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D8.2 Ethics and Safety Manual II

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[2] A deliverable can be in one of these stages: Draft, Peer-Reviewed, Submitted and Approved.

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Abbreviations and Acronyms

AWB	Dutch General Administrative law Act
CCMO	Dutch Central Commission for Research Involving Humans
CODEX	Swedish Research Council's research ethics guidelines
DPD	Data Protection Directive
DoH	The Declaration of Helsinki
DoW	Description of Work
D*x.x*	Deliverable *x.x*, as described in DoW
EDPS	European Data Protection Supervisor
EMC	Electro Magnetic Compatibility
HP	Health Professional
MREC	Dutch Medical Ethical Research Committees
PUL	Swedish Personal Data Act
QR code	Quick Response Code
RPN	Risk Priority Number
PSS	Primary Screening Stage
T*x.x*	Task *x.x*, as described in DoW
WMA	World Medical Association
WMO	Dutch Medical Research Involving Human Subjects Act
WP*x*	Work package *x*, as described in DoW
WHO	The World Health Organization
WBP	Dutch Data Protection Act

Executive Summary

One of the main tasks of the SPLENDID project is the performance of reliable scientific studies and testing for the evaluation of the usability and the functionality of the SPLENDID platform with human subjects. Ethical considerations were a concern from the very beginning of SPLENDID, acknowledging the existence of different EU legislation on ethics in research trials. This is the second and final format (II) of an Ethical manual including guidelines to everyone who will conduct research trials and testing in the settings of SPLENDID.

Three of the main directives, which support the ethical use of human subjects in research, are: The Declaration of Helsinki, The EU Charter of Fundamental Rights and The EU Directive 2001/20/EC on clinical trials. These regulations are the basis of many national guidelines in EU and they promote the ethical treatment of human subject research by defining guidelines with the sole purpose of maintaining ethical standards within research. Additionally, the Regulation (EC) No 45/2001 regulates the protection of individuals with regard to the processing and transferring of personal data by community institutions and bodies in the European Union, while the Directive 2002/58/EC sets out rules to ensure security in the processing of personal data through electronic communications.

In this document, key ethical issues concerning research activities are identified and defined according to EU and national directives. This issues are examined from the SPLENDID point of view and include *recruitment of participants*, *information to participants*, *informed consent*; *volunteer compensation*, *data handling and transfer*, *safety of equipment* and *adverse event handling* during the planned research activities. A reference list of the scheduled testing activities and the relevant key issues is presented and specific strategies for the management of these issues are proposed.

The document continues describing the technological aspects of data handling and device safety in the projected final version of the SPLENDID system. The manual finishes with a presentation of the Ethical administration procedures in SPLENDID.

1 Introduction

1.1 Purpose of the document

Deliverable 8.2: Ethics and Safety Manual II is part of WP8, Project Management and Ethical Issues. The document aims to:

- Review the ethical principles and the relevant legal and regulatory framework which are related to the research in SPLENDID
- Clearly identify the ethical issues for key elements of the SPLENDID research and define strategies to address them.

The above points are especially considered in relation to research involving humans and personal data. Therefore, the main impact of this deliverable will be in the area of the research studies that are conducted in WP6. However, there are also considerations that have an impact on the technical development, namely in the areas of sensor safety (WP2) and data management (WP3, WP4 and WP5).

The manual presents a detailed outline of the state of the research activities, especially highlighting the required ethical awareness indicated by the European Union Directives and guidelines. Consecutively, we have identified key methodological aspects of SPLENDID which are connected to the described ethical issues and we are proposing specific practises to mitigate possible ethical issues that might arise.

Note that, while the Ethical Issues relevant to the future use of the SPLENDID platform have regularly been considered, this manual focuses on the ethical considerations relevant to the *development phase* of SPLENDID. This version of the document (II), incorporates updated information about the functional details of the platform and the specifics of the projected uses, collected throughout the first two years of the development of the SPLENDID platform.

1.2 Project description

SPLENDID aims to provide personalized services, guiding young individuals to adopt healthy eating behaviours and activity patterns, thus preventing the onset of obesity and eating disorders. In particular, SPLENDID will combine measurements of eating and activity behaviour in real life conditions. Three types of sensors will be integrated to the SPLENDID platform, namely, a scale on which the plate with the food is placed, measuring the rate of food consumption during a meal, an acoustical sensor capturing chewing generated sounds and a wearable activity meter recording body motion. Subjective logs for fullness, intake and daily activities will also be used. The two target uses of the developed platform include use by high-school users (SPLENDID @ School) and young adults (SPLENDID for Adults; see D1.1 [1] for more information).

To achieve its aim, SPLENDID concentrates on a set of activities, including prospective studies and tests, as well as use of existing data from previous experiments. In summary the activities, expressed as Tasks and sub-Tasks in WP6 in DoW, relevant to this manual include:

- *Data sharing* for pre-existing data:
    - Task T6.1: “Acquisition and standardisation of existing data”. In this Task, pre-existing clinical and experimental anonymized data acquired by MANDO and KI respectively have been provided to AUTH for further analysis and

use for algorithm development. Details about this Task have been presented in D6.1.
    - Task T6.3: Sensor testing with different foods. In this Task, pre-existing experimental anonymized data acquired by KI will be provided to AUTH to be analysed further and used for algorithm development. Details about this protocol will be presented in D1.3 "Protocols of Evaluation Studies"

- Studies and tests:
    - Task T6.2: Preliminary testing of the functionality of new sensors (*preliminary sensor testing*). This activity (T6.2) will take place independently in two separate study sites, i.e., in the Netherlands (WU) and in Sweden (KI, MANDO). Young adult volunteers for all testing will be recruited.
    - Task T6.3: Testing the sensors with different types of foods (*food testing*). This activity will also take place in the Netherlands (WU) and in Sweden (KI, MANDO). Young adult volunteers for all testing will be recruited.
    - Task T6.4: Testing the first version (V1) of the platform in semi-controlled and real-life settings (*V1 testing*). Similarly, this activity will take place in Sweden (KI, MANDO and possibly IEGS; T6.4a) and the Netherlands (WU; T6.4b) In the Netherlands young adult volunteers will be recruited for the testing. In Sweden, a mix of adolescents (if possible; the protocol of the testing will be finalised before July 2014) and young adults will be recruited.
    - Task 6.5: Testing the final version of the platform (V2) in real-life settings (*V2 testing)*. This activity is divided according to the two projected system uses, i.e., SPLENDID @ School, taking place in Sweden (KI, MANDO and IEGS; T6.5a) and SPLENDID for Adults, taking place in the Netherlands (WU; T6.5b). In the two sub-activities, high-school students and young adults will be recruited respectively.

1.3 Structure of the document

This document was written by KI, incorporating valuable feedback and material provided by WU, Mando Group, IEGS, CSEM, TSB and AUTH. Work on the first version of the manual (I) started as early as the DoW writing and it was complemented through the focus groups that took place in the SPLENDID kick-off meeting in Thessaloniki, October 2013. Follow-up work was completed through tele-meetings that took place towards the end of 2013 and the beginning of 2014 among the relevant partners, administered by KI and AUTH. The same work plan was followed for the creation of the second version of the document, with repeated communications among the partners, especially after the completion of the testing planned for the second year of the project, when more specific ethical considerations arose.

Communication and content creation for this document was parallel with the consortium activities that led to the D1.1 [1] and D1.2 (Use Case Specifications) and the preparatory activities concerning the finalization of D1.3 (Protocols of Evaluation Studies) and all the relevant WP6 work tasks (e.g., T6.1-T6.4).

The different chapters of the document include:

- ***Chapter 1*** is the introduction.
- ***Chapter 2*** provides an overview of the legal and ethical aspects, as well as guidelines, including national and international directives and conventions. The presented references are tightly related to the SPLENDID practice.
- ***Chapter 3*** elaborates on key identified ethical issues, relevant to SPLENDID, including *recruitment of participants*, *information to participants*, *informed consent*; *volunteer compensation*, *data handling*, *data transfer* and *adverse event handling*. Each issue is explored based to relevant national, international and EU directives. Afterwards, the specific aspects of the issues relevant to SPLENDID are described in detail and the proposed actions to mitigate the ethical risks are presented.
- ***Chapter 4*** deals with the technological safety in SPLENDID. Technological details about *data handling* and the *safety of the novel sensors* are presented.
- ***Chapter 5*** presents the details of the Ethical administration in SPLENDID

Changes in the version II of the document: In its current version (II), the Manual has been modified in order to incorporate:

i) Some additional information on current and future European Directives and Regulations related to the handling of SPLENDID data (sections 2.1 & 3.2.5 respectively).

ii) A more detailed presentation of the national regulations concerning personal data collection, handling and transfers in Sweden and the Netherlands (sections 2.3.1, 3.2.6 & 2.3.2).

iii) Updated information on the procedures of the second year of the project, when relevant to the ethical considerations presented here (sections 3.2.1, 3.2.4 & 4.1.4 and in Table 1).

iv) A small evaluation of the proposed strategy for the avoidance of *stigmatization* in SPLENDID @School, based on the comfortability ratings of the students during the T6.3 testing @School (section 3.2, paragraph: *Stigmatization*).

