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myAirCoach - Analysis, modelling and sensing of both physiological and environmental factors for the customized and predictive self-management of Asthma"

(myAirCoach, Grant Agreement No. 643607)

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Executive Summary

This report constitutes the Deliverable "D8.5 – Ethics, Safety and mHealth Barriers (Regulation, Legislation, etc.) Manual" of the myAirCoach project (Grant Agreement No.: 6436071), and aiming to outline the project's plan towards addressing issues related to the safety and privacy of asthma disease as well as to ensure the fulfilment of high ethical standards during the project duration.

The current deliverable is mainly connected with the "Task 8.3 Ethical, Safety and mHealth Barriers Issues" within the WP8. So, the main outcomes of this deliverable will be applied to all the work that is planned under the myAirCoach project.

In this direction, the deliverable has two main functions, a) to analyse and identify privacy, safety and legal issues that are related to the myAirCoach project and especially to the components compromising in novel area of mHealth, b) to provide a first version of the project's strategy towards the ethical issues in order to minimise any related risks that may rise in the course of the project.

In this basis, the current deliverable is considered as a living document and will be continuously updated during the course of the project in order to address any emerging needs and requirements and cover any additional risks identified within the project duration. Furthermore, and as the test campaigns and pilots of the project are forming and their procedures are accurately defined, this document will be adapted by the responsible partners in order to include the pilot requirements that are needed for the two pilot countries participating in the project, namely the United Kingdom and the Netherlands.

The final and consolidated version of the document will be available by Month 35 as described in the project's Description of Work.

Table of contents

List of figures

List of Tables

List of abbreviations and acronyms

(*in alphabetic order*)

AIMD	Active Implantable Medical Devices Directive
AmI	Ambient Intelligence
BT	Blue Tooth
EAB	Ethics Advisory Board
EHR	Electronic Health Records
GCP	Good Clinical Practice
HCP	Health Care Professionals
ICT	Information Communication Technology
ISO	International Organisation for Standardisation
IVD	In vitro diagnostic
IVDMD	In Vitro Diagnostic Medical Devices Directive
LAN	Local Area Network
MDD	Medical Device Directives
OECD	Economic Co-operation and Development
P2P	Peer-to-Peer
PCC	Project Coordination Committee
PETs	Privacy Enhancing Technologies
SoA	Service Oriented Architecture
SOUP	software with unknown provenance
WAN	Wide Area Network
WBAN	Wireless Body Area Network
WHO	World Health Organisation
WMA	World Medical Association

1 Introduction

The myAirCoach project seeks to create a patient centred mHealth environment in order to support the self-management approaches for the disease of asthma. The patient oriented nature of the project's objectives connects its tasks with a variety of ethical, privacy and safety requirements that should be taken into account in all the phases of the work plan and guarantee the avoidance of possible risks to the patients..

One of the main goals of the project is to help patients managing their health condition through the adoption of user-friendly tools that will increase their awareness of their clinical state as well as the adherence and effectiveness of the medical treatment they follow. In this direction modern sensing capabilities will be integrated with the system and a novel sensor-based inhaler will be implemented during the source of the project. Through these components, the central system of myAirCoach will collect and analyse the data and propose tailored asthma treatment plans. The sensing capabilities of the final system will include physiological, behavioural and environmental factors that will be crossed with asthma data. Thanks to the latest analysis, processing and computational modelling techniques, myAirCoach will be able to present raw measurements, extracted features, indicators, and personal profile data, depending on the user's choice. All these data will be aggregated to give a picture of the patient's condition and will ensure clinical state awareness and optimal treatment.

All this mechanisms of data collection, storage and processing indicate the importance of a thorough plan and detailed methodologies that will protect the privacy of users, secure their data and strengthen the confidentiality between patients and doctors when using the myAirCoach system. **Chapter 2** of the current document tries to address these issues, through the formulation of the data security and privacy protection framework that spans across the data collection and information processing of the project. Furthermore, the use of novel medical devices healthcare approaches may create significant risks to the medical safety of patients. In this scope the developed software and hardware components should be used with caution during all the phases of the project, and always after the informed consent of participants and the supervision by healthcare professionals. Finally, the detailed definition of and effective patient safety plan will be a fundamental step towards the commercialization of myAirCoach components since it is expected to support their successful approval by the responsible regulation organizations. **Chapters 3** and **4** try to provide an initial version of the safety and risk management plan as a first step towards this direction.

The myAirCoach framework will be quantified in appropriate test campaigns with clearly defined cohorts of patients in three different testing sites. The validation of these results will serve to increased confidence in myAirCoach and in technology support for health decisions and self-management systems in general. Furthermore, the project's work plan includes evaluation campaigns that will not only assess quality and utility of the system but will also allow its further improvement. All the above, indicate the high importance of user involvement in the project and underline the importance of an ethical plan that will allow the deployment of test according to the highest of standards. **Chapter 5** of the current document focuses on these issues and tries to set the basis for the ethical strategy of the myAirCoach project. Generalized templates for questionnaires and forms protecting the user involvement are also attached in the annexes so as to help formulate a common basis for the different sites of trial deployments in the project.

1.1 Barriers and Obstacles of mHealth solutions

A recent global survey of the World Health Organization assessed, among many other parameters of mHealth, the barriers of its development and implementation[1]. In the region of Europe legal issues are proven to be the greatest obstacle for the deployment of mobile health solutions (Green Paper on mHealth, April 2014)[2]. The heterogeneity of the European framework further magnifies this issue and asks for careful design of the myAirCoach system on every level of its architecture and every step of its development. Based on the results of the aforementioned study and also on a recent report of the European Commission[3] and the GSM Association[4] as well reports of private organizations[5], the possible barriers of the myAirCoach project can be outlined by 9 main components as described in the following table together with the contributions of the myaircoach in this direction.

Table 1: Barriers of mHealth technologies and contributions of myAirCoach

	mHealth Barriers	Expected contributions of the myAirCoach project and specific contributions of the current document
1	**Financial issues** in terms of initial investments and reimbursement policies),	The support of the myAirCoach project by the European Commission addressed this barrier and created the optimum environment for the development of a novel solution for the patient engagement in the treatment of asthma through innovative mHealth approaches
2	**Legal and legislation issues** concerning the liability of the service providers and the security of private data,	The current deliverable takes the first step towards the mapping of the related legal and legislative environment surrounding mHealth technologies in the European Union.
3	**cultural issues** (resistance by traditional healthcare systems and institutions),	This issues will be identified and addressed during the deployment of testing trials and evaluation campaigns
4	**Lack of acceptance by the users** due to the often invasive approach of the currently available solutions and their lack of accessibility and user friendliness (often the user feels "inadequate" rather than	The careful study of privacy, safety and ethical issues is very a very important component for the acceptance of any new technology, and especially for the case of health oriented applications. The current deliverable takes the first

[1] Kay, et al. "mHealth: New horizons for health through mobile technologies." World Health Organization (2011).

[2] EC Green Paper on mobile health ("mHealth"),Available at: http://ec.europa.eu/digital-agenda/en/news/green-paper-mobile-health-mhealth (Assessed 2014

[3] European Commision "European Innovation Partnership on Active and Healthy Ageing " (2011)

[4] GSM Association on mHealth. Available at: http://www.gsma.com/connectedliving/mhealth/ (Assessed 2014)

[5] PwC. "Socio-economic impact of mHealth: An assessment report for the European Union" (2013)

	"empowered"),	step in this direction and tries to formulate the basis for the project's strategy to address these issues.
5	**Lack of common regulations** valid on a worldwide level, making even the development of viable solutions even more challenging (only big groups can afford the initial costs),	The review of EU regulations related to mHealth, as presented in this document, will be followed by a more detailed study of the local regulations in the United Kingdom and Netherlands and is expected to contribute to the identification of differences that may help towards a harmonised legal framework across Europe.
6	**Lack of suitable and consolidated business models**,	These issues will be addressed in the WP7 "Dissemination and Exploitation"
78	**Technical issues** (accuracy and stability of the measurements, system architecture, robustness of the solution also in terms of wireless connectivity and other),	These issues will be addressed in the technical Work Packages of the Project (WP2-WP5) and always inside framework of data protection and patient safety, as included in this deliverable.
8	**Lack of standards** specifically devoted to personal healthcare and fostering interoperability of the available solutions and finally,	Standardisation will be addressed in WP7 "Dissemination and Exploitation"
9	**Reluctance of healthcare stakeholders** to embrace new technologies and methods.	The compliance with legal, privacy, safety and ethical requirements described in the current document are expected to contribute positively in the involvement of stakeholders

According to partners' experience, the current project intends to address all above issues and contribute greatly towards the establishment of the enabling conditions for a successful deployment and exploitation of mHealth in Europe with specific reference the personalised monitoring and controlling of asthma disease. MyAirCoach will provide a large quantity of asthma related information, data, interventions and models allowing the **assessment of all the characteristics of the proposed solutions** such as clinical value, healthcare improvements, usability, integration, restraints, applicability of the business models and technological aspects related to its operation. In addition all the data and models produced through the myAirCoach timeline will be analysed and disseminated towards the **creation of guidelines** to be utilised by a far wider spectrum of applications than the ones addressed under the scope of the current project. Finally, myAirCoach will continuously provide to vendors and medical providers with all the needed information for the reassurance of the **system's interoperability** with related software and hardware components. All the above together with the technological,

economic and clinical validation of myAirCoach project as a whole and the well-established dissemination plan are promising bring this approach to a **widespread diffusion.**

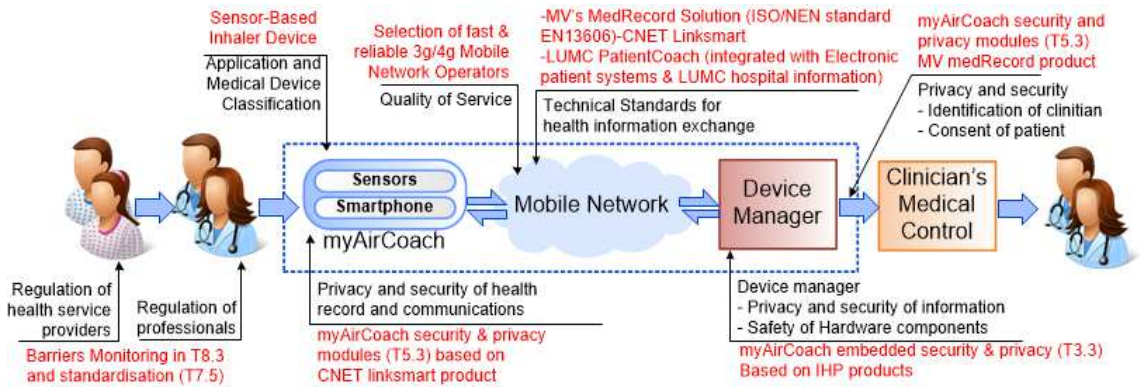

Figure 1: Addressing mHealth Barriers in the scope of myAirCoach Project

2 Data Security and Privacy Protection

MyAirCoach aims to help asthma patients manage efficiently and optimally their disease through the use of novel sensing approaches and their innovative positioning in the modern mHealth environment. In this direction myAirCoach will collect important health and lifestyle parameters of patients and provide them with an accurate outline of their asthma condition. Furthermore, myAirCoach system will develop the required infrastructure for the sharing of this information with the responsible doctor and the easy interpretation by both patients and their healthcare professionals. Based on the collected data and their transformation to useful and personalised knowledge, the myAirCoach project promises to target the fundamental difficulties in modern asthma treatment methodology, bringing it closer to the new age of mHealth and self-care approaches.

Related Project Objectives
Objective 1: Continuous, context-aware, multi-parametric monitoring of asthma related parameters, activity, lifestyle, and environment: Continuous physiological and clinical state monitoring of patients based on both physiological and environmental sensors will be achieved within myAirCoach. The aggregated physiological, behavioural, environmental, and treatment compliance indicators will be captured by different sensors integrated on the inhaler and a mobile device. Correlation of these parameters will clear the picture of the patient's clinical and physiological status and help to determine whether the patient's condition responds to the prescribed treatment procedure.   ***Objective 4: To develop patient-specific physiological and environment-aware computational model for asthma disease***   Development of a multi-scale patient-specific physiological and environment-aware computational model through correlation of physiological, environmental, lifestyle parameters, and biomarkers coupled with practical clinical experience, to help patients and their healthcare providers better understand and control their asthma symptoms. The patient models will be quantified through extensive clinical measurements performed in the very beginning of the project and will be able (1) to associate dynamically complex parameters and factors with the risk of developing asthma and (2) to assess the proximity of an individual's behaviour to the goals set by a supervising health professional.   ***Objective 6: Exploration of predictive value of new physiological markers that may enhance predictability of asthma***   Simulated continuous estimation of the patient's clinical biomarkers will be based on the patient records, the computational models and the measurements that will be unobtrusively captured during everyday activities. This information will be processed and analysed by a novel Clinical Prediction module as well as through the myAirCoach Decision support system that will be able to estimate the influence of specific treatments in the patient's quality of life, proposing new metrics to analyse and also to evaluate methods for future medical treatment.

All the above make evident the importance of data security and privacy protection in the proposed myaircoach framework. In order to address the issues connected to the management of personal information and especially health related data, the myAirCoach system will be designed to handle the collected data with extreme safety and under modern security preserving approaches. Security of data and privacy preservation components will be addressed in all the different layers of the system starting from the design the smart sensor based inhaler and wireless sensor network (WP3) to the implementation of computational models and Decision Support module (WP4), and from the integration of the personalised guidance system (WP5) to the initial test campaigns (WP2) and the final evaluation of the system (WP6).

The current section focuses on the different aspects of a data security and privacy and takes the initial step toward the formulation of a strategy that will help the evolution of the project and the development of the related system components. However, as is often the case, there are some important trade-offs that need to be taken into account for the final design of the system. For example, security requirements can lead to decreased performance and thus jeopardise not only the usability of the system, but also decrease the positive impact that it can have on the patients' health. This comes to no surprise, since in the majority of cases, data security components increase the complexity of systems.

The level of security that should be included in the myAirCoach system involves some judgement about the dangers associated with the system and the resource implications of various means of avoiding or minimising those dangers. Several major questions arise, for example:

- How to safeguard the integrity of the information?
- How to safeguard the confidentiality of the information (i.e. who should be allowed to see what and under what conditions)?
- How to publish scientific results without compromising the protection of patient health records?
- How to improve the availability of information to legitimate users?

Therefore the protection of data security in the framework of the myAirCoach project is expected to be a continuous process that will aim for the optimum balance between usability, performance, patient privacy and data protection and will always conform with the requirements of the European legislation framework.

The structure and content of the current chapter was based on the work of recent EU projects (where project beneficiaries contributed) in the field on ICT supported health tools and reflects the combination and extension of previous methodologies in order to cover the data security and privacy challenges introduced by the novel mHealth approaches. Analytically the outcomes and followed strategies of PeerAssist, Ask-IT, SPLENDID and HUMABIO projects where combined for the formation of the data security and privacy protection plan of myAirCoach. The following table summarises the objectives of these projects and their relation to myAirCoach Data Protection Strategy.

Table 2: Connection of myAirCoach data protection plan with previous approaches

Mobiguide[6]	
	The aim of the MobiGuide project is to develop an intelligent decision-support system for patients with chronic illnesses. The system accompanies the patients wherever they go and helps them and their care providers in managing their illness, whether they are at home, at work, out and about or travelling abroad on holiday or for business. The patients wear sensors that can monitor biosignals. The MobiGuide decision-support tools, which have access also to the patient's' historical clinical data, alert the patient about actions that should be taken, ask the patient questions, and make recommendations regarding lifestyle changes or contacting care providers.
Peer-Assist[7]	
	The main objectives of the proposed PeerAssist project were the implementation of a flexible Peer-to-Peer (P2P) platform, which will allow elderly people (not necessarily familiar with ICT technologies) to build virtual communities dynamically based on interests and needs they share. The PeerAssist platform will facilitate establishing on demand ad-hoc communities with friends, family, neighbours, caregivers, facilitators, care providers, etc., based on shared interests and communication needs.
ASK-IT[8]	
	The ASK-IT integrated project established Ambient Intelligence (AmI) in semantic web enabled services, to support and promote the mobility of Mobility Impaired people, enabling the provision of personalised, self-configurable, intuitive and context-related applications and services and facilitating knowledge and content organisation and processing
SPLENDID[9]	
	The aim of SPLENDID is to provide personalised services guiding adolescents and young adults to healthy eating and activity behaviours, preventing the onset of obesity and eating disorders. This requires an interactive system that accurately tracks eating and physical activity behaviour,

[6] MobiGuide Project. Available at: http://www.mobiguide-project.eu/ (Assessed 2015)

[7] Peer-Assist Project. Available at: http://www.aal-europe.eu/projects/peer-assist/ (Assessed 2015)

[8] ASK-IT Project. Available at: http://www.ask-it.org/index.php%3Fpage=about.html (Assessed 2015)

[9] SPLENDID Project. Available at: http://splendid-program.eu/project-aims/ (Assessed 2015)

	and provides goal oriented feedback to the user. It will also require a system that does not prevent the user from partaking in any activities related to regular life. The success of the project also depends on its implementation in the community, which is regarded an equally important objective.
HUMABIO[10]	
	The project developed a modular, robust, multimodal biometric security authentication and monitoring system which utilizes a biodynamic physiological profile, unique for each individual, and advancements of the state-of-the art in behavioural and other biometrics, such as facial, speech, gait recognition and seat based anthropometrics. HUMABIO also aims at creating the necessary enhanced security framework for the integration of the biometric authentication system to a corporate security grid or other controlled and monitored ambient intelligence environments, in order to guarantee trust and privacy concerning the citizen's personal biometric template and data.
Connections and Relations with myAirCoach Data Protection Plan	
Similarly to all above projects, myAirCoach will be highly dependent on the gathering of data and support of users through online available resources. Therefore, the data protection approaches of these projects have provided important insights related to the protection of privacy in the online environment and especially for the protection of medical information and helped for the initial formation of data protection and privacy preservation of the myAirCoach project.	

2.1 Categorisation of Data

As a first step in the direction of data protection the data manipulated by the myAirCoach should be classified so as to outline the important characteristics and requirements of the data protection plan.

- ***Personal Profile Data***: These data will be inserted to the system by the patient or the responsible healthcare professional, identifying important aspects of his health record (e.g. date of birth, gender, address, contact information) and will include space for free text information to be used by both doctors and patients themselves.
- ***Behavioural Data***: These data will include both the self-assessment of patients regarding their activity levels, smoking and eating habits in addition to the parameters measured by sensors such as accelerometers that will be used to accurately outline the activity levels of patients. This category will also include the measurements related to the proper use of the inhaler.

[10] HUMABIO Project. Available at: http://www.humabio-eu.org/index.html (Assessed 2015)

- ***Health Data:*** Similarly this category of data will include self-assessments of patients about known symptoms of asthma in addition to the objective measurements of the related sensors such as Nitric Oxide sensor. In addition this category of data will include the diagnosis and commends of doctors in addition to the measurements done in the clinical environment.
- **Environmental Data:** Asthma is highly related to the quality of air that the patients are breathing and especially the presence of allergens that can trigger exacerbation responses. Therefore this category will include the measurements of the patient's environment as assessed by myAirCoach sensors and also collected by online resources.
- **Personalised Patient Models:** The combination of all the above data will be used for the formulation of personalised patients' models that will be the centre of the accurate prediction and tailored decision support tools of the myAirCoach system. Because this type of information will stem from the processing of all the aggregated data, special focus will be given to the protection of patient models.
- **Statistics per Patient:** This category will include statistical results and outcomes for each patient and will be based on the processing of all the above data collections.
- **Overall statistics:** This category will include the statistical outcomes of the study of a group of patients and the extraction of useful results both for the validation of the myAirCoach system but more importantly for the formulation of treatment guidelines that will help asthma treatment.
- **Procedural:** This information is related to the operation of the myAirCoach system and includes both data related to the system requests of users, and service related data that will be used for the functionalities offered by the system.

The following table summarises all the above types of data already identified and stored in the myAirCoach system with some indicative examples of data and their collection mode. It is important to mention that the final selection of the collected data will be decided based on the identification of technical and legal barriers and taking into account their clinical significance for the assessment and treatment of asthma.

