A Personalised Integrated Care Platform

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1 Executive Summary

The PICASO project aims to build a service oriented, ICT based integration platform that will support collaborative sharing of care plans across sectors based on dynamic and personalised orchestration of care services. The PICASO project will conduct two separate but complementary use case driven trials for proof-of-concept demonstrators of integrated care. As the trials involve real patients the PICASO project is committed to follow standard ethical guidelines for research involving human subjects. This deliverable and the establishment of the PICASO Ethical Board represent two important initiatives to ensure that the project and its trials are conducted in an ethically responsible and sound manner.

This deliverable presents the PICASO Ethical Guidelines which have been defined for the project and which all project partners have committed to honour. The PICASO Ethical Guidelines are based upon four Ethical Principles: Respect for Persons, Beneficence, Justice, and Respect of Confidentiality and Privacy.

The PICASO Ethical Board, consisting of both project partners and external experts, and its Terms of Reference were on 25 May 2016; the board also had its first board meeting on this date. The content of this deliverable stems in large part from the discussions and agreements made at the board meeting. The PICASO Ethical Board will act to ensure that the PICASO project trials are executed in an ethically sound manner and in accordance with relevant national and international ethical and legal requirements for trials involving human subjects (here patients). The PICASO Ethical Board is an *advisory body* to both project partners and to the participating patients in the trials. As such, it cannot make any formal decisions that affect the entire project status or the trials; these can only be made by the PICASO Project Board or the European Commission.

Certain ethical issues are particularly relevant in the context of the PICASO trials and special attention will be given to these in order to ensure that trial participants' ethical rights are protected and that any concern of ethical nature is resolved. The ethical issues are: Informed Consent, Autonomy, Dignity, Stigmatisation, Inclusion, Privacy and Data Protection, and Clinical Incidental Findings.

In order to support the ethical execution of project trials, an Ethical Check List has been defined which should be used as a support tool for trial owners to check if they have considered the issues that have ethical implications. The Ethical Check List is a tool to protect the patients who participate in the trials, but it can also be used as a tool for evaluation of the trial's ethical obligations. Informed Consent is a prerequisite for ethically sound trials, and the process that should be followed by trial owners when obtaining informed consent has therefore been described in detail.

When conducting a trial involving human subjects, there are a number of local, national and international policies, regulations and laws. The most relevant ones are listed in this document and will be taken into account in the project. The project has a moral and ethical responsibility to ensure compliance with applicable laws.

2 Introduction

The PICASO project aims to build a service oriented, ICT based integration platform that will support collaborative sharing of care plans across sectors based on dynamic and personalised orchestration of care services. It will further provide a method for sharing patient information across all relevant formal and informal care providers using a unique, trust federated solution to the problem of data privacy in cloud based health systems.

The vision of the PICASO project is that it will become a Europe-wide Continuum of Care service platform that will:

- improve cooperation and exchange of knowledge between professional caregivers in health, rehabilitation and social care domains and actively include patients and their relatives in the integrated care settings to support patient empowerment and self-care;
- bring about improvements in health outcomes, daily activities, and quality of life of people with multi-morbidities by personalising care management programmes to specific characteristics of the patients' profiles and support adherence to care plans at the point of need;
- reinforce medical knowledge and create new care models for management and treatment of patients with multi-morbidity conditions;
- allow more cost-effective care management through increased skills and collaboration of care professionals and more automated and efficient workflows, which eventually will lead to better health outcomes and a reduction in hospitals admissions, and thus contribute significantly to the sustainability of health and social care systems in Europe.

The PICASO platform development will be complemented by sociological and economic research aimed at understanding ethical, social and business aspects of the integrated care platform. Research on patient involvement will provide insight into ethical localism focusing on opportunities in patient empowerment and issues such as autonomy, privacy, fear of surveillance, and stigmatisation. Further, usability aspects, inclusion and techno-animism will be studied to help improve the design.

The PICASO project will conduct two separate but complementary use case driven trials for proof-of-concept demonstrators of integrated care. The purpose of the trials is 1) to demonstrate the concept of the PICASO platform and its components, and 2) to validate the impact on the effectiveness of care systems and acceptance by the wider group of stakeholders, patients, relatives and the society at large.

The trials will involve actual patients who have been diagnosed with either Rheumatoid Arthritis (Trial 1) or Parkinson Disease (Trial 2). Both groups will also have been diagnosed with cardiovascular disease as a co-morbidity. Trial 1 will be run by project partner UDUS in Germany and Trial 2 will be run by project partner UTV in Italy. A preliminary description of the two trials is available in Appendix A and B. The forthcoming deliverable, D8.1 Trial Definitions for Integrated Care Management, will provide a detailed description of the trial layout and protocols.

2.1 Purpose, context and scope of this deliverable

As the trials involve real patients the PICASO project is committed to follow standard ethical guidelines for research involving human subjects. In the beginning of the project, the PICASO Ethical Board was therefore established as an advisory entity. The PICASO Ethical Board consists of both of internal members (i.e. project partners) and external members to ensure a degree of objectivity. The PICASO Ethical Board had its first meeting on 25 May 2016 where the ethical issues relevant to the project and the two trials were discussed and the PICASO Ethical Guidelines and Principles were defined. The discussions and conclusions from this first Ethical Board meeting form the basis for this deliverable. The agenda is available in Appendix C.

This deliverable documents the PICASO project's Ethical Principles and as such is aimed at all project partners. Project partners have a common interest in working together in accordance with the project's Ethical Principles. The Ethical Guidelines that are set out in this deliverable are primarily directed towards the trials and how they are to be conducted. In particular, the partners directly involved in the trials and with the trial participants are expected to follow the guidelines and consult these as necessary. Overall, it is presumed that this document will be consulted and referred to throughout the PICASO project's lifetime as a reference guide to ensure that the PICASO project and its trials upheld a high ethical standard.

2.2 Content and structure of this deliverable

Chapter Three defines the PICASO Ethical Boards Terms of Reference and the members of the Ethical Board are briefly presented. In Chapter Four the ethical issues that are considered most relevant in the PICASO context are briefly described in general terms and in the context of the PICASO trials. The PICASO Ethical Principles and Guidelines are presented in Chapter Five. The Guidelines are particularly aimed at the trial owners and their main purpose is to protect the ethical rights of the patients who will participate in the trial. Finally, in Chapter Six the most relevant International and EU policies, charters and regulations which PICASO must comply with are listed. The appendices contain descriptions of the two trials and the agenda for the Ethical Board meeting.

3 PICASO Ethical Board Terms of Reference

The PICASO Ethical Board Terms of Reference were defined and agreed at the Ethical Board meeting on 25 May 2016.

3.1 The PICASO Ethical Board Roles and Responsibilities

The PICASO Ethical Board will act to ensure that the PICASO project trials are executed in an ethically sound manner and in accordance with relevant national and international ethical and legal requirements for trials involving real patients. The PICASO Ethical Board is the highest authority on ethical matters *within* the PICASO project, only subject to mandatory EU, national, institutional ethical principles and regulations. The PICASO Ethical Board will of course also be subject to the trials' internal ethical boards, principles and regulations.