1.4 Intended audience

The intended audience consists of all the individuals in the SPLENDID consortium, together with the general public. It is natural that different partners will focus on the parts of the manual that specifically concerns them. This manual should be consulted in relation to all the planned research studies and testing activities in WP6. SPLENDID investigators should read and consider the content of this manual in each and every research protocol design and practice. Members of the technical teams of WP2, WP3, WP4 and WP5 should focus in section 4. The general public should consult the manual for answering any concerns about the ethical treatment of SPLENDID subjects and their collected data.

2 Ethical guidelines and rules on human research

This chapter presents (very briefly) the current legalisation and ethical considerations regarding human research from EU and international conventions and declarations and their relevance to the SPLENDID project. Secondly, since the research trials described in the DoW and D1.1 [1] will be taking place in Sweden and The Netherlands, this chapter presents overview information on ethical considerations and practices in these countries. Due to the European character of the SPLENDID platform, the ethics and the regulations of personal data transfers among institutions in different European countries were also considered.

2.1 International conventions and declarations

This chapter provides a relevant outline of regulations to the ethical aspects of SPLENDID regarding protections of human subject research in accordance with international conventions and declarations:

- ***The Declaration of Helsinki*** (DoH) (1964) [2] is the World Medical Association's (WMA) medical principles for research involving human subjects (2013), which is an important landmark for ethical research standards. The specified guidelines will be applied to the SPLENDID research trials to ensure respect for all human subjects and protect their health and rights.
- **UN Convention on the Rights of the Child**, (2002) [3]. The Convention deals with the child-specific needs and rights. It requires that states act in the best interests of the child. According to this convention on involving children in social activities "*children should be given an opportunity to participate in everything that is related to their lives. This includes the right to freedom of expression and an opportunity to make their views known and take part in decision-making about matters that have a bearing on them."*

2.2 Ethical legislation and Guidelines

This manual is composed in accordance with EU legislations and directives, and relevant national and international ethical guidelines:

- ***The EU Charter of Fundamental Rights*** (2001) [4] is one of the principle charters in the EU legal order that guarantees protection of human rights and fundamental freedoms. The legal status of this manifestation contains main rights listed under headings of freedom, equality, solidarity, citizens' rights, justice and dignity.
- ***World Medical Association. Medical Ethics Manual (2nd edition 2009)*** [5]. The manual is built on the foundation of the physician's relationships with others and covers a wide range of issues in medical ethics. These include an introduction to what medical ethics is and why it ought to be studied; the principal features of medical ethics, and how the WMA decides what is ethical; ethical issues arising from the physician/patient encounter; ethics concerning physicians and society; ethical issues arising from physician/colleague interactions, and medical research ethics.
- ***The EU Directive 2001/20/EC on clinical trials*** [6]. Its main objective is to simplify and harmonise the administrative provision regarding clinical trials. Thus, each EU country member has been required to adopt the provisions of the Directive into the national law by 1 may 2003. On the practical level, following this directive

establishes procedures which prevent complications linked to the multinational character of clinical trials. Even if the research studies in SPLENDID do not fill the strict criteria for being Clinical Trials, the main considerations of the directive concerning participant rights and medical data handling are very relevant to the SPLENDID study protocols.

- ***The EU Directive 95/46/EC on the data protection of individuals (DPD)*** [7] is the most important text on the EU level on the protection of personal data. The Directive establishes a legal framework aimed at achieving a balance between a high level of privacy and free movement of personal data within the EU. The Directive sets strict limits on the collection and use of personal data.
- ***The EU Directive 2002/58/EC on Privacy and Electronic Communications*** [8] and its amendment, **Directive 2009/136/EC** [9] establishes the basic legal framework for data privacy. This directive, together with Directive 95/46/EC, stands out as being of particular importance on legal and administrative points. In accordance to this Directive, the provider of an electronic communications service must protect the security of its services by: 1) ensuring personal data is accessed by authorised persons only; 2) protecting personal data from being destroyed, lost or accidentally altered; 3) ensuring the implementation of a security policy on the processing of personal data. The SPLENDID system will abide on all these requirements.
- ***The EU Regulation (EC) No 45/2001 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data*** [10] sets specific rules based on Data Protection Directive 95/46/EC [7] and the E-privacy Directive [8, 9]. It also establishes the European Data Protection Supervisor [11] as an independent supervisory authority with the responsibility of monitoring the processing of personal data by the Community institutions and bodies. The SPLENDID system will abide on all these rules.
- ***The EU Directive 97/66/EC on Protection of Privacy in the Telecommunication Sector*** [12]. According to this Directive, companies need to ensure that adequate data protection measures are applied and that the company is compliant with relevant data protection laws. The SPLENDID system will be developed in order to provide high level of data protection in accordance to both national laws and EU Directives.
- ***The EU Low Voltage Directive (LVD) 2006/95/EC*** [13] seeks to ensure that electrical equipment within certain voltage limits provides a high level of protection. This directive addresses the safety aspects of electrical appliances, such as household appliances, but also industrial equipment, laboratory instruments as well as information technology apparatus. This Directive is relevant for SPLENDID, since novel sensors will be used in different experimental settings.
- ***The EU Directive 2001/95/EEC*** [14] describes the general safety requirements for manufactures and distributors. Produced products should with the general safety requirement and the necessary information should be provided to consumers. The general principles and safety requirements of this directive will be followed during the production of the novel sensors to ensure health and safety of participant who are going to use them. That will also facilitate possible acquisition of relevant certifications for the final SPLEDID platform after the end of the project.
- ***The EU Directive 2007/47/EC (i.e. an amendment of the EU Directive 93/42/EEC) on clinical investigations on medical devices*** [15]. This directive harmonises the laws related to the manufacturing, use and commercialisation of medical devices in EU. Due to the fact that the SPLENDID platform is early in its developmental cycle, it

will not meet the criteria to be characterised as a medical device for the duration of this project. However, parts of the platform are registered medical devices; i.e., the Mandometer and the same is the case for some of the research tools that will be used in the described functionality tests (e.g., Bodymedia armband accelerometer [16]). These devices are going to be used in accordance to this directive. Additionally, the platforms' projected functionality is relevant to this directive. Thus, in order to develop physical activity as well as chewing sensors, the technical development partner in SPLENDID (CSEM) will strictly follow the guidelines relevant to this directive to ensure participants safety, hence good research practice.

2.3 National guidelines and regulations

While human research is, in many cases, international, the ethical guidelines of research on humans vary worldwide. Many countries' legislation and guidelines have The Nuremberg Code (1947) [17] and DoH [2] as staring points. Common to most is the emphasis on the importance of the informed consent, on the prevention of hazardous risks, on balancing the benefit/risk ratio and on confidentiality issues. The regulations for the transfer of personal data out of Sweden and the Netherlands are also considered. Note that no major legislative change took place in the two countries during the first and the second versions of this document.

2.3.1 Sweden

In Sweden research involving humans needs to be executed according to the Act concerning the Ethical Review of Research Involving Humans (*Riktlinjer för etisk värdering av medicinsk humanforskning*) [18]. This Act, in which the EU Clinical Trial Directive 2001/20/EC [6] is incorporated, provides an ethical review of research involving humans and human biological material. It also contains provisions regarding consent to such research. The purpose of the Act is to protect the individual and respect human dignity in research. The act also applies to doctoral work in graduate school (relevant in the case of KI). CODEX [19] is the Research Council's portal for research ethics guidelines in Sweden. The site is run in partnership with the Center for Bioethics (Karolinska Institute & Uppsala University) [20] and contains links to research ethics and for overviews of ethics in research. Ethical approval for every relevant study in Sweden is obligatory. Six Regional Ethical Review Boards [21] are responsible for reviewing the applications for ethical approval. Since KI, MANDO and IEGS partners are located in Stockholm, all the applications for ethical approvals for the SPLENDID studies in Sweden will be handled by the Stockholm Ethical Review Board [22].

Concerning the handling of personal information, Swedish legislation is harmonised with the EU directives 95/46/EC [7] and 2002/58/EC [8], and 2009/136/EC [9]. The Swedish Personal Data Act (PUL) [23] aims to protect people from having their privacy violated when personal data is processed. PUL covers the collection, recording, storage, processing, distribution, extinction of data and more. Additionally, he Swedish Data Inspection Authority (*Datainspektionen* [24]), has issued specific guidelines for personal data transfer out of Sweden with electronic means (including cloud storage) and supervises their implementation.

