D1.3.1

Manual Ethics and Privacy Issues for PLAYTIME

Work package	**WP1 User Centered Design for Social Innovation**
Task	**T1.3 Ethics & Privacy Manual**
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Project PLAYTIME

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Contents

1 Introduction

Ethical issues as well as preconditions to develop the enabling and key technologies for the final achievement of the PLAYTIME objectives has to be investigated. Furthermore, privacy, trust and data security will be investigated and determined in order to strengthen the confidence in the service. Privacy is a highly important issue for the end user's confidence in the technological solution. This document sets out the ethical principles and privacy procedures underlying professional performance and attitudes at the PLAYTIME consortium. It provides concrete actions for the PLAYTIME consortium how to take ethical and privacy issues into account. Therefore, the national guidelines, codes and laws about medical research in The Netherlands and Austria were the basics for this document.

2 Research Ethics Committees

2.1 European Research Ethics Committees

Today, the ethical review of medical research projects which involve human participants has become a mandatory standard that is reflected in national laws as well as in supranational and international documents. Not only those people who are willing to participate as subjects in research projects, but also both researchers undertaking projects and the general public have come to expect that an independent review process is in place which ensures the highest degree of protection possible and, more generally, that research is carried out in an ethically acceptable manner. This has been a relatively short journey. In the early second half of the 20th century review bodies started to emerge, mainly as a form of self-regulation of the medical profession and often in an ad-hoc form responding to concrete problems. However, in the past decades Research Ethics Committees (RECs) have, in most European countries and worldwide, been established as permanent and independent bodies. As such they build, at least in Europe and other western countries, the core of a robust infrastructure which monitors and reviews research projects. (http://www.eurecnet.org)

2.2 National Research Ethics Committees

2.2.1 Dutch Medical Research Ethics Committee system

There are 24 accredited Medical Research Ethics Committees (MRECs) in the Netherlands that review medical/scientific research proposals. The majority are linked to an institution such as an academic medical centre or a hospital. Research covered by the Medical Research Involving Human Subjects Act must be submitted to an accredited MREC for approval before it is carried out. In some cases, the Central Committee on Research Involving Human Subjects (CCMO in Dutch: 'Centrale Commissie Mensgebonden Onderzoek') acts as the MREC. The MREC reviews protocols in accordance with the rules laid down in the Dutch law; the Medical Research Involving Human Subjects Act (WMO).

Research subject to the WMO cannot be carried out without a positive judgment. Drugs trials, medical devices and genetic research are all covered by the above-mentioned WMO. The MREC's review all clinical trials on investigational medicinal products as well as non therapeutic observational studies, and the CCMO reviews medical research in the field of gene therapy, iRNA, anti-sense oligonucleotides, (stem) cell therapy, xenotransplantation and non-therapeutic interventional studies with minors and incapacitated subjects. Research with spare embryos and IVF technology (e.g., embryonic stem cell research) is covered by the Embryos Act and are reviewed by the CCMO http://www.ccmo.nl. Both the accredited MREC's and the CCMO are independent governmental bodies with a legal status that reach a legally

binding decision on research protocols, and thus are not advisory boards. Only accredited research ethics committees (MREC's or the CCMO) can review biomedical research with human subjects. The criteria for accreditation are laid down in the WMO.

The Central Committee (CCMO) is responsible for the accreditation of MREC's. If an MREC no longer fulfills the criteria, the CCMO can withdraw the accreditation. Only one decision of one accredited MREC is required for research projects in the Netherlands including multicentre research.

Networking between RECs:
The Dutch Association of Medical Research Ethics Committees (NVMETC in Dutch: 'Nederlandse Vereniging voor Medisch Etische Toetsingscommissies') is a platform for MREC's in the Netherlands. The goals of the NVMETC are fostering best practices in judgment by MREC's, fostering the quality and harmonizing the implementing of legal criteria, discussing medical ethical issues, maintain relationship with other relevant bodies like the CCMO and provide information for its members. One of the main goals of the Association is quality improvement of the accredited MREC's. The NVMETC developed a quality improvement programme for MRECs by peer-to-peer review. Another main task is supplying relevant news and information to its members by a Newsletter (Forum) and organizing seminars for information and discussion on actual topics and practical issues. Furthermore the NVMETC set up a training programme for MREC members and its secretaries. All the Dutch MREC's are member of the NVMETC (24 accredited and 34 not-accredited local committees). More information can be found on http://www.nvmetc.nl.