The Ethical Board has a responsibility to ensure that the PICASO Ethical Principles are known to all project partners and that they are committed to work according to these principles. The Ethical Board is thus responsible for advising project partners as required to ensure that agreed procedures are implemented and conducted correctly. The Ethical Board will act both as an evaluator and as support to the project trials in all matters of an ethical nature.

The Ethical Board also has a high responsibility towards all potential and actual patients who will participate in the project trials to protect their rights. The Ethical Board must thus safeguard the privacy, dignity, informed consent, and confidentiality of all trial participants The Ethical Board must ensure that trial participants are given information about the board and its role in the project trial and how to contact board members if necessary.

The Ethical Board will thus be available on demand meaning that should a project partner or a trial participant have any ethical concerns in relation to the project/trials, they may contact the Ethical Board in writing stating the nature of the concern and its potential consequences for the project. The Ethical Board will subsequently consult the project's Ethical Guidelines as well as the relevant national and international regulations (if necessary), in order to determine the nature of the issue and propose a resolution. The Ethical Board will always strive to find a resolution that is acceptable and/or feasible for the project partner(s) in question and will therefore consult with the project partner(s) before a resolution is finally determined. In addition, in particularly complex situations, the Ethical Board may want to consult with additional external experts. This may also be the case if the Ethical Board members cannot agree on a solution.

If a violation of the Ethical Guidelines or of a participant's rights is at stake as a result of the running of a pilot, and cannot be resolved within the pilot, the Ethical Board may request that the pilot is temporarily stopped until the matter is resolved.

Specifically, the Ethical Board will carry out the following activities:

- Define the Terms of Reference;
- Define the PICASO Ethical Principles and see too that they are honoured by all project partners;
- Establish the Ethical Guidelines for the project trials and monitor that the trials comply. This includes approving the Annual Compliance Monitoring Reports, collect the Ethical Check List from each trial, and monitor that informed consent forms have been collected from all trial participants;
- Check that necessary approval from national/local ethical committees have been obtained by the trial owner prior to their start;
- Ensure that clinical protocols for the trials follow the ICH-GCP as well as the European (Directive 2001/20/EC) and national legislations and monitor that the trials are being carried out in accordance with the clinical protocols;
- Act as *advisor* for project partners if or when ethical concerns appear and, in cooperation with the relevant project partner(s), come up with a way to resolve the issue at hand and define a way forward. This also means that the Ethical Board may intervene by giving advice and suggestions if it judges that i) there is a potential ethical issue arising which requires attention or ii) if a trial is not complying with the project's Ethical Guidelines;

- Act as *advisor* for patient participants in the trial (potential or actual) on questions, concerns and/or problems of an ethical nature. If a violation of the Ethical Guideline or of a participant's rights is at stake as a result of the trial, and cannot be resolved within the trial, the Ethical Board may advice the PICASO Project Board and the trial owner to temporarily stop either the particular patient's participation in the trial or the entire trial until the matter is resolved. Only the PICASO Project Board has the authority to temporarily (or permanently) stop the patient's participation or the trial (in accordance with the consortium agreement and relevant contracts), or to make any final decisions that would affect the project and the trials;
- The Ethical Board will ensure that the appropriate action is taken if any ethical problems are reported by project partners and/or other participants. The Ethical Board is obliged to take action within two weeks from the receipt of the report and/or complaint. The rapporteur/complainant must be informed hereof at the same time and be kept updated of the progress and final resolution. The PICASO Project Board must also be informed. The Ethical Board will in this respect be the direct point of contact for the European Commission in cases of ethical issues.
- The Ethical Board will have regular meetings throughout the duration of the PICASO project;
- Call for extraordinary board meetings if so required.

The first Ethical Board meeting took place on 25 May 2016, which prior to the start of any trials. The main aim of this first meeting was to agree on the Terms of Reference, Ethical Principles and Applications, and the Ethical Check List (see agenda in Appendix C).

3.2 Membership of the Ethical Board

The Ethical Board will consist of a Chair, a minimum of three and a maximum of six internal members (project partners), and a minimum of two external members and a maximum of five. The internal members must include at least one trial representative from each of the two trials. Members must be both men and women.

The Chair and the members have been (are) appointed by consensus by the PICASO consortium. The external experts are proposed by project partners and subject to acceptance by the consortium.

The internal members who have been selected to sit on the PICASO Ethical Board are:

- Trine F. Sørensen – Chair (IN-JET)
- Jutta Richter (UDUS) – Trial 1 Owner
- Agostino Chiaravalloti (UTV) – Trial 2 Owner
- Paul Quinn (VUB) – Legal expert

The external expert members who accepted to sit on the PICASO Ethical Board are:

- Christopher Buckingham, Senior Lecturer, Computer Science, Aston University, Birmingham, UK.
- Robin Wilton, Technical Outreach Director for Identity and Privacy, The Internet Society's Trust and Identity Initiatives group
- Dieter Wiek, Chair of EULAR (The European League against Rheumatism) Standing Committee of PARE (People with Arthritis/Rheumatism in Europe).

4 PICASO Ethical Issues

The most relevant ethical issues to PICASO are briefly described here. The list is by no means exclusive nor does it imply that other ethical issues will not be considered nor dealt with in the project. However, as the most relevant ethical issues, they are closely linked to the Ethical Principles (see Chapter 4). The issues should not be seen as completely separated; rather they can be interlinked in various ways, as well as implicating other matters of an ethical nature.

4.1 Informed Consent

Informed Consent is generally seen as guaranteeing that research involving human subjects, especially in a clinical or medical context, is ethically sound; however, Informed Consent per se can raise ethical issues. It is thus important to address the context and manner in which informed consent is collected, and it is important to be aware of the inherent power relations within the informed consent process. For example, power and authority structures are deeply embedded in the doctor-patient relationship and can easily affect the informed consent process.

In the context of PICASO and the technologies that will be developed and tested, informed consent is an important step towards overcoming the ethical problems related to privacy and data protection, surveillance, and autonomy. Informed consent allows the user/patient to exercise control over his/hers personal data by determining who has access to what information and when.

Informed Consent will be collected from all participants in the PICASO trials prior to their commencement in the trial. Informed Consent will be collected following the three steps outlined in the “Application” of the Ethical Principle: “Respect for Persons” (see Table 1). This process includes guidelines for the manner and context in which Informed Consent should be collected in order to ensure that the process per se is ethically sound.

4.2 Autonomy

An essential ethical problem with the use of ICT in healthcare concerns the notion of autonomy. On the one hand, healthcare and assistive ICT may reduce patients’ dependency on consultation with physicians to enable a less restricted daily life, and/or increase patient’s self-determination. On the other hand, the technology may threaten the patient’s autonomy in the sense that it generates a new type of dependency, i.e. on the new technology, and creates a huge amount of personal data beyond the patient’s control. However, dependency may vary with respect to the use of the technology in question. To enable self-determined use of the technology, patients should be educated in understanding its purpose and how to use it effectively.