2.3.2 The Netherlands

In the Netherlands the Medical Research Involving Human Subjects Act (*Wet Medisch-wetenschappelijk Onderzoek met Mensen*; WMO) [25], governs research involving humans. Research needs to be executed according to it if the following conditions are met:

- It concerns medical-scientific research, which is defined as: "*All research that aims to provide answers regarding health and disease, by systematically collecting and studying data. Furthermore, it aims to add to the medical knowledge that is also applicable / relevant to populations outside the direct research population.*"
- People participating in the study are subjected to treatment/actions and/or a mode of conduct is imposed on them.

The WMO, in which the EU Clinical Trial Directive 2001/20/EC [6] is incorporated, is a law that has been enacted to protect people participating in a study and requires medical-scientific research to get medical-scientific and ethical approval before its execution. The Central Commission for Research Involving Humans, called *Centrale Commissie Mensgebonden Onderzoek* (CCMO) [26], is the executive body of the WMO. One of their main functions is appointing Medical Ethical Research Committees (*Medisch-ethische toetsingscommissies*; MRECs). A MREC consists of at least: a doctor, a methodologist, a legal expert, an ethicist and a person representing a person participating in a study. All research proposals need to be submitted for approval to a MREC. A research file with a standardised format should be submitted, including a complete justification of why and how the research will be performed. The General Administrative Law Act (AWB) [27] is a Dutch law which lays down the general rules for the relationship between the government and individual citizens, businesses and the like. According to it, the MREC has a 'reasonable period of time' (i.e., 8 weeks) to come to a decision on the proposed study, but if that is not enough that they can extend it with another 'reasonable period of time'. Without approval from the MREC it is illegal to perform studies covered by the WMO [25] in the Netherlands.

WMO [25] also includes statements on how participants should be recruited for medical/scientific research in which participants are subjected to treatment/actions and/or a mode of conduct is imposed on them. Regarding the people to be recruited the WMO states the following:

- Section 4+6: It is illegal to perform scientific research on people below the age of 18 or participants that are not mentally competent. However, there are some exceptions.
- Section 5: It is illegal to perform scientific research on people of which it can be reasonably assumed that, as a result of the factual or legal relationship to the person that recruits the participants or executes the study, they cannot freely decide on participating in the study. There, however, are some exceptions.
- Section 6: It is illegal to perform scientific research on people without their or their legal representative's written consent.

Again, the legislation in the Netherlands concerning the collection, processing and handling of personal data is harmonised with the relevant European directives [7-9]. Thus, the Dutch Data Protection Act (WBP; Wet Bescherming Persoonsgegevens [28]), describes codes of conduct on how to deal with personal data. The Dutch Data Protection Authority (DPA; *College Bescherming Persoonsgegevens*) [29] supervises the processing of personal data, in

order to ensure compliance with the provisions of the law on personal data protection and advises on new regulations.

3 Ethical aspects of user involvement

This chapter gives a detailed overview of research ethics involving humans in SPLENDID project. Information in this chapter should be supplemented with more practical instructions from the respective research sites (KI, Mando and WU). Confidence in research is essential. It is a prerequisite for people to set up as volunteers, whether they are patients or healthy volunteers. To further improve and strengthen confidence, it is necessary that the research trials are conducted in a manner that meets the highest ethical standards.

3.1 Principles of research ethics

There are some common basic ethical principles that apply in all human relationships. The Belmont Report (1979) [30] summarizes the basic ethical principles and guidelines for research involving human subjects. The SPLENDID ethics manual should be related to these principles and thus to be respected in all research trials. These principles are:

- ***Autonomy principle***. Everyone should respect others' ability and right to Self-determination (autonomy), empowerment and integrity that they have the ability to independently assess the information to alternative actions.
- ***Goodness principle.*** Respect for persons and their autonomy necessarily must give birth to doing the good; "*doing of the good upon respect for persons*".
- ***Principle of not to harm.*** Considering the balance between doing no harm and always doing the good
- ***Principle of justice.*** This extends beyond the legal protection of the subject. Justice also means that the benefits of research cannot be distributed unequally.

These principles are central to human research ethics. They are not a regulatory legislation and they address the practise, but also the overall integrity of conducting research. These principles must be interpreted anew in each age and each context, so that research is shaped by the preservation of human dignity. Accordingly, the SPLENDID research trials planning are shaped and preserved by implementing these basic ethical.

3.2 Key ethical issues

Since SPLENDID deals predominantly with human behaviour, in all its activities the human involvement is a prerequisite. Thus, in order to ethically justify the aim of these activities, it is necessary to consider a very basic question relevant to all research with human subjects. *What conditions have to be met so that these research activities subjects are ethically responsible?* The aim of this chapter is to summarise the common ethical issues and corresponding conditions, based on the most important guidelines and regulations, so that research activities in SPLENDID are ethically substantiated and justified. According to WMA [2], a study must have sociological value and meet the requirements of scientific methodology. The research design and realisation of the intended trials should be conducted so that they are capable of leading to reliable and valid results. For SPLENDID, the societal value and scientific methodology of the intended research trials and activities have extensively been warranted in detailed in the DoW and D1.1 [1]. All research protocols have been/are going to be submitted for approval. The following conditions should be met in every case, in accordance to Directive 2001/20/EC [6]:

- It is probable that the scientific activity will result in new insights in the field of medical science;
- It is probable that these insights cannot be obtained through methods that do not require the use of subjects or research that uses less invasive methods;
- It is probable that the interests of the subject involved are proportionate to the objections and risks for the subjects involved;
- The activity meets the requirements of a correct methodology of scientific research;
- The activity is performed by an appropriate institution and by or under expert guidance of persons that are competent in performing scientific research, and of which at least one is well able to perform the operations that are required with respect to the subjects involved;
- The compensations of the subjects do not disproportionately influence the subjects to give consent for participating in the study;
- The persons performing the scientific study and the institution at which the study is performed do not receive a compensation that exceeds an amount proportionate to the nature, extent and purpose of scientific research;
- In the research protocol it is indicated to what extent subjects can benefit from participating in the scientific study;
- In the research protocol for the scientific study, criteria for recruiting subjects are included;
- The study meets all reasonable requirements.

From an ethical perspective, research with underage individuals as volunteers is subject to specialised considerations. Inherently, it is more difficult to obtain adequate informed consent from underage participants, since their ability to assess risks and consequences is limited and they can be persuaded by others more easily. In these cases the decision for participation in research is jointly shared between the participant (who provides assent) and their parents (who provide consent). In order to facilitate this, the researcher has the responsibility to provide adequate information to both parties in understandable language. In SPLENDID, all the planned research activities will be implemented respecting the specific guidelines relating to good clinical practice, in accordance to Directive 2001/20/EC [6], in conducting of research trials involving both children at school environment and adults.

The following sub-chapters summarize the ethical requirements for key elements of a research study. All of the presented elements are relevant with the research testing included in SPLENDID. Each issue is defined with the help of EU and national directives, examined from the perspective of SPLENDID. Finally, actions in SPLENDID to mitigate the ethical risks are presented in each case.

3.2.1 Recruiting participants

This issue is relevant to *preliminary sensor (T6.2) & food (T6.3) testing* and *V1 (T6.4) & V2 (T6.5) testing.*

In accordance with WMA guidelines [5], justice is important in the process of selection of subjects in research. Test subjects must be chosen such that the project results will be useful for society. In conducting research trials, for all intents and proposes, recruiting the appropriate participants is critical. The research protocol should contain information on participants' eligibility to determine who among them is eligible to be in the study (i.e., well

defined inclusion criteria). The research protocol might also provide reasons that justify why a specific trial procedure is not practicable/ appropriate for some individuals and obtain a Waiver for Recruitment (i.e., well defined exclusion criteria). One possible problematic case arises when data is collected while participants who are later found to be ineligible to participate. In this case, the research protocol should have explicit outlined procedures for dealing with participant and collected data.

Recruitment of adolescents*: V1 (T6.4a) & V2 (T6.5a; SPLENDID @ School) testing.*

Children are vulnerable as a participant group as they are in dependence of others and have reduced ability to assess benefits and risks of participating in research. SPLENDID has identified some specific ethical issues relating to both participant group and purpose of research trials:

Participants with pre-existing problems.

SPLENDID @ School includes a behavioural screening (Primary Screening Stage - PSS) of a broad population (i.e., high school students), and it is projected that the system will have the means to analyse behaviours leading to either obesity or eating disorders. Thus, it is plausible that individuals with pre-existing problems will be identified. Also, as is usual in this type of research, it is expected that some of the test subjects will reach out to the researchers voluntarily, suspecting or even admitting to have relevant pre-existing conditions (predominantly eating disorders). Finally, judging by the reported prevalence of obesity in European schools [31], it is possible that fully-fledged obese students will exist in the initial test samples.