Table 3: Data stored by the myAirCoach system

Data Category	Type of Information	Indicative Data	Collection Mode
Personal Profile		Date of Birth, Gender, Address, Contact Information	Reported by Doctor
		Free Text Information	Reported by Doctor & Patient
Behavioural	Activity	Accelerometer, Location	Measured
	Daily habits	Smoking Habits, Nutritional Habits	Reported by Patient
	Proper inhaler use	Accelerometer, Time	Measured

Health	Asthma Symptoms	Coughing, difficulty to breath	Reported by Patient
	Physiological measurements	Breath Nitric Oxide Levels, Breath Temperature	Measured
	Clinical Measurements	Spirometry	Measured in clinical environment
	Diagnosis	Asthma severity, Allergens	Reported by Doctor
Environmental	Environment parameters	Humidity, Temperature, Pollution	Measured or assessed online
Models		Personalised Patient Asthma Models	Extracted from data collections
Patient statistics		Statistic results on patients asthma condition	Extracted from data collections
Overall statistics		Statistic results on the results of different treatment approaches	Extracted from data collections
Procedural	User requests	Data presentation, Decision support, Prediction etc.	Reported by the myAirCoach system
	User Account	Account credentials	

2.2 General Guidelines Concerning Data Management

Purpose of the data protection plan: The data protection plan outlines the crucial components of the proper use of data in the framework of myAirCoach. The fundamental goal of the rules and requirements outlined in this plan is to guard and protect the privacy of all users of the system allowing at the same time the proper function of the system and the stimulation of research in this field.

What should be covered by the plan: The data protection plan applies to both the raw data files assessed by the system in addition to the health data provided by the project consortium. The plan should also address how the results and outcomes derived from these data will be kept secure and pose no threat to the privacy of patients when used for scientific studies.

Components of the plan: myAirCoach data protection should be based on the three main components of data use as outlined in the following subsections.

2.2.1 Data Storage, Encryption and Anonymisation

Medical research increasingly revolves around real time and objective assessment of patient's condition (physiological and behavioural parameters) derived from sensors, health records, scientific tests, surveys and interviews. Unfortunately, this information may be also used for unintended purposes if it falls to the hands of unauthorised

persons, posing a significant risk to the privacy of patients. The protection of the privacy of patients should always be a fundamental responsibility for all the people involved in the myAirCoach project. Privacy also means that the participant can control the access to her/his personal information.

The protection of data should play an important role in every stage of their use starting with the lower stage of storage. Information should be anonymized so that individual identities cannot be revealed. Anonymisation provides a safeguard against accidental or mischievous release of confidential information.

There are different ways in which personal data can be modified to conceal identities:

- **Data encryption**: This approach uses modern encryption methodologies to protect the privacy of data, In this case the data are algorithmically encrypted using a public key and they can only be decrypted by the owner or the respective private key.
- **Data Anonymisation**: In this approach, identifying information (e.g. name, address etc.) is replaced with ID numbers , while their correspondence with the real data is kept in a different location or even in paper format in order to minimize any risk of their publication.
- **Overlap with generated noise**: This approach is an addition to the data anonymisation, in the case where large data collections can be used for the identification of a person. For example the continuous measurement of a patient's position can be used to reveal his address and consequently his identity. A solution in this case would be the addition of a constant on coordinates, which will protect the patients' identity but will allow the extraction of activity levels as a changes of position will remain the same.

The researchers and database developers should always consider whether the collected data contain combinations of such information that might lead to identification of individuals or very small groups of people and make the appropriate changes before publishing or sharing these data.

For the research purposes of myAirCoach the collected data will be anonymised and random noise will be added to them when the measurements can identify the patient information without affecting the informational quality of the final dataset. Furthermore, unique IDs will be assigned to patients and their correspondence with accurate profile details (name, address, phone number etc.) will be always encoded before sharing among the consortium. Finally, the online platform will use modern log-in approaches and frequent prompts will be sent to the users to change their passwords for optimal security and proper functionality of the system.

2.2.2 Data Handling and Processing

The following recommendations will be presented to the users of the myAirCoach system in order to minimise the risk unintentionally jeopardising her/his privacy:

- Use of antivirus programs and avoidance of risky mails and webpages.
- Never send the credentials of the myAirCoach platform to anyone.
- Contact with the responsible administrator of the online platform when strange system behaviour is detected.

In addition the myAirCoach consortium should follow some basic rules regarding the processing of data towards the goals of the project:

- Minimise the any specific personal information of any participant/patient from communication messages within the consortium. Encrypt data when such communication absolutely necessary (e.g. encrypted compression and sharing of the key via other communication media).
- Delete any specific personal information of any participant/patient from publications (scientific or not). When absolutely necessary require written permission by the participants for the specific publication and after a detailed explanation of the procedure.
- Protection of privacy of participants/patients within the organisational structure of all partners (employees, volunteers, etc.) a throughout all processes such as, communications, data exchange, presentation of findings, etc.

2.2.3 Data Destruction

The Destruction of data is a crucial component for the protection of the patients and participants of the campaigns and trials of the myAirCoach project. Specifically all partners will comply with the following couple of guidelines.

- Destruction of paper/electronic documents revealing patient identity and health data once the purposes for which the documents were authored and for which the consent form was signed is over.
- Erasing of electronic documents containing medical information once the purposes for which the data were obtained and for which the consent form was signed is over.

Furthermore, the final myAirCoach system will offer to the users the possibility to delete data and measurements that they consider not significant. Finally, if a patient choses to terminate her/his account on the myAirCoach system, all the collected data should be automatically deleted.

2.3 Data Security Framework

2.3.1 The need for security

The myAirCoach system will handle sensitive information, comprising of medical and lifestyle parameters characterising both the patient's health condition and lifestyle. Therefore, the provision of myAirCoach services requires a secure operational environment that will protect all the sensitive information of its users. Without an appropriate level of security in place, no such a system can be operational. Security is therefore considered as one of the cornerstones of the myAirCoach project

Different stages of security levels should be included in the myAirCoach system which includes judgment about the dangers associated with the system and the resource implications of various means of avoiding or minimizing those dangers. Several major questions arise including the integrity of the information, the confidentiality of the information (i.e. who should be allowed to see what and under what conditions) and the availability to legitimate users. Participants of the project test campaigns and evaluation trials need to be made aware that their information assessed during all the project experiments will be shared between the consortium members and only for the achievement of the goals of the project

In order to address the above concerns of the myAirCoach system it is necessary to:

- Identify the specific security requirements / threats / vulnerabilities associated to the various categories of users and data types.
- Study the related technology available.
- Define an appropriate security policy for protecting sensitive information.
- Study the impact of adding security on the availability/performance of the system.
- Propose the conceptual structure and specific measures required to improve the security of the system.

2.3.2 The security issue

It is widely accepted today that security is a basic requirement for the appropriate introduction and use of information and communication technologies especially for applications of health. The increasing employment of advanced technologies makes information systems more efficient, yet more complex, posing new challenges to ensure the protection and confidentiality of data and their integrity and availability. The new technologies contribute to improving the efficiency and quality of services offered to the patient and they are valuable tools for their management. They create however new situations regarding security that should be dealt with in a thorough and convincing manner.

Networking and communication security issues arise when a variety of different sensors and devices interact with local or remote applications. The foreseen network of myAirCoach can be separated in three main levels: the Body Area Network (BAN), the Local Area Network (LAN) and the Wide Area Network (WAN). Data security and privacy concerns are applicable in all three network levels and should be studied separately during the development of the respective software and hardware components of myAirCoach.

The basic security requirements of myAirCoach system are following previous approaches of health oriented systems. The following is a list of such technical security requirements for the security of the myAirCoach system:

- The security considerations must take into account both **software and hardware** components of the system that are parts of the system information flow.
- **Data integrity** is a key requirement. The system must preserve the integrity of the data stored in it.
- **Physical integrity**, so that the data of the myAirCoach system is immune to physical problems, such as power failures.
- **Logical integrity**, so that the structure of the myAirCoach databases is preserved. With logical integrity, a modification to the value of one field does not affect other fields, for example.
- Data should not be destroyed or altered either **accidentally**, as in a system crash, or maliciously, as in some **unauthorized person** modifying the data.
- **Element integrity**, so that the data contained in each element is accurate.
- **Data should be available when needed**. This implies system fault tolerance and redundancy especially for the system components that are related to critical health issues.

- Confidentiality, so that users are allowed to **access only authorized** data and so that different users can be restricted to different modes of access (e.g., read or write).
- **User authentication**, in order to be sure that every user of the myAirCoach system is positively identified and is granted access to specific data and functions.
- **Availability**, so that users can access the myAirCoach system in general and all the data for which they are authorized.
- **Auditability**, so that it will be possible to track who has accessed (or modified) the elements in the myAirCoach databases.

2.3.3 Components of the myAirCoach Security Design

Any discussion of computer security necessarily starts from a statement of requirements. In general, secure systems need to control the access to information or processes through the use of specific features, tools and approaches. Six fundamental requirements form the basis of information security:

- **Security Policy:** There must be an explicit and well-defined security policy enforced by the system. Given identified subjects and objects, there must be a set of rules that are used by the system to determine whether a given subject can be permitted to gain access to a specific object. Computer systems of interest must enforce a mandatory security policy that can effectively implement access rules for handling sensitive (e.g., classified) information. These rules include requirements such as: No person lacking proper personnel security clearance shall obtain access to classified information. In addition, discretionary security controls are required to ensure that only selected users or groups of users may obtain access to data (e.g., based on a need-to-know).
- **Marking**: Access control labels must be associated with objects. In order to control access to information stored in a computer systems, according to the rules of a mandatory security policy, it must be possible to mark every object with a label that reliably identifies the object's sensitivity level (e.g., classification), and/or the modes of access accorded those subjects who may potentially access the object.
- **Identification/Authentication**: Individual users must be identified. Each access to information must be mediated based on who is accessing the information and what classes of information they are authorized to deal with. This identification and authorization information must be securely maintained by the computer system and be associated with every active element that performs some security-relevant action in the system.
- **Accountability**: Audit information must be selectively kept and protected, so that actions affecting security can be traced to the responsible party. A trusted system must be able to record the occurrences of security-relevant events in an audit log. The capability to select the audit events to be recorded is necessary to minimize the expense of auditing and to allow efficient analysis. Audit data must be protected from modification and unauthorized destruction to permit detection and after-the-fact investigations of security violations.
- **Continuous Protection:** The trusted mechanisms that enforce these basic requirements must be continuously protected against tampering and/or unauthorized changes. No system can be considered truly secure if the basic

hardware and software mechanisms that enforce the security policy are themselves subject to unauthorized modification or subversion. The continuous protection requirement has direct implications throughout the computer system's life-cycle.

- **Integrity:** Data Integrity assures that information stored on a system is reliable and can be trusted. Data Integrity is a measure of the quality of that information. Most important factors of this measurement are: consistency, accuracy, and correctness of data stored in a database. Accordingly, it must be an integral part of myAirCoach security module.

When security is viewed globally and from a technical perspective, data security techniques have been developed over many years and range from the basic application of passwords to sophisticated encryption techniques and will encompass issues such as human factors and physical protection. The degree to which they are applied within individual systems is variable. Formal standards exist for defining system security (e.g. ISO 27001 and 270021) in the general domain. In addition the ISO standard 27009 provides regulations specific for healthcare. ISO 27009 is a comprehensive regulation that is complex to apply in full. Hence there is a need for understandable and acceptable “good practices” demonstrating realistic implementations of that standard.

In addition, there is increasing concern about the security weaknesses inherent in mobile devices which seems to be a crucial component of the myAirCoach project.

The benefits of **modern smart devices** include increased convenience and productivity, but they also contribute to the worsening of data security issues and risks.

Mobile computing is inevitably linked to the use of **cloud computing**. Cloud computing also implies specific security risks and triggers e.g. privacy and liability concerns. On the other hand, cloud computing – or more broadly outsourcing to large computing centres – offers also substantial opportunities for security improvements: As security is often not a priority for stand-alone systems (no back up, no policy of access etc…) those aspects are usually integrated in professional service level agreements offered by cloud-based solutions; the quality of those services is then subject to monitoring, quality assurance and certification. While the technical aspects are usually managed in a professional manner (strict privacy rules, access policy, mirroring of data etc..) there may be cultural challenges for health professionals as well as legal and liability challenges when health care data become virtual and are stored outside medical institutions.

Given the overall power of mobile and cloud solutions their risks should be assessed and overcome. Furthermore, strategies for securing the continuity of medical care in case of network outages should be established. The myAirCoach online mobile and web user platform will be developed using open source tools and environments of high security standards. Every myAirCoach system module should be evaluated and marked with access control labels. Although tracking of the activity of users will be useful from a security point of view, it will always be done by taking into account the protection of the user’s privacy and therefore audit methods should be discussed thoroughly before their application. For proper managing a myAirCoach services, detecting denial of service attacks and dealing with inter-provider relations the myAirCoach system needs to collect usage information related to the use of services.

2.4 Privacy Preservation Framework

2.4.1 The right of Privacy in the Modern Technological Environment

Modern smart devices are increasingly becoming fundamental components of our lives and they formulate an environment of constant and ambient monitoring that promises to facilitate citizens, help with a variety of issues and improve our quality of life. Unfortunately, all these technologies came with an important disadvantage as they pose significant risks for the preservation of the privacy of their users. It is no surprise that modern technology has been strongly criticised from this perspective, prompting engineers and legislators to protect the privacy of users in the modern technological environment.

2.4.2 Many facets of personal privacy

Even though, the security of personal information can significantly complicate the design and development of modern systems, modern systems cannot bypass any of the related requirements sins privacy is still a universally considered as a fundamental component of democracy.

The motives behind the protection of privacy can be distinguished in the following:

- ***Privacy as empowerment***: When seeing privacy as the protection of personal information, its aim is to give people the power to control the publication and distribution of information about themselves.
- ***Privacy as utility***: From the viewpoint of the person involved, privacy can be seen as utility, providing more or less effective protection against nuisances, such as unsolicited phone calls or emails.
- ***Privacy as dignity***: Dignity not only entails a free and independent life, but also focuses on the equilibrium of information, available between two people.
- ***Privacy as a regulating agent***: Privacy laws and moral norms can also be seen as a tool for keeping social balances.

Ambient intelligent technologies are slowly transforming the privacy environment and the redefining the impact of privacy protection as it exists today. In order to protect personal information it is important to make the principles of data gathering, storing, etc., transparent and to highlight the security measures that are used to protect the data management.

2.4.3 Components of the myAirCoach Privacy Protection Framework

2.4.3.1 Authentication

Authentication is the process of determining whether someone or something is, in fact, who or what it is declared to be. And it is also a fundamental security requirement. In private and public computer networks (including the Internet), authentication is commonly done through the use of login passwords. Knowledge of the password is assumed to guarantee that the user is authentic. A second approach is to use something that users possess to present proof, such as a dedicated authenticator or smart card, special authentication software or a digital certificate. Still another approach to authentication utilizes biometrics — fingerprints, voice prints, retinal scans, etc. Two-factor authentication, which utilizes two of these approaches (e.g. password and authenticator), is generally considered the optimum way to ensure an adequate level of security. In the scope of myAirCoach login authentication will be

utilised. In addition, doctors will be prompted to prove their education and experience before becoming a member of the platform since their suggestions can lead to health problems if they do not have adequate experience. All users will be also reminded to seek the help of a trained professional and not rely on comments of patients about their experience with asthma.

2.4.3.2 Authorization

Authorization is the process of controlling what information, applications and services a user can access. Authorization is sometimes seen as both the preliminary set of permissions by a system administrator and the actual checking of the permission values that have been already set up. The different categories of users within the myAirCoach system (doctors, nurses, patients, family etc) are relatively complicated authorization environment that needs to be studied in detail before the finalisation of the system's design and architecture.

2.4.3.3 Confidentiality

Confidentiality has been defined by the International Organization for Standardization (ISO) as "ensuring that information is accessible only to those authorized to have access" and is one of the cornerstones of information security. myAirCoach needs high level of confidentiality protection mechanisms based on the fact that it focuses on healthcare applications. Specially, medical and lifestyle data must be secured from unauthorized access with highest priority and should cover the full spectrum of activities extending beyond the protection of data as described in the previous sections.

2.4.3.4 Anonymity

Anonymity assures that sensitive data cannot be associated with a particular individual, either from the data itself, or by combining the user transaction with other data. It is very important to assure, that while the publication of statistic data, does not pose any risk to the anonymity of the users of the myAirCoach system.

2.4.3.5 Non-repudiation

Non-repudiation ensures that a transferred message has been sent and received by the parties claiming to have sent and received the message. Non-repudiation is a way to guarantee that the sender of a message cannot later deny having sent the message and that the recipient cannot deny having received the message. Assuring of non-repudiation is of critical importance in healthcare applications especially for the communication between patients and their doctors.

2.4.4 Directive on the Protection of Personal Data (2012/0010 COD)

In 2012, the Commission proposed a major reform of the EU legal framework on the protection of personal data, stimulating the discussion for new proposals will strengthen individual rights and tackle the challenges of globalisation and new technologies.

Every day within the EU, businesses, public authorities and individuals transfer vast amounts of personal data across borders. Conflicting data protection rules in different countries would disrupt international exchanges. Individuals might also be unwilling to transfer personal data abroad if they were uncertain about the level of protection in other countries. Therefore, common EU rules have been established to ensure that your personal data enjoys a high standard of protection everywhere in the EU. You have

the right to complain and obtain redress if your data is misused anywhere within the EU.Under EU law, personal data can only be gathered legally under strict conditions, for a legitimate purpose. Furthermore, persons or organisations which collect and manage your personal information must protect it from misuse and must respect certain rights of the data owners which are guaranteed by EU law.

2.5 European instruments in the field of data protection

The Council of Europe Convention for the protection of individuals with regard to automatic processing of personal data is the first European instrument in this field. It laid down the basic principles of a lawful data processing addressing the threats from the invasion of information systems, such as the data aggregation. The Organisation of Economic Co-operation and Development (OECD) is also actively participating in the issues of data protection on the Internet as well as the protection of consumer rights with regard to ecommerce[11].

2.5.1 Data Protection Working Party

The Data Protection Working Party has been established by art. 29 of Directive 95/46/EC and is the independent advisory body on data protection and privacy. Its tasks are laid down in art. 30 of Directive 95/46/EC and in art. 14 of Directive 97/66/EC. The opinions and recommendations of the Working Party are not legally binding, reflect, however, the current trends on European level and influence the decisions taken by the European Commission and the Committee established by art. 31 of Directive 95/46/EC.

This working document seeks to raise awareness and to promote the public debate on issues of on-line data protection. It therefore provides detailed information on technical aspects of how the Internet and the communications through the Internet are organised and what are the main privacy risks arising from the use of the Internet. In this context, it aims at the same time to provide an interpretation of the data protection Directives in that field. It follows a "holistic" approach by basing the analysis of privacy risks, the obligations and rights of the involved parties on both the general data protection Directive 95/46/EC and the privacy and telecommunications Directive 97/66/EC.

2.5.2 Directive on Data Protection in the Telecommunications (97/66/EC)

This Directive applies to data processed in connection with the provision of telecommunication services in public telecommunications networks, in particular via ISDN and public digital mobile networks, and is aiming to protect the privacy right of natural persons, as well as the legitimate interests of legal entities. Non-publicly available telecommunications services fall within the scope of the general data protection Directive 95/46/EC (Recital 11 Directive 97/66/EC).

The Directive imposes to the telecommunications network provider and the provider of a publicly available telecommunications services a duty to safeguard the privacy of the

[11] OECD Guidelines on the Protection of Privacy and Transborder Flows of Personal Data. Available at: http://www.oecd.org/sti/ieconomy/oecdguidelinesontheprotectionofprivacyandtransborderflowsofpersonaldata.htm (Assessed 2015)

users. This means that the service provider - if necessary in conjunction with network provider - shall ensure the security of its services in a similar way as under the Directive 95/46/EC.

2.5.3 Data Protection Directive (95/46/EC)

In 1995, the EC Directive on the protection of personal data has been adopted by the Council. The Directive is the first attempt on EC level to recognise the right to privacy and harmonise the national laws. Some main characteristics of the Directive are that it applies equally to public and private bodies, to both automatic and non-automatic data processing, and that the protection is restricted to natural persons (as opposed to legal entities). The directive regulates the processing of personal data, regardless if the processing is automated or not.

2.5.3.1 Scope of Directive 96/46/EC

Personal data is defined as "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/her physical, physiological, mental, economic, cultural or social identity;" (art. 2 a).

This definition is meant to be very broad. Data is "personal data" when someone is able to link the information to a person, even if the person holding the data cannot make this link. Some examples of "personal data" include address, credit card number, bank statements, criminal record etc.

The notion *processing* means "any operation or set of operations which is performed upon personal data, whether or not by automatic means, such as collection, recording, organization, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, blocking, erasure or destruction;" (art. 2 b).

The responsibility for compliance rests on the shoulders of the "controller", meaning the natural or artificial person, public authority, agency or any other body which alone or jointly with others determines the purposes and means of the processing of personal data; (art. 2 d)

2.5.3.2 Principles

Personal data should not be processed at all, except when certain conditions are met. These conditions fall into three categories: transparency, legitimate purpose and proportionality.