Autonomy includes having control of the system/devices, i.e. that the (informed) user is able to switch it on or off. One may here ask what is the point if users can freely switch the system/device on or off? However, the issue is in reality not different from the traditional healthcare setting where the patient may choose whether or not to follow the doctor’s orders. The ethical requirement here is that the patient is made fully aware of the consequences of non-concordance.

The participants in the PICASO trial must be informed of their free choice to opt out at any point in time and that it will have no consequence for their “pre-trial” treatment plan. Participants should also be made aware of what will happen after the trial ends, e.g. what will happen to the devices they have been using or had installed. There is an obvious ethical problem of offering a service for a limited time only and participants should therefore be made fully aware of any limitations, particularly with respect to post-trial.

Another interesting aspect is the notion of techno-animism which may also have some ethical implications and it will thus be studied during the trials. This aspect is particularly relevant in the context of the home-monitoring that will be part of the PICASO trials. Overall, Techno-animism refers to when people assign human features to computers/technologies. In the PICASO context, techno-animism is relevant because it may imply two aspects that have ethical implications: 1) the potential of technologies replacing human contact, and 2) the probability of technologies becoming so saturated into our lives (that the boundary is blurred somehow. Both aspects are particularly relevant in the context of the planned home-monitoring set-up in patients’ home in connection with the trials. The former as the home-monitoring of health parameters

can replace visits to the clinic in the future[1], and the latter because patients may forget that certain health parameters are being monitoring and that data is being collected, thus affecting their autonomy, but potentially also their dignity. The project will therefore continuously evaluate if the notion of Techno-animism has had any implications for the trials and how so.

4.3 Dignity

The notion of dignity is closely related to the notion of integrity. Treating people with integrity helps to avoid violating their dignity. Dignity is also linked to inclusion in society. According to the European Charter of Fundamental Rights, dignity includes i) the right to life and ii) the right to the integrity of the person, which also implies the right to the free and informed consent of the person concerned. Also, the Universal Declaration of Human Rights adopted in 1948 states that all people are "free and equal in dignity and rights".

Dignity has a special meaning in the context of health care. For example, in the Declaration of Helsinki article 11 states: "It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects." This article in many ways sums up PICASO's commitment to conduct ethically sound trials that do not violate participants' dignity.

4.4 Stigmatisation

Stigmatisation, or stigma, is something that can be present either directly or indirectly. It is also possible to distinguish between public stigmatisation and self-stigmatisation, although the latter will usually result from the former. Stigma means "label" and refers to the labels that can be imposed on others, perhaps most evident and often due to ethnic and/or social background, which then lead to discrimination and social exclusion. In a medical context, patients suffering from e.g. life-style disease may often experience that they are being stigmatised (labelled).

In the context of PICASO, the implementation of devices in the home (intrusion of the home) and/or the use of wearable devices could potentially stigmatise participants. It is therefore important to consider not only the design and location (in homes) of devices but also to consider and respect participants' feelings towards using these devices during the trial. The notion of techno-animism may also be relevant here (see 4.2)

4.5 Inclusion

The notion of inclusion used here is adopted from social sciences, where inclusion is used to signify a process, de facto and/or de jure, of including people in a given social structure, most often, in society at large.[2] In the context of ICT, a lot of attention has been given to the notion of e-inclusion, particularly so in the context of assistive and medical technologies aimed at the elderly and frail groups of people.[3] In this context, access is key and becomes an acute ethical issue. For example, access to assistive technologies targeted at the elderly is not simply about making these technologies available or offer them; access is here dependent on the person's ICT literacy.

The PICASO project is thus aware of the ethical issue of excluding some patients from participating in the project trials based on an assessment of their ICT literacy. It is important to stress that the tested ICT solutions for participating patients should be presented as a supplement, and not a replacement to non-ICT solutions and support. Further, usability aspects will be studied and used to improve the design. This will allow the platform to be adapted to the needs of various groups, including the needs and vulnerabilities of key minority groups.

4.6 Privacy and Data Protection

Privacy and data protection are ensured by law but it is nevertheless useful to examine the ethical implications of this issue. These include: what information is collected and how, controlled (not excessive) use, for what purpose the information is used, to whom it may be transferred, user's access to information and the possibility to correct personal information, storage, etc. Healthcare and assistive technology may

[1] As mentioned in 4.5, the tested ICT solutions for participating patients should be presented as a supplement, and not a replacement to non-ICT solutions and support.
[2] Mordini et al. 2009.
[3] e-inclusion is the promotion of computer use by all members of society, so as to avoid a reduction in opportunities for those who do not have or cannot understand the technology (https://en.wiktionary.org/wiki/e-inclusion)

cause an erosion of privacy and it is therefore crucial that proper measurements (including those embedded within the technology per se) are taken to protect the individual's data and privacy.

With respect to data-protection, technical and policy provisions should be developed to protect the confidentiality of the processed data, while simultaneously enabling efficient access to the information for diagnostic and therapeutic purposes. Moreover, as far as medical data are involved, issues of medical confidentiality are obviously involved as well. How such a system would impact on the patient-doctor relationship and on the trust level presupposed in such a privileged relationship must be assessed.

Another related issue is the right to check the accuracy on one's personal data. In this regard, the OECD guidelines say that personal data should be accurate, complete and kept up-to date, which is similar to Article 6 of the EU's Data Protection Directive.

Patients must be fully informed of all relevant issues concerning their data. This includes which data will be collected, why, how, when, by whom, where and how it will be stored and how long for, how and when it will be deleted, how data will be used, who will have access to their data, which devices are used for collection of which data, etc. (see also the Ethical Check List).These issues must be made clear during the informed consent process.

The PICASO trials must take all participants' concerns about the protection of their privacy and personal data that will be collected during the trial seriously. This includes providing adequate explanation and assurances that their privacy and data will be protected and handled with confidentiality (e.g. referring the Ethical Check List – see below).

In PICASO there is a heightened focus on privacy and data protection, and the project will therefore establish a special advisory board to oversee this issue in the context of the development work that will be carried out.

4.7 Clinical Incidental Findings

Incidental Findings (Ifs) are considered those, which occasionally arise unexpectedly in the course of a research and are unrelated to its original purpose. No consensus yet exists on how to handle IFs in human subjects' research. Yet empirical studies document IFs in a wide range of research studies, where IFs are findings beyond the aims of the study that are of potential health or reproductive importance to the individual research participant. Often, incidental findings are associated to biomedical research such as this but can appear in other fields as well.

In the context of the PICASO project and trials, Incidental Findings refer to clinical incidental findings and this term will thus be used for our purposes. Clinical Incidental Findings (CIFs) may arise during the life of the PICASO project and the trials. These may have significance for the health or well-being of the research subjects.

The PICASO trials will consider if and which CIFs are possible and inform participants of those possibilities as part of the informed consent process. Thus participants must be informed of this possibility prior to the signing of the Informed Consent form.

If a CIF appears during the project trials (whether expectantly or un-expectantly), the trial owner will follow their standard clinical guidelines for verifying the findings and for informing the patient. If the CIF is directly linked to data handled by the PICASO platform or any other trial related data collection procedure, the trial owner must also check and verify (usually in co-operation with technical project partners) that the PICASO platform is functioning and handling the data collection correctly.