In order to avoid stigmatisation, as well as in order to evaluate the usability of the test protocol in a real-life school environment, no exclusion criteria were set for participating in the V1 testing in the school (T6.4a; see report D6.3 - *Preliminary evidence on objective assessment of eating and activity behaviour of Swedish adolescents and Dutch adult population at risk for weight gain*). While the protocol for the V2 testing in the school (T6.5) has not been finalised yet (the finalised version will be described in D1.3 - *Protocols of Evaluation Studies*, version 3), it has been proposed that 2 or 3 school classes will be participating in the Training and Test meals, included in the PSS, indiscriminately. However, only healthy participants, identified to be at-risk, will be accepted for the Behavioural assessment and Guidance phases of SPLENDID @ School.

Nevertheless, whenever it is deemed necessary (through data analysis or personal communication and/or observations), professional consulting and care to the student will be provided. The participation of IEGS as an educational partner in SPLENDID, provides access to experienced consulting school personnel (e.g., school nurses/teacher mentors etc.), which will help SPLENDID to handle the personal communication with the relevant students and their parents in the optimal manner. Additionally, MANDO is a registered health care provider, specialised in eating disorders and obesity. If it is requested, professional medical assessment and treatment (up to the usual MANDO standards) may be offered in one of the Mando clinics and the treatment costs will be covered by the Swedish Health Care System, since Swedish students are covered by the Swedish Health insurance by default [32]. Alternatively, after the first, free of charge, consultation, the concerned individuals will be given the choice to select any other registered Swedish health care provider (as required by Swedish Health Care legislation [33]). Note that the described methodology has been previously approved numerous times by the local Ethical authorities, as part of the protocol for joint KI & MANDO research projects.

Stigmatization.

The experience of stigma is common among human beings [34]. Stigmatization has also been associated with assistive technology for monitoring or evaluating behaviour [35]. The risk for stigmatization has been identified in the early on during the research planning in SPLENDID and has actively affected the design of every component of the proposed platform use of sensors and medical devices for collecting data (more info in D1.1 [1]). Overall, it has already been agreed that the active participation and endorsement of the testing by the educational institution (IEGS) is required to mitigate the risks of stigmatisation.

In the school environment, three main key actions in order to reduce the risk of stigma during the testing in school have been proposed:

A) Early and widespread delivery of information about the purpose of the project using all internal media channels available in the school environment. This strategy provides clarification on the project and prevents misunderstanding, which always appears prior to stigmatization. Based on this strategy, the information about the specific aims and proposes of the testing will be announced using available media channels in the school:

- School website
- Flyers to inform staff and students
- Informational meetings with students and teachers
- Informational meetings with health school personnel (i.e., school nurse and psychologists)

B) Indiscriminate participation of whole classes in the V1 testing and the PSS during the V2 testing. Afterwards, the students that will not be selected to participate in the follow up phases will be given the opportunity to participate in parallel (but not directly linked to SPLENDID) research activities that will be organised by KI and MANDO in the school environment.

C) Carefully selected common and secluded school areas to be used for meetings and running the tests. One of the main SPLENDID's aims is the seamless integration of the developed methodology with the normal school life. Working together with the school authorities (IEGS), the protocols for the testing inside the school environment will be specifically tailored to the available facilities. Thus, the testing will not disturb the everyday life in school and the participating students will not be singled out from their peers.

In practice, the measures above have proven to be effective during the V1 testing (T6.4a), during which the participating students felt very comfortable participating to the SPLENDID tasks (figure 1). Specifically, 100% of the students (n=41) rated their comfort more than 5 (in a scale from 1 to 9) and 73% of the students rated their comfort either 8 or 9 out of 9. No occurrences of stigmatisation were observed/reported to either the SPLENDID investigators or the school personnel. For more details on the protocol and the collected data from the V1 testing in IEGS see D1.3 (*Protocols of Evaluation Studies*) and D6.3 (*Preliminary evidence on objective assessment of eating and activity behaviour of Swedish adolescents and Dutch adult population at risk for weight gain*).

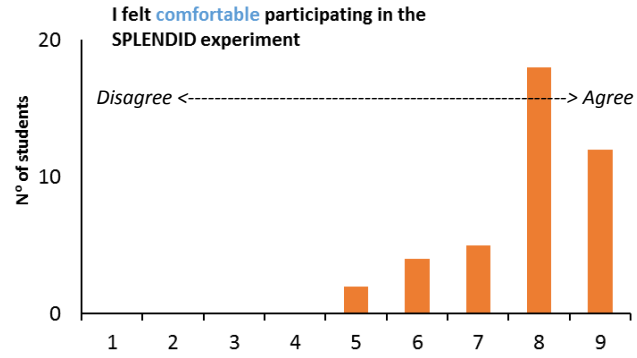

Figure 1: When IEGS students (n=41) were asked to rate their comfort while participating in the SPLENDID V1 testing in their school, they were overwhelmingly comfortable.

Additionally, an obvious out-of-the-school practise, which is very important in minimising the stigmatisation risks, is the final design of the SPLENDID sensors and the functionality of the platform. This has been a major focus point of the consortium since the initiation of the project. The necessity of having user-friendly, minimalistic and modern designs has been identified early on. The presence inside of the consortium of partners with experience in dealing with human subjects (KI, MANDO, WU) and more importantly of the educational partner (IEGS) will help SPLENDID achieve this goal. Note that this point is equally important in the:

Recruitment of young adults: *preliminary sensor (T6.2) & food (T6.3) testing and V1(T6.4b) & V2 (T6.5b; SPLENDID for Adults testing.*

Recruitment of participants in the relevant sites will be done through posters, emails and other relevant online services (e.g., web-portals for subject recruitment [36], social media etc.). More specifically, the WU has access to a database of people interested in participating in research. On the other hand, KI and MANDO have easy access to two university campuses at close proximity to their facilities. Individuals that fulfil the relevant criteria for each test and show interest in participating will be properly informed before they sign an informed consent-form and will be included in the study. The specifics of the information to be provided to potential participants are presented below.

3.2.2 Information to participants

This issue is relevant to all testing activities in SPLENDID including volunteers, i.e., the *preliminary sensor (T6.2) & food (T6.3) testing* and the *V1 (T6.4) & V2 (T6.5) testing.*

The fundamental requirement for good information to the participants [6] states that the researcher shall ensure that subjects are informed in a manner and with a language they understand. In Sweden guidelines for the information provided to the participants are available by CRB [20]. In the Netherlands, the written information distributed among potential participants should contain information according to the CCMO [26]. All informational material will be reviewed by the Central Ethical Review Board in Stockholm [22] and the responsible MREC in Wageningen. The information flow from the researcher to the participant should take account of the following elements (in general, not SPLENDID-specific):

General info:

- *Title*; the title of the protocol (or a simplified version of it).

- *Introductory information*; the need for participants, the type of participants needed (i.e., inclusion/exclusion criteria), the location of the study and the number of participants needed.

What the study entails:

- *Purpose of the study*.
- *Background*; a description of the study, the relevance of the study, the stage of development and the product/agent/treatment that is being investigated.
- *Nature and duration of the study*.

What does the participation in the study entails for the participants:

- *Contents of the study*; intervention/s (what, how often), number of visits, questionnaires, test procedures, time investment, study schedule and difference between intervention and research.
- *Alternatives for intervention*; other options of treatment, with advantages and disadvantages.
- *Disadvantages for the participant*; risks, side effects, responsibilities, possible consequences.
- *Advantages for the participant* (also mentioning 'no advantages' is relevant).

The arrangements made for participation:

- *Voluntary participation*; before and during a study a participant is allowed to drop-out without giving a reason and with no consequences attached (participation can also be terminated prematurely by the investigator).
- *Insurance* (if applicable); amounts, exclusions, insurer contact details, exoneration (if applicable).
- *Resistance of minors and mentally incompetent*: when any resistance is shown participation is terminated (if applicable).
- *Interim information*; timely provision of information that can influence the consent.
- *Results*; processing of research data, publication, message to participant, right to know or not to know and possible use of research material/interventions after the study.
- *Confidentiality of personal information & personal information transfer*; processing of information, right of access, possible reporting to general practitioner/specialist, storage time, use of excess material.
- *Compensations*; travel expenses, compensation, possible costs.
- *Proof pf approval from the ethical authorities*.

Considerations when giving consent:

- *Request for cooperation*
- *Time to think about/consider participation*
- *Presence/availability of independent physician* (if applicable)
- *Complaint procedure*
- *Contact details;* means to reach the investigators/research team
- *Attachments*; informed consent-form, insurance text, general brochure for participants, rare side effects (if applicable), local information (in case of a multicentre study).

For testing involving **adolescents**, i.e., *V1 (T6.4a) & V2 (T6.5a; SPLENDID @ School) testing*, the information will be provided to the students and their parents using a language that is comprehensible and suitable for each group. The information should be clear and

adequate in order for the student to make decision about participation. The specific information provided to the participant group should include:

- Aim of the test/study
- The overall aims of SPLENDID @ School
- Type of data that will be collected and information on the processing of data, including information about right of access from different partners
- Benefits and risks of the test/study and SPLENDID @ School in general
- Information that participation is voluntary and the right to withdrawal at any time of the project
- Contact details to the investigator team and the responsible project leader

Information in paper/electronic formats will be provided to the students and their parents/guardians. Informational meetings at school will be held with all the students scheduled to participate in the Primary Screening, when all the relevant information will be passed along in detail. It is SPLENDID's responsibility to ensure that the participants understand the information provided to them. If the student has not understood the information, s/he should not participate in the project.