2.5.3.3 Transparency

The data subject has the right to be informed when his personal data are being processed. The controller must provide his/her name and address, the purpose of processing, the recipients of the data and all other information required to ensure the processing is fair (art. 10 and 11).

Data may be processed only under the following circumstances (art. 7):

- when the data subject has given his/her consent;
- when the processing is necessary for the performance of or the entering into a

contract;

- when processing is necessary for compliance with a legal obligation;
- when processing is necessary in order to protect the vital interests of the data subject.

Processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller or in a third party to whom the data are disclosed;

Processing is also necessary for the purposes of the legitimate interests pursued by the controller or by the third party or parties to whom the data are disclosed, except where such interests are overridden by the interests for fundamental rights and freedoms of the data subject.

The data subject has the right to access all data processed about him/her. The data subject even has the right to demand the rectification, deletion or blocking of data that is incomplete, inaccurate or isn't being processed in compliance with the data protection rules (art. 12).

2.5.3.4 Legitimate Purpose

Personal data can only be processed for specified, explicit and legitimate purposes and may not be processed further in a way incompatible with those purposes (art. 6 b).

2.5.3.5 Proportionality

Personal data may be processed only insofar as it is adequate, relevant and not excessive in relation to the purposes for which they are collected and/or further processed. The data must be accurate and, where necessary, kept up to date; every reasonable step must be taken to ensure that data which are inaccurate or incomplete, having regard to the purposes for which they were collected or for which they are further processed, are erased or rectified; The data shouldn't be kept in a form which permits identification of data subjects for longer than is necessary for the purposes for which the data were collected or for which they are further processed. Member States shall lay down appropriate safeguards for personal data stored for longer periods for historical, statistical or scientific use (art. 6).

When sensitive data is being processed, extra restrictions apply (art. 8).

The data subject may object at any time to the processing of personal data for the purpose of direct marketing (art. 14).

A decision which produces legal effects or significantly affects the data subject may not be based solely on automated processing of data (art. 15). A form of appeal should be provided when automatic decision making processes are used.

2.5.3.6 Supervisory authority and the public register of processing operations

Each member state must set up a supervisory authority, an independent body that will monitor the data protection level in that member state, give advice to the government about administrative measures and regulations, and start legal proceedings when data protection regulation has been violated. (art. 28) Individuals may lodge complaints about violations to the supervisory authority or in a court of law.

The controller must notify the supervisory authority before he/she starts to process

data. The notification contains at least the following information (art. 19):

- the name and address of the controller and of his/her representative, if any;
- the purpose or purposes of the processing;
- a description of the category or categories of data subject and of the data or categories of data relating to them;
- the recipients or categories of recipient to whom the data might be disclosed;
- proposed transfers of data to third countries;
- a general description of the measures taken to ensure security of processing.

3 Patient Safety

MyAirCoach aims to empower asthma patients to manage their condition though the development of a novel inhaler device and innovative software tools for personalised guidance. Both this objectives create issues of patient safety that should be addressed during the course of the project so that none of the foreseen task can jeopardise the overall health of the patients and trial participants.

Related Project Objectives
Objective 2: To Design and integrate miniaturised sensors into a novel small and lightweight inhaler prototype device
The appropriate measuring infrastructure will be designed and developed so as to monitor physiological parameters and biomarkers of clinical significance. In order to address this challenge, the project will develop beyond state-of-the-art sensing device that will be integrated into a novel small and lightweight prototype device that will be easy to mount securely on most commonly inhaler. This device will connect to the wireless body area network and be able to communicate with a smart mobile device.
Objective 3: To develop a personalised monitoring and guidance mHealth platform
Implement a mHealth platform for the personalised monitoring and guidance of patients with asthma. Communication with the patients' family and also supervision by the responsible doctor are two other fundamental components of the system. The platform will employ innovative analysis and modelling tools the outcomes of which will be accessible through intuitive graphical user interfaces. Optimal medical treatment approaches and concepts will be also used to inform and encourage the patients towards the avoidance of asthma triggers, healthier lifestyle and daily habits.

It is therefore evident that the importance of user safety is highly important in the framework of the current project, both in terms of the foreseen software tools (personalised guidance) and hardware components (novel smart inhaler). In order to address these issues the development of all the related components should be done under the corresponding requirements and in accordance with the related legislations.

The structure and content of the current chapter was based on the work of recent EU projects in the field on ICT supported health tools and reflects the combination and extension of previous methodologies in order to cover the safety challenges introduced by the novel mHealth approaches. Analytically the outcomes and followed strategies of eHGI Initiative, INTERSTRESS, REACTION, RENEWING-HeALTH and Sustains projects where combined for the formation of the data security and privacy protection plan of myAirCoach. The following table summarises the objectives of these projects and their relation to myAirCoach Safety Protection Strategy.

Table 4: Connection of myAirCoach safety plan with previous approaches

eHealth Governance Initiative eHGI[12]	
eHealth Governance Initiative eHGI	The eHealth Governance Initiative is working to establish a governance structure for eHealth within Europe in order to ensure continuity of healthcare both at home and across borders. It is achieving this through the development of strategies, priorities, recommendations and guidelines designed to deliver eHealth in Europe in a co-ordinated way. This work involves all stakeholders but especially patients and healthcare professionals.
INTERSTRESS[13]	
INTERSTRESS	The INTERSTRESS project aimed at developing innovative ICT-based solutions for addressing the problem of psychological stress in professional and social life. From a technological standpoint, the project involves a combination of virtual reality, non-invasive biosensors and mobile tools to provide personalised healthcare devices for stress prevention and management. The specific objectives of this approach are: 1) quantitative and objective assessment of symptoms using biosensors and behavioural analysis; 2) decision support for treatment planning through data fusion and detection algorithms; 3) provision of warnings and motivating feedback to improve compliance and long-term outcome.
PALANTE[14]	
PALANTE PAtients Leading and mANaging their healThcare through EHealth	Patient empowerment enables patients to take an active role in their own healthcare provision which allows them to stay easily informed and self-manage their own health services. In the context of an ageing population and increasing number of chronic patients, patient empowerment is a key tool to reduce healthcare costs and improve quality and efficiency of the health delivery

[12] eHealth Governance Initiative Project. Available at: http://www.ehgi.eu/default.aspx (Assessed 2015)

[13] SPLENDID Project. Available at: http://splendid-program.eu/project-aims/ (Assessed 2015)

[14] PALANTE Project. Available at: http://www.palante-project.eu/ (Assessed 2015)

	process. PALANTE seeks to empower patients so they are able to make informed decisions about their health, take an active role in their care and collaborate effectively with their healthcare team through the use of information and communication technologies.
REACTION[15]	
REACTION	The aim of the REACTION project was to develop an integrated ICT platform that supports improved long term management of diabetes based on wearable, continuous blood glucose monitoring sensors and automated closed-loop delivery of insulin. The REACTION platform presents an interoperable peer-to-peer communication platform based on Service Oriented Architecture (SoA) using cloud-enabling midddleware. It will feature a Model Driven Application Development environment based on extensive use of dynamic ontologies.
RENEWING HeALTH[16]	
RENEWING HeALTH REgioNs of Europe WorkING toGether for HEALTH	RENEWING HEALTH aims at implementing large-scale real-life test beds for the validation and subsequent evaluation of innovative telemedicine services using a patient-centred approach and a common rigorous assessment methodology.
Sustains[17]	
sustains	SUSTAINS comprises an array of services based on giving citizens online access to their Electronic Health Records (EHR). The services proposed have been distilled from the experience of regions which have already pioneered such access. Overall, SUSTAINS contributes to three major healthcare related issues in modern society: 1) Empowerment of patients: There is a growing tendency by patients and the public to question information from the health system, ask for a second opinion, demand respect and dignity in their treatment, expect convenience, etc. 2) Quality of care: New progress in healthcare means that patients demand, and healthcare professionals want to offer, the best quality of care. 3) Efficiency and economy: There is a growing demand from patients/citizens for improved efficiency and economy.
Connections and Relations with myAirCoach Data Protection Plan	
The above initiative and projects are related to the development of health oriented	

[15] REACTION Project. Available at: http://www.reaction-project.eu/news.php (Assessed 2015)

[16] RENEWING HeALTH Project. Available at: http://www.renewinghealth.eu/ (Assessed 2015)

[17] Sustains project. Official website: http://www.sustainsproject.eu/ (Assessed 2015)

online services and the development and use of novel devices and therefore can offer highly useful insights for the protection of patient/participant safety from both the software and hardware point of view in the framework of myAirCoach project.

3.1 Safety of Software Components

This section focused on the characteristics of software components that outline the requirement of user safety

3.1.1 Application Characteristics and Safety

3.1.1.1 Usability

The International Organisation for Standardisation (ISO) defines usability as, "The extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use". In the paper, "Usability 101 – Introduction to Usability"[18], usability is defined as consisting of five quality components, namely:

- Learnability: How easy is it for users to accomplish basic tasks the first time they encounter the design?
- Efficiency: Once users have learned the design, how quickly can they perform tasks?
- Memorability: When users return to the design after a period of not using it, how easily can they re-establish proficiency?
- Errors: How many errors do users make, how severe are these errors, and how easily can they recover from the errors?
- Satisfaction: How pleasant is it to use the design?

Based on the fact that asthma patients and their doctors will be the primary users of myAirCoach systems, these five components are expected to strengthen the trust on the myAirCoach system and allow its efficient use.

A recent European project, namely RENEWING HeALTH[16], has identified three key elements that increase usability:

- A patient-centred approach in which applications enable a partnership among practitioners, patients, and their families (when appropriate) to ensure that procedures and decisions are made based on patients' needs and preferences;
- Encouraging patient commitment to treatment and monitoring regimes, particularly when dealing with self-administered devices;
- Learnability as the ability to easily memorise tasks to be performed within the telemedicine service / application and that these are easy to understand.

3.1.1.2 Patient Access to Data

Patient access refers to the right and ability of individual patients to access their medical records either held as a full or summary record. Such access may be enabled

[18] Nielsen, J. (2003). Usability 101: Introduction to usability.

through the provision of a paper transcript or copy, or through electronic access to the record. The purpose of such access is to engender trust in the accuracy and completeness of the record and implies the provision of some mechanism or process whereby the patient may request and obtain changes to factual errors in the record. There are implications both for patient safety and professional liability if the process of deletion or suppression of a record prevents comprehensive care based on full knowledge of the patient's history. Nevertheless, access to personal medical records is a major step forward in empowering patients. The right to see what has been written about you, and the opportunity to correct errors of fact, are very strong drivers of trust. The concept of providing access to records is now enshrined in both national and EU legislation and is a key component in the EU Directive 2011/24/EU on patients' rights in cross-border healthcare.

3.1.1.3 Training and User Empowerment

In order for the benefits of myAirCoach to be fully realised and for its full potential to be re-leased, the meaningful involvement of patients is essential. Such involvement only becomes possible if myAirCoach developments and implementation meet the needs and expectations of professionals and patients who will ultimately use them.

The European Commission in its report, "European Countries on Their Journeys Towards National myAirCoach Infrastructures: Final Progress Report" published in 2011, recognises that education, training and continuous professional development for all, including for those citizens and patients which are capable and motivated to become engaged in their own care, must be strongly promoted: "There is a strongly felt need to improve myAirCoach training and education for professionals, but also to focus on reducing the asymmetry in capabilities, in-formation and knowledge between health professionals and patients, and thereby strengthen stakeholder engagement". The report further acknowledges that skills of health-care staff and ICT suppliers' staff also need to be expanded

For professionals, education and training in the delivery and support of more personalised healthcare and the use of myAirCoach solutions in the home are likely to come to the fore in the following years. This has implications for the medical curriculum and the need to include the use of tele-health services. This has already been recognised, notably by the British Medical Association, which issued its own recommendations for training in this area in 2007.

For patients such training needs to ensure that they:

- Understand how to use such systems;
- Understand the benefits associated with such systems and how they can enhance the patient/professional relationship;
- Learn how the use of myAirCoach systems can improve their own health literacy and thus promote personal healthcare and healthier lifestyles;
- Are fully informed about information flows;
- Have trust in the safety of such systems either both from a privacy and a safety perspective.

More specific objectives for such a training -supporting patient empowerment – can be derived from focus group work within the EU-co-funded large scale pilot SUSTAINS[17]

(Support Users TI Access Information and Services). Preliminary findings indicate the following dimensions and elements:

- Health literacy
    - to understand specific health information better
    - to understand their disease/condition and its implications better
    - to distinguish between quality health information from information pollution
    - to understand how changes in lifestyle could impact on patient health
- Patient control
    - to monitor their treatment progress
    - to feel less anxious about the health condition
    - to feel more responsible for the management of their disease
    - to be more aware and understand test results and the relevance of the tests done
- Patient participation
    - to better prepare for consultations with health professionals and meaningful engage in discussions with Health Care Professionals (HCP)
    - to participate in defining treatment plans in partnership with HCP (concordance)
    - to be able to attract HCP attention to issues considered important by the patient

In order to meet these requirements within myAirCoach services, the final system will need to integrate training approaches that are specifically designed for the asthma disease and on the basis of mHealth and towards efficient self-management of asthma condition.

3.1.1.4 Mobility

Information mobility can be viewed in two ways. First, information can follow the patient as he or she travels either within their country of residence or within the European Union. Secondly, mobility can refer to the use of mobile devices to improve efficiency and convenience. In the first case much work has been carried out at the legal level to preserve the rights of patients as they travel across borders. Projects such as CALLIOPE[19] and epSOS[20] have already considered in considerable detail the many technological legal and ethical issues associated with cross-border mobility.

In the case of mobile devices, the advantages of being able to input, store and access clinical and general health information are still being investigated within a developing technical environment. Perceived benefits of mobile technology within myAirCoach include:

[19] Calliope network. Official website: http://calliope-project.org/ (Assessed 2015)

[20] epSOS project. Officiela website: http://www.epsos.eu/ (Assessed 2015)

- Reduced paperwork;
- Increased time on patient care;
- Efficient communication links between patients and doctors;
- Efficient communication within the patient community;
- Support of self-management approaches;
- Increased care at home, meaning less travel for patients;
- Optimised treatment of asthma;
- Greater access to general health care information;
- Asthma assessment in the real life environment of patient.

The UK recently conducted a national study into the use of mobile devices by community care workers, "The National Mobile Health Worker Project"[21] that investigated the use of mobile technology by home and community care workers across a number of different locations

Among others, this study concluded that:

- The majority of sites demonstrated increased productivity after mobile devices were implemented (contacts increased) ;
- More time was spent with patients following deployment of mobile devices;
- Journeys and total journey time were increased, although to a lesser degree than activity, indicating improved efficiency

In terms of financial savings the project concluded:

> *"Whilst there are some clear financial benefits associated with the adoption of mobile working, it is stressed that just as the solutions are not 'one size fits all', neither are the benefits. Financial savings will vary greatly across different sites and the different services within them, as demonstrated by this report."*

The security of data held on mobile devices, and the legal issues surrounding their use are barriers to their implementation. A WHO reported that "The European (56%) and Americas (50%) Regions reported the absence of legal guidelines on privacy and confidentiality in the mHealth domain as the two most important barriers to mHealth implementation. Legal frameworks that govern the integrity of health data transfer and storage, in addition to identifying access control and medical liability, are critical to enabling myAirCoach (and therefore mHealth) in countries in these regions."

3.1.2 Medical Device Software – Software Life-Cycle Processes (EN/IEC 62304)

This standard defines the life cycle requirements for safety of medical device software. The set of processes, activities, and tasks described in this standard establishes a common framework for medical device software life cycle processes.

[21] The national mobile health project. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213313/mhwp_final_report.pdf (Assessed 2015)

The myAirCoach platform will comprise many software items that will manage patient information and therefore fall under EN/IEC 62304. Although some of the software components of myAirCoach will be developed research purposes, EN/IEC 62304 should be applied as good practice, and may be necessitated in some countries for compliance with Medical Device Directives (MDD) (See Section 3.2).

3.1.2.1 Scope of standard EN/IEC 62304

The standard emphasizes the combination of three principles for safety of medical device software, namely risk management, quality management and software engineering, and aims to focus on software engineering aspects.

This standard provides a detailed development and maintenance process for high quality and safe medical device software when software is itself a medical device or when software is an embedded or integral part of the final medical device. EN/IEC 62304 uses a software risk management process compliant with ISO 14971, as a part of medical device risk management process. If a medical device contains software that can lead to a hazard, then EN/IEC 62304 should be taken into account. This is because ISO 14971 does not specifically address the risk control in the software development life cycle. EN/IEC 62304 provides additional requirements for software risk control including software contributing to a hazardous situation or software that is used to control medical device risks.

This standard does not cover validation and final release of the medical device, even when the medical device consists entirely of software.

Plans, procedures and documentation for risk management activities can be a series of separate documents or a single document or they can be integrated with the medical device risk management activities and documentation.

3.1.2.2 Terms and Definitions

Architecture: organizational structure of a system or component.

Change request: a documented specification of a change to be made to a software product.

Medical device software: software system that has been developed for the purpose of being incorporated into the medical device being developed or that is intended for use as a medical device in its own right.

Regression testing: the testing is required to determine that a change to a system component has not adversely affected functionality, reliability or performance and has not introduced additional defects.

Safety: freedom from unacceptable risk.

Security: protection of information and data so that unauthorized people or systems cannot read or modify them and so that authorized persons or systems are not denied access to them.

Serious injury: injury or illness that directly or indirectly:

- is life threatening,
- results in permanent impairment of a body function or permanent damage to a

body structure, or

- necessitates medical or surgical intervention to prevent permanent impairment of a body function
- or permanent damage to a body structure.

Software development life cycle model: conceptual structure spanning the life of the software from definition of its requirements to its release for manufacturing, which:

- identifies the process, activities and tasks involved in development of a software product,
- describes the sequence of and dependency between activities and tasks, and
- identifies the milestones at which the completeness of specified deliverables is verified.

Software item: any identifiable part of a computer program.

Software product: set of computer programs, procedures, and possibly associated documentation and data.

Software system: integrated collection of software items organized to accomplish a specific function or set of functions.

Software unit: software item that is not subdivided into other items.

3.1.2.3 General Requirements

Quality Management System

The manufacturer of the medical device software shall demonstrate the ability to meet the applicable regulatory requirements to ensure reliable software (e.g. compliance with ISO 13485 or a national quality management system standard).

Risk Management

The manufacturer shall use a software risk management process compliant with ISO 14971 standard, as a part of medical device risk management process.

Software Safety Classification

The manufacturer shall assign to each software item a software safety class based on severity and document it into the risk management file. There are three software safety classes; class A: no injury or damage to health is possible, class B: Non-serious injury is possible, class C: death or serious injury is possible. If a software failure leads to a hazard, then the probability of such failure is assumed to be 100%. After a risk reduction process, a new software safety classification should be carried out. When a software system is decomposed into software items, such software items shall inherit the software safety classification of the original software item.

3.1.2.4 Software Development Process

This part includes all the stages of software development and testing from planning to software release, i.e. software development planning, software requirements analysis including functional specifications and risk control measures, software architectural design, software detailed design, software unit implementation and verification, software integration and integration testing, software system testing and software

release.

3.1.2.5 Software Maintenance Process

This includes establishing software maintenance plan (identify procedures for implementing maintenance activities and tasks), problem and modification analysis and modification implementation.

3.1.2.6 Software Risk Management Process

This includes analysis of software contributing to hazardous situations, risk control measures, verification of risk control measures implemented in software and risk management of software changes. The process shall be compliant with ISO 14971.

3.1.2.7 Software Configuration Management Process

This process includes configuration identification (i.e. establishing means to identify configuration items, identifying of software with unknown provenance (SOUP), identifying system configuration documentation), change control (approval of change requests, implementation and verification of changes, means of traceability of change), configuration status monitoring and documentation.

3.1.2.8 Software Problem Resolution Process

This includes preparation of problem reports, investigation of the problem, advising relevant parties, use of change control process, maintaining records, analysing problems for trends, verification of software problem resolution and inclusion of test documentation.

3.2 Safety of Medical Devices

The Medical Device Directives (MDD) harmonise the rules on the free circulation of medical devices in the EU. In order to conduct a clinical investigation of a medical device, researchers must prove they meet the applicable safety and administrative requirements detailed in the respective directives. Within the EU's framework of regulation, the Medical Device Directive is of the most importance with regards to the development of the inhaler prototype. In the final stages of commercialisation of the myAirCoach must include the required documentation and labels with the device. Regarding the use of commercial devices their manufactures must also provide a statement to the relevant competent authorities indicating how it has complied with the essential requirements of the MDD.