5 PICASO Ethical Principles and Guidelines

The PICASO Ethical Guidelines are based upon the Ethical Principles, or in other words, they are description of actions and activities that must be carried out in order to apply the Ethical Principle in practice.

The following subchapters first define the PICASO Ethical Principles and how they should be applied (the guideline). Next, the Ethical Check List is presented which will be consulted and used to support the application of the Ethical Principles. Finally, the process that should be used to obtain Informed Consent from trial participants is described in more detail.

5.1 Ethical Principles

The PICASO Ethical Principles are guided by the Belmont Report which defined three ethical principles for research involving human subject. The Belmont Report was created in 1978 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and it is still used widely as a reference for defining ethical principles for research involving human subjects.

In the annual deliverable D3.7 Annual Compliance Monitoring Report will contain a report of how the PICASO Ethical Principles have been applied in practice.

Principle	Application
Respect for Persons Includes respect for autonomy and personal integrity[4]. Respect for persons demands that subjects enter into the research voluntarily and with adequate information.[5]	• Inform and seek advice (from Project Board and/or Ethical Board) if there are concerns related to the integrity and quality of the project and the trials • Treat participants as autonomous agents and respect their right to determine their own best interests • Participation in the project trials is voluntary and follows from informed consent • Enable participants to make reasoned informed choices and decisions • The obtainment of informed consent must follow three consecutive steps (prior to the signing of the informed consent form) : 1. *Information:* Detailed information of the trial, including potential benefits, risks and limitations, must be provided; 2. *Comprehension:* The information must be given both verbally and written in clear lay language, in a precise and calm manner and in the proper context. Participants should be invited to ask any questions they may have; 3. *Voluntariness:* The informed consent form must stress that that participation is voluntary and that participants are free to withdraw at any time at their own discretion and at no cost (without reprehension) • Participants will be informed about the PICASO Ethical Board and that they can, in addition to their field trial contact, always contact the board directly if they have concerns of an ethical nature.
Beneficence Persons are treated in an	• Clarify any probable benefits and harms to participants during the PICASO field trials

[4] Convention on Human Rights and Biomedicine (art.1) states that "Parties to this Convention shall protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine".
[5] Belmont Report, 1978

ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being.[6]	• Explain the limitations of the PICASO field trials, particularly in terms of probably personal and/or health benefits during and after the field trial[7] • Inform of possible Clinical Incidental Findings prior to signing of Informed Consent Form and how these will be handled • Follow standard clinical practices for consulting relevant specialist and for informing patients of actual Clinical Incidental Findings and take appropriate actions • If applicable, perform a PICASO platform check for the accuracy of data related to the Clinical Incidental Findings • Maximise probable benefits and minimise probable harms • Continuously assess probable risks and benefits. The probable benefits must be deemed higher than the probable harm. • Put the health and welfare of participants as the highest priority.
Justice This includes the process of selecting participants in a justifiable manner.	• The selection of participants must be fair and equal, i.e. inclusion/exclusion in the trial must not be denied a person without good reason but must be based on reason directly related to the objectives of the trial.
Respect of confidentiality and privacy In addition to adherence to applicable laws and regulations (national and international), this principle entails a moral and ethical commitment to respect confidentiality and privacy	• The PICASO Project (all project partners) must treat participant information with confidentiality • Participants may exercise control over personal information by consenting to, or withholding consent for, the collection, use and/or disclosure of information at any time during the trial • Participant information must be protected from unauthorized access, use, disclosure, modification, loss or theft • Implement the Privacy by Design principle • Follow the guidelines and decisions from the PICASO Data Advisory Board • Adherence to national and international regulations on privacy and data protection.[8]

Table 1: PICASO Ethical Principles and their application

5.2 Ethical Approval from local committees

The PICASO trials will apply for approval for the trials with the relevant local ethical committee. Approval must the obtained prior to the trial start.

Ethics Committee “Comitato Etico Indipendente – Policlinico Tor Vergata” for every research and trial involving ethical issues as required. The principal investigator for this trial will be Prof. Schillaci and the main responsible for the trial is Dr. Agostino Chiaravalloti, Department of Biomedicine and Prevention, UTOV.

In the case of PICASO trials in Germany, the principal investigator for the field trial (from UDUS) will apply for approval to the Ethics Committee “Ethikkommission an der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf” for every research and trial involving ethical issues as required. The principal

[6] The Belmont Report, 1978.

[7] E.g. the devices and sensors installed in participants’ homes for home- and self-monitoring purposes in connection with the field trial will only be available and active during the field trial.

[8] E.g. Charter of Fundamental Rights of the European Union and Directive 2002/58/EC on data protection. A full list of relevant directives and regulations are provided in the Appendix A.

investigator for this trial will be PD Dr. Jutta Richter of UDUS, Policlinic of Rheumatology. Trials will be performed in line with Good Clinical Practise (GCP) / International Conference on Harmonization (ICH) Guidelines; well-known harmonized standards that need to be followed in randomized controlled trails (RCTs). The principal investigator holds a GCP certificate, as required in Germany, which was attached as Annex 3 to the proposal.

5.3 Clinical Protocol

For each pilot a specific protocol will be written following the ICH-GCP13 as well as the European (Directive 2001/20/EC) and national legislations. The protocols will be documented in D8.2 Trial Protocol for RA and Comorbidities Trial in Germany and D8.3 Trial Protocol for PD and CVD trials in Italy.

5.4 PICASO Ethical Check List

A useful way to check if the Ethical Principles are being implemented in the project work and the trials is to ask a number of questions related to each ethical issue that has been defined as particularly relevant to PICASO (see Chapter 3). In PICASO, the trials will therefore implement an Ethical Check List which will be consulted by the trial owner at the onset of the trial. Here the function is primarily for the trial owner to check which issues to consider when planning the recruitment process and defining the information that is to be given to patients (verbally or written). It might also be used as a useful reference tool that can be consulted during the recruitment interview with a potential trial participant in order to ensure that all issues have been raised and possibly clarified to the patient.

If the trial owners report any ethical problems for their own trial on the Ethical Check List (e.g. in comment field), they must submit the list to the Ethical Manager who must initiate action within 2 weeks from the date the list was received.

In addition to functioning as a consultancy tool for the trial owner, the Ethical Check List will be used by an evaluator to assess if the trial has followed the project's ethical principles. The evaluator would then ask the trial owner if they have considered the issues in the list and how and possibly ask for documentation, e.g. the informed consent form that has been used. The evaluator would be either the trial owner from the other trial, or a member of the PICASO Ethical Board.

If a participant or health professional expresses a concern at any time during the PICASO project and/or trial, the Ethical Check List should be consulted. If the issue raised is on the list, the trial owner should fill in the comments field and submit it to the Ethical Manager. In this case, the Ethical Check List is used as a means to document that an ethical issues has been raised. It is then the responsibility of the Ethical Manager to take action on the issue. If the actual ethical issue that has been raised is not represented on the Ethical Check List, this should be noted in the "Other comments field" at the bottom of the list.