Similar information will be provided to **young adults** that will participate in testing activities for *preliminary sensor (T6.2) & food (T6.3) testing and V1(T6.4b) & V2 (T6.5b; SPLENDID for Adults).* Apart from the written information to the participants, the main volume of the information will be passed along to interested individuals in face to face meetings which will be held in WU and KI/MANDO facilities.

3.2.3 Informed Consent

Again, this issue is relevant to all human-related testing activities in SPLENDID, i.e., the *preliminary sensor (T6.2) & food (T6.3) testing* and the *V1 (T6.4) & V2 (T6.5) testing.*

The consent procedure is one of the most important aspects of the Ethics in research involving humans. Aligned with the Directive 2001/20/EC [6], the procedure of getting informed consent from people to participate in an investigative activity needs to be described in the research protocol that is reviewed by the relevant Ethical authorities in each EU country. Before requesting consent, the investigator should make sure that the potential participant (or their legal representative) has received written, and if desirable oral, information. This information should be provided in such a way that it is probable that the potential participant (or legal representative) did understand the contents. Furthermore, s/he should be given sufficient time to make a proper decision on the requested consent. According to the CCMO [26] (in accordance to the American Psychological Association [37]) in the Netherlands and the CRB [20] in Sweden, in seeking informed consent according to the, the following information (in addition to the points covered in chapter 3.2.1) shall be provided to each participant:

- Confirmation on having read the study information.
- Confirmation on having been able to ask questions, and which were answered satisfactorily.
- Confirmation on having had enough time to think about and consider participation.
- Reminder that participation is voluntary and one can withdraw at any time, without giving a reason.

Similarly, the following permissions should be asked from the participant:

- Permission to inform a general practitioner/treating specialist in case of an identified mishap (if applicable).
- Permission for authorized persons, approval committees and authorities to access data (if applicable).
- Permission on transfer of data to another country inside or outside the EU (if applicable).
- Permission to process the (anonymous) data like mentioned in the information letter.
- Permission to store data for future research (if applicable).
- Permission for participation in the study.
- Date, name, and signature of the subject.
- Confirmation by or on behalf of the investigator on having offered both oral and written information, and being available for future questions.
- Date, name, and signature of the investigator or their representative.

Concerning the special case of adolescents who are to participate in SPLENDID testing; *V1(T6.4a) & V2(T6.5a; SPLENDID @ School*, the WMA's Declaration of Ottawa on the Rights of the Child to Health Care [38] discusses, among other things, children's right to refuse to participate in research. Accordingly, rights of young people to information and informed consent should be considered when conducting scientific research. In accordance to the Swedish CODEX [19], if a child is under 15, written informed consent will be needed from parent/guardian. In SPLENDID, the students, as well as their guardians, will need to consent to participation and usage of collected data before the projects starts by signing a written consent form. If the parent/ guardian opposes, the student will not be able to participate. By signing the written consent form, the participant has consented to having understood the procedure of the project and gives the researchers of SPLENDID right to use the data collected. The consent form should be documented with the student's and their guardian's identity, including their full name, date of birth and signature, and date and place. If the participant decides to withdraw during the course of project, all data that have been collected will be erased. The researcher must respect the participant and cannot object to the decision.

3.2.4 Incentives for research participants

Like before, this issue is relevant to the *preliminary sensor (T6.2) & food (T6.3) testing* and the *V1 (T6.4) & V2 (T6.5) testing* in SPLENDID.

In research involving humans incentives are used to encourage participation in a research project, or to honour a participant's contribution. Incentives are anything offered to participants, monetary or otherwise, for participation in research. However, a description of the incentives, including its monetary value and the rationale for its use is required in accordance with WMA's ethics guidelines [5]. It is important that participants are not tempted to take risks by being offered a large financial gain from participating in research trials. In order to avoid this Wageningen University has developed a formula, based on standard compensations for study elements (e.g. the number of visits to the university, and the number of questionnaires to fill out) to calculate appropriate compensations.

The researcher when seeking informed consent "*should not put undue pressure on the participants/parent(s)/legal representatives*". For example, Article 4 of the directive 2001/20/EC [6] requires that "*there must be no inducement to enter a trial, either for the parents, legal representatives or children. Parents/legal representative can only be*

compensated for their time and expenses". In the Netherlands, according to section 3 of the WMO [25], the compensation that participants receive for participating in a study, should not disproportionately influence a person to give consent for participating in the study.

In SPLENDID we have decided to use small non-monetary (e.g., a gift card) or comparable modest monetary compensations according to current practices of the involved partners.The compensation will preferably be given at the beginning of the research encounter in order not to connect the compensation to the performance of the participant. It will also be stressed in the informed consent that this does not affect participants' right to withdraw at any point during the research encounter.

3.2.5 Data confidentiality and anonymity

This issue is relevant to all the SPLENDID related activities (*T6.2-T6.5*), including *data sharing (T6.1 & T6.3)*.

The World Health Organisation (WHO) has published the *Ethical Guidelines for Biomedical Research Involving Human Subjects* [39], which provides explicit provisions for respecting the privacy of research participants and maintaining the confidentiality of their personal information. Privacy has been defined in terms of "*a person having control over the extent, timing, and circumstances of sharing oneself (physically, behaviourally, or intellectually) with others"*, hence limitation of access to these data by others. Confidentiality defines as "*the process of protecting an individual's privacy"*.

Confidentiality, in a research setting, refers to managing of information that an individual has disclosed in a relationship of trust, with the expectation that this information will not be passed to others without permission. National guidelines in Sweden and Netherlands are aligned with the Directive 95/46/EC [7], describe codes of conduct on how to deal with personal data with respect to privacy and confidentiality. The common rule is that collected data from participant need to be protected.

Anonymity in scientific research refers to a set of procedure that describes how to de-link the identifiers from originally collected data. Therefore, it is important to check national as well as EU regulation to determine whether the procedure used to secure anonymity prevail. The EU Directive 95/46/EC on the data protection of individuals [7] is the main act on the protection of personal data on the EU level. The directive establishes a legal framework aimed at achieving a balance between a high level of privacy and free movement of personal data within the EU. The directive sets strict limits on the collection and use of personal data.

In practise the Swedish Personal Data Act [23] and the Dutch Data Protection Act (WBP) [28], describe codes of conduct on how to deal with personal data. In both and in the directive 95/46/EC [7], personal data is defined as any information relating to an identified or identifiable natural person. Furthermore, in DPD [7] an identifiable person is defined as one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity.

The codes of conduct entail the following regarding research:

- All personal data should be managed as described in the research protocol and according to possible instructions and conditions
- Before collecting any data the investigator should have gotten informed consent; while having explained what data will be stored, for what purpose, where and for how long

- Data needs to be made anonymous. Personal data should not be stored in a way that enables identification of the subjects, once it is no longer necessary for the purpose the data have been collected

In SPLENDID, all the collected and shared data will be treated confidentially and only authorised researchers will have access to them. During all steps of data processing each participant will be given a new identification code that cannot be linked to him/her. While the data will become available to other SPLENDID partners, the coding list will be stored separately on each research site and it will not, under any circumstances, be shared with the whole project. All data will be encoded to ensure that the participant is unidentifiable. The collected data will be stored securely and kept/deleted according to the national guidelines for each research site (see 3.2.6). All access to data will be password protected. Details about technical aspects of data confidentiality and anonymity in SPLENDID are presented below (3.2.6) and in chapter 4.1.

Note that, at the moment of writing this manual (September 2015), the planned European Regulation *on the protection of individuals with regard to the processing of personal data and on the free movement of such data* [40], which is a comprehensive reform of the EU's 1995 [7] data protection rules to strengthen online privacy rights, has not been finalised. However, the proposed procedures for Data confidentiality, anonymity and handling in SPLENDID are fully in agreement with the principles of the current proposed draft of the regulation [40].

3.2.6 Data handling

This is a complementary issue to 3.2.5 and is relevant to the *data sharing (T6.1 & T6.3)*, the *preliminary sensor (T6.2) & food (T6.3) testing* and the *V1 (T6.4) & V2 (T6.5) testing* in SPLENDID.