2.2.2 Austria Research Ethics Committee system

There are about 26 ethics committees (ECs) in Austria including 9 federal state regional ECs and a number of local ECs. For multi centre drug trials 7 so called 'leading ECs' may provide a single opinion: EC of the Medical University of Vienna, EC of the City of Vienna, EC of the Medical University of Innsbruck (Federal State Tyrol), Medical University of Graz (Federal State Styria), EC of the Federal State Lower Austria, EC of the Federal State Upper Austria, EC of the Federal State Salzburg.

The 3 university ECs are established under the University Act, most of the others under the Hospital Acts of the provinces (federal states).

In 8 of the 9 states (Vienna is city and state) the EC of the state (Landes-Ethikkommission) is also responsible for research outside of hospitals (according to the Drug Act and the Medical Devices Act). Only in one state (Styria) an EC is established solely for research outside of hospitals under the Drug Act and the Medical Devices Act. In Vienna the university EC is responsible solely for the university hospital and the EC of the city of Vienna serves as state EC (responsible for other hospital of the City of Vienna = State of Vienna) and for research outside of hospitals. In Tyrol the university EC (Innsbruck) serves also as state EC and is responsible for research outside of hospitals. In Styria the university EC (Graz) is responsible for the university hospital and for all other state hospitals, but not for research outside of hospitals. Aside from the university and the state ECs there are smaller ECs responsible for only one (non-state) hospital and one EC was established by the Association for Clinical Pharmacology (Österreichische Arbeitsgemeinschaft für Klinische Pharmakologie und Therapie

und Institut für Hypertoniker).The supervising authority for the ECs is the Federal Office for Safety in Health Care (Bundesamt für Sicherheit im Gesundheitswesen).

The central EC in the province of Styria with the city o Graz being its capital is the "Ethikkommission der Medizinischen Universität Graz" [1] (MEDUNI Graz). There is a meeting of the board members[2] approximately every month[3] with a submission deadline being approximately 3 weeks before that meeting date.

Partner JOANNEUM RESEARCH has experience in receiving ethical approval for many years and from this is highly knowledgeable about how to prepare and process an application to the EC at the MEDUNI Graz.

Networking between RECs:
Since 1997 the Austrian ECs are represented by the 'Forum of the Austrian Ethics Committees'. It provides a list with 26 ethics committees, registered with the Forum and which use and accept the forms and guidelines, distributed by Forum.

The Forum provides a basis for exchange of experiences and for the harmonisation of the functioning of the ECs. It issues forms for the communication with the ECs as well as guidelines on various topics.

In 2000 the Forum initiated an annual advanced training course for members of ethics committees which is organised by the Centre of Ethics and Medicine of the Lower Austria State Academy (Zentrum für Ethik und Medizin der Niederösterreichischen Landesakademie).

Moreover, the Forum serves as contact for the legislative and the supervising authorities. The organs of the Forum are the general assembly and the board. The general assembly meets once a year during the annual Forum meeting, board meetings are scheduled once or twice a year. External Link: http://www.ethikkommissionen.at/

[1] https://www.medunigraz.at/ethikkommission/Graz/

[2] https://www.medunigraz.at/ethikkommission/Graz/Mitgl/index.htm

[3] https://www.medunigraz.at/ethikkommission/Graz/SitzTerm/index.htm

3 Contents of the Ethical Guidelines

3.1 Ethical aspects

The relationship between researchers and research participants is the ground on which human research is conducted. Values and principles including respect for human beings, research merit and integrity, justice, and beneficence, help to shape that relationship as one of trust, mutual responsibility and ethical equality. The WMO was set up to protect human subjects on the following aspects:

- Research that falls under the WMO must be reviewed on its medical/scientific and ethical aspects.
- The research subject must be provided written information on the research.
- An independent expert must be present to inform the research subject.
- Written consent must be obtained by the research subject prior to participating in the research.
- Insurance must be taken out to cover damage endured by the research subject.
- The law imposes requirements on research involving subjects under the age of 16 and incapacitated adults.
- Those carrying out the study must ensure that the privacy of the research subject is protected to the greatest degree.