The Ethical Check List should of course be consulted at any time during the PICASO project.

If an ethical problem is reported, the Ethical Board must assess if the participation of the concerned patient should be temporarily stopped until the issue has been resolved. The Ethical Board should in this case inform and discuss the best solution with the trial owner and the PICASO Project Board. The Ethical Board can only advise a temporary withdrawal of a patient; only the Project Board can decide to withdraw a patient from participating in the trial. The same procedure applies if the issue reported concern the trial as a whole.

Check list	Compliance (yes/no/not applicable)	Comments
Informed Consent		
Participants have been given detailed information about the trial, including its purpose, limitations, and potential benefits and risks.		
The information has been given verbally with supporting written information and in clear lay language.		
Participants have had the opportunity to rethink if they want to participate or not and were given a week to decide; thus, they did not have to sign the		

informed consent form immediately.		
Participants have been informed that participation in the trial does not replace existing and usual treatment.		
The trial's informed consent form included all the issues that were identified in D3.3 The PICASO Ethical Guidelines (Chapter 5.5.1 and 5.5.4)		
The informed consent process defined in D3.3 The PICASO Ethical Guidelines (Chapter 4.5) has been followed and copies of all participants' signed informed consent forms have been forwarded to the PICASO Ethical Manager.		
Autonomy		
The voluntariness of the participation has been stressed as have the option to withdraw at any time without further explanation and without any repercussions.		
The trial will not use a technology/device that constrains a person or curtails their freedom of movement or association.		
Participants are able to control the technologies/devices used for home monitoring, i.e. they can switch them off or choose not to send the data.		
In the recruitment process and during the trial participants are/have been treated as autonomous agents and their right to determine their own best interests is respected.		
Dignity		
Participants' personal information is treated with confidentiality.		
The trials recognise and respect the right of participants to lead a life of dignity and independence and to participate in social and cultural life.		
Inclusion/exclusion in the trial has been based on the medical inclusion/exclusion criteria and are thus directly related to the objectives of the trial and the PICASO project.		
Stigmatization		
Upmost efforts have been made to ensure that the least intrusive, physically and aesthetically, devices and technologies are used in the trials.		
The trials do not require participants to use a technology that marks them in some way as cognitively or physically disabled.		
Inclusion		
Participants' needs and requirements have been defined and used to guide the selection of technologies/devices as usability is a priority.		
Technical partners in the project have been informed and consulted on usability issues to ensure the participants' needs and IT literacy have been considered.		
Participants have been instructed thoroughly in how to use the technologies/devices and have access to support as necessary.		
Participants have been made aware that the technologies/devices used in the trial are used to		

support, and not replace, human interaction and information sharing.		
Privacy and Data Protection		
Participants have been given detailed information on all aspects related to the handling of personal data in the trial and the project.		
Participants have been informed how they can exercise control of their personal data.		
Participants have been enabled to exercise flexible and granular data access.		
The trial adheres to local, national and international regulations on privacy and data protection.		
Clinical Incidental Findings		
If any Clinical Incidental Findings have been discovered, the trial owner has verified the PICASO platform and data accuracy in cooperation with PICASO technical partners.		
If any Clinical Incidental Findings have been discovered, the trial has followed their institution's standards clinical procedures for dealing with these and for informing the patient in question.		

Table 2: PICASO Ethical Check List

5.5 Informed Consent Process

Informed consent is the process by which a participant will be fully informed about the research/trial in which he/she is going to participate. It originates from the legal and ethical right that the participant has to direct what happens to his/her personal data and from the ethical duty of the researcher to involve the participant in the research. This means that the subject has the right to be involved in the research process.

5.5.1 Step One: Information

Following the PICASO Ethical Principle of Respect for Persons, the first step in the informed consent process is to ensure that the potential participants receive proper information about the trial and what it would entail should they accept to participate. Below is a list of questions (as seen from the end-user's perspective) that the trial owner should explain to participants before they sign the informed consent form and thus prior to their active participation in the trial.

1. Title / reference / place of the trial
2. What is the purpose of this trial?
3. Who can take part in this trial?
4. Why should I consider joining this trial as a research participant?
5. Do I have to become a participant in this trial? If I joined the trial, can I change my mind and drop out before it ends?
6. What exactly will be done to me, and what kinds of treatments or procedures will I receive, if I agree to be a research participant in this trial?
7. How will my personal data be collected, when, and by whom/by what, and how, where and for how long will it be stored?
8. How can I give/retract/limit access to my personal data and level of data (granularity of data)?

9. What kinds of harm can I experience in this trial, and what will the investigators do to reduce the chances of harm?

10. What will the investigators do to make sure that the information they will collect on me will not get in the wrong hands?

11. What kinds of benefit can I expect personally from taking part in this trial?

12. What kinds of benefit to others can come out of this trial?

13. What will the investigators do, if I get injured in the trial?

14. Will I get paid for taking part in this trial?

15. Will I or my health insurance company be charged for any of the costs of this trial?

16. Once I start in this trial as a participant, what do I do if I want to find out more about the trial/project, or to complain about the way I get treated?

17. What happens after the trial ends?

18. What would happen if the project/trial is ended earlier than planned?

19. Who gets to keep this document, once I sign it?

20. Which others may view or use the data in this document, if any?

5.5.2 Step Two: Comprehension

In addition to the information given orally, the trial owner should provide a brief written outline of the trial, basically covering the main issues as in the above list. The information must be given in clear and concise language and manner, and the trial owner must ask if the participant has any questions or other points/doubts that need clarification. This step is important to ensure that participants have a clear understanding of the trial, what is expected of them as participants, and what they can expect from the trial.

5.5.3 Step Three: Voluntariness

The trial owner must stress that participation is fully voluntary and that participants are free to refuse to participate and/or withdraw at any time without any consequences. This should also be clearly stated on the Informed Consent form presented to the participants. The trial owner should not exercise any pressure on the participants to accept or sign the Informed Consent form; they should be offered some time to consider before agreeing.

5.5.4 The Informed Consent Form

The Informed Consent Form used by the PICASO trial will be in the local language (German or Italian), however an English translation should be provided to the Ethical Board for the record (will be also be included in the deliverable D3.7 Annual Compliance Monitoring Report 1).