In Sweden, in general, public authorities' documents are public and are to be archived according to the archives law [41]. According to Swedish National Archives, data generated by a research project is regarded as public documents. The archive law's basic principle is that "*the authorities' archives belong to the national cultural heritage and are to provide for, among other things, the right to examine public documents as well as the needs of research"*. On a personal level, the Swedish Personal Data Act (PUL) [23] aims to protect people from having their privacy violated when personal data is processed. Concerning data transfer among European countries, The Swedish Data Protection Authority [24] instructs that, after the correct anonymising procedures have been followed data may be transferred freely and without restrictions between the EU-member states and the EES countries. Finally, the

According to PUL, the person in the research trials is to be informed as to which information will be used. The data generated in Sweden will be treated in accordance to the PUL's code of conducts which demand that:

- Data files do not contain references to names of the subjects.
- Connection between data file names/information and subject names (i.e. encryption key) should be kept at separate files stored at different password protected locations (i.e., computers).
- The data are be deleted, ten years after publication of the results in scientific papers, so that they cannot be retrieved.

Similarly, WU-generated data (including type of data stored, way of protection and persons that can access the data) will be registered at the Dutch Data Protection Authority (DPA) [29], which supervises compliance with legislation regulating the use of personal data. Additionally, WU's Division of Human Nutrition has a code of conduct which every person working with the personal data of the subjects has to sign. This code of conduct dictates that data files will not contain references to names of the subjects. The connection between data file names/information and subject names (i.e. encryption key) will be kept at separate files stored at different password protected locations (i.e., computers). Five years after publication of the results in scientific papers, the data will be deleted so that they cannot be retrieved. Furthermore, when data is shared with other partners of the SPLENDID project, this data will be made anonymous and will only include the required information. Details for the technical management of information are presented in chapter 4.1.

3.2.7 Risk of harm assessment, adverse events and insurance

Once more, this issue is relevant to the *preliminary sensor (T6.2) & food (T6.3) testing* and the *V1 (T6.4) & V2 (T6.5) testing* in SPLENDID.

Regarding the testing activities in SPLENDID adverse effects due to the testing activities themselves are unforeseen, but we cannot rule out that they will occur. Examples of such adverse events might be: allergy for the used materials, headaches due to continuous wearing of the system, etc. However, we foresee such adverse events will be identified early in the development of the equipment and will subsequently be minimised (e.g., using hypoallergenic materials or modifying the fit of the sensor). An adverse event is considered serious if it:

- is fatal
- is life-threatening
- makes hospital admission or an extension of the admission necessary
- causes persistent or significant invalidity or work disability
- manifests itself in a congenital abnormality or malformation

Technical information about the development of novel sensors in SPLENDID are presented in chapter 4.2.

In Sweden, patients and healthy volunteers participating in clinical investigations of medical devices are covered by the Patient Injury Compensation Act [42] which regulates compensations to participants for damage in connection with related research. Any unexpected adverse events that may impact on the wellbeing of participants should be reported ethical committee that approved the protocol after first knowledge of the event [43].

In the Netherlands, Section 7 of the WMO [25] states that before the start of a study an insurance policy has to be taken out to cover damage by the study caused by death of injury of the participants and to cover liability for damage caused by the study. However, possible damages unrelated to the study, do not have to be covered. Furthermore, it states that the insurance that has been taken out should be described in the research protocol that has to be reviewed by a MREC (submitted within 15 days after first knowledge of the event through www.toetsingonline.nl). In case an adverse event (i.e., any undesirable experience occurring to a subject during the subject, whether or not related to the investigational product or the experimental intervention) is reported spontaneously by the subject or observed by the investigator it should be recorded and reported when it is considered serious.

3.3 Summary of ethical issues per research study

In order to make the manual easier for the SPLENDID partners to use, the table below summarizes the ethical issues relevant to each study including counter-references in the main body of text of this report.

Table 1. Synopsis of relevant ethical issues in SPLENDID per research activity (Q: yearly quarter; T*x.x*: Task *x.x*)

Title of research activity	Scheduling of research activity	Relevant ethical issues	Ethical application	
			Submitted	Approved
T6.1; Acquisition and standardisation of pre-existing data (KI, MANDO, AUTH)	Completed Dec 2013	Data confidentiality and Anonymity (3.2.5) Data management (3.2.6)	Sep 2013 (Sweden)	Oct 2013
T6.2; Standardisation of the new sensors				
T6.2a – Sound-based chewing/swallowing sensors versus EMG (WU)	Completed August 2014	Recruiting participants (3.2.1) Information to participants (3.2.2) Informed consent (3.2.3) Incentives for research participants (3.2.4) Data confidentiality and Anonymity (3.2.5) Data management (3.2.6) Risk assessment and insurance (3.2.7)	March 2014 (the Netherlands)	June 2014
T6.2b – Activity sensor versus commercially available sensor (KI, MANDO)	Completed August 2014	Recruiting participants (3.2.1) Information to participants (3.2.2) Informed consent (3.2.3) Incentives for research participants (3.2.4) Data confidentiality and Anonymity (3.2.5) Data management (3.2.6) Risk assessment and insurance (3.2.7)	March 2014 (Sweden)	May 2014
T6.3; Sensor testing with different foods				
T6.3a – Testing the chewing/swallowing sensors with different foods (WU)	Completed August 2014	Recruiting participants (3.2.1) Information to participants (3.2.2) Informed consent (3.2.3) Incentives for research participants (3.2.4) Data confidentiality and Anonymity (3.2.5) Data management (3.2.6) Risk assessment and insurance (3.2.7)	March 2014 (the Netherlands)	June 2014
T6.3b – Testing the Mandometer with different foods (KI, MANDO)	Completed August 2014	Recruiting participants (3.2.1) Information to participants (3.2.2) Informed consent (3.2.3) Incentives for research participants (3.2.4) Data confidentiality and Anonymity (3.2.5) Data management (3.2.6) Risk assessment and insurance (3.2.7)	March 2014 (Sweden)	May 2014
T6.4; Testing V1 of the system in semi-controlled environments				

T6.4a; Testing in adolescents (MANDO, KI, IEGS)	Completed April 2015	Recruiting participants (3.2.1) Information to participants (3.2.2) Informed consent (3.2.3) Incentives for research participants (3.2.4) Data confidentiality and Anonymity (3.2.5)* Data management (3.2.6)* Risk assessment and insurance (3.2.7)	November 2014	January 2015
T6.4a; Testing in young adults (WU)	Completed July 2015	Recruiting participants (3.2.1) Information to participants (3.2.2) Informed consent (3.2.3) Incentives for research participants (3.2.4) Data confidentiality and Anonymity (3.2.5) * Data management (3.2.6) * Risk assessment and insurance (3.2.7)	January 2015	March 2015
T6.5; Testing V2 of the system in real-life environment				
T6.5a; Testing in adolescents; SPLENDID @ School (MANDO, KI, IEGS)	Q2 2016	Recruiting participants (3.2.1) Information to participants (3.2.2) Informed consent (3.2.3) Incentives for research participants (3.2.4) Data confidentiality and Anonymity (3.2.5) Data management (3.2.6) Risk assessment and insurance (3.2.7)	Q4 2015 (projected date; Sweden)	Q4 2015 (projected date)
T6.5b; Testing in young adults; SPLENDID for Adults (WU)	Q2 2016	Recruiting participants (3.2.1) Information to participants (3.2.2) Informed consent (3.2.3) Incentives for research participants (3.2.4) Data confidentiality and Anonymity (3.2.5) Data management (3.2.6) Risk assessment and insurance (3.2.7)	Q4 2015 (projected date; the Netherlands)	Q4 2015 (projected date)

* During the *V1 (T6.4)* testing @School and in young adults, a SPLENDID-specific sensitive case of data processing, handling and sharing was identified. After the completion of the studies, during the analysis of the acoustical signals from the ear-worn chewing sensor, it became obvious that the sensor could potentially pick environmental sounds, especially relevant since human speech was sometimes audible, creating the risk for potential identification of the user. Since the data analysis at this point of the development required transfer of the raw data for the development of the first algorithm for chewing indicators, all the acoustical data were played back and checked manually by on-site investigators in order to ensure absence of identifiable information before they were passed forward to the rest of the consortium. This risk will not be relevant in the final version of the platform, since the raw acoustical information is transmitted (encrypted) to the user's mobile, where the indicator extraction takes place. The raw signal is then deleted and only the extracted indicators (non-identifiable) are transferred "downstream".

4 Data handling and device safety in the final system

In this chapter technical information about the SPLENDID practises relating to the *Data confidentiality and anonymity* (3.2.5), the *data management* (3.2.6) and the *sensor safety* (directly connected to the *risk of harm assessment, adverse events and insurance*) are presented. The presented information concerns the final version (V2) of the system, as described in D1.1 & D1.2 (*Use Cases Specifications*).