3.2 Research Conditions

A committee can only issue a positive decision if the following conditions are met (section 3 WMO):

- The scientific research contributes to new insights in the field of medicine.
- There are no simpler or less intrusive alternatives (for example; preferably no minors or incapacitated subjects).
- The importance of the research is in proportion to the objections (burden) and the risks to the research subjects.
- The study meets the scientific requirements for research.
- The research is led or carried out by professionals.
- Any financial compensation for the research subject does not form part of the reason for participating in the research.
- The protocol states the extent of the benefits for the subjects as a result of participation in the study (in the case of group therapy: the benefits for the group to which the subject is assigned).

3.3 Research Protocol

This chapter provides a description on how to build a research protocol. From the Dutch and Austria ethical committees there is a template available for the admission of a research protocol. The following topics have to take in consideration;

1. INTRODUCTION AND RATIONALE

The research protocol must contain an introductory section explaining why the research is to be carried out. The scientific and social relevance of the project should be indicated.

2. OBJECTIVES

The objectives of the study are the questions that the study is intended to answer and are based on the scientific rationale and/or hypothesis formulated.

3. STUDY DESIGN

Provides a description of the study design (examples of intervention studies are: double-blind randomized placebo-controlled trial, cross-over trial; examples of observational studies are: (nested) case-control study, cohort study), the duration and setting of the study.

4. STUDY POPULATION

The research population should be clearly defined. From what source population will the subjects be drawn? What is the likelihood that the planned number of patients can be recruited from the defined source population? If relevant, prevalence/incidence number should be given. The characteristics of the study population should be given (age, sex, ethnic background (if relevant), etcetera)

The number of subjects required for the study should be justified. The number of subjects should always be large enough to provide a reliable answer to questions addressed. Also the size of detectable differences should be of clinical relevance. The number of subjects is usually determined by the primary objective of the trial. If the sample size is determined on some other basis, then this should be made clear and justified. There are many formulas to calculate the size of the study population. It should be clear which method is used and the reasons why this method has been chosen.

5. TREATMENT OF SUBJECTS

Intervention studies are studies in which the investigator deliberately intervenes in the consisting situation, in order to study the effect of that intervention.

6. INVESTIGATIONAL PRODUCT

This chapter is not applicable for PLAYTIME but for research with any product; medicinal product, food product, medical device or other.

7. NON-INVESTIGATIONAL PRODUCT

This chapter is applicable for any other product that is used in the study, like challenge agents or products used to asses end-points in the trial . This can be a medicinal product or a food product or a chemical compound or stable isotope or other product.

This chapter does not include co-medication or escape medication, these are already mentioned in chapter 5. For products to be used as in usual clinical practice the information can be limited to specific chapters

8. METHODS

Describe the main study parameter/endpoint, for example number of events/relapse, blood hormone levels, etcetera. The protocol must contain a detailed description of the procedures that subjects will undergo in the course of the research. It should be clearly indicated which procedures are part of the medical treatment and which are extra for this study and whether diagnostic procedures or treatment will be postponed. Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

9. SAFETY REPORTING

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

10. STATISTICAL ANALYSIS

Describe in detail how the primary analysis will be done for the primary outcome parameter(s) in order to avoid subjective choices to be made during the analysis. Discuss how the type I error will be controlled in case of multiplicities and what the impact is of the multiplicity corrected alpha if needed, with regard to the power of the study. Any other analyses of the primary study parameter(s) should be labeled as such and must be separated in the text from the description of the main analysis above. If multivariable methods are used the list of covariates needs to be specified.

11. ETHICAL CONSIDERATIONS

In this chapter it can be stated that the study will be conducted according to the principles of the Declaration of Helsinki (version, date, see for the most recent version: www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts (if applicable).

Give a description of the recruitment and informed consent procedures. How and by whom (investigator, supervising doctor, other person) will subjects be informed about the study and asked for their consent? How much time will they be given to consider their decision? The patient information letter and informed consent form should be attached as a separate document.

Specify which code of conduct is applicable for minors and/or incapacitated adults participating in non-therapeutic research. This should also be specified in the informed consent letter.