Prior to the introduction of the EU framework on Medical Devices in the 1990s, the regulation of medical devices was subject to the differing regimes of each member state. This created barriers towards the functioning of the internal market. As a consequence the Commission decided to harmonise regulation in the area of the medical devices so as to remove obstacles to the internal market. The framework on medical devices consists of three directives:

- The Medical Devices Directive (MDD) 93/42/EEC (as amended by Directive 2007/47/EC),
- The Active Implantable Medical Devices Directive (AIMD) 90/385/EEC (as amended by Directive 2007/47/EC)

- The In Vitro Diagnostic Medical Devices Directive (IVDMD 98/79/EEC.

The MDD is applicable to most medical devices, with the AIMD and the IVDMD applying in only more narrowly defined circumstances. The focus of this section is therefore on the MDD as it is likely that it will apply mainly to the novel inhaler device of myAirCoach. In order to be placed on the market all products that fall within the scope of the directive and meet its requirements are required to bear an EC conformity mark to show compliance with the directive. The aim of this is to allow products that conform to the directive's requirements to be sold freely throughout the European Union without hindrance from national governments. As Callens points out, the MDD was important for the e-health sector especially with regard to medical software that is used in many applications5[22]. The directive is not only of importance however for devices which are ready to be placed on the market. This is because there are, broadly speaking, two regimes for the use of devices under the MDD, one is for clinical evaluation/clinical investigations, the other is for general release on the market with the *CE* stamp. The following sections will focus on the provisions of the directive that might have a possible impact on the myAirCoach project. Devices which are to be used in clinical investigations under the myAirCoach project must comply with these requirements in order to be used in such investigations. Evidence of compliance with such requirements must be included in a statement to the relevant authorities before authorisation is granted for clinical investigations.

The Medical Devices Directive (MDD) has been subsequently amended by four directives and one regulation. In reviewing the Medical Device Directive the following analysis also takes into account the amendments made to it by subsequent directives. These include:

- Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998
- Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000
- Directive 2001/104/EC of the European Parliament and of the Council of 7 December 2001
- Regulation (EC) No 1882/2003 of the European Parliament and of the Council of 29 September 2003
- Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007

3.2.1 Definition of a 'Medical Device' (93/42/EEC)

In order decide whether a device is subject to the rules of the directive it must be discerned whether it is a 'medical device' or not. The definition of what exactly is a medical device is described as any "instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application".

[22] Callens, S. (2010). The EU legal framework on e-health.

Such a device should be intended by the manufacturer for one of a number of defined purposes, one of which is, “diagnosis, prevention, monitoring, treatment or alleviation of disease”. Devices not used for this purpose, including software, would therefore not be classed as a ‘medical device’ and therefore not be governed by the directive. However, software that does not perform one of the above functions itself will still be considered a medical device if it is used in combination with another medical device that does.

3.2.2 Requirements for Medical Devices used in Clinical Investigations.

The directive contains special requirements for the manufacturers of Medical Devices intended for use in Clinical investigations.

3.2.2.1 Statement of Purpose

For such devices the manufacturer must produce a statement for the authorities of the relevant member state. Such a statement must contain the following items (if applicable);

- data allowing identification of the device in question;
- the clinical investigation plan;
- the investigator's brochure;
- the confirmation of the subjects’ insurance status;
- the documents used to obtain informed consent;
- a statement indicating whether or not the device integrates as an integral part a substance or human blood derivative;
- A statement indicating whether the device is manufactured utilising tissues of animal origin as referred to in directive 2003/32/EC;
- the opinion of the ethics committee concerned and details of the aspects covered by its opinion;
- the name of the medical practitioner or other authorized person and of the institution responsible for the investigations;
- the place, starting date and scheduled duration for the investigations;
- a statement that the device in question conforms to the essential requirements apart from the aspects covered by the investigations and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient.

3.2.2.2 Documentation for Devices used in Clinical Investigations

In addition to producing the statement described above manufacturers must provide documentation for the medical devices that are involved in clinical investigations that meets the following relevant requirements:

- a general description of the product and its intended use;
- design drawings, methods of manufacture envisaged, in particular as regards sterilisation, and diagrams of components, sub-assemblies, circuits, etc.;
- the descriptions and explanations necessary to understand the above mentioned drawings and diagrams and the operation of the product;
- the results of the risk analysis (with a list of the standards of the relevant national standards if relevant, applied in full or in part, and descriptions of the

solutions adopted to meet the essential requirements of the directive if the standards referred to have not been applied. ;

- it must state whether the device incorporates as an integral part or substance human blood or one of its derivatives;
- It must state whether the device is manufactured utilising tissues of animal origin as referred to in Directive 2003/32/EC and that the relevant risk management measures have been taken to reduce the risk of cross infection;
- the results of the design calculations, and of the inspections and technical tests carried out, etc.

Copies of the manufacturer's statement and the documentation should be retained for at least 5 years. The product produced by the manufacturer should match the description given in the documentation. The manufacturer is obliged to take all necessary steps to ensure that the manufacturing process meets that which it described in its statement and in the device's documentation. Manufacturers should be meticulous in ensuring that all required documentation is enclosed. If the manufacturer meets these requirements member states are not permitted to create obstacles for the use of a medical device in a clinical investigation.

3.2.2.3 Requirements of the Clinical Investigation

Clinical investigations themselves must be conducted according to certain principles. According to the Directive the clinical investigation must be carried out on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge in such a way as to be able to confirm or refute the claims of the manufacturer. The procedures used must be appropriate for the device in question and the conditions must be similar to the normal conditions of use for the device. All appropriate features including the device's safety, its performance and its effect on the patients must be examined during the investigation. All adverse events must be fully recorded and immediately notified to all competent authorities in the Member State in question. Investigations must be carried out under the supervision of an appropriately qualified practitioner who has access to the technical and clinical data regarding the device and in an appropriate environment. The practitioner's report must be signed and contain a critical evaluation of all the data collected during the investigation. As a result of the recent amendment of this directive, manufacturers are obliged to keep this report 'at the disposal of the competent authorities'.

Manufacturers are obliged to notify the authorities of the termination of clinical investigations, with a justification if a trial was terminated early. If such termination was on safety grounds such a termination must be communicated to the relevant authorities of all member states and the Commission.

3.2.3 Essential Requirements of Medical Devices

3.2.3.1 General Design Requirements

In order to be placed onto the market devices must meet the 'essential requirements' of the directive. Devices intended for clinical investigation must also meet the directive's essential requirements; however with the obvious exception of those it is not possible to do so because the device in question is still at the investigation stage. The manufacturer of a device must include a description of how the product in question complies with the general requirements in its statement to relevant authorities of a

member state when applying for a clinical investigation or to be placed on the market. In addition to meeting the requirements laid down in the 'Essential Requirements of the Medical Device Directive member states must assume that a medical device is compliant with the 'essential requirements' if it meets the relevant national standards adopted pursuant to the harmonized standards, the references of such having been published in the Official Journal of the European Communities. Member States are obliged to publish the references of such national standards.

The primary aim is to ensure that devices are manufactured is such a way as to not compromise the clinical conditions of the patient, in addition to the safety and the health of those using such devices. Any risks that are created by the use of a device (including side effects) must be acceptable when weighed against the benefits to the patient and be compatible with a high level of health and safety. In order to achieve this, risks arising out of the ergonomic nature of the project must be considered in addition to the technical knowledge, experience and education of users and where applicable the physical condition of users. The solutions selected by the manufacturer must conform to recognised safety principles taking account of the state of the art. The following principles should be applied by the manufacture (in the following order) in order to achieve this;

- To eliminate or reduce risks in so far as is possible using an inherently safe design and construction;
- To take protection measures where appropriate including alarms if necessary, in relation to risks that cannot be eliminated;
- Users should be informed of any residual risks that cannot be eliminated by the protection measures adopted.

All devices should achieve the performances intended by the manufacturer and should be designed and packaged in such a manner as to be suitable for one of the functions described in the definition of a 'medical device'. These aspects of a device should be expected even with all the stresses and strains of normal use. Devices should be designed, manufactured and packed so that their performance during their intended use will not be adversely affected during transport (including the products instructions)51. The pages below describe the responsibilities of manufacturers with regards to several specific but important aspects of the medical devices.

3.2.3.2 Requirements Linked to Specific Hazards

In addition to the generalised requirements described above the directive contains a number of requirements in order to ensure against more specific hazards as they may be connected with the materials of functionalities of the myAirCoach smart inhaler.

Chemical, Physical and biological properties

The manufacturer must pay close attention to the choice of materials, with regards to such issues as flammability, the compatibility with biological tissues, and where appropriate the results of biophysical or modelling research. The design, manufacture and packaging must minimize risk of contamination in the transport, storage and use of devices. Particular attention should be paid to such problems that might arise with regards to exposed tissues and should take into account the nature and length of exposure. Design should also take into account all foreseeable interaction with other substances during the normal use of the device. If a device is designed to administer

medicinal products it must be designed to be compatible with such products according to the previsions and restrictions governing such products, allowing such products to function normally.

Special requirements exist if a medical device incorporates as an integral part a medicinal product. If the substance acts in an ancillary manner upon the body to a medical device it must meet the requirements laid out in Directive 2001/83/EC, the quality, safety and usefulness of the substance must be verified by analogy with the methods specified in Annex 1 of that directive. The relevant notified body is then obliged to verify the usefulness of the substance, taking into account the purpose of the relevant device, and then seek a scientific opinion from one of the competent authorities designated by the member states or the European Medicines Agency acting through its committee in accordance with regulation (EC) No 726/200453 Such an opinion will be based upon the quality and safety of the substance including the benefit/risk profile of the incorporation of the substance into the device as determined by the notified body. If a device incorporates a human blood derivative the notified body must also seek an opinion on a similar basis. The notified body should be notified of any changes made to a medical device. It will then have to consult the medicines authority involved in the initial consultation in order to confirm that the ancillary substance retains the same level of quality and safety. All devices must be designed so as to minimise the risk due to the leakage of substances from them5. If the parts of the device are intended for use with the treatment of children, pregnant or nursing women, the manufacturer must provide a specific justification for the use of substances. The manufacturer should also provide information in its documentation on residual risks for these patients groups and if available any precautionary measures that should be taken.

Infection and Microbial Contamination

Devices must be designed to eliminate risks, insofar as is possible to the users of the device and to third parties from infection. The design must however allow easy handling but where needed minimise the risks of contamination of the device by the patient during use or vice versa. Devices should be manufactured and sterilised by an appropriate and validated method and under appropriate conditions. Again there are specific requirements for devices that use tissues of animal origin. Devices which are to be delivered in a sterile state must be designed, manufactured and packaged in a non-reusable bag or according to the relevant procedures to ensure that they are sterile when placed on the market and remain so throughout transport and storage and until the protective packaging is opened. If the device is to be sterilised prior to use, the packaging should still aim to keep microbial contamination to a minimum. Packaging and labelling of devices should clearly distinguish between identical or similar products sold in both sterile and non-sterile conditions.

Construction and Environmental Properties

A device should be designed in a way that (if intended) it can be used in combination with other devices and not impair its, or their intended function. If such restrictions are unavoidable they should be clearly labelled or included with the device’s instructions. All devices must be designed to reduce risk of fire or explosion, particularly those intended for uses where exposure to flammable or combustible substances is possible. Devices should be designed so as to avoid or minimise the following risks;

- risk of injury, taking into account volume/pressure ratio, dimensional and where appropriate ergonomic features;
- risks connected with reasonably foreseeable environmental conditions such as magnetic fields, external electrical influences, electrostatic discharge, pressure, temperature or variations in pressure;
- risk of interference with other devices normally used in similar investigations or treatments as the device in question;
- risks arising where maintenance or calibration is not possible. Care should be taken to avoid risks brought about by the aging of materials or the loss of accuracy any measuring or control mechanism.

Devices with a Measuring Function

Such devices must be designed to provide appropriately sufficient levels of accuracy and stability for the intended use of the device in question. The limits of a device's accuracy should be clearly stated by a manufacturer. Measurement, monitoring and display scales must be designed in line with ergonomic principles taking account of the device's intended use. Measurements made by the device should be expressed in the correct legal units.

Requirements for Medical Devices Connected to or Equipped with an Energy Source

Devices incorporating systems that are electronically programmable must be designed to ensure the repeatability, reliability and performance of their systems according to their intended use. Devices that include software, or are software themselves, must be validated according to the state of the art, taking into account the principles of development lifecycle, risk management, validation and verification. If devices are dependent upon an internal power supply those devices must be equipped with a means of determining the state of such a supply. If the device is dependent upon an external power supply the device should be equipped with an alarm mechanism to indicate disruption to that supply. In addition if the device is meant to monitor clinical parameters of a patient, of which problems could lead to deterioration or death, it should be fitted with alarm systems to alert the patient of such situations. It is important that devices are designed and manufactured in such a way to avoid the creation of electromagnetic fields, which could interfere with the operation of other devices or equipment in the usual environment. The risk of electric shock should also be minimised as much as is possible through the design and manufacture of devices. The directive is also concerned with potential mechanical and thermal risks from such powered devices. The manufacturer should ensure that terminals and connectors to energy sources are designed in such a way to minimise risk. Devices are expected to be designed and manufactured to exclude as much as is possible risks associated with:

- Resistance, stability and moving parts;
- Vibrations;
- Noise;
- Heat from accessible parts of the device.

Devices that intended to supply energy to the patient should be designed in such a way that the flow of energy can be set or maintained at a rate that is safe for the patient. Such devices should also be fitted with a means for detecting problems with the flow rate. Manufacturers should incorporate suitable properties to prevent accidental

releases of excessive amounts of energy or substances. Devices that have visual systems or instructions indicating the required parameters for its operation should present such information in a way that is readily understandable to the user.

3.2.3.3 Information Supplied by the Manufacturer

All devices must be accompanied by the information needed for safe and proper use, taking into account the training and knowledge of potential users. The information available should also allow the manufacturer to be identified. Such information should be composed of a label and also instructions for use. If possible the information should be set out on each unit or packaged with each unit. If this is not practicable a leaflet should be sent with one or more devices. Instructions should be included in the packaging for every device. This is however not required for devices in Classes I or IIa which can be used safely without such instructions. Where symbols are used they must conform to harmonised standards. If no such standards exist the symbols must be clearly described in the documentation supplied with the device.

Labels

Labels are required to display the following information (if applicable):

- the name or trade name and address of the manufacturer71;
- the details strictly necessary to identify the device and the contents of the packaging, especially for the users;
- were appropriate, the word ‘STERILE’;
- where appropriate, the batch code, preceded by the word ‘LOT’, or the serial number;
- where appropriate, an indication of the date by which the device should be used safely, expressed as the year and month;
- where appropriate, an indication that the device is for single use. A manufacturer's indication of single use must be consistent across the Community;
- if the device is custom-made, the words ‘custom-made device’;
- if the device is intended for clinical investigations, the words ‘exclusively for clinical investigations’;
- any special storage and/or handling conditions;
- any special operating instructions;
- any warnings and/or precautions to take;
- year of manufacture for active devices other than those supplied with a use by date72;
- where applicable, method of sterilization;
- an indication that the device contains a human blood derivative (if that is the case).

If the purpose of the device is not obvious to the user, the manufacturer is obliged to clearly state it on the label and in the instructions for use. The devices and attachable components must be identified, where appropriate in terms of batches to allow all appropriate action to detect and risk posed by such detachable components.

Instructions for use Instructions for use are required to contain the following particulars:

- The same date required to be placed on labels except for batch number and use by date (if appropriate);
- The expected performances of the device and any undesirable side effects;
- If the device must be installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct devices or equipment to use in order to obtain a safe combination;
- All the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the device operate properly and safely at all times;
- Where appropriate, information to avoid certain risks in connection with implantation of the device;
- Information regarding the risks of reciprocal interference posed by the presence of the device during specific investigations or treatment;
- The necessary instructions in the event of damage to the sterile packaging and, where appropriate, details of appropriate methods of re-sterilisation;
- If the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and, where appropriate, the method of sterilization of the device to be re-sterilised, and any restriction on the number of reuses. Where devices are supplied with the intention that they be sterilized before use, the instructions for cleaning and sterilization must be such that, if correctly followed, the device will still comply with the basic principles of the essential requirements74.
- If the device bears an indication that the device is for single use, information on known characteristics and technical factors known to the manufacturer that could pose a risk if the device were to be re-used75.
- Details of any further treatment or handling needed before the device can be used (for example, sterilization, final assembly, etc.);
- In the case of devices emitting radiation for medical purposes, details of the nature, type, intensity and distribution of such radiation. The instructions for use must also include details allowing the medical staff to brief the patient on any contra-indications and any precautions to be taken. These details should cover in particular:
- Precautions to be taken in the event of changes in the performance of the device;
- Precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharge, pressure or variations in pressure, acceleration, thermal ignition sources, etc.;
- Adequate information regarding the medicinal product or products which the device in question is designed to administer, including any limitations in the choice of substances to be delivered;
- Precautions to be taken against any special and unusual risks related to the disposal of the device;
- Medicinal substances, or human blood derivatives incorporated into the device as an integral part;
- The degree of accuracy claimed for devices with a measuring function;

- The date of issue or the latest revision of the instructions for use.

3.3 Transmission Protocols and Safety

3.3.1 Cabled Protocols

The home sensors that will be used for the myAirCoach system will maintain a continuous connection with the central system and therefore the used transmission protocols should be included in the safety investigation.

IEEE 802.3 and IEEE 11073-30400:2010

IEEE 11073-30400:2010 provides for devices that are connected using IEEE 802.3 cabled Ethernet. It defines the clauses of IEEE 802.3 that apply. It further defines the connection sockets, plugs and cables for medical devices. There are no specific issues in IEEE 11073-30400:2010 of concern to medical devices in the myAirCoach project.

3.3.2 Wireless Protocols

Wireless Body Area Networks will be the centre of the myAirCoach system and will be used to transfer information from and to the patients in their daily living environment and during usual activities of daily living. As a result the effects of the transmitted electromagnetic radiation should be investigated.

IEEE 802.11

IEEE 802.11, commonly known as WiFi, provides the radio physical layer for high speed local area networks, and is normally seen as the wireless form of IEEE 802.3 cabled Ethernet. However, unlike IEEE 802.3 cabled Ethernet, IEEE 802.11 suffers from all issues relating to radio communication. Specifically this includes not only issues of correct data transmission; range, interference, error, data throughput; but also issues of the interference to other equipment through electromagnetic compatibility (EMC). This is seen as particularly important for medical equipment. There are also issues relating to security.

The problems of wireless are well known and general guidelines are available for use in the clinical setting. Specific guidelines relating to the issues of the use of wireless communication for medical devices connected to a network are to be addressed within a report in the IEC 80001 family. The recommendations made in this report will be adopted in myAirCoach.

Blue Tooth

There is little guidance on the use of Blue Tooth (BT) for medical devices. Recent development of a health care profile for Blue Tooth that has been adopted by the Continua Alliance will lead to an increase in availability of devices and this will lead to an increase in experience of its use. It is anticipated that at that time, guidelines will become available from appropriate standards bodies. Until that time, medical devices in the myAirCoach project will require careful risk analysis.

Zigbee

There is little guidance on the use of Zigbee for medical devices. Recent development of a health care profile for Zigbee that has been adopted by the Continua Alliance will lead to an increase in availability of devices and this will lead to an increase in experience of

its use. It is anticipated that at that time, guidelines will become available from appropriate standards bodies. Until that time, medical devices in the myAirCoach project will require careful risk analysis.

4 Risk Assessment and Management of Medical Devices

Risk Assessment is a core element in the research domain, and especially in projects that explore integrated intelligent solutions. Various opportunities and risks exist in every project providing a complex and often inter-related risk environment that researches have to address. After being identified, possible risks have to be mitigated. Furthermore, and especially for the case of medical applications, significant risks and challenges may arise and should be assessed and managed efficiently in order to reduce the possibility of harmful consequences on patients and healthcare personnel.

This section is based on the outcomes of the REACTION[15] project and outlines the legal environment for the assessment and management of risk related to medical devices.

4.1 Application of Risk Management to Medical Devices

4.1.1 Background

ISO 14971 provides a logical sequence of stages for risk management to ensure safety of medical devices and is addressed to medical device manufacturers. ISO 14971 emphasizes that the risk management process is an ongoing process of review and risk assessment throughout the medical device life cycle, and therefore sees post-market surveillance as a key tool in this process. Different from IEC 80001-1, which applies to medical devices on the same IT Network by a third party, ISO 14971 applies to medical devices that are on a physically isolated IT Network.