The informed consent form that the trials use must basically cover the questions that were listed above in chapter 5.5.1 including:

1. Title / reference / place of the trial
2. The purpose of the trial
3. Inclusion/exclusion criteria (why the patient is invited to participate)
4. The expected duration of the trial (start/end date)
5. Participation is voluntary and how to withdrawal from the trial at any point (no repercussions and no explanation necessary)
6. The possible benefits and risks to the participant and/or others (family members, etc.) associated with participating in the trial

7. The limitations of the trial (e.g. devices used during the trial must be returned, the trial has a time limit, post-project implementation of PICASO cannot be guaranteed, etc.)
8. What is expected of the participant, e.g. allowing devices to be installed, using the home monitoring equipment provided, allowing access to data etc.
9. How data is handled (collected, stored, shared, deleted etc.)
10. How access to data and level of data (granularity of data) is given/retracted
11. Confidentiality of data and personal information
12. Costs and insurance issues
13. Trial contact person (details) and role
14. PICASO Ethical Board contact person (details) and role

The informed consent form should also contain the following:

- A statement where the patient agrees to the use of anonymised personal data for the project's research purposes (e.g. publications).
- A statement where the patient agrees to allow the relevant ethics committee and authorities access to anonymised personal data for control purposes, e.g. that data is handled according to the law and regulations.
- "Name of the person who has collected the informed consent (and given the information to the patient)
- "I agree to take part in the trial" statement for the participant to mark/fill in
- Name, signature and date

All the informed consent forms will be collected by the field trial owner and a copy given to the participants. The Ethical Board will also receive a copy of the signed informed consent forms.

6 Relevant EU legislation

The main EU and international policy documents that are relevant to PICASO are:

- WMA Declaration of Helsinki
- Oviedo Bioethics Convention
- Charter of Fundamental Rights of the European Union
- European Convention for the Protection of Human Rights and Fundamental Freedoms
- The UN Convention on the Rights of Persons with Disabilities
- 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
- Opinions of the Article 29 working party concerning the implementation of the EU data protection framework
- Directive 2000/58/EC concerning the processing of personal data and the protection of privacy in the electronic communications sector (Directive on privacy and electronic communications)
- Regulation No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use
- Medical Device Framework including but not limited to; Medical Device Directive (Council Directive 93/42/EEC of 14 June 1993 [1] concerning medical devices, OJ No L 169/1 of 1993-07-12)
- General Data Protection Regulation (pending)
- Directive 2011/24/EU on patients' rights in cross-border healthcare (the 'Patient's Rights Directive')

6.1 Charter of Fundamental Rights of the European Union (2000/C 364/01)

The fundamental rights of data protection and the right to privacy of the volunteer research participants will strictly followed. Furthermore, the developments and tests performed within PICASO project life will observe the Charter of Fundamental Rights of the European Union11 (2000/C 364/01). The following articles of this Charter apply directly to this project:

- Article 1: Human dignity is inviolable. It must be respected and protected.
- Article 7: Everyone has the right to respect for his or her private and family life, home and communications.
- Article 8.1: Everyone has the right to the protection of personal data concerning him or her
- Article 8.2: Such data must be processed fairly for specified purposes and on the basis of the consent of the person concerned or some other legitimate basis laid down by law. Everyone has the right of access to data, which has been collected concerning him or her, and the right to have it rectified.
- Article 8.3: Compliance with these rules shall be subject to control by an independent authority
- Article 23: Equality between men and women must be ensured in all areas, including employment, work and pay. The principle of equality shall not prevent the maintenance or adoption of measures providing for specific advantages in favour of the under-represented sex
- Article 25: The Union recognises and respects the rights of the elderly to lead a life of dignity and independence and to participate in social and cultural life.

6.2 The European Convention of Human Rights (ECHR)

In addition to the European Charter (EU) the PICASO project will observe all rights and obligations relating to the provisions of the ECHR and case law relating thereto. The following articles in particular of this Charter apply directly to this project:

- Article 2 – A Right to Life
- Article 8 - Right to respect for private and family life

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8 References

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Appendix A: Trial 1 Rheumatoid Arthritis with Cardiovascular Disease

The first trial will be performed by the Policlinic of Rheumatology and Hiller Research Unit Rheumatology at the Heinrich-Heine-University (HHUD) / University Hospital of Düsseldorf (UDUS). The Policlinic of Rheumatology focuses on inflammatory rheumatic diseases. UDUS has access to the local clinical register at the Policlinic of Rheumatology and Hiller Research Unit Rheumatology with currently approximately 20,500 patients with rheumatic diseases, whose clinical characteristics are routinely documented in a web-based application. The trial will perform cross-sector workflows involving the Centre for Health and Society; an interdisciplinary association of several departments at the Medical Faculty of the University of Düsseldorf. The centre will engage as the professional, public provider of social care, which reflects the dominant social care system in Northern Europe.

Pathologies: Rheumatoid Arthritis and comorbidities such as Cardiovascular Diseases
Inflammatory rheumatic diseases are mostly chronic diseases that may start at any age. Almost one-quarter of the European population (more than 120 million) live with some form of rheumatism or arthritis. Rheumatoid Arthritis (RA) is the most frequent inflammatory rheumatic disease, affecting approximately 1% of the German adult population. Mid age at disease onset in Germany is approximately 48 years. People with rheumatic diseases very often face severe limitations on their independence and autonomy as individuals and discriminatory policies and attitudes that exclude their full participation. The costs of treatment exceed 240 billion Euros per year in the EU (EULAR 2011). The most prevalent co-morbidities are cardiovascular disease, arterial hypertension, diabetes, and chronic pulmonary diseases, which by itself influence the rheumatic process.

Treatment in RA predominantly includes immunosuppression (e.g. glucocorticosteroids, conventional disease modifying drugs and biologicals) that might influence the co-morbidities (e.g. by interaction with medication that is given to treat the co-morbidities) or even leads to co-morbidities (e.g. diabetes). Other risk factors for developing co-morbidities are the chronic inflammation and a high disease activity that might persist in patients even though treated aggressively. The treatment of RA requires an integrated multidisciplinary team approach, recommending complementary treatments like physical and occupational therapy, social workers etc. Thus, RA care is by itself very complex and furthermore complicated by multi-channel and multi-actor (e.g. in- and out-patient care and rehabilitation) interdisciplinary junctions (general and specialised care) as well as other players (e.g. health insurances) that are involved in the treatment process.

Care plans
The care of newly diagnosed patients with arthritis should follow the evidence-based guideline 'Management of Early Rheumatoid Arthritis' (RA) directed by the Policlinic of Rheumatology in UDUS since 2002 (Schneider et al. 2011). Other guidelines such as those from the EULAR (European League Against Rheumatism) define the optimal care of patients according to the present scientific level of knowledge. They have been developed to assist physicians and patients with their decisions on appropriate health care, and thus they are useful tools for clinical decision making, process standardisation and quality of care improvement. Major developments in treatment and prevention are 'new' medications like biologics, which enable a greater chance for remission, the detection of the benefits of an early diagnosis and efficient care plan, facilitated by new classification criteria, and invention of new strategies like treat-to-target and remission as the important target. However, they rarely include the concomitant treatment of existing co-morbidities despite various German evidence-based guidelines being available (see http://www.awmf.org/).

Trial layout
The prototype of the ICT integration platform will be applied to patients with RA. From M6 of the first year, 30-50 patients that meet the inclusion criteria will be enrolled in the UDUS pilot. Until M14 a baseline is established for each patient including number of hospital visits and bed days, family integration in care etc. 15 patients and their treating physician will start directly with the devices installed in M14, involving data transfer and the evaluation of functionality/usability of the platform; they will stop their active participation after 9 months but will be followed for the rest of the use case to get an idea of sustainability of the system when stopped. Another fifteen patients and their treating physician will start in M26, after the deployment of the updated platform, and will run for another 9 months. All patients will be followed to report on the sustainability. Within the pilot study patients and physicians will answer (online) questionnaires that record the primary and secondary endpoint items (e.g. SF-36, EQ5D).