Give a justification of the proposed study and about the liability insurance and the insurance for the subjects participating in the study. The sponsor or investigator should also have a liability insurance.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

Data should be handled confidentially and if possible anonymously. Where it is necessary to be able to trace data to an individual subject, a subject identification code list can be used to link the data to the subject. The code should not be based on the patient initials and birth-date. The key to the code should be safeguarded by the investigator or an independent person/committee (e.g. notary) in case the data or human material is kept for a longer period of time(see also the code of proper use: www.fmwv.nl). The handling of personal data should comply with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp). On the website of the CCMO (www.ccmo.nl) the CCMO

statement on publication policy can be found. This statement contains the basic principles of the CCMO's position on the disclosure/ publication of research results obtained form studies involving human subjects. It is the opinion of the CCMO that the results of scientific research involving human subjects must be disclosed unreservedly.

13. STRUCTURED RISK ANALYSIS

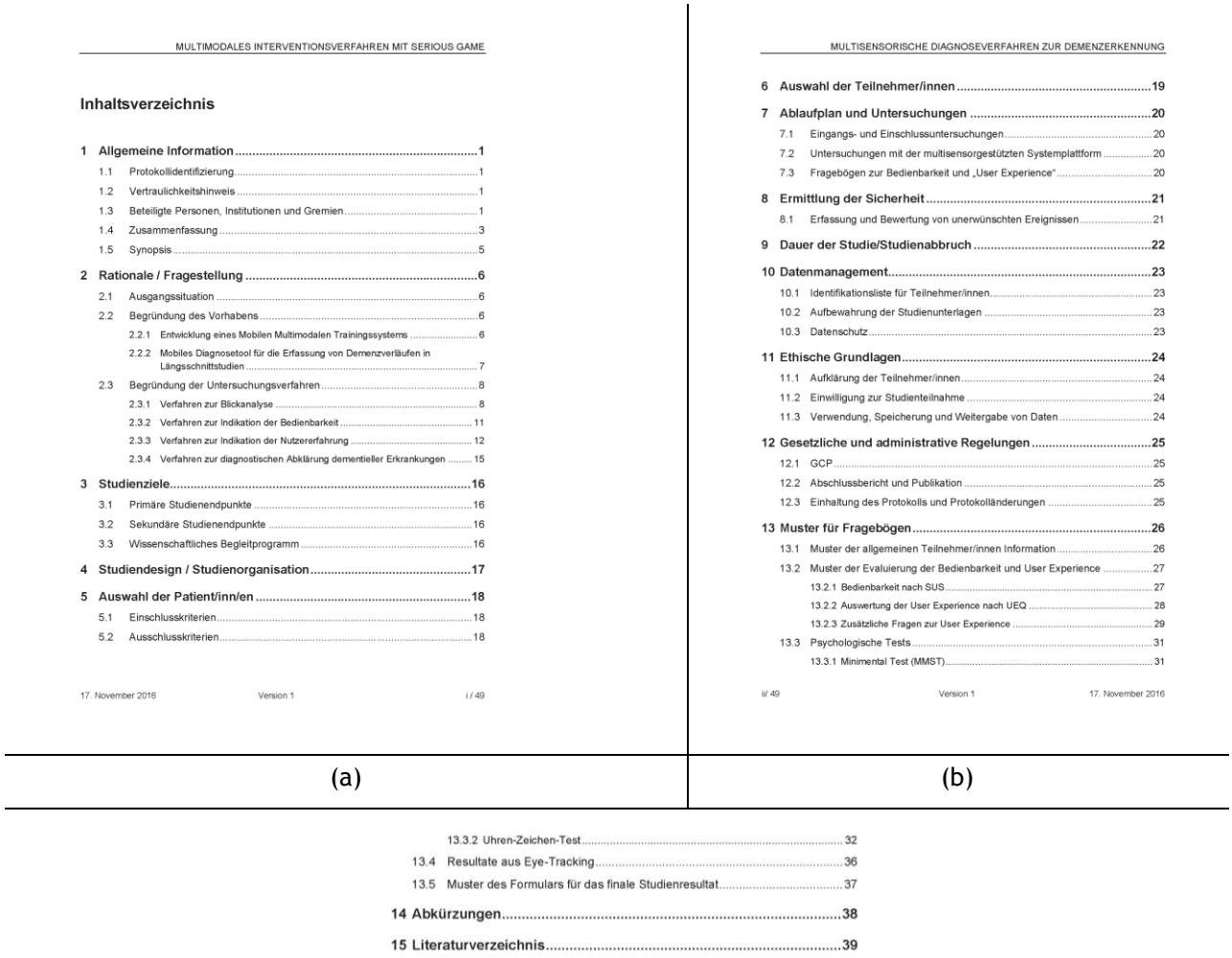
In this final paragraph of the research protocol a structured risk analysis which consists of a number of steps is required. The analysis should result in a comprehensive overall synthesis of the direct risks for the research subjects in this study. The risk considerations on the various issues (http://www.ccmo.nl/en/standard-research-file) should be supported by up to date information and should be clearly described to allow a thorough review by the METC. For details one may refer to the previous chapters, the Investigator's Brochure or a similar document (if applicable), peer reviewed papers in (biomedical/scientific) journals.