4.1.2 Relevance of ISO 14971:2007 to myAirCoach

ISO 14971 is very specific in its application and intent, and places direct responsibility of risk assessment and management on the device manufacturer, where a device is used within an isolated system.

ISO 14971 shall apply to the inhaler device to be developed within myAirCoach, and positions to the medical device manufacturer the responsibility to ensure compliance with the standard where the device is used for intended purpose. In the framework of myAirCoach, ISO 14971 will not apply to the manufacturer, since the responsibility for risk assessment and management will also be a responsibility of the complete myAirCoach consortium and through the entire length of the project.

Where a medical device is employed within myAirCoach for a purpose for which was not designed or intended, then ISO 14971 will not apply to the manufacturer, and the responsibility for risk assessment and management will fall upon the Ethical Committee of the myAirCoach project. All non-intended use of medical devices will be subject to receiving ethical approval from the appropriate national organisation.

4.1.3 Scope of ISO 14971:2007

4.1.3.1 Terms and Definitions

Risk management: systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk.

Harm: Physical injury or damage to the health of people, or damage to property or the environment.

Hazard: potential source of harm. Risk: combination of the likelihood of harm and the severity of that harm. Intended use/purpose: use for which a product, process or service is intended according to the specifications, instructions and information provided by the manufacturer.

Residual risk: Risk remaining after risk control measures have been taken.

Risk analysis: systematic use of available information to identify hazards and to estimate the risk.

Risk evaluation: process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk.

Risk assessment: overall process comprising a risk analysis and a risk evaluation.

Risk control: process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels.

Risk estimation: process used to assign values to the probability of occurrence of harm and the severity of that harm.

Use error: act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

In vitro diagnostic medical device (IVD medical device): medical device intended by the manufacturer for the examination of specimens derived from the human body to provide information for diagnostic, monitoring or compatibility purposes.

Top management: person or group of people who direct(s) and control(s) a manufacturer at the highest level.

Life cycle: all phases in the life of a medical device, from the initial conception to final decommissioning and disposal.

4.1.3.2 General Requirements for risk management

Risk Management Process

The risk management process involves identification of all potential hazards associated with the medical devices, including in-vitro diagnostic (IVD) medical devices, assessment of the associated risks, risk control, i.e. minimisation of risks or reducing them to an acceptable level, evaluation of overall residual risk for acceptability and documentation.

The risk management process needs to be iterative, covering each risk in turn and returning to the earlier steps if the risk control measures introduce new hazards or when new information that could affect the device safety becomes available or if any modifications have been carried out.

Management Responsibilities

The top management shall provide an overall guidance on the risk management process. They are responsible for defining the policy for risk acceptability based on applicable national or regional regulations and relevant international standards, establishing a risk management process as a part of the design, carrying out periodic reviews of the risk management activities for their effectiveness and suitability and rectifying weaknesses, and documenting decisions and actions taken.

The top management shall provide adequate resources and assign qualified personnel for risk management.

Qualification of personnel

The risk management process should be performed by a multi-disciplinary team, consisting of people with complementary skills, such as people who are knowledgeable of the design/construction/use of the particular device/service or similar devices/services, technologies involved and risk management techniques.

Risk Management Plan

The manufacturer shall establish and maintain a risk management plan for each medical device in accordance with the risk management process. The risk management plan shall provide an organised approach for the risk management process and shall include:

- description of the particular medical device including its intended use and expected benefits
- mapping of all elements of the risk management process to the manufacturer's defined product life-cycle
- Assignment of responsibilities and authorities for the execution of specific risk management activities, e.g. reviewers, experts, independent verification specialists, approval authorities
- Requirements for monitoring the risk management activities
- Criteria for risk acceptability, based on the manufacturer's policy for determining acceptable risk, including criteria for accepting risks when the probability of occurrence of harm cannot be estimated
- Risk management report (Details of the verification activities, effectiveness of the risk control measures, etc)
- Methods of gathering relevant post-production information from various sources such as users, service personnel, training personnel, reports and customer feedbacks (and this information will be fed back to the risk management process)

Risk Management File

The manufacturer shall establish and maintain a risk management file. This file shall provide traceability for each identified hazard to demonstrate that the risk management process has been applied correctly and to assure completeness of the risk management process. Incompleteness at any stage of the risk management process, e.g., unidentified hazard, risks not assessed, unspecified risk control measures, unimplemented or ineffective risk control measures might jeopardize safety. The risk

management file, in essence, provides an evidence of conformance to the requirements of the standard. The following are documented in the risk management file:

- Project description and plan
- Risk management plan
- Requirements for risk management activities
- Scope of any planned changes
- Identified hazards/hazardous situations and their consequences
- Risk control measures chosen and effectiveness of these measures
- Any decisions made including the rationale throughout the risk management process
- Evaluation of the new risks arising from risk control activities, e.g. changing a part of the device, change of medical network or decommissioning of the device

4.1.3.3 Risk Analysis

The manufacturer should think about and shall identify and document all characteristics affecting safety of the medical device by taking into account the intended users and situations other than those intended/foreseen by the manufacturer.

The manufacturer shall identify known or foreseeable hazards and estimate the associated risks using available information or data. If the likelihood of the hazard cannot be estimated, the possible consequences shall be listed for use in the risk evaluation and risk control.

Intended use and any foreseeable misuse, the implementation of the planned risk analysis activities results of these activities shall be recorded in the risk management file.

4.1.3.4 Risk Evaluation

The manufacturer shall evaluate risk associated with each identified hazard and hazardous situation, and decide whether the estimated risk is acceptable using the risk acceptability criteria defined in the risk management plan. Unacceptable risks shall be passed onto the risk control procedure for risk reduction.

The decision and rationale for each decision shall be documented in the risk management file.

4.1.3.5 Risk Control

The manufacturer or responsible organisation shall identify appropriate risk control measures and record them for each unacceptable risk until the residual risk is judged to be acceptable. The manufacturer shall use one or more of the following risk control measures listed in priority order:

- Inherent control by design
- Protective measures (e.g. including alarms, barriers)
- Information for safety (e.g. warnings, user documentation, training)

If practicable, the medical device should be designed to be inherently safe. If this is not

possible then protective measures such as barriers or alarms are appropriate.

The risk control may trade-off key properties, in priority order of safety, effectiveness and data and system security.

If the manufacturer determines that required risk reduction is not practicable, the manufacturer shall employ a risk/benefit analysis, i.e. determine whether the benefit of the medical device to the patient outweighs the residual risk.

The manufacturer/responsible organisation shall select risk control measures and verify their implementation and effectiveness, and document decisions, rationale for decisions and the results.

After the risk control measures are applied and verified, the manufacturer shall assess both individual risks and combined impact of the individual risks, i.e., overall residual risk, for acceptability using the criteria defined in the risk management plan.

The manufacturer shall review and document the effects of risk control measures to identify any new or increased, and follow all necessary steps of the risk management process for these risks.

4.1.3.6 Evaluation of overall residual risk acceptability

The manufacturer shall decide if the combined effect of the individual residual risks, i.e. overall residual risk, is acceptable based on the criteria defined in the risk management plan.

For a risk judged unacceptable, the manufacturer may gather and review data and literature to determine whether the benefits of the intended use outweigh the overall risk and decide whether to proceed with the medical device. If the manufacturer decides benefits outweigh the overall residual risk, then the overall residual risk can be judged acceptable.

For residual risks that are identified as acceptable, the manufacturer shall decide which residual risks to disclose, to whom the information is provided, how much detail is needed and how it will be disclosed. Users should be informed of significant residual risk and resulting benefits so that users can make informed decisions or can take appropriate actions to minimise the risk (refer to Annex J of ISO 14971).

4.1.3.7 Risk Management Report

Prior to release for commercial distribution of the medical device, the manufacturer shall review the risk management process to ensure correct implementation of the risk management process and to confirm that the required objective(s) have been achieved.

The responsibility for review should be assigned in the risk management plan to persons having the appropriate authority.

The results of this review shall be recorded as the risk management report and included in the risk management file.

4.1.3.8 Production and Post-production information

The manufacturer should monitor post-production information for data that affect risk estimates in order to improve the risk management process. Therefore, the manufacturer shall

- maintain a scheme to gather information about the particular medical device in

the production and post-production phases

- evaluate the information for possible relevance to safety and effects on the risk estimates
- determine if new risk(s) appear when the device is in use and/or reassessment of risk is necessary
- review new or revised standards
- review publicly available information about similar medical devices on the market

The results of this review and evaluation shall be recorded in the risk management file.

4.2 Risk Assessment for IT Networks of Medical Devices (IEC 80001-1)

4.2.1 Introduction

This section summarises aspects of IEC80001 that are different from ISO 14971. The IEC 80001-1 standard requires the use of a risk management process that is compliant with ISO 14971 and addresses specifically how medical devices can be connected to IT Networks, including general purpose IT Networks, to achieve interoperability without degrading the delivery of health care in terms of safety, effectiveness, and with increased security of data and system components. There are a number of potential risks associated with the incorporation of medical devices into IT Networks, including lack of support from manufacturers of medical devices for the incorporation of their products into IT networks, incorrect operation resulting from combining medical device software and other software applications, lack of security controls across many medical devices and the threat of possible cyber-attacks.

IEC 80001-1 is addressed to responsible organisations, to manufacturers of medical devices and to providers of other information technology, and is therefore particularly related to the myAirCoach system as a whole.

4.2.2 Relevance of IEC 800001-1 to myAirCoach

The myAirCoach platform will be designed to allow the connection of different medical devices within an IT Network. Furthermore, the platform will be defined for use in a number of environments, including; in the hospital; in primary care health centres. Hospital and primary care are both clinical settings, and would be expected to be subject to the same risk management processes.

myAirCoach will also have to consider risk management for medical devices in an IT Network in the living environment of patients. Although not intended for such a setting, IEC 80001-1 can provide essential guidelines that should be followed in determining risk for operation of myAirCoach devices in such a manner.

4.2.3 Scope of IEC 80001-1

4.2.3.1 Terms and Definitions

Change-release management: process that ensures that all changes to the IT Network are assessed, approved, implemented and reviewed in a controlled manner and that changes are delivered, distributed, and tracked, leading to release of the change in a controlled manner with appropriate input and output with configuration management.

Change permit: an outcome of the risk management process consisting of a document that allows a specified change or type of change without further risk management Activities subject to specified constraints.

Configuration management: a process that ensures that configuration information of components and the IT Network are defined and maintained in an accurate and controlled manner, and provides a mechanism for identifying, controlling and tracking versions of the IT Network.

Data and systems security: an operational state of a medical IT Network in which information assets (data and systems) are reasonably protected from degradation of confidentiality, integrity, and availability.

Event management: a process that ensures that all events that can or might negatively impact the operation of the IT Network are captured, assessed, and managed in a controlled manner; a property permitting diverse systems or components to work together for a specified purpose.

IT Network (information technology network): a system or systems composed of communicating nodes and transmission links to provide physically linked or wireless transmission between two or more specified communication nodes.

Key properties: three risk managed characteristics (safety, effectiveness, and data and systems security) of medical IT Network.

Medical device software: software system that has been developed for the purpose of being incorporated into the medical device or that is intended for use as a medical device in its own right.

Medical IT Network: an IT Network that incorporates at least one medical device.

Medical IT Network risk manager: person accountable for risk management of a medical IT Network Responsibility agreement: one or more documents that together fully define the responsibilities of all relevant stakeholders.

Responsible organization: entity accountable for the use and maintenance of a medical IT Network.

Top management: person or group of people who direct(s) and control(s) the responsible organization accountable for a medical IT Network at the highest level.

4.2.3.2 Roles and Responsibilities

Responsible organisation shall maintain a medical IT Network risk management file. The responsible organisation shall have overall responsibility for risk management for a medical IT Network, i.e. planning, design, installation, device connection, configuration, use/operation, maintenance, and device decommissioning. Compliance will be assessed by the responsible organisation.

The responsible organization shall obtain the accompanying documents and additional documentary information for a medical device incorporated in an IT Network as necessary to perform risk management for the medical IT Network, including any known hazardous situations that need to be managed by the responsible organization. These documents shall be maintained in the medical IT Network risk management file.

The top management shall be responsible for establishing policies (risk management policy and risk acceptability policy), allocating resources including assignment of qualified personnel, monitoring the risk management process to ensure suitability and effectiveness of the process and review the results.

Different from ISO 14971, IEC 80001-1 defines another role, *medical IT Network risk manager*. The IT Network risk manager shall be appointed by the top management and be responsible for managing the risk management process during design, putting the network into use, managing necessary communication between the internal and external participants of the risk management process (like medical device manufacturers, other suppliers of IT equipment/software/services, clinical users, technical support team like biomedical engineers), change-release management and change management throughout the entire life cycle. Although the risk management tasks may be delegated, the medical IT Network risk manager remains responsible for ensuring their adequate performance. The medical IT Network risk manager is responsible for consolidating all project risk management activities into a single risk management file for the medical IT Network.

Each *medical device manufacturer* shall provide accompanying documents to the responsible organisation that describe the intended use and give instructions necessary for safe and effective use of the medical device. The accompanying document shall include required characteristics and configuration for the IT Network incorporating the medical device, technical specifications of the network connection, intended information flow between device(s) on the medical IT Network and a list of hazardous situations resulting from a failure of the IT Network.

Providers of other information technology (e.g. infrastructure components/services, client devices (non-medical), servers, applications software or middleware) shall provide accompanying documentation with essential information such as technical description or manuals, information for network connectivity, product configuration, operating requirements and cyber security notices.

4.2.3.3 Life Cycle Risk Management in Medical IT Networks

The policy for risk management for incorporating medical devices in IT Networks shall be defined and documented by the top management. The policy shall include criteria for risk acceptability and a description of processes relevant to IT Networks (e.g. event management, change-release management, configuration management and monitoring).

The risk management process shall be carried out by the medical IT Network risk manager. Compliance is checked by inspection of the medical IT Network risk management file.

The responsible organisation shall plan the risk management by maintaining risk-relevant asset description, i.e. list of assets including hardware, software and data Medical IT Network documentation: this document shall include network configuration

(both physical and logical), applied standards, network communication requirements, etc.

The responsible organisation shall determine the need for responsibility agreement(s) defining the responsibilities of all relevant stakeholders. The responsibility agreement may cover project(s) and maintenance of medical IT Networks, and shall identify responsibilities and activities for all aspects of the medical IT Network life cycle. The responsibility agreement shall contain at least the definition of roles and responsibilities in the risk management process, a list of the medical devices incorporated into the medical IT Network and a list of accompanying documents to be supplied by the device manufacturers together with the names of organisations responsible for the provision of technical information necessary for the completion of the project. The agreement shall also identify the nature of the co-operation required and responsibilities if any co-operation of manufacturers and/or other organisation is required.

The risk management plan for the medical IT Network: the responsible organisation shall establish and maintain a risk management plan for the medical IT Network. The plan shall contain a description of the medical IT Network (including intended use, expected benefit and identified stakeholder), a description of activities, roles and responsibilities for all parties involved with respect to the risk management and criteria for risk acceptability.

IEC 80001-1 applies a risk control management process that is compliant with ISO 14971. The medical IT Network risk manager is responsible for managing the risk management process. Change-release management and configuration management: For any change to an existing medical IT Network, the responsible organisation shall apply and document a change-release management process. The medical IT Network risk manager shall: Ensure that a change-release management process includes the risk management process. Assess the results of the risk management process for approval and acceptability.

In order to control the versions of the medical IT Network, the responsible organisation shall document and apply a configuration management process across all risk management processes. The responsible organisation shall decide whether the change requirements are met by an applicable change permit. If no applicable change permit exists, a medical IT Network project shall be initiated.

A change permit is a way of avoiding unnecessary repetition of risk management for some frequent activities. Based on the results of risk management activities, the responsible organisation may decide that a specified type of routine change (e.g. adding a user) may be performed with acceptable risk, subject to specified constraints (e.g. a limit on the number of users) and may define a change permit which allows such routine changes and specifies the constraints.

Change permits shall be maintained in the medical IT Network risk management file.

Medical IT Network projects: The responsible organisation shall establish and maintain a project plan for change and activity that has the potential to introduce new risk. The project plan shall provide requirements for risk management activities, a description of the project including the parts affected by the project and the scope of the planned changes to the medical IT Network. The scope shall include, but not limited to, specifications of components (both software and hardware) relevant to the project, and

physical and logical configuration of the medical IT Network before and after the planned changes.

The project plan shall be kept in the medical IT Network risk management file in accordance with the life cycle processes of event management, change-release management, and configuration management.

Go-live: Before going live, the medical IT Network risk manager shall approve the specified change to the medical IT Network and the responsible organization shall review the medical IT Network residual risk. The approval of the medical IT Network residual risk shall be documented in the medical IT Network risk management file.

5 Ethical Issues

Any medical research has to be compatible with legal as well as ethical requirements. For this reason the documentation of work of myAirCoach determines that the objectives of the whole project will only be achieved by respecting the rights of patients and the legal and ethical requirements in the EU. The entire project has set itself as its primary goal to adhere to the highest ethical standards.

Related Project Objectives
Objective 5: Test campaigns with beneficiaries
Evaluation and quantification of the patient specific computational models will be made in test campaigns with patients. The aim of myAirCoach test campaigns will be twofold. In the first half of the project they will be performed so as to quantify and fine-tune the developed computational models and the clinical prediction and DSS framework. In the second half of the project, they will involve pilot execution in two highly challenging scenarios and will serve both model optimization and validation purposes.
Objective 7: To validate myAirCoach project results in real-life scenarios Validation of the project results with the active involvement of patients with asthma in realistic application environments. The entire validation procedure will exploit (1) relevant clinical measurements and data that are already available in the clinical partners and (2) the experimentation that will take place in three different pilot sites under specific approval of Ethics Advisory Boards.

The above deployments of trials, involving the full spectrum of user groups, highlight the importance of the appropriate ethical framework for the myAirCoach project, both for the test campaigns and the evaluation pilots. The following part of this deliverable will therefore deal with ethical requirements. The main source of arguments used will be the Declaration of Helsinki (appendix 6) – "Ethical Principles for Medical Research Involving Human Subjects"[23]) which is also adopted by the World Medical

[23] Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html (Assessed 2015)

Organization[24]. This represents and promotes highest ethical standards for medical research involving human subjects, including research on identifiable human material and data. The study of the relevant national ethical standards will be performed in parallel with the design and deployment of trials and will be integrated in the following versions of the document.

The structure and content of the current chapter was based on the work of recent EU projects in the field on ICT supported health tools and reflects the combination and extension of previous methodologies in order to cover the safety challenges introduced by the novel mHealth approaches. Analytically the outcomes and followed strategies of PeerAssist, ASK-IT, Linked2Safety, RECODE, SPLENDID, EHICAL, NoTremor, REACTION and INTERSTRESS projects where combined for the formation of the ethics plan of myAirCoach. The following table summarises the objectives of these projects and their relation to myAirCoach Ethical Strategy.