Integration of care

The prototype of the PICASO platform will be applied to patients with RA for integration of care. The trial will perform cross-sector workflows involving rheumatologists in the UDUS outpatient clinic, physicians and scientists from the Centre for Health and Society (CHS), and physiotherapists at the Heinrich-Heine-University Düsseldorf. Through the latter, the full spectrum of general practitioners, occupational therapist, physicians and experts in medical sociology will be integrated in the trial. This approach allows us to include a full assessment of stressful employment conditions on health in midlife as this has an impact on cardiovascular risk and rheumatic disease and depression as major health outcomes. CHS will be integrated via the various participating stakeholders of the centre. Predominantly, the large group of general practitioners will be the most relevant interacting partners with Rheumatology in- and outpatient care and they will be involved in the clinical trial (e.g. in terms of better interaction when handing over the patient to the GPs for necessary regular controls that cannot be guaranteed by the rheumatologists themselves).

Due to better medical treatment and explicit treatment goals today patients with inflammatory rheumatic diseases have a greater chance to stay employed and keep their work productivity but the diseases remain associated with a high financial and social burden. Thus, the PICASO driven interaction with the physicians and other healthcare providers associated with another CHS member the “Institute of Occupational and Social Medicine” becomes even more important because the occupational physician rarely participate in today’s health care plan, due to missing communication with the rheumatologist or GP. This is where the Institute of Medical Sociology’s involvement is important because it is well known that working life factors influence humans’ (life) satisfaction and well being. Their well-known and accepted model assumes that a perceived imbalance between high effort spent at work and low rewards may lead to stress reactions with unfavourable consequences for individual’s health, including co-morbidities as CVD. Integration of the Institute of Medical Sociology model is reasonable when assessing patients’ outcomes and preventive co-morbidity management. The department of Public health and the Coordination Center for Clinical Trials might support us e.g. when evaluation aspects need to be taken into account.

Trial endpoints
The quantitative primary endpoints are: reduced number of admissions to hospital and bed days. The qualitative endpoints are: improved quality of life assessed via validated QoL instruments. The secondary endpoints are qualitative and include: usability (both assessed by patients and physicians), integration into care systems, and patient participation and their social interaction. In addition, this trial will generate information on the increase of medical knowledge about the management of co-morbidities in the caring physicians, but also in the RA patients.

Patient profiles: Inclusion and exclusion criteria
Inclusion: Patients above 18 years of age that: have at least one known, documented co-morbidity (e.g. CVD and diabetes) at study entry; are willing to participate and sign data transfer agreements; are willing to use the sensors and devices and interact with the platform; and have a sufficient understanding of the German language, which will be included in the trials. Exclusion: Patients without any co-morbidity are excluded.

Recruiting patients
A cohort of UDUS’s RA patients creates an excellent use case scenario for the prototype of the ICT integration platform. The RA cohort treated in UDUS routine patient care is very familiar with information technology related studies that address improvement of patient care in clinical practice as well as the application and evaluation of new media developments. In addition, this is a unique cohort as RA patients are active in self-management, self-empowerment, and self-care. They take their personal responsibilities seriously.

Appendix B: Trial 2 Parkinson's Disease with Cardiovascular Disease

The second trial will be performed by The University Hospital of Tor Vergata in Rome (UTV) in conjunction with the institute of treatment and research Santa Lucia in Rome. The hospital has access to 300+ patients from which they routinely select patients for research studies. In terms of risk prediction, the hospital has genetic data available in addition to clinical data in order to provide risk estimates based on clinical, genetic, as well as the social/environmental data. Integration of care flows will be demonstrated by involving a nursing home as a non-clinical care provider. Moreover, the hospitals will engage the "family structure" as a provider of social care, which reflects the dominant social care system in Southern Europe.

Pathologies: Parkinson's Disease with Cardiovascular Disease
Parkinson's Disease (PD) is a neurodegenerative disorder with an incidence that rises steeply with age; from 17.4 in 100,000 persons between 50 and 59 years of age to 93.1 in 100,000 persons between 70 and 79 years old17. The main histo-pathological feature of this disease is a neurodegenerative process that affects the neurons of the substantia nigra that primarily affect motor symptomatology. If one considers that the diagnosis of PD is usually performed in adult subjects (with the highest peak of incidence being detected in patients over 65 years old), Cardio Vascular Disease (CVD), diabetes and kidney failure are among the most frequent co-morbidities in subjects affected by PD. As far as these diseases are concerned, diabetes is a known risk factor for CVD (with diabetes being related to an increases atherosclerosis and to an altered functioning of platelets) however, co-occurrence of diabetes with CVD can also happen by chance. Usually hypertension (another clinical condition that is usual in patients affected by PD) is responsible of kidney damage with a subsequent kidney failure, anaemia and disturbed mineral metabolism that also contribute to the worsening of PD.

Together with the relatively common co-morbidities mentioned above, the clinical course of PD in characterized by a major involvement of deep brain structures that govern autonomic functions of cardiovascular, genitourinary and digestive system. In particular it has been recently demonstrated that the accumulation of pathological protein aggregates as alpha synuclein and amyloid may lead to the dysfunctions of those nervous system involved in the governance of several autonomic functions as blood pressure and cardiac frequency. Up to 60 percent of people with Parkinson's disease experience mild or moderate depressive symptoms. In fact, research suggests that the disease itself causes chemical changes in the brain that may lead to depression. PD affects many parts of the brain that are important in controlling mood. One of these is the area that produces serotonin, a brain chemical implicated in depression. Another part of the brain important in regulating mood—the frontal lobe—is known to be under-active in PD. Commonly prescribed antidepressants can help. In addition to medications, cognitive-behavioral therapy has also been shown to help some people with PD. Other researchers have found that people with PD who were depressed had more trouble with daily activities, and were more likely to begin medication for motor symptoms sooner than those without depressive symptoms. Depression decreased their quality of life and made their motor symptoms worse—but treating the depression, rather than the motor symptoms, improved both quality of life and movement. If you feel you are doing very poorly, yet your doctor finds only mild physical impairments during your exam, you may be depressed. Depression can range from feelings of sadness and discouragement to extreme hopelessness. These feelings generally are different from the grief and frustration you may feel as a result of your diagnosis.

Care plans
Shared risk factors for hypertension, hypercholesterolemia and diabetes promote co-occurrence of these diseases and strengthen the association between them. These risk factors do not just affect disease onset but also disease progression and likelihood of complications. For example, it has been recently shown that the onset of diabetes before the onset of PD appears to be a risk factor for more severe PD symptoms20 21. Clinical treatment for people with comorbidity is much more complex and time consuming than for those with a single condition, especially for people affected by neurodegenerative diseases as PD where the treatment is very individualized for this complicated condition; patients must work closely with doctors and therapists throughout the course of the disease to customize a programme suitable for their particular and changing needs. Levodopa (L-dopa) has been used for years and is the gold standard for treating Parkinson's disease by increasing brain levels of dopamine. It is probably the most effective drug for controlling symptoms and is used in nearly all phases of the disease. Dopamine agonist drugs mimic dopamine to stimulate the dopamine system in the brain and monoamine oxidase B (MAO-B) inhibitors can be used in the treatment of PD as well.