Make clear what measures have been taken to reduce what risks. Make clear why in your opinion the remaining risks are acceptable for the subjects participating in the study.

14. REFERENCES

Include all key references published in peer reviews journals that are relevant for the study and are discussed in the protocol. Do make sure that the references are up to date.

Figure 1 depicts an example of an Austrin research protocol, processed with ethical approval within the national project "AktivDaheim".



MULTIMODALES INTERVENTIONSVERFAHREN MIT SERIOUS GAME

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MULTISENSORISCHE DIAGNOSEVERFAHREN ZUR DEMENZERKENNUNG

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(b)

(c)

Figure 1. Contents from an Austrian research protocol ("Studienplan") that identifies formal details of an intervention study.

3.4 Patient Information

Potential human subjects must be provided with written information on the research prior to being asked for consent. The following aspects must be covered:

- Aim, nature and duration of the research (how, what and why with regards to the study, but also which procedures, when, for how long and how often).
- The risks and objections to the research subject with regards to the research.
- The possibility to withdraw from the study during its course, taking into consideration any risks to the participant in doing so.
- The necessary information on the independent expert.
- The necessary information on the patient insurance.

The patient information must be written in such a manner that every participant can understand it. The language level of the texts must be written with the target group in mind. In cases of

research incapacitated subjects such as people with advanced dementia, mentally handicapped, or people with a severe psychological disorder, they will be excluded at PLAYTIME.

See the **codes of conduct** put together by the groups of professionals.

- Code of conduct minors
- Code of conduct mentally disabled
- Code of conduct incapacitated elderly

3.5 Informed Consent

Persons who participate in medical/scientific research must give prior written consent. They must be given enough time to come to an informed decision between the moments of being informed and being asked to provide consent. The period of time deemed reasonable to come to this decision depends on the type of study. Adults, capable subjects sign their own form of consent. When people with advanced dementia, mentally handicapped, or people with a severe psychological disorder, they will be excluded at PLAYTIME.

3.6 Independent expert

Subjects have the right to information and to ask questions. Not just prior to, but also during the research. The sponsor of the study is responsible for providing this information and answering difficult questions. He/she is also compelled to appoint an independent doctor or other independent expert to whom the participant can go to with questions. An independent doctor or other independent expert is:

- preferably not employed as partner of the sponsor, and
- not employed by the sponsor's company, and
- if employed by the institution where the research is being carried out, then should not be involved in the research

The expert may not have personal interests in the (inclusion of patients in the) research. He/she must be adequately knowledgeable in the field of the specific research and be easily contacted by the participants.

3.7 Insurance

Research that falls under the scope of the WMO must be provided with primarily two insurances. Subject insurance (see standard research file, part G1) and liability insurance (see standard research file, part G2)

3.8 Research data, coding and privacy

3.8.1 Personal data

The Medical Research Involving Human Subjects Act (WMO) states that the person responsible for carrying out the study must ensure that the privacy of the participating subject is protected to the highest possible degree. Part of this is ensuring that registration of research data must in principal take place anonymously, in such a way that no personal information is stated during the gathering of data.

If it is necessary to trace back research data to a person, then a unique fictive code must be used. This code must prevent the data being traced back to the person involved. Initials and/or date of birth as part of or in addition to the code are detrimental to the aim of the code, so much so that the CCMO has deemed this to be principally non-acceptable. The encryption key must be secure. The protocol must state who has access to the key.