4.1 Data management practices

Concerning data management the following requirements have been stated in the Ethics Section of the DoW:

1. In SPLENDID, every precaution will be taken to respect the privacy of the subjects in accordance with the **PDD 95/46/EC** [7] on the protection of individuals with regard to the processing of personal data and on the free movement of such data. Data transfer will be handled in accordance to the e-privacy directives **2002/58/EC** [8] & **2009/136/EC** [9] following the rules described in the regulation **No 45/2001** [10].
2. During all steps of data processing **each research subject will be de-identified** and will be given a **new identification code**. The coding list will be stored separately. All data will be encoded to ensure that the research subject is unidentifiable. Only the researchers involved in the study will have access to the collected data.
3. **No user identifiable information is supposed to be stored on the server's side**. All identifiable information will only be stored on local computers of the healthcare professionals and/or the investigators.
4. An access policy will be defined specifying **data access rights of each type of user**, such as researcher, study assistant, subject.

In line with these requirements the current section will present:

- The definition of personal data according to the DPD
- The description of the data to be collected, processed and stored by the SPLENDID system and the access rights of each type of user per data type (based on D1.1 [1] and D1.2; *Use Cases Specifications*).
- Description of the subjects' registration and authentication procedure ensuring that user identifiable information will not be handled by the system (D1.2; *Use Cases Specifications*).
- Data safety requirements that should be addressed during system development in D5.1 (*Services, Components and System Specification*), D5.2 (*SPLENDID Integrated System*) and D5.3 (*SPLENDID System Prototype*).

4.1.1 Personal data definition

According to the DPD *"'personal data' shall mean any information relating to an identified or identifiable natural person ('data subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity"*.

A data subject has a number of characteristics such as name and date of birth. A data subject is identified within a set of data subjects if he/she can be singled out among other data subjects.

A personal data set can be split up in two parts:
- A *non-identifiable data part*, containing characteristics that in itself do not allow unique identification of the data subject. This is commonly referred to as the "payload". The payload contains anonymous data. In SPLENDID, such data includes for example, all the behavioural and health data of each subject (see Section 4.1.3).
- An *identifying part* that contains information that allows unique identification of the data subject. Such information includes: name, address, phone/fax numbers, email address, full postcode, date of birth, social security number, photograph, names of relatives, etc.

Due to its functionality, the SPLENDID platform only utilises with the subjects' *non-identifiable data part*. Thus, no *identifying data* will be handled (collected, processed or stored) by the system. Identifiable information will only be kept on the local computers of the healthcare professionals and/or the investigators, who by law have the right to access such data.

4.1.2 The SPLENDID users

In the final SPLENDID platform there four distinct categories of system users have been identified (D1.1 [1] and D1.2; *Use Cases Specifications*):

Student: An adolescent from the school population. The primary screening process at school is the entry point for the Student into the SPLENDID. If the Student is considered to be in a high risk category then he/she may participate in the secondary screening process and if the risk is verified he/she may continue with personal guidance monitoring. He/she interacts with the SPLENDID system via a smartphone and a web interface.

Adult: A young health concerned adult that uses SPLENDID as a lifestyle product. A Health Professional (HP) registers an Adult user into SPLENDID since the Adults do not have a primary screening process like the one of the Students. The Adult starts with the behavioural assessment process and if he/she is considered as high risk he/she continues with the personal guidance monitoring. He/she interacts with the SPLENDID system via a smartphone and a web interface.

Health Professional: A doctor, a school nurse or a nutritionist. Through the SPLENDID system he/she is able to setup the screening processes and the personal guidance monitoring for the Students and the Adults. He/she is responsible to verify the system predictions and prescribe behavioural goals. He/she interacts with the SPLENDID system via a web interface. For the needs of the planned testing activities SPLENDID investigators in each research site also belong to this category.

Assistant: The Assistant users are engaged by the HPs. They are responsible for running the primary screening process at schools and they may assist in other tasks (e.g. preparing the devices, arranging meetings). He/she interacts with the SPLENDID system via a web interface.

From the technical perspective, Student and Adult have been merged to a single user, the Student/Adult, following the decision to design interfaces that are common for both (D1.2;

Use Cases Specifications). Subjects data in SPLENDID refer to the data of the Student/Adult user. For HPs and Assistants the only data stored in the system are: usernames, passwords and accoundIDs. No other personal information related to these users is either processed or stored in the system.

4.1.3 Categorization of data

Table 2 below shows in detail the subjects' data that is stored in the SPLENDID system. Data may have been collected in 3 different ways:

- **Reported data**: Through user input. Students or adults may enter it via the smart phone and the health care professionals and the assistants via the web interface.
- **Recorded data**: Through the sensors, namely the activity sensor, the chewing sensor and the Mandometer.
- **System generated data**: Data may have been generated by the SPLENDID algorithms, such as behaviour indicators, risk for obesity or ED and proximity to goals. This type of data also includes system generated parameters such as accountIDs, eventIDs, usernames and passwords.

Data has been classified in five main categories:

- **Personal Profile Data:** this is information related to personal characteristics of students and adults, such as age, height and weight. This information is *Reported* by the users.
- **Behavioural data:** this is information related to the students/adults eating and activity behavior. The majority of SPLENDID data belong to this category. It may be data *Reported* by the users, *Recorded* by the sensors or *Generated* by the SPLENDID algorithms.
- **Health data:** the only types of health data in SPLENDID are the risk for obesity or ED for the students and the risk for obesity for the adults.
- **Procedural data:** this is information related to the management of the different stages and events during the usage of SPLENDID.
- **Statistics:** this information is generated by the system and includes data statistics from the subjects that have used SPLENDID.

Personal profile, behavioural and health data are personal data according to the DPD definition. However, they are anonymous without identifying information included. Procedural data and statistics are not personal data.

The data access rights, namely Read or Write, of each type of user for each data type have been identified and are presented in Table 2. As shown, the subjects' personal data can only be accessed by the HP.

4.1.4 Authentication procedure

Students Authentication in Primary Screening Phase

During this phase, the students will use cards with QRcodes to login to the smartphone application. QR code (Quick Response Code) is the trademark for a two-dimensional barcode first that is a machine-readable optical label containing information about the item to

which it is attached. In our case it is simply another coding of the StudentID which can be easily read by a device such as the smartphone.

The procedure is as follows: Before the Primary Screening event takes place at school, the HP, via the web interface, selects to generate a list of Student IDs. The system generates the StudentIDs and respective QRcodes. StudentIDs and QRcodes are printed in cards. The HPs, in collaboration with the Assistants, match each QRcode to a specific name (outside the system), write the students' names on the cards and give each student their card. The students then scan the cards with the smartphone, so that the system will link their data to the corresponding StudentID. The file listing the names and respective ID numbers will be stored locally by the HP.

An early, non-integrated version of such a system, following a very similar information flow, was deployed in V1 testing in adolescents (in IEGS, March/April 2015; D6.3). In this instance, the generation of the QR codes was manual. Also, each participant's code was linked with the Mandometer V4 and the accelerometer/data-logger that was used in every instance. The correspondence list of the Student-QR codes, with the Equipment-QR codes was stored in KI computers, separately from the collected data.

In practice, this system has proven to be both very secure and flexible enough for use in the school environment.

Student/Adult authentication in Behavioural Assessment and Personalized Guidance

During these phases, the students/adults will need to login either to their smartphone or to the web interface. They will use a Username & Password, provided to them by the HP. Usernames and Passwords, linked to subject IDs are generated by the web interface of the HP. The HP, outside of the system will assign specific names to the respective Username/Passwords and ID numbers. The file capturing this information will be stored locally by the HP.

4.1.5 Data Security

The main data security questions that arise in SPLENDID, as in all computing systems are:

- How to safeguard the *confidentiality* of the information (i.e., information is accessible only to those authorized to have access to it).
- How to safeguard *the integrity* of the information (i.e. information stored on a system is reliable and can be trusted).
- How to improve *the availability* of the information to its users.

The requirements in SPLENDID concerning these aspects are listed below.

Confidentiality:
- Access control should be in place so that a user is allowed to access only authorized data as per Table 2.
- User authentication should be in place in order to ensure that every user is positively identified.
- Log files should be kept so that it will be possible to track who has accessed or modified elements in the databases.
- Use secure protocols, antivirus products, firewalls.

Integrity:

- Physical integrity; data in SPLENDID should be immune to physical problems such as power failures and possible to reconstruct in case of system failures. The servers should be kept in secure areas, the database should be protected through firewall and backup procedures should be in place.
- Structure of the databases should be preserved. Modification to the value of one field should not affect other fields.
- Data from the sensors should be checked for validity (e.g. data in allowable value ranges) prior to be stored to the database.
- The user interfaces should be designed with proper validation for input data.

Availability

- Data should be available when needed. The Smartphone application should be designed so that it will continue to operate if there is no internet connection for periods during the day.