Table 5: Connection of myAirCoach ethical plan with previous approaches

Peer-Assist[25]	
PeerAssist	The main objectives of the proposed PeerAssist project are the implementation of a flexible Peer-to-Peer (P2P) platform, which will allow elderly people (not necessarily familiar with ICT technologies) to build virtual communities dynamically based on interests and needs they share. The PeerAssist platform will facilitate establishing on demand ad-hoc communities with friends, family, neighbours, caregivers, facilitators, care providers, etc., based on shared interests and communication needs.
ASK-IT[26]	
ASK-IT	See above for more detailed information about this project.
Linked2Safety[27]	
Linked2Safety	The main goal for he Linke2Safety project is to build the next-generation, semantically-interlinked, secure medical and clinical information space in the enlarged Europe, that will facilitate stakeholders with the appropriate access rights at pan-European level to dynamically discover,

[24] WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects Available at: http://www.wma.net/en/30publications/10policies/b3/ (Assessed 2015)

[25] Peer-Assist Project. Available at: http://www.aal-europe.eu/projects/peer-assist/ (Assessed 2015)

[26] ASK-IT Project. Available at: http://www.ask-it.org/index.php%3Fpage=about.html (Assessed 2015)

[27] Linked2Safety Project. Available at: http://www.linked2safety-project.eu/ (Assessed 2015)

	fruitfully combine and easily access medical resources and information contained in spatially distributed Electronic Health Records (EHRs), ensuring successful cooperation and proper, real-time integration and synthesis of patient and clinical data supplied by different healthcare organizations and hospital information systems across Europe, always respecting patients anonymity, data ownership and privacy, as well as European and national legislation.
RECODE[28]	
RECODE	The Policy RECommendations for Open Access to Research Data in Europe (RECODE) project will leverage existing networks, communities and projects to address challenges within the open access and data dissemination and preservation sector and produce policy recommendations for open access to research data based on existing good practice.
SPLENDID[29]	
SPLENDID	The aim of SPLENDID is to provide personalised services guiding adolescents and young adults to healthy eating and activity behaviours, preventing the onset of obesity and eating disorders. This requires an interactive system that accurately tracks eating and physical activity behaviour, and provides goal oriented feedback to the user. It will also require a system that does not prevent the user from partaking in any activities related to regular life. The success of the project also depends on its implementation in the community, which is regarded an equally important objective.
ETHICAL[30]	
ETHICAL	The value of privacy that is reflected in the protection of data is crucial in the area of biometric and health applications. Today's networked environment changes the landscape and the very essence of privacy is transformed. Whilst innovative information and communication services are constantly improving people's lives and generating growth throughout the global economy, they also create new risks. The critical issue of protecting personal data is becoming more crucial. Personal data processed over distributed networks poses the threat of misuse. How

[28] RECODE Project. Available at: http://recodeproject.eu/ (Assessed 2015)

[29] SPLENDID Project. Available at: http://splendid-program.eu/project-aims/ (Assessed 2015)

[30] ETHICAL Project. Available at: http://www.ethical-fp7.eu/ (Assessed 2015)

	technology can assist in the protection of integrity and privacy of this shared data is a critical question. The **ETHICAL vision** is an international consensus on the ethical use of personal data as a basic human right in the information society.
NoTremor[31]	
NoTremor	NoTremor aims to provide patient specific computational models of the coupled brain and neuromuscular systems that will be subsequently used to improve the quality of analysis, prediction and progression of Parkinson's disease. In particular, it aspires to establish the neglected link between brain modelling and neuromuscular systems that will result in a holistic representation of the physiology for PD patients. A significant breakthrough of NoTremor is that these models will not be used for abstract representation of the physiology or as a match between theory and clinical measurements. On the contrary, they will be used with a totally new perspective; predictive simulation.
REACTION[32]	
REACTION	See above for further details of this project.
INTERSTRESS[33]	
INTERSTRESS	See above for further details of this project.
Connections and Relations with myAirCoach Data Protection Plan	
The above projects create a multidimensional basis for the Ethical Plan of the myAirCoach project as they include issues concerning both patients and researchers and provide detailed templates of questionnaires and informed consent forms as they are presented in the annexes of the deliverable after their adaptation to the needs of the myAirCoach project.	

5.1 Ethical Principles

The work of the ETHICAL project[30] covered a wide range of topics and involved a large

[31] NoTremor Project. Available at: http://notremor.eu/notremor/ (Assessed 2015)

[32] REACTION Project. Available at: http://www.reaction-project.eu/news.php (Assessed 2015)

[33] SPLENDID Project. Available at: http://splendid-program.eu/project-aims/ (Assessed 2015)

amount of research consisting of literature reviews, desk research and one-to-one interviews with stakeholders. However, in the body of the research (encapsulated in the project deliverable, “Code of Conduct for FP7 Researchers on medical and biometric data privacy” a concise number of common principles emerged. These six principles will be also form the ethical basis of the myAirCoach project, namely:

- Trust
- Privacy
- Ownership
- Dignity
- Equity
- Proportionality.

5.1.1 Trust

Modern eHealth technologies are becoming more and more widespread in health systems across Europe. However, while most health professionals and other health workers are familiar with their purpose and operation, this is not yet the case for most patients. Some groups of patients will be familiar with information and communications technology while others may be less (e.g elders and illiterate individuals). Both health and care professionals and patients will have questions regarding safety and the use of data and information.

A recurring theme in eHealth, and therefore an important requirement of mHealth applications, is the need for transparency in order to engender trust among members of the patient or user community regarding the way in which information about them is handled and used by health professionals, researchers, health organisations and institutions and commercial organisations. This requirement affects all those involved

The practical implication of this concept is the need for openness regarding the use of data and honesty in terms of how data will be used. This is particularly the case if new or secondary purposes of that use are to be considered or implemented in the future. In addition, patients and citizens need to be reassured that international transfer of sensitive information is handled appropriately, that financial considerations do not override ethical data handling and that data quality is maintained in order to provide accurate and safe treatment.

5.1.1.1 Openness and transparency about security risks

Openness and transparency are a particular requirement in this area for researchers, who should be completely open to inform the public and other project participants about the security risks related to any research and should discuss the scope and implications of their work. This openness should also include the provision of third-party consultation for participants in the research activity to receive an independent briefing. These are seen as important ethical principles that could help significantly to engender trust. Issues of trust also emerge in guaranteeing the security of sensitive medical data in terms of their confidentiality, integrity and availability (i.e. when required).

5.1.1.2 The case of international transfer and sharing of medical information

Transparency also features in discussions regarding the international transfer and sharing of medical information. It has been suggested that a database of all transfers should be established. Such a database would enable individuals and organisations to determine how, where and why their data has been transferred. Indeed, manipulating individuals' data without their knowledge could be considered as dishonest and the manipulator therefore seen as untrustworthy.

The international or cross-border transfer of information raises interesting issues regarding the need for a harmonisation of rules, processes and safeguards both in Europe and globally. This would imply holding international discussions and creating international agreements. It would need a body to be involved which is recognised as being impartial and trustworthy. The World Health Organisation (WHO) was suggested as one possible body, although other bodies such as UNESCO, OECD and ISO might also be considered.

5.1.1.3 Risks with data quality

A final aspect of trust relates to data quality. The responsibility for data quality lies with all handlers of sensitive personal medical information who need to ensure that data is accurate. Such accuracy ensures that false conclusions cannot be drawn from the research or that individuals cannot be incorrectly identified, for example, of being at risk. This implies not only that there should be appropriate data quality mechanisms in place but also that software processing systems are properly assessed and appropriate integrity checks included.

5.1.2 Privacy

As already addressed in chapter 2the protection of privacy holds an important position in the framework of the current project. Furthermore, this section will position the issue of privacy in the ethical context of the projects work. Individuals are private people who possess knowledge about themselves and have private thoughts. Individuals have a choice as to whether to impart information about themselves and, indeed, to choose what information to disclose. Having revealed that information, they can place a duty of confidentiality on the person to whom they have revealed it. They must trust that person to abide by that duty. In the ethical context of healthcare, this is why the patient/professional relationship embodies a strong ethical duty of confidentiality on the part of the doctor, nurse or allied carer. This ethical duty is reinforced by international data protection legislation.

5.1.2.1 Impact of a breach of privacy

The impact of a breach of privacy may vary depending on the size and nature of the breach and on the sensitivity of the data held on the individual(s) concerned. For example, the single disclosure of a non-sensitive medical condition about one person may be embarrassing but not life-threatening. However, a well-publicised large-scale disclosure of such information could have societal consequences that might lead to a lowering of trust in the system and those working within it. Long-term retention of medical data means that violations of privacy can take place many years after the data was collected.

5.1.3 Ownership

Data ownership is an important ethical principle that applies in many areas including medical information. The debate about who owns medical records and/or the information they contain has been discussed for many years. Opinions vary. These opinions can also vary from the legal status of personal medical data internationally:

5.1.4 Dignity

5.1.4.1 Dignity of the person

The European Group on Ethics in Science and New Technologies to the European Commission (1999) have put forth an opinion stating that personal health data form part of the personality of the individual, and must not be treated as mere objects of commercial transaction. This is, essentially, a rephrasing of the categorical imperative: as medical data are constitutive of an individual's identity, they should be treated with dignity, rather than as currency that can be bought and sold.

5.1.4.2 Dignity at home

Issues of dignity also arise in relation to eHealth applications concerned with remote monitoring involving audio and video technologies, technologies that may offer significant clinical benefits that stem from the accurate assessment of the patient health. However, it must be understood that there are times and places when the individual will not wish to be monitored. Even though, neither audio nor video measurements will be collected by the myAirCoach system, its sensing capabilities pose some reduced risks. This implies the need for respect in terms of the installation of remote monitoring technologies and their operation. Such operational issues either might or should include placing the control of the monitoring technology with the individual and (if appropriate) providing the functionality to switch it off.

5.1.5 Equity

At a meeting in 1986, the WHO stated, "Equity in health implies that ideally everyone should have a fair opportunity to attain their full health potential and, more pragmatically, that no one should be disadvantaged from achieving this potential, if it can be avoided" Through its flexible and innovative nature, eHealth has the potential to support and promote equity in healthcare. It can do this through:

- Improved access.
- Health promotion and awareness.
- Remote monitoring.
- Health needs assessment.

EHealth in general and mHealth in particular have a number of key features that can be exploited to deliver more equitable delivery of healthcare. For instance, telemedicine enables remote communities to benefit from access to expert medical services in a way that was not possible previously as a result of geographical and transportation difficulties. The provision of tools for self-management means that people with chronic diseases, such as asthma, can have more control over their conditions. They are no longer excluded from society by the fact that they are unable to consult with a medical professional as often as desired. Remote monitoring can also improve the quality of life for certain groups in society enabling them to spend longer in their own homes rather

than being treated or cared for in nursing homes or other care centres. All of these features can work towards reducing health inequities.

5.1.6 Proportionality

When considering eHealth developments or, more importantly, implementing them, it is necessary to bear in mind the principle of proportionality. There are several definitions of this principle many of which are rooted in law or military action. An online reference to the Collins English Dictionary gives the definition as, “the idea that an action should not be more severe than is necessary, especially in a war or when punishing someone for a crime”. More formally, the European Union has a principle of proportionality laid down in Article 5 of the Treaty on European Union that regulates the exercise of powers by the European Union. It seeks to set actions taken by the institutions of the Union within specified bounds. Under this rule, the involvement of the institutions must be limited to what is necessary to achieve the objectives of the Treaties. In other words, the content and form of the action must be in keeping with the aim pursued.

A number of requirements for international data-sharing that were subsequently validated with regard to existing research and established policies include:

- Ethical guidelines should be sensitive and flexible depending on the purpose of the use of the data;
- Data should not be retained longer than necessary in the recipient country;
- Data-sharing should be unobstructed when there is an urgent need to obtain data, particularly to prevent loss of life.
- Data should not be shared across borders via an unsecured network except in life-threatening emergencies.

5.2 Ethical aspects of user involvement

This chapter gives a detailed overview of research ethics involving humans in myAirCoach project. Information in this chapter should be supplemented with more practical instructions from the respective research sites. 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.

Key ethical issues

Since myAirCoach deals predominantly with physiological measurements and lifestyle parameters, 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.

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 myAirCoach are ethically substantiated and justified. 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 myAirCoach, the societal value and scientific

methodology of the intended research trials and activities have extensively been warranted in detailed in the DoW. All research protocols are going to be submitted for approval during the course of the project and the final selected methodologies are going to be integrated in the future versions of this document. The following conditions should be met in every case, in accordance to the clinical trials directive of the European Parliament (2001/20/EC)

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.

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 myAirCoach. Each issue is defined with the help of EU and national directives, examined from the perspective of myAirCoach. Finally, actions in myAirCoach to mitigate the ethical risks are presented in each case.

5.2.1 Recruiting participants

In accordance with World Medical Association (WMA) guidelines[34], 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

[34] World Medical Association. Medical Ethics Manual; 2nd edition. (2009). Available at: http://www.wma.net/en/30publications/30ethicsmanual/pdf/intro_en.pdf (Assessed 2015)

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.

Additionally, it is very important to minimise the stigmatisation risks, is the final design of the myAirCoach 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 decided early on.

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, social media etc.). 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.

5.2.2 Information to participants

The fundamental requirement for good information to the participants states that the researcher shall ensure that subjects are informed in a manner and with a language they understand. The information flow from the researcher to the participant should take account of the following elements, which are also included in the informed consent form (see Appendix 3:: Template of Informed Consent Form):

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*; 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).

5.2.3 Voluntariness

Consent must be voluntary and freely given consent so that it corresponds to the ethical requirements of the Declaration of Helsinki (See Appnedix 6).

There must be no external pressure on the patient to make a certain decision. External pressure occurs when consent is given under coercion, duress, pressure, manipulation or undue influence. Physician should be in particular cautious when seeking consent in situations when the individual is in a dependent relationship relative to him in. In such a case, the Declaration of Helsinki recommends seeking the informed consent through an appropriately qualified individual who is completely independent of this relationship. That means an independent person of the physician - patient relationship decides on the voluntariness of the informed consent.

5.2.4 Informed Consent

The consent procedure is one of the most important aspects of the Ethics in research involving humans. Aligned with the Directive 2001/20/EC , 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.

The following issues should be covered for every 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.

5.2.5 Data anonymity

The World Health Organisation (WHO) has published the *Ethical Guidelines for Biomedical Research Involving Human Subjects*[35], 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"*.

[35] World Health Organization's International Ethical Guidelines for Biomedical Research Involving Human Subjects. (2002). Available at: http://www.cioms.ch/publications/layout_guide2002.pdf (Assessed 2015)

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 aligned with the Directive 95/46/EC, 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 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.

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 myAirCoach, 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 myAirCoach 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 guidelines outlined in chapter 2.

5.2.6 Risk of harm assessment, adverse events and insurance

Regarding the testing activities in myAirCoach 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, misuse of guidance tools, 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 casing 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

5.3 Principles of research ethics

There are some common basic ethical principles that apply in all human relationships. The Belmont Report (1979) summarizes the basic ethical principles and guidelines for research involving human subjects. The myAirCoach 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 myAirCoach research trials planning are shaped and preserved by implementing these basic ethical.

5.3.1 Data handling

The Data Protection Act is based on common rules adopted within the European Union, known as the Data Protection Directive 2002/58/EC. 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 to be deleted, five years after publication of the results in scientific papers, so that they cannot be retrieved.

(Section 2.3 provides a detailed description of the data security framework of myAirCoach)

5.3.2 Incentives for research participants

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.

5.4 Ethics strategy in myAirCoach

5.4.1 Structure of Project Management

CERTH/ITI is the project coordinator and is authorized by the consortium to execute the project management and will be responsible for the preparation of the meetings and decisions and the chairing of the Project Board. Further, a project office located at CERTH/ITI will provide the necessary support for day-to-day project management for the Project Board, for Work Package Leaders as well as for reporting activities to the European Commission.

The project's structure will ensure that the expected outcomes are according to its objectives. The work in the project is divided into Work Packages and further in Tasks. Each work package is led by one of the consortium partners, who designate responsible for leading the partner's work package(s). The management work is defined and distributed among a number of persons in the project to ensure effective management operation, consisting of the Project Coordinator, project manager and as well as the project's Ethics Advisory Board. Work package leaders are chosen according to their expertise in reference to the main subject of a work package. The ethical advisor will ensure that investigations and trials with volunteer participants and handling of personal data will be in the according to ethical standards, relevant national regulation, EU regulations and international. The ethical advisor will ensure consistence between the project overall decisions and the ethics obligations.

5.4.2 Ethics Advisory Board

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

5.4.2.1 Terms of reference

- The board is a voluntary group with representation from multidisciplinary fields relevant to the three main areas of project work (computer modelling, clinical trials, and commercial exploitation) as well as a patient representative and an ethicist.
- All members of the board must provide a disclosure statement regarding their relationship(s) to any of the participating organisations in myAirCoach, as well as any commercial interests.
- The EAB will convene regularly as an independent forum and representatives will also be invited to take part in Project Coordination Committee (PCC) meetings.
- Established or anticipated areas of concern and standards for both regulatory compliance and good practice are set out in the ethics manual, which will serve as a basis for the board's work. The EAB will ensure that requirements are met and standards are maintained by receiving and reviewing documents and

protocols and recording any local regulatory approvals, such as those required by ethics committees.

- The EAB will also be responsible for reviewing and advising on other issues that may arise in the course of the project, which are either referred to them by project members or are elicited as part of work package reports or in the course of ensuring regulatory compliance.
- Although the EAB provides guidance and oversight and will assist with requests for advice, clarification and information, it remains the responsibility of individual project partners to keep informed about the legal and ethical regulations relevant to their own area of expertise in the myAirCoach project, and to obtain any necessary local approvals. Similarly, the responsibility to ensure integrity and ethical practice in the conduct of research rests with individual researchers on the project. The EAB will monitor observance and can act as arbitrating body in the case of uncertainties or conflicts that may arise in relation to research integrity.
- All assessment tools and protocols to be used within myAirCoach test campaigns will be reviewed in advance by the Ethics Advisory Board.
- Where appropriate, the EAB may contribute to ethics training of project partners, or take on other governance roles requested by the Project Coordination Committee (PCC).
- The EAB will report to the Project Coordination Committee and will refer any non-compliance, misconduct, or disregard of its advice to the PCC.
- Communication will be maintained between board members by a member's only distribution list. Communication with members of the myAirCoach project will be through the normal channels established for project communication.
- Reports of the EAB will also be included in the periodic reports and in the final reports to the European Commission. It will report to the Project Coordination Committee by means of board meeting minutes and an annual report.
- The EAB will undertake an annual self-evaluation and will review, in particular, timelines for responding to items to be monitored as set out in the project ethics guidance as well as issues raised independently; quality and adequacy of responses.
- In the interests of transparency, the business of the EAB may be discussed outside of the board itself, unless there is explicit agreement that an item or issue is confidential. Minutes will be copied to the Project Coordination Committee and made available more widely on request.
- Public statements and any oral or written presentations on behalf of the EAB are to be corporate in nature, and distinguished from any representations made in a personal capacity.

5.4.2.2 Board composition

Members of the board are drawn from project partners contacts (internal and external) and augmented by lay members. Board members will include at least one individual representing each of the following:

Table 6: Composition of Ethics Advisory Board

Ethical Field	Name of main responsible
Ethics and Governance	Mr. Dimos Ioannidis (CERTH, ethical expert for the EC)
Clinical Trials in the United Kingdom	Rob Niven (UMAN)
Clinical Trials in the Netherlands	Dr. Jacob Sont (LUMC)
Asthma Patients	One member (asthma patient) of the patients 'forum (EFA, Asthma UK)

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

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

5.4.2.3 Awareness of ethical issues

Ethics will be on the agenda at board meetings and consortium meetings. This will ensure an on-going discussion about ethical issues throughout the project and facilitating reporting of ethical matters.

There will be a continuous watch of new laws and legislations that may arise during the project development, regarding the ethical management of research with humans within national and European levels, to ensure that if new legislations arise during the project, they will be immediately applied to the myAirCoach research strategy. Especially the work of the European Group on Ethics in Science and New technologies concerning the requested Opinion on the ethical implications of Information Communication Technology (ICT) will be followed. This opinion will take into consideration different possible applications of ICT, such as widespread uptake and use by citizens of the Internet, e-health and mHealth.

Through the work of the project and based on the ethics manual as described in the current section , the project consortium will update and adjusts the ethical guidelines for the user studies including issues relating to informed consent; documentation; data protection; freedom of information; dealing with complaints and will.

5.4.2.4 Treatment of ethical issues

Before each user investigation the responsible researcher at the test site will send the test plan together with the informed consent form to the Ethics Advisory Board for a final quality check against the guidelines outlined in this document.

The myAirCoach participant should not hesitate to approach the Ethics Advisory Board or the project board with any questions or issues. Moreover, the European commission offers an Ethics Help Desk[36], which allows people to obtain expert advice and guidance

[36] European Commission: Ethics Helpdesk. Information available at: http://ec.europa.eu/research/participants/portal/desktop/en/support/other_help_services.html#ohs4 (Assessed 2015)

should ethical issues arise in the course of their research.

5.4.2.5 Collection of ethical issues

Any confusion, ambiguity or complaints occurring during user investigations and experiments shall be reported to the Ethics Advisory Board. The ethical advisor will keep a journal of such issues and consider clarifications in or revision of the ethics manual based on these issues. In general, project members are encouraged to contact the ethical advisor or the coordinator if in doubt in any question concerning ethical aspects of the project.

6 Conclusion

This deliverable outlines an initial version of the plans for the privacy protection of patient data, the safety of project participants and the compliance with ethical requirements. It is important to mention once again that this document will follow a gradual approach and will be continuously modified and extended to cover the project needs as they will be faced during the course of the myAirCoach system development and the deployment of test campaigns and pilot trials. The goal of this manual is to compose a basic guide for the entire myAirCoach Consortium and will be presented in its final and accurate form at the final stages of the project in M35 as described in the project's description of work.

After a short introduction to the myAirCoach project and the description of mHealth barriers the current document describes the connection of these issues with the project objectives outlining the positioning of this deliverable in the overall work plan of the project. The next chapter outlined the important issues of data protection and privacy preservation and took the first step towards the formulation of the system requirements and project methodologies that will address these issues. The following chapters formulate the structure of the plan for the safety protection of patients and trial participants and will be used development of personalised guidance framework of both patient and doctors and will also play a crucial role for design and testing of the smart inhaler device. Finally the last chapter outlines the ethical issues that are expected in the design of the testing campaigns and evaluation pilots, and formulated an initial generalised strategy that will be adapted and accurately fitted to the final design of trials and campaigns.