3.8.2 Processing personal information

Data which can be traced back to a person can only be used in order to determine the age of a participant if this is necessary for the specific research or if using this data is necessary for controlling the accuracy of the data. This may be part of the date of birth together with the unique code number on research forms. It concerns situations whereby a different coding is not sufficient and the importance of controlling the data on the basis of the date of birth is so great, that this cannot be sufficiently solved in another manner.

Using the full date of birth is not necessary. Using a part of the date, such as the year of birth, is then sufficient. And even then this is only allowed for the sake of gathering data and not for use in all documentation – otherwise personal information would always form part of the coding.

If the use of initials may lead to the direct identification of a research subject, they should not be used. However, there might be cases in which the omission of initials may increase the risk of failures in the data collection. In that case the use of initials is acceptable, provided this is mentioned explicitly in the informed consent.

The Personal Data Protection Act (Wet bescherming persoonsgegevens, Wbp, in Dutch) applies to the handling of personal details.

4 Material on privacy drafts

4.1 Privacy functionalities and issues for using PLAYTIME

Concerning the privacy of subjects working with playtime, especially patient information we should be aware of some privacy functionality and issues.

- Server security and monitoring
  - Servers have to be up to date and the software used should be standardized
  - Different monitoring scenarios should ensure that
    - ✓ The provided service is always available
    - ✓ Security breaches are detected (process monitoring, data transfer monitoring, IP checking)
- Secure data storage (Intrusion, data loss)
  - Data loss must be made impossible (realized via RAID-system and backups)
  - If the data storage is compromised some data should be hashed or encrypted so that the intruder will not have direct access to this data
  - It should be checked of data pseudonymization can be done on database level too
- Encryption of communication
  - All communication between the apps, servers and backend must be encrypted (via SSL)
  - It should be checked if we want to use a VPN for the connection to the server too
- Data anonymization
  - Especially for tasks or exports (API) on data it must be possible to anonymize the data (k-anonymity!)
  - It should be checked if a different scope of anonymization in the backend is possible
- Data pseudonymization
  - Should patients personal data ever be entered in the backend or should we work always and only with data pseudonymization within the playtime system?
  - Especially for tasks or exports (API) on data it must be possible to pseudonymize the data

5 Conclusions and Outlook

5.1 Flowchart ethical approval PLAYTIME

1) Writing a research proposal based on the following format http://www.ccmo.nl/attachments/files/model-onderzoeksprotocol-08102015.docx

2) Investigate if the research is fulfilling the National guidelines of the Netherlands and/or Austria has to approved by the national ethical boarder (MREC). If so, following the national procedure of MREC.

3) If the research proposal don't met the criteria for medical research, the research proposal have to approved by the Psychological ethical commission in the Netherlands via Tilburg University (PETC). The PETC will check the scientific value of the proposal and the practical feasibility of the research.

4) Submission of the research proposal, example of an informed consent and an information letter for the people living with dementia at the internal science committee of GGzE. In the Netherlands all University Medical Centers and large mental healthcare centers do have a internal science committee. This committee check the substantive value of the research, and the feasibility of the research. Furthermore, it issues a statement of the conducted organizations requested by the MREC.

Researchers have to be aware that the duration of an approval process takes three to six months. This is important for starting to include participants for the research.