Table 2. Data stored by SPLENDID (HP: Health Professionals; S&A: Students and Adults; ASS: Assistants; R: Read permission; W: Write permission)

Data Category	Type of information	Data	Collection Mode	Access Permissions		
				HP	S & A	ASS
Personal profile		age, height, weight, gender, free text information	Reported	W	W	
Behavioural	self-assessment	desired weight, desired diet	Reported	R	W	
		self-ranking of: weight category, eating and of physical activity; fear of loosing control while eating	Reported	R	W	
	daily habits	sleep time, wake-up time, eating instances & physical activity level (while Smartphone turned off), workdays and days-off	Reported	R	W	
	sensor raw data	raw Mandometer data; raw Chewing sensor data; raw Activity meter data	Recorded	R		
	auto recorded meal data	meal time, quantity of consumed food	Recorded	R	R	
	registered meal data	meal type, type of consumed food, estimated quantity of consumed food, type of consumed liquid, estimated volume of consumed liquid, meal identification, meal location (home/restaurant), food picture	Reported	R	W	
	beverage data	beverage type, estimated volume of consumed beverage, beverage consumption time	Reported	R	W	
	registered activity	physical activity level (while sensor missing)	Reported	R	W	
	meal characteristics	meal detection, meal quantity, meal duration, original eating curve	Generated	R	R	
		corrected eating curve & coefficients	Generated	R	R	
	performance feedback	feedback on eating performance per meal, on physical activity performance per physical activity period, on eating, physical activity & system usage performance per day	Generated		R	
	sensor use/compliance	sensor removal	Generated	R	R	
	indicators	(categories:) end-user compliance, aggregate physical activity, meal characteristics per meal type, eating habits, self-rated fullness, discrepancy between objective & self-rated data	Generated	R		
	eating goals	workdays meal schedule, days-off meal schedule, energy per meal, quantity per meal	Reported	W	R	
	physical activity goals	physical activity periods, activity level per period, activity level for entire day, suggested activity per period	Reported	W	R	
	system usage goals	target time period per day for wearing the Chewing Sensor, for wearing the Activity Meter, target number of instances per day for using the Mandometer, target number of questions answered per day	Reported	W	R	
	goal proximity	proximity to eating goals, physical activity goals and system usage goals	Generated	R	R	
Health	obesity or ED risk	automatically assigned risk category	Generated	R		
		finalized risk category, justification	Reported	W		

Data Category	Type of information	Data	Collection Mode	Access Permissions		
				HP	S & A	ASS
Procedural	stage/event	event ID	Generated	R		
		stage name, start/end date, location, plate weight, description	Reported	W		
		introductory meeting location & date, start/end date, time/date of next appointment, free text	Reported	W		
		measurement mode (test/train)	Reported	W	R	W
	users accounts	account credentials (Username Password), subjectID, QRcode	Generated	R	R	R
Statistics		meal vs. fullness before/after meal, average indicator values, average satiety levels before/after meal, male/female ratio, average food quantity consumed for males/females, average meal coefficients for males/females	Generated	R	R	

4.2 Devices and sensors

In SPLENDID, two novel sensors will be developed, one for quantification of physical activity and one for quantification of chewing and swallowing. However, a number of additional devices will be used during the scheduled testing. The Mandometer® and the Bodymedia armband [16] (both also registered as a medical devices) devices are CE certified.

Concerning the development of the novel chewing/activity sensors involved in SPLENDID, certain directives are applied in order to provide measures for the protection of human subjects attending the research studies.

4.2.1 Classification of the sensors

The sensors developed in the framework of the project have to be firstly classified, even if they are not considered as medical devices.

According to:

- Directives 90/385/EEC, 93/42/EEC, 98/8/EC and 2007/47/EC [15], concerning medical devices
- Medical devices guidance document: Classification of medical devices (MEDDEV 2. 4/1 Rev. 9 June 2010) [44]

and given that the sensors are not invasive, with a lithium polymer battery used for power supply, it is concluded that the sensors are all Class IIb devices.

4.2.2 Legal directives

The principal applicable standard for CE certificated device is shown in Table 3:

Table 3. Applicable CE Certificated Device Directives [45]

Standard	Description
IEC 60601-1	General requirements for safety – Collateral standard: Safety requirements and essential performance for medical electrical systems

Beside this standard, a User Manual and a Manufacturing File shall be edited.

Since a Bluetooth™ device will be embedded into the data logger, EMC (ElectroMagneticCompatibility) analysis will be carried out to the final device.

Different tests are required to be performed as shown in:

Table 4. EMC tests and corresponding standards [46]

Standard	Test
CISPR 11	RF emissions
IEC 61000-3-2	Harmonic emission
IEC 61000-3-3	Voltage fluctuation/ flicker emissions
IEC 61000-4-2	Electrostatic discharge (ESD)
IEC 61000-4-4	Electrical fast transient / burst
IEC 61000-4-5	Surge
IEC61000-4-11	Voltage dips, short interruption and voltage variations on power supply lines
IEC 61000-4-8	Power frequency (50/60 Hz) magnetic field
IEC 61000-4-5	Conducted RF
IEC 61000-4-3	Radiated RF

In the case of medical devices, the following directives are to be respected during the development and system validation, as shown in Table 5.

Table 5. Applicable Medical Device Directives [15, 45, 46]

Directives	Description
93/42/EEC	European Council Directive concerning medical devices
2007/47/EC2	Amendment of the European Council Directive 93/42/EEC concerning medical devices
EN ISO 13485:2012	Medical devices QMS - Requirements for regulatory purposes
EN ISO 14971:2012	Medical devices - Application of risk management to medical devices
IEC 62366:2007	Medical devices – Application of usability engineering to medical devices
IEC 62304:2006	Medical device software – Software life cycle processes

Particularly, note that in terms of software development of the sensors, risk management is carried out, guided by the standard IEC 62304:2006.

An internal procedure of CSEM, responsible for development of sensors, is applied in the framework of the standard ISO 9001:2008. This procedure applies to all products designed and manufactured by CSEM that are qualified as medical devices or that might be used at a later stage as medical devices. This includes all devices that could be used in research project on human being and which are not considered as medical device.

At CSEM, the risks are evaluated on the basis of the severity of harm, the probability of occurrence of the hazard and on the detectability of the hazardous situation. The harm is defined as a physical injury or damage to the health of a patient or of the healthcare professional using the device.

A Risk Priority Number (RPN) qualifies the risk level. It is obtained by taking into account of severity of potential harm, probability of occurrence of harm and detectability of a hazardous situation.

Mitigation measures and risk control shall be performed according to the value of the calculated RPN in order to reduce risk level.

5 Ethics administration in SPLENDID

5.1 Ethical advisor

In SLENDID, Dr Ioannis Ioakimidis is appointed as Ethics Advisor on his merit of having extensive experience in designing, administrating (including acquiring the required ethical permissions) and conducting many research studies in relative scientific fields. He will be responsible for upholding the ethical code and instructing others involved in research trials to do so as well. The advisor also assists the SPLENDID in maintaining high ethical standards of conduct in research planning.

5.2 Ethical permission applications

Each research site in SPLENDID has an Ethics Committee (Chapter 2.3), to which ethical application will be send for approval. The default national standard operating procedures will be followed in every case. The Ethics Advisor should be contacted if any questions about the procedure arise and, if necessary, he should even review a pre-submission draft of the application. The application should be submitted to the Ethics Committee by the responsible research partner, who has the final responsibility about the quality of the application, but also for the actual research.

5.3 Managing Ethical Issues

"The best defence against an ethical problem is a good offence". Ethics will be on the agenda at consortium meetings to ensure an on-going discussion about ethical issues throughout the project and facilitating reporting of ethical matters.

From the initiation of SPLENDID, every aspect of the project has been evaluated from an ethical viewpoint, recognising the importance ethics in the scheduled testing, especially in sensitive populations like students.

Prior to each research trial the responsible researcher at the study site will send the study protocol, together with the informed consent form to the Ethics Advisor for a final quality check against the guidelines outlined in this document. The Ethical Advisor will study the protocol in detail and will provide feedback and instructions for adjustments (if necessary).

Furthermore, if needs arises, the Ethics advisor is responsible for initiating contact with the Ethics Review Help Desk of the European Union Commission [47] and the European Data Protection Supervisor (EDPS) [11]. The Help Desk will provide information, expert advice and guidance on ethics should ethical issues arise in the course of the project. Finally, the EDPS provides more general advice on the policies and legislation that affect privacy of personal data and will be contacted if the need arises.

6 Conclusions

The current document serves as a comprehensive reference manual, specific to the SPLENDID system.

It starts with a compact presentation of International, European and national guidelines and directives, relating to the ethical handling of all the aspects of research with human subjects.

It raises and defines and key ethical issues, cross references them with the planned research and testing activities in SPLENDID and presents guidelines for their management. Specifically, the concepts of *recruitment of participants*, *information to participants*, *informed consent*, *volunteer compensation*, *anonymity* and confidentiality of personal information, *data handling*, *safety of equipment* and *adverse event handling* are covered in great detai l.

Similarly, the technological details of data management and sensor safety in the final SPLENDID system are portrayed in detail and the Ethical Administration of the project is described.

In summation, this document will be a helpful tool for every member of the SPLENDID consortium in acting ethically during the project.

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