The impact of myAirCoach is expected to set the basis for the widespread adoption of sensor-based self-management systems across the spectrum of respiratory diseases and therefore the adopted approach for addressing privacy, safety and ethical issues will be expected to create a crucial link in this direction, and hopefully accelerate the adoption of mHealth approaches.

Appendix 1: Lists of Legislation Material relevant to myAirCoach

UK Legislations and Guidance

- Guidelines for Good Clinical Practice (GCP)
- Department of Health Research Governance Framework for Health and Social Care 2005
- Data Protection Act 1998
- Mental Capacity Act 2005
- Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments 2006a, 2006b, 2008 and 2009
- The Medical Devices Regulations 2002.
- Framework for Research Ethics. Economic and Social Research Council, Mar 2010.
- Research Governance Framework for Health and Social Care. Department of Health, Social Services and Public Safety, Dec 2006.
- NRES. Defining Research. National Patient Safety Agency, Dec 2009.

Netherlands Legislations and Guidance,

- Wet Medisch-Wetenschappelijk Onderzoek met Mensen (WMO)
- Wet persoonsregistraties (WPR) naar Wet Bescherming Persoonsgegevens
- Medical Research (Human Subjects) Act, http://www.ccmo.nl/attachments/files/wmo-engelse-vertaling-29-7-2013-afkomstig-van-vws.pdf

Communications from the European Commission to the Parliament and Council

- Promoting Data Protection by Privacy Enhancing Technologies (PETs) Brussels, 2.5.2007 COM(2007) 228 final
- Follow-up of the Work Programme for better implementation of the Data Protection Directive, Brussels, 7.3.2007 COM(2007) 87 final
- First Report on the implementation of the Data Protection Directive, COM (2003) 265(01), 15.5.2003,
- Communication on a strategy for a secure Information Society, COM(2006) 251 of 31 May 2006
- Implementing The Hague Programme: the way forward, COM(2006) 331 final Brussels, 28.6.2006
- 93/42/EEC: European Council Directive concerning medical devices
- 2007/47/EC2: Amendment of the European Council Directive 93/42/EEC concerning medical devices

EC Green Papers

- Green paper on detection technologies in the work of law enforcement, customs and other security authorities COM(2006) 474, September 2006
- Green Paper on a European Programme for Critical Infrastructure Protection - COM(2005) 576, November 2005

Opinions of the European Data Protection Supervisor

- Opinion of 26 September 2005 on the Proposal for a Directive of the European Parliament and of the Council on the retention of data processed in connection with the provision of public electronic communication services and amending Directive 2002/58/EC (COM (2005)438 final), OJ C 298, 29.11.2005
- Opinion of 28 February 2006 on the Proposal for a Council Framework Decision on the exchange of information under the principle of availability (COM (2005)490 final), OJ C 116, 17.05.2006

Opinions of the Article 29 Working Party

- Recommendation 1/2007 on the Standard Application for Approval of Binding Corporate Rules for the Transfer of Personal Data
- Working Document on the processing of personal data relating to health in electronic health records (EHR)
- Seventh report on the situation regarding the protection of individuals with regard to the processing of personal data and privacy in the European Union and in third countries covering the years 2002 and 2003

European Conventions and Regulations

- Convention for the Protection of Human Rights and Fundamental Freedoms Council of Europe, Rome, 4th novembre 1950, ETS n° 5 http://conventions.coe.int/treaty/en/Treaties/Html/005.htm
- Charter of Fundamental Rights of the European Union, http://www.europarl.europa.eu/charter/docs/default_en.htm
- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, OJ L 281, 23.11.1995. http://ec.europa.eu/justice/data-protection/index_en.htm
- Directive 2002/58/EC of the European Parliament and of the Council of 12 July 2002 concerning the processing of personal data and the protection of privacy in the electronic communications sector, OJ L 201, 31.07.2002
- Regulation (EC) 45/2001 of the European Parliament and of the Council of 18 December 2000 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, OJ L 8, 12.1.2001 www.europarl.europa.eu/register/pdf/r1049_en.pdf

International Conventions and Declarations

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

- EN ISO 13485: Medical devices QMS - Requirements for regulatory purposes
- EN ISO 14971: Medical devices - Application of risk management to medical devices
- IEC 62366: Medical devices – Application of usability engineering to medical devices
- IEC 62304: Medical device software – Software life cycle processes

Appendix 2:: Questionnaire on ethical and legal issues

	**HORIZON 2020** **Self management of health and disease:** **citizen engagement and mHealth**

Project:

myAirCoach - Analysis, modelling and sensing of both physiological and environmental factors for the customized and predictive self-management of Asthma"

(myAirCoach, Grant Agreement No. 643607)

Questionnaire on ethical and legal issues	
Summary	This is a tool to monitor the fulfilment of the ethical and legal requirements by the investigators and the project partners responsible for the myAirCoach trials.
Partner	Full Name (Partner short name)
Status	□ completed / □ pending

Introduction

This is a template on ethical and legal issues that has to be completed by all partners who conduct trials. The questions and the documents of the different sections are based on the myAirCoach Ethics, Safety and mHealth Barriers Manual D8.5, in which background information concerning the different questions and subsections is provided in more detail. Within the Ethics manual the content of the template will also be justified on scientific and legal basis in depth.

The questionnaire on ethical and legal issues has to be filled in by the investigator who conducts experiments. It is a sort of checklist in which the researcher is reminded to take into account relevant ethical aspects before conducting any experiment. This questionnaire on ethical and legal issues is divided into different subsections (Informed consent, ethical control instruments, privacy, safety, risk assessment).

All filled-in questionnaires will be sent to the project the Ethics Advisory Board (EAB). Then the EAB will carefully scrutinise the results. Within further versions of the ethics manual, the results are reported.

This template is based on the related outcomes of the ASK-IT project[37], and will be revised during the preparation and deployment of the myAirCoach trials by the responsible partners and for the specific legislation environments of UK and NL.

Questionnaire on ethical and legal issues

1. Is your experiment approved by a local research ethics committee?

Yes__ / No__

If ***yes***, please continue with question 1.

If ***no***, please contact the Ethics Advisory Board.

Informed consent clarifications

Note: If private information is recorded, please use the additional document 'myAirCoach informed consent' concerning private information.

2. Do you conduct experiments with *mentally* incapacitated participants (people unable to understand the informed consent form)?

Yes__ / No__

If *yes*, no experiment will be performed.

If *no*, please continue with the next question.

3. Is there any doubt about the individual's mental capacity to consent?

Yes__ / No__

If *yes*, no experiment will be performed.

[37] ASK-IT Project. Available at: http://www.ask-it.org/index.php%3Fpage=about.html (Assessed 2015)

If *no* please continue with the next question.

4. a) Is the informed consent provided in very simple language

Yes__ / No__

If *no*, why not?

b) Will the participant be given a lot of time to reflect his/her decision of giving or withholding consent?

Yes__ / No__

If *no*, why not?

5. Is the participant unable to consent?

Yes__ / No__

If *yes*, no experiment will be performed.

If *no*, please continue with the next question.

6. Does the participant included in research object in either words or action?

Yes__ / No__

If *no* (no objection) please continue with the next question.

If *yes* (he/she does object) no experiment will be performed!

7. Is the participant unable to read the form?

Yes__ / No__

If *yes*, please continue with b)

If *no*, please continue with the next question.

b) There are a range of people who are unable to read the consent form; these include those who have a severe visual problem, those with severe dyslexia, those who are illiterate and those whose knowledge of the language may be limited (eg a recent immigrant). For these people the information will be provided in appropriate alternative media (eg large print, audio tape, braille).

8. Is the participant deaf?

Yes__ / No__

If *yes*, please continue with b)

If *no*, please continue with the next question.

b) The information has to be provided to the participant in a modality with which he is able to understand the informed consent form information (e.g. in written form)!

An oral explanation of the informed consent is not appropriate.

9. Is the participant illiterate?

Yes__ / No__

If *no*, please continue with the next question.

If *yes*, please note that the informed consent information has to be provided in a modality that the illiterate participant is able to understand (e.g. the statements have to be read to the participant) the informed consent form information.

The participant has to give oral consent which has to be witnessed at least by one person Informed consent form 3.6 has to be used.

Legislation

10. Is an oral consent of an illiterate participant that is witnessed in accordance with your national legislation?

Please comment:

11. Is there an international or national legislation, which you must follow when performing tests?

a) with healthy and able-bodied human participants?

Yes__ / No__

If ***Yes***, please give details (reference number and short description of procedure):

b) with participants with cognitive impairments / learning difficulties?

Yes__ / No__

If ***Yes***, please give details (reference number and short description of procedure):

c) with *blind*, *deaf, motor disabled* or *illiterate* participants?

Yes__ / No__

If ***Yes***, please give details (reference number and short description of procedure):

Ethical control instruments

12. At which level of organization, *ethical controls* are audited?

__ laboratory or workgroup

__ division or department

__ institution

__ regional

__ national

13. Is there an ethics controlling body in your country?

Yes__ / No__

If ***Yes***, please give details about the procedure:

14. Is there a local ethics controlling committee, that your organisation is obliged to get approval from, for the experimental procedures before beginning with the experiment?

Yes__ / No__

If ***Yes***, please give details about the procedure:

15. Is there an established ethical control procedure which you must follow before performing tests with:

a) human participants?

Yes__ / No__

If ***Yes***, please give a brief description of it:

b) with blind, deaf, motor disabled or illiterate participants?

Yes__ / No__

If ***Yes***, please give a brief description of it:

Privacy

Please note: If private information will be recorded, the myAirCoach informed consent template; has to be filled-in and signed by the participant and the investigator.

16. Is private information recorded?

Yes__ / No__

If yes, please use also the informed consent template concerning private information.

If no, please continue with question no. 16.

17. Is the risk of identifying users in profiles and scenarios being minimised?

Yes__ / No__

If ***No***, please explain the reasons briefly, or what corrective actions are taken.

18. Are all social and demographic identification data encrypted ?

Yes__ / No__

If ***No***, please explain the reasons briefly, or what corrective actions are taken.

19. Is there an established Data Protection Authority which you must follow before performing tests with human participants and their personal data?

Yes__ / No__

If ***Yes***, please give a brief outline of it:

If ***No***, please explain the reasons briefly or what corrective actions are taken?

20. Do you follow written procedures for protecting privacy?

Yes__ / No__

If ***Yes***, please give a brief outline of it:

If ***No***, please explain the reasons briefly or what corrective actions you take?

21. Do you follow any official national or international guidelines on protecting privacy?

Yes__ / No__

If ***Yes***, please give a brief outline and provide references.

22. Do you clarify to the participants that all data collected in the activities they are participating is kept confidential and that their anonymity will be protected?

Yes__ / No__

If ***Yes***, please give a brief outline and provide references.

23. Do you identify persons and their professions who are authorised to have access to the data collected?

Yes__ / No__

If ***Yes***, please give a brief outline and provide references.

24.Are the data collected in the user requirements questionnaire necessary (but also are the minimum, in order to avoid asking for non-relevant, but sensitive, information) for the subsequent development of the myAirCoach platform?

Yes__ / No__

If ***No***, please give details about additional parameters assessed.

25. Is the site where the statistical results and computational models of myAirCoach users' information are stored password protected?

If ***No***, please give details about the reasons that lead to this deviation

26. Has social and demographic identification data been dissociated from the rest of information about the users?

If ***No***, please give details about the reasons that led to this deviation

Safety

27. Will you provide information to the participants if you get aware of an illness?

Yes__ / No__

If ***Yes***, please give a brief outline of it and provide some references

28. Is every experiment evaluated for any side-effects?

Yes__ / No__

If ***Yes***, please give a brief outline of it:

29. Do have written procedures for safety for employees and volunteers within your own group or institution?

Yes__ / No__

If ***Yes***, please give a brief outline of it:

If ***No***, please explain the reasons briefly or what corrective actions you take?

Risk assessment

30. Do you have procedures to perform risk-assessment concerning breach of privacy, and safety?

Yes__ / No__

If ***Yes***, please give a brief outline of it:

If ***No***, please explain the reasons briefly or what corrective actions you take?

31. Is your organisation insured against risks as a result of breach of privacy and safety?

Yes__ / No__

If ***Yes***, please give a brief outline of it:

If No, please explain the reasons briefly or what corrective actions you take?

32. For conducting research and manage the risk, do you need to involve other organisations (unit, division, department etc.) that also control your research activity?

Yes__ / No__

If Yes, please give a brief outline of it:

Appendix 3:: Template of Informed Consent Form

	**HORIZON 2020** **Self management of health and disease:** **citizen engagement and mHealth**

Project:

myAirCoach - Analysis, modelling and sensing of both physiological and environmental factors for the customized and predictive self-management of Asthma"

(myAirCoach, Grant Agreement No. 643607)

Consent Form of Participant	
Summary	This is a tool for the documentation of the consent of participants in the research studies of myAirCoach
Partner	Full Name (Partner short name)
Participant	Full Name
Status	□ completed / □ pending

Introduction

The informed consent is a process through which the participant will be given information about the research. In seeking informed consent , the following information shall be provided to each subject:

1. The purpose of the research, expected duration, and procedures;

2. Explanations on confidentiality of the data and the protection of privacy see; ' myAirCoach informed consent concerning private information;

3. The possible risks, discomfort, adverse effects, and side-effects (if any);

4. A description of any benefits to the subject or to others which may reasonably be expected from the research;

5. Their right to decline to participate and to withdraw from the research once participation has begun and the foreseeable consequences of declining or withdrawing.

6. Whom to contact for questions about the research and research participants rights.

This template is based on the related outcomes of the ASK-IT[38] and PeerAssist[39] project and will be revised and extended in view of the specific characteristics of each trial and by the responsible partner for the deployment of thes trial.

1. General Information

This part will be pre-filled by the investigator for each study. *The original will be given to the participant; a copy will be kept by the investigator.*

The myAirCoach Ethics Advisory Board reviewed this pilot study from the standpoint of the protection of human research participants. The myAirCoach Ethics Advisory Board found the study to be in compliance with the relevant regulations.

This version of the consent document was prepared on:	
This trial was approved by the myAirCoach Ethics Advisory Panel on:	
Names of the investigators responsible for this project:	

2. Information on the research study in the form of Q/A?

Before the start of the research study all participants should be informed about the

[38] ASK-IT Project. Available at: http://www.ask-it.org/index.php%3Fpage=about.html (Assessed 2015)

[39] Peer-Assist Project. Available at: http://www.aal-europe.eu/projects/peer-assist/ (Assessed 2015)

following questions. The following section should be filled using easily understandable language and avoiding specialised technical terminology.

- What is the title of the study?

- What is the purpose of this research study?

  - The research study is being directed by

  - Other professional persons who work with him/her may assist or act for them.

- Who can take part in this study?

- Why should I consider joining this study as a research participant?

- Do I have to become a participant in this study? If I joined the study, can I change my mind and drop out before it ends?

- 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 study?

  - What kind of data will be recorded, stored and why?

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

- What will the investigators do to make sure that the information they will collect on me will not get in the wrong hands?
    - To whom will the data be transferred?
    - How long is the length of storage?
    - Where data will be stored, - according to which national legislation?
    - Who will access the data?
    - Who will supervise the data protection?
    - How has the data ownership?
    - Is the data connected to other information?
- What kind of benefits can I expect personally from taking part in this study?
- What kinds of benefit to others can come out of this study?
- Will the data possibly commercially exploited?

- What will the investigators do, if I get injured in the study?

- Will I get paid for taking part in this study?

- Will I or my health insurance company be charged for any of the costs of this study?

- Once I start in this study as a participant, what do I do if I want to find out more about the study, or to complain about the way I get treated?

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

- Which others may view or use the data of this document?

Investigators' confirming statement

I have given this research participant information on the study, which in my opinion is accurate and sufficient for the participant to understand fully the nature, risks and benefits of the study, and the rights of a research participant. There has been no coercion or undue influence. I have witnessed the signing of this document by the participant.

Investigator's Name:	
Investigator's Signature:	

Date:	

3. DOCUMENTATION OF PARTICIPANT'S CONSENT

Introduction to the myAirCoach study

This section will be filled in by the participant. *The original will be kept be the investigator; a copy will be given to the participant.*

Title of the study:	
Place of the study:	

Participants in this study

You are being asked to volunteer in a research study. This consent/information form includes information about this study. We want to make sure that you are informed on the purpose of this study and what it means for you to participate in this study.

Please ask us for clarification on any point in the following information sheet. If you do not understand certain contents, please do not sign this form before you feel confident that you are aware of the study and its goals.

The participation in the study is totally voluntary. You can quit at any moment without being penalized or losing your benefits.

Project Goals

myAirCoach is a project funded by European Commission under the Horison 2020 programme. The myAirCoach project aims to develop a holistic asthma monitoring system based on personalised mHealth capabilities. One of the main goals of the project is to empower patients to manage their own health by providing user friendly tools to increase the awareness of their clinical state and the adherence and effectiveness of medical treatment. Towards this direction an ergonomic, compact and efficient sensor-based inhaler will be developed that will be in continuous communication with the patients smart devices and through them with the central system of myAirCoach. The intuitive user interfaces of the components will offer to the patients the possibility to customize their treatment towards preset goals and guidelines, either automatically or driven by healthcare professional in a telemedicine manner.

The sensing infrastructure of myAirCoach will have the capability to automatically monitor several clinical, behavioral and environmental factors in realistic conditions and combine them with the aggregated knowledge of asthma. A pipeline of advanced analysis, processing and computational modelling techniques will integrate under the same framework raw measurements, extracted features, indicators, and personal profile data representation. All these sources of data will be transformed into useful knowledge about the patient's condition and will ensure clinical state awareness and optimal treatment. Furthermore, myAirCoach is aiming to empower doctors, offering

them the possibility to supervise the condition of their patients and adjust the prescribed medication. In this context, myAirCoach will give to the clinicians early indications of increasing symptoms or exacerbations, while making an important contribution for the understanding of the mechanisms underlining the progression of asthma disease.

Aims of the current study

The myAirCoach framework will be quantified in two test campaigns with carefully designed cohorts of patients in three testing sites. Besides the obvious necessity of the test campaigns to ground the myAirCoach patient models and framework with data, the objective formal validation of the results is expected to lead to increased confidence in the myAirCoach approach and in the decision support tools and self-management systems in general. The impact of the holistic and innovative approach of myAirCoach is expected to lay the foundations for the widespread adoption of sensor-based self-management systems across the full spectrum of respiratory diseases.

Procedures

In the initial phase, your participation will consist of an interview. The goal will be to gather knowledge about: demographic data, quality of life, their physical, psychological and social health, and skills and interests about new technologies. Moreover, after making a brief presentation of the myAirCoach project and its main objectives, it will be develop a focus group to collect their point of view and opinions.

This procedure will last two hours. The main purpose of the evaluation is to achieve information about your daily needs and your opinion about the new technologies in order to improve and to adapt the platform to your needs. In this way, these needs can be taken into account and your actual needs will be achievable by the device developed in the myAirCoach project. At the end of the study, if you want, you can receive information about the results of this evaluation.

Risks and inconveniences

No risks or damages are foreseen during the assessment.

Benefits

You will probably not receive any personal benefit for your participation in this study. In any case, the data collected in this study might result in a better knowledge of asthma and the development of tools for the efficient self-management of the disease by patients.

Privacy and Confidentiality

We will record your answers to our notes in a way that it will not hold any identification of yourself nor it will not be possible to identify you later on. In other words, when someone agree to participate in the research, they receive a code-number, and since that moment every personal data are under that code, because of that no one could know to whom the data belongs to. The information will be processed during the analysis of the data obtained and will appear in the project deliverables in the way that it will not be possible to identify the participant from the information presented.

The results of this research can be published in scientific magazines or be presented in clinical sessions, always guaranteeing your complete anonymity.

The authorization for the use and access of the information for the aim of research is totally voluntary. This authorization will apply to the end of the study unless you cancel it before. In this case we will stop the use of your data.

If you decide to withdraw your consent later on, we ask you contact principal investigator of this study and let him know that you are withdrawing from the study.

Since the moment of your withdrawal, your data will not be processed again in any further phases of the research project. However, it will not be possible to alter already existing published documents or completed project deliverables.

CONTACT PERSON

For further information about your rights as a research participant, or if you are not satisfied with the manner in which this study is being conducted or if you have any questions or suffer any injury during the course of the research, please contact the Principal Investigator.

Research participant's identity

Research participant's identity and the identity and dated signatures of the participant affirming that consent was given

The information shown below identifying the participant should be entered in the designated spaces at the time of execution of the consent document.