The conditions associated with non-motor impairment symptoms of PD may need a variety of treatments (depression, dementia, constipation and drooling could require treatment with different drugs such as

antidepressants, laxatives or botulinum) and the side effects that derive from the conjunctions of these drugs could be relevant. For example, the tricyclics have problematic anticholinergic effects, especially for the elderly. Selective serotonin reuptake inhibitors are tolerated in many, but some patients find them to have a stimulating, uncomfortable effect.

Trial layout
From M6 of the first year, 30-50 patients that meet the inclusion criteria will be enrolled in the UTV pilot. Until M14 a baseline is established for each patient including number of hospital visits and beddays, family integration in care etc. In M13, the first version of the platform will be installed in the homes of 10 patients for the first phase of the trial (M14-M23). Data obtained in this phase of the pilot will be used for updating the requirements definition. In M25, an updated version of the platform will be installed and the second phase of the trial (M26-M30) will commence The PICASO platform (devices, data transfer capabilities etc.) will be introduced to a subset of the patients as well as their treating physicians and relevant care providers, in particular their families. The remaining patients serve as a control group.

Integration of care
The complexity introduced by the co-morbidities does not only affect the patient from a clinical point of view but has a huge impact on the patient's care providers outside the hospital. In Italy - like in many Mediterranean countries - the largest section of home care consists of licensed and unlicensed non-medical personnel who are often relatives of the patient. Care assistants may help the patient with daily tasks such as bathing, eating, cleaning the home and preparing meals. Caregivers work to support the needs of patients who require such assistance, and this care helps them stay at home instead of living in a facility. Co-morbidities significantly increase the complexity for families to understand, evaluate and react to the situation of the patient. This increases uncertainty and stress, and reduces the willingness to comply with treatment plans. Therefore the trial will make a strong effort to include the family as an active participant in the treatment.

A dedicated, user-friendly smart phone application (PICASO App) will be developed and provided to the non-professional carers to give them access to the PICASO platform. The PICASO App will enable them for example to receive alerts if there are indications of problems at the patient's home, to receive treatment plan based reminders, to provide data on behalf of the patient, and to send messages with their own observations and concerns to the treating doctors. The goals are to empower the patient's family in their role as primary care givers, to support and improve the social aspects of patient – family interactions by increasing transparency and to obtain better, more structured and more regular feedback from the patients and their families.

Clinical visits provide only a brief snapshot of the condition of PD patient in a particular situation. However, PD is notorious for its fluctuations, which may occur both within and across days. Moreover, performance during the clinical visit does not always reflect how patients perform at home. A well-known example is freezing of gait, which is often difficult to elicit in the examination room, even in patients who are severely debilitated by frequent freezing episodes at home. Several features of PD or associated disorders are absent during routine clinical visits, such as night time disability caused by axial akinesia.

Trial endpoints
The quantitative primary endpoints are: reduced number of admissions to hospital and bed days. The qualitative endpoints are: quality of life assessed via validated QoL instruments (WHOQOL-BREF) and by means of detailed questionnaire for patients, relatives/caregivers, home nurses, family physicians, neurologists, cardiologists etc. In particular, these questionnaires will be filled by both subjects of the experimental and "standard" arm respectively in order to compare the performance in terms of satisfaction of the monitoring system. The secondary endpoints are qualitative and include: usability (both assessed by patients and physicians), integration into care systems, patient participation and their social interaction. In addition, this trial will generate information on the increase of medical knowledge about the management of co-morbidities in the caring physicians, but also in the PD patients.

Patient profile: Inclusion and exclusion criteria
Inclusion: Patients above 65 years of age with CVD (hypertensive disease, heart failure etc) and Parkinson's disease and at least one of the following co-morbidities: Respiratory disease (obstructive sleep apnoea syndrome, lung failure etc.), arthritis and rheumatisms, back problems, diabetes, thyroid dysfunction, kidney failure. The patient and the patient's family as primary care giver must agree to participate and use the provided medical devices including the PICASO App targeted at non-professional carers, understand the Italian language, and sign the necessary agreements (informed consent). Exclusion: Patients younger than 65 years, patients without co-morbidity of CVD and Parkinson or patients with the following co-morbidities: oncological history, history of transplant (i.e. lung or kidney), chronic therapy for immune diseases,

psychiatric diseases, chronic infectious diseases (i.e. tuberculosis) and dementia. Patient's where the family as primary care giver is not willing to participate.

Recruiting patients

UTV has access to more than three hundred patients from which they can select a suitable number of patients for the trials. PD is sufficiently widely spread not to be considered a "niche" diagnosis and the presence of co-morbidities is relatively frequent in these patients considering the age of onset. UTV will enrol a cohort of 30 or more subjects that are compliant with the aim of the study. In terms of risk prediction UTV also has genetic data available in addition to clinical data in order to provide risk estimates based on clinical, genetic, as well as the social/environmental data. Genetic data for both PD and CVD will be collected.

Appendix C: PICASO Ethical Board Meeting Agenda

Meeting Subject:	PICASO Ethical Board Meeting
Venue:	Building C5, room 120 Fraunhofer Institute for Applied Information Technology (FIT), Schloss Birlinghoven, 53754 Sankt Augustin (close to Bonn)
Date:	25 May 2016
Chair:	Trine F. Sørensen (IN-JET)
Distribution:	The Ethical Board and PICASO Clinical Partners
Participants	Trine F. Sørensen (Chair), Markus Eisenhauer, Jutta Richter, Paul Quinn, Christian Schunck (representing trial 2), Robin Wilton, Dieter Wiek.
Apologies	Christopher Buckingham, Agostino Chiaravalloti

Time	Subject	Topics to be covered	Time (mins)	Lead participant
8:45	**Welcome**	Arrival and coffee	15	ALL
9:00	**Introduction**	**The PICASO Project** • Desired outcomes of today • Brief overview of PICASO and the two trials	15	Trine F. Sørensen (IN-JET)
9:15	**Ethical Board Terms of Reference**	**Definition of PICASO Ethical Board Terms of Reference** • Comments and amendments to the proposed text	15	ALL
9:30	**Main Ethical Issues at Stake**	**Ethical Issues in the PICASO context** Comments and amendments to: • The predefined issues • Additional issues • The proposed Informed Consent Form • The proposed Ethical Check List	40	ALL
10:10	**The PICASO Ethical Principles**	**Definition of the PICASO Ethical Principles and Guidelines** Comments and amendments to: The proposed Ethical Principles and their Application	35	ALL
10:45	**Coffee break**		15	
11:00	**Ethical Board reporting to Consortium**	**Presenting the main issues & discussion**	45	ALL
11:45	**Close of meeting**			