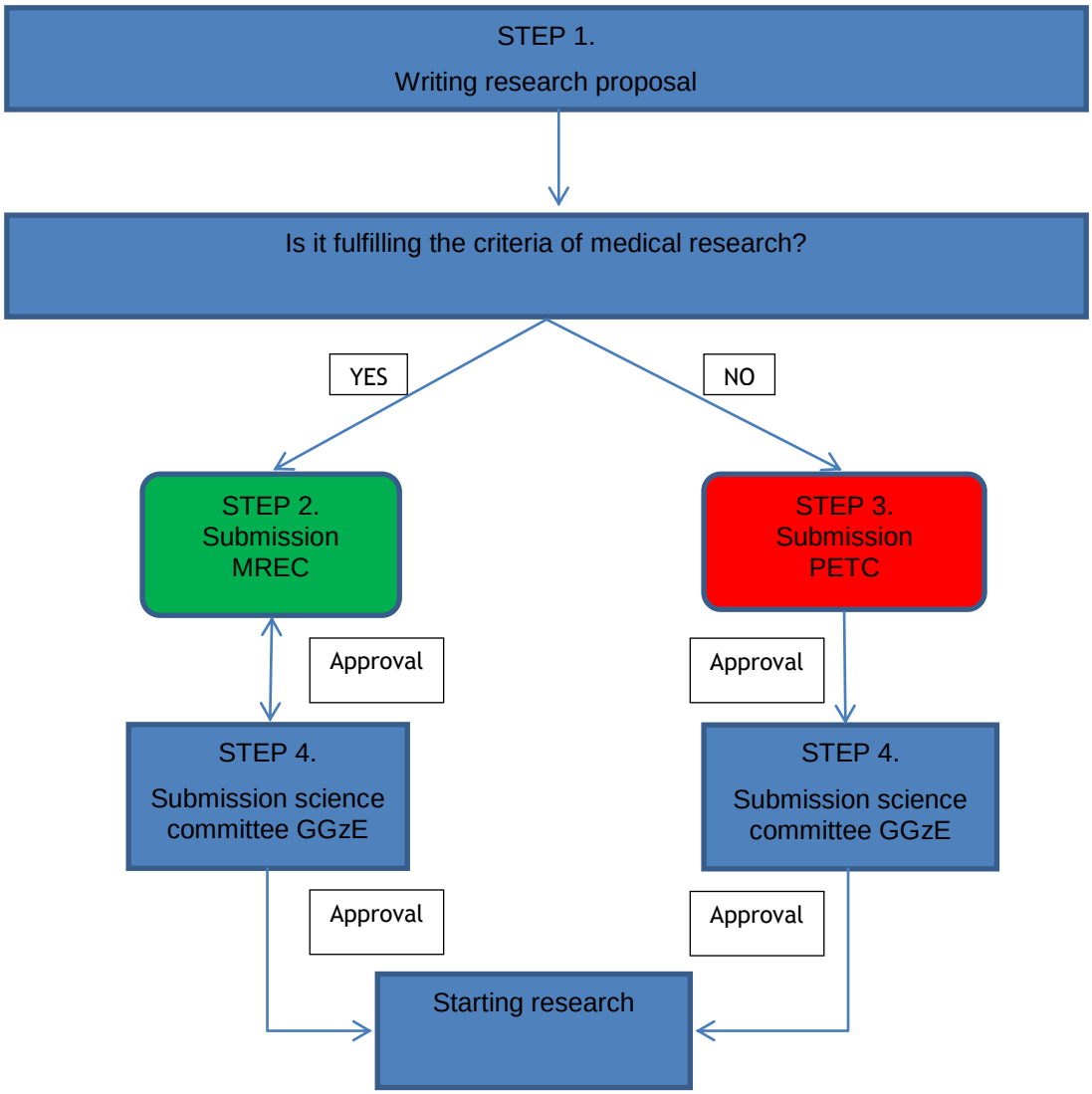

Figure 1. Flowchart ethical approval.

6 Glossary

Table 1. *Glossary.*

Notion	Description
Ethics	Ethics or moral philosophy is a branch of philosophy that involves systematizing, defending, and recommending concepts of right and wrong conduct. (Internet Encyclopedia of Philosophy "Ethics")
Human Research	Human subject research is systematic, scientific investigation that can be either interventional (a "trial") or observational (no "test article") and involves human beings as research subjects. Human subject research can be either medical (clinical) research or non-medical (e.g., social science) research. (Research Administration, University of California, Irvine. Retrieved 2012-01-04).
Information privacy	Information privacy, or data privacy (or data protection), is the relationship between the collection and dissemination of data, technology, the public expectation of privacy, and the legal and political issues surrounding them. (Wikipedia)

7 Abbreviations

Table 2*. Abbreviations.*

Abbreviation	Description
REC	Research Ethics Committees
MREC	Medical Research Ethics Committee
CCMO	Central Committee Human Research (In Dutch; Centrale Commissie Mensgebonden onderzoek)
WMO	Medical Research Involving Human Subjects Act (In Dutch; Wet Medisch Onderzoek)
iRNA	Inference ribo nucleic acid
IVF	In-Vitro Fertilisation
NVMETC	In Dutch: 'Nederlandse Vereniging voor Medisch Etische Toetsingscommissies
EC	Ethics Committees
IP	Internet Protocol
RAID	Redundant Array of Independent Disks
SSL	Secure Sockets Layer
VPN	Virtual Private Network
API	Application Programming Interface
PETC	Psycological ethical commission

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