Participant's Name:	
Participant's Birth Date:	
Participant's Reference Number:	

Participant Consent Form

	YES	**NO**
I was informed about the effect to be expected, about possible disadvantages and about possible risks verbally and in writing by the test leader of the study.		
I was informed about the purpose of research, the expected duration and the procedures verbally and in writing by the test leader of the study.		
I was informed about the of any benefits to me or to others which may reasonably be expected from the research.		
I was informed about the explanations on confidentiality (and limits) of the data.		
I was informed about the right to decline to participate and to withdraw from the research once participation has begun and the foreseeable consequences of declining or withdrawing.		
was informed about whom to contact for questions about the research		

	YES	NO
and research participants rights.		
I have read and understood the written information handed out for the study mentioned above. My questions in connection with the study have been answered satisfactorily. I can keep the written information and receive a copy of my written declaration of consent.		
I understood and agreed with the handling of incidental findings.		
I had sufficient time to take my decision.		
In case an incident arises contrary to expectation, insurance consists for me in the legally specified scale.		
I understand that I am free to withdraw from the study • at any time • without having to give a reason for withdrawing • and without affecting my future medical care		
I agree to take part in the study.		
The confidentiality of my personal data was assured to me. Personal date will used anonymised at the publication of the study's results. I approve of the fact however under a strict compliance with the confidentiality that the responsible experts of the authorities and the ethics commission may take a look for examining and control purposes of my original data.		

CONFIRMATION

Your participation in the study is possible only if you sign a stand-alone consent form that will authorize us to use your personal and health information and the information on your health status. If you do not wish to do so, please do not take part in this study.

I have read the information written in this consent report or has been adequately read to me. All my questions about this study and about my participation on it have been met.

Tick one of the following:

I read all the information in this form and all my questions were answered.

I authorize the use and dissemination of my answers to the aforementioned entities and for the above mentioned purposes. The signing of this consent report does not imply the renunciation to any legal right. I voluntarily agree to participate in this research study.

I understand that I am entitled to and will be given a copy of this signed Consent Form.

Signature	
Date	
Name (in block letters)	

Appendix 4:: Integrated Research Application Filter (UK)

Full Set of Project Data IRAS Version 4.0.0

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
myAirCoach dummy UK ethics

1. Is your project research?

(•) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product
( ) Clinical investigation or other study of a medical device
( ) Combined trial of an investigational medicinal product and an investigational medical device
(•) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
( ) Basic science study involving procedures with human participants
( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
( ) Study involving qualitative methods only
( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
( ) Study limited to working with data (specific project only)
( ) Research tissue bank
( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (•) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ( ) Yes (•) No
b) Will you be taking new human tissue samples (or other human biological samples)? ( ) Yes (•) No
c) Will you be using existing human tissue samples (or other human biological samples)? ( ) Yes (•) No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

1

☑ England
☐ Scotland
☐ Wales
☐ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

◉ England
○ Scotland
○ Wales
○ Northern Ireland
○ This study does not involve the NHS

4. Which review bodies are you applying to?

☑ NHS/HSC Research and Development offices
☐ Social Care Research Ethics Committee
☑ Research Ethics Committee
☐ Confidentiality Advisory Group (CAG)
☐ National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

5a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

○ Yes ◉ No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see information button for further details.

◉ Yes ○ No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP) and you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before completing and submitting other applications.

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of

identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Other clinical trial or investigation

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
myAirCoach dummy UK ethics

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

A3-1. Chief Investigator:

Title Forename/Initials Surname

Post
Qualifications
Employer
Work Address

Post Code
Work E-mail
* Personal E-mail
Work Telephone
* Personal Telephone/Mobile
Fax

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.

Title Forename/Initials Surname

Address

Post Code
E-mail
Telephone
Fax

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):
Sponsor's/protocol number:
Protocol Version:
Protocol Date:
Funder's reference number:
Project website:

Registry reference number(s):
The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

Additional reference number(s):

A5-2. Is this application linked to a previous study or another current application?

○ Yes ○ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, this summary will be published on the website of the National Research Ethics Service following the ethical review.*

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

A6-3. Proportionate review of REC application *The initial project filter has identified that your study may be suitable for proportionate review by a REC sub-committee. Please consult the current guidance notes from NRES and indicate whether*

- [ ] Design of the research
- [ ] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [ ] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.

A14-2. Have you tested the acceptability of using patient identifiable data in this study without consent?

Please give details.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [ ] Cancer
- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [ ] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender: Male and female participants

Lower age limit: Years

Upper age limit: Years

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ○ No

A21. How long do you expect each participant to be in the study in total?

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

○ Yes ○ No

A24. What is the potential for benefit to research participants?

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

A26. What are the potential risks for the researchers themselves? *(if any)*

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? *For example, identification may involve a disease register, computerised search of social care or GP records, or review of medical records. Indicate whether this will be done by the direct care team or by researchers acting under arrangements with the responsible care organisation(s).*

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

○ Yes ○ No

Please give details below:

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ○ No

A29. How and by whom will potential participants first be approached?

A30-1. Will you obtain informed consent from or on behalf of research participants?

○ Yes ○ No

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-3. Why is it not practicable for either the researcher's organisation, or the current holder of the information required by the researcher, to seek or obtain patient consent for proposed use of patient identifiable information?

A31. How long will you allow potential participants to decide whether or not to take part?

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

- ○ Yes
- ○ No
- ○ Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

- ○ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- ○ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- ○ The participant would continue to be included in the study.
- ○ Not applicable – informed consent will not be sought from any participants in this research.
- ○ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- ☐ Access to medical records by those outside the direct healthcare team
- ☐ Access to social care records by those outside the direct social care team
- ☐ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☐ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices

☐ Storage of personal data on any of the following:

- ☐ Manual files (includes paper or film)
- ☐ NHS computers
- ☐ Social Care Service computers
- ☐ Home or other personal computers
- ☐ University computers
- ☐ Private company computers
- ☐ Laptop computers

Further details:

A37. Please describe the physical security arrangements for storage of personal data during the study?

A38. How will you ensure the confidentiality of personal data? *Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

A39. Please specify whether identifiers will be held in the same database as the clinical data, or in a separate database and linked through a unique study or case number. *If held separately, please specify how and at what point the separation will occur. If held in the same database, will the identifiers be encrypted? If so, specify what will be encrypted and who will continue to have access.*

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

A42. Who will have control of and act as the custodian for the data generated by the study?

Title Forename/Initials Surname

Post
Qualifications
Work Address

Post Code
Work Email
Work Telephone
Fax

A43. How long will personal data be stored or accessed after the study has ended?

- ◯ Less than 3 months
- ◯ 3 – 6 months
- ◯ 6 – 12 months
- ◯ 12 months – 3 years
- ◯ Over 3 years

A44. For how long will you store research data generated by the study?

Years:
Months:

A45. Please give details of the long term arrangements for storage of research data after the study has ended. *Say where data will be stored, who will have access and the arrangements to ensure security.*

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

◯ Yes ◯ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

◯ Yes ◯ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

◯ Yes ◯ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◯ Yes ◯ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50-1. Will the research be registered on a public database?

The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials.

Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◯ Yes ◯ No

Please give details, or justify if not registering the research.

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- ☐ Peer reviewed scientific journals
- ☐ Internal report
- ☐ Conference presentation
- ☐ Publication on website
- ☐ Other publication
- ☐ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

A53. Will you inform participants of the results?

◯ Yes ◯ No

Please give details of how you will inform participants or justify if not doing so.

5. Scientific and Statistical Review

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

- ☐ Review by independent statistician commissioned by funder or sponsor
- ☐ Other review by independent statistician
- ☐ Review by company statistician
- ☐ Review by a statistician within the Chief Investigator's institution
- ☐ Review by a statistician within the research team or multi−centre group
- ☐ Review by educational supervisor
- ☐ Other review by individual with relevant statistical expertise

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title Forename/Initials Surname

Department

Institution
Work Address

Post Code
Telephone
Fax
Mobile
E-mail

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

A58. What are the secondary outcome measures? *(if any)*

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:
Total international sample size (including UK):
Total in European Economic Area:

Further details:

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

A61-1. Will participants be allocated to groups at random?

○ Yes ○ No

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

A64. Details of research sponsor(s)

A65. Has external funding for the research been secured?

☐ Funding secured from one or more funders

☐ External funding application to one or more funders in progress
☐ No application for external funding will be made

What type of research project is this?

◯ Standalone project
◯ Project that is part of a programme grant
◯ Project that is part of a Centre grant
◯ Project that is part of a fellowship/ personal award/ research training award
◯ Other

Other – please state:

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

◯ Yes ◯ No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

◯ Yes ◯ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

Title Forename/Initials Surname

Organisation
Address

Post Code
Work Email
Telephone
Fax
Mobile

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A68-2. Select Comprehensive Local Research Network for this NHS organisation:

To support communication between the REC and R&D contacts for this study, please select the Comprehensive Local Research Network (CLRN) for this NHS organisation. This CLRN will be the Lead CLRN for your study.

For information about support and advice available through the Lead CLRN and the CLRNs for participating sites see http://www.crncc.nihr.ac.uk/about_us/processes/csp. A map showing the CLRNs is available at

http://www.crncc.nihr.ac.uk/about_us/ccrn.

A69-1. How long do you expect the study to last in the UK?

Planned start date:
Planned end date:
Total duration:
Years: Months: Days:

A69-2. How long do you expect the study to last in all countries?

Planned start date:
Planned end date:
Planned end date (clinical interventions):
Planned end date (all trial procedures):
Total duration:
Years: Months: Days:

A71-1. Is this study?

○ Single centre
○ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

☐ England
☐ Scotland
☐ Wales
☐ Northern Ireland
☐ Other countries in European Economic Area

Does this trial involve countries outside the EU?
○ Yes ○ No

A72. Which organisations in the UK will host the research? *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☐ NHS organisations in England
☐ NHS organisations in Wales
☐ NHS organisations in Scotland
☐ HSC organisations in Northern Ireland
☐ GP practices in England
☐ GP practices in Wales
☐ GP practices in Scotland
☐ GP practices in Northern Ireland
☐ Joint health and social care agencies (eg community mental health teams)
☐ Local authorities
☐ Phase 1 trial units

☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)
☐ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☐ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ○ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ○ No ○ Not sure

A79. Please select the level of commercial participation in this project.

○ None
○ Industry funding, but not industry sponsored
○ Industry funding and industry sponsored
○ Industry sponsored, but not industry funded

A80. Please select the main subject area of research. Additional sub-topics may be selected, if required

☐ Age and Ageing
☐ Anaesthetics
☐ Cancer (includes malignant haematology
☐ Cardiovascular
☐ Clinical
☐ Critical Care
☐ Dementias and Neurodegenerative Diseases
☐ Dermatology
☐ Diabetes
☐ Ear, Nose and Throat
☐ Gastrointestinal

- ☐ Genetics
- ☐ Health Services Research
- ☐ Hepatology
- ☐ Immunology and Inflammation
- ☐ Infectious Disease and Microbiology
- ☐ Injuries and Accidents
- ☐ Medicines for Children (does not include Paediatrics)
- ☐ Mental Health
- ☐ Metabolic and Endocrine
- ☐ Musculoskeletal (Rheumatoid Arthritis is a separate category)
- ☐ Nervous System Disorders
- ☐ Non-malignant Haematology
- ☐ Ophthalmology
- ☐ Oral and Dental
- ☐ Paediatrics (does not include Medicines for Children)
- ☐ Primary Care
- ☐ Public Health Research
- ☐ Renal
- ☐ Reproductive Health and Childbirth
- ☐ Respiratory
- ☐ Rheumatoid Arthritis
- ☐ Stroke
- ☐ Surgery
- ☐ Urogenital

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

12. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further

information. We would be grateful if you would indicate one of the contact points below.

- ○ Chief Investigator
- ○ Sponsor
- ○ Study co-ordinator
- ○ Student
- ○ Other – please give details
- ○ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

Signature: .....

Print Name:

Date: *(dd/mm/yyyy)*

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*
7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.
8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

Signature: .....

Print Name:

Post:

Organisation:

Date: *(dd/mm/yyyy)*

Appendix 5: Templates for Ethics in Netherlands

ccmo Centrale Commissie Mensgebonden Onderzoek

Sluiten | Opslaan | Verwijderen | Maak definitief | Help ... Dr J.K. Sont - c2a08f

Formulier voor medisch-ethische beoordeling en registratie

ABR-formulier, versie april 2014

Onderzoeksdossiernummer

ABR Nummer	**53836**	Status	**Concept**
Versie	**concept**	Status per	**29-05-2015**

Het is raadzaam de ingevoerde gegevens tijdens het invullen van dit formulier tussentijds regelmatig op te slaan. Dit voorkomt eventueel verlies van gegevens bij een verbreking van de internetverbinding.

Selecteer de secties die U wilt bewerken:

Alles selecteren Alles de-selecteren

- B. Administratief
- C. Onderzoek
- D. Proefpersonen
- E. Voor- en nadelen
- F. Informatie en privacy
- G. Financieel
- I. Indiening en beoordeling
- J. Aanvullende opmerkingen
- K. Samenvatting
- L. Ondertekening

A. Sectie - Openbaar maken gegevens medisch wetenschappelijk onderzoek

A1. Het CCMO-register is een voor ieder toegankelijk openbaar trial register. De antwoorden op de vragen gemarkeerd met een wereldbol en de samenvatting bij dit formulier worden openbaar gemaakt in het CCMO register.

B. Sectie - Administratief

B1. Betreft het onderzoek met geneesmiddelen (inclusief gentherapie, somatische celtherapie, vaccinonderzoek, GGO's, zie verder toelichting) als bedoeld in de Wet medisch-wetenschappelijk onderzoek met mensen (WMO)?

- ja
- nee

B2. Houdt het onderzoek verband met een eerder door een erkende METC of door de CCMO beoordeelde studie of is het onderzoek reeds eerder bij een erkende METC ter beoordeling voorgelegd?

- ja, het onderzoek houdt verband met – of is het vervolg op – een eerder beoordeelde studie
- ja, het onderzoek is eerder ter beoordeling aan een erkende METC of de CCMO voorgelegd (stuur kopie besluit mee)
- nee

B4. Is het protocol (nog) in een ander openbaar trial register geregistreerd?

- ja
- nee

B5. Naam indiener/contactpersoon voor de oordelende toetsingscommissie

B5a.	Achternaam indiener/contactpersoon	Sont
	Titel en voorletters	Dr J.K.
	Tussenvoegsel	
B5b.	Type Organisatie/Bedrijf	Universitair Medisch Centrum
	Organisatie/Bedrijf	Leids Universitair Medisch Centrum
	Afdeling	Medische Besliskunde
	Adres/straatnaam (geen postbus)	Albinusdreef 2
	Adres/huisnummer (geen postbus)	
	Postcode en plaats	2333 ZA Leiden
	Postbus	
	Postcode en plaats	
	Land	Nederland

B5c. Intern adres J-10-86
Telefoon 071-5264578
Fax 071-5266838
E-mail j.k.sont@lumc.nl

B6. Is de indiener werkzaam bij de opdrachtgever/sponsor (verrichter) van het onderzoek?

Ja Nee

Ga naar boven Opslaan

C. Sectie - Onderzoek

C1. Volledige titel van het onderzoek
C1a. In het Engels

C1b. In het Nederlands

C2. Verkorte titel van het onderzoek/acroniem
C2a. In het Engels

C2b. In het Nederlands (Let op: deze korte titel wordt vermeld binnen ToetsingOnline)

C3. Trefwoorden (maximaal 4, plaats elk trefwoord op een aparte regel)
C3a. In het Engels

C3b. In het Nederlands

C4. Beschrijf het belang van het onderzoek en de beoogde toepassing van de resultaten (verwijs eventueel naar de relevante pagina's in het protocol).

C6. Betreft het onderzoek een multicenter-onderzoek?

nee
ja - alleen in Nederland
ja - internationaal binnen de Europese Unie
ja - internationaal ook buiten de Europese Unie

C8. Wie is/zijn medisch verantwoordelijk voor de proefpersonen die deelnemen aan het onderzoek

C9. In welk centrum/welke centra (incl. huisartsenpraktijken) in Nederland wordt het onderzoek uitgevoerd? Geef per centrum op: aantal proefpersonen, naam hoofdonderzoeker, naam onafhankelijk arts.

Voeg centrum toe Het ABR-formulier dient eerst opgeslagen te worden, alvorens een centrum toegevoegd kan worden.

Ga naar boven Opslaan

C10. Betreft het onderzoek met:

- mensen
- geslachtscellen
- (rest-)embryo's
- foetussen in utero

C11. Beoogd totaal aantal proefpersonen/(rest)embryo's/foetussen in utero:
C11a. In Nederland

C13. Onderzoeksgebied

- etiologie
- organisatorisch/zorgonderzoek
- diagnostiek
- preventie
- therapie
- veiligheid
- werkzaamheid
- farmacokinetiek
- farmacodynamiek
- bio-equivalentie
- dosis-respons
- farmacogenomics
- farmaco-economie
- anders

C14. Type onderzoek

- observationeel onderzoek zonder invasieve metingen
- observationeel onderzoek met invasieve metingen
- interventie-onderzoek

C15. In welke fase kan het onderzoek worden ingedeeld?

- fase I (a)
- fase II (b)
- fase III (c)
- fase IV (d)
- overige onderzoeken waarbij geneesmiddelen worden toegepast (e)
- niet van toepassing

C17. Is er sprake van een andere interventie dan met geneesmiddelen zoals bedoeld in de Wet medisch-wetenschappelijk onderzoek met mensen (WMO) (zie toelichting)?

- Ja
- Nee

C18. Worden de onderzoeksproducten voor deze studie door de verrichter gratis verstrekt?

- ja
- nee
- gedeeltelijk namelijk
- niet van toepassing

C19. Is/zijn er (een) controlegroep (en)?

- ja
- nee

C20. Betreft het een gerandomiseerd onderzoek?

- ja
- nee

C21. Op welke klasse(n) van aandoeningen heeft het onderzoek betrekking (maximaal 3)

- hartaandoeningen
- congenitale, familiaire en genetische aandoeningen
- bloed- en lymfestelsel aandoeningen

- zenuwstelsel aandoeningen
- oogaandoeningen
- evenwichtsorgaan- en ooraandoeningen
- ademhalingsstelsel-, thorax- en mediastinumaandoeningen
- maagdarmstelselaandoeningen
- nier- en urinewegaandoeningen
- huid- en onderhuidaandoeningen
- skeletspierstelsel- en bindweefselaandoeningen
- endocriene aandoeningen
- voedingsstoornissen en metabole ziekten
- infecties en parasitaire aandoeningen
- letsels, intoxicaties en verrichtingscomplicaties
- neoplasmata, benigne, maligne en niet-gespecificeerd (incl cysten en poliepen)
- chirurgische en medische verrichtingen
- bloedvataandoeningen
- algemene aandoeningen en aandoeningen op de plek van toediening
- zwangerschap, perinatale periode en puerperium
- sociale omstandigheden
- immuunsysteemaandoeningen
- lever- en galaandoeningen
- voortplantingsstelsel- en borstaandoeningen
- psychische stoornissen
- overig, namelijk

C22. Geef twee synoniemen voor de aandoening die bestudeerd wordt, waarvan tenminste één lekenterm.

In het Engels:
In het Nederlands:

C23. Beoogde start- en einddatum van het onderzoek

C23a. Start Datum (dd-mm-jjjj)
C23b. Eind Datum (dd-mm-jjjj)

Ga naar boven Opslaan

D. Sectie - Proefpersonen

D1. Is er een proefpersonenverzekering conform de WMO-eisen afgesloten of wordt aan de oordelende toetsingscommissie ontheffing gevraagd?

- proefpersonenverzekering is afgesloten bij verzekeringsmaatschappij
- ontheffing van de verzekering wordt gevraagd
- niet van toepassing - onderzoek valt onder de Embryowet en niet onder de WMO

D2. Gezonde proefpersonen en/of patiënten

- Gezonde proefpersonen
- Patiënten

D4. Voornaamste inclusiecriteria

D4a. In het Engels

D4b. In het Nederlands

D5. Voornaamste exclusiecriteria

D5a. In het Engels

D5b. In het Nederlands

D6. Bij welke categorie proefpersonen wordt het onderzoek uitgevoerd (meerdere antwoorden mogelijk)

- [ ] 18 jaar of ouder en wilsbekwaam
- [ ] 18 jaar of ouder en wilsonbekwaam
- [ ] 12 t/m 17 jaar en in staat tot het geven van geïnformeerde toestemming
- [ ] 12 t/m 17 jaar en niet in staat tot het geven van geïnformeerde toestemming (wilsonbekwaam)
- [ ] jonger dan 12 jaar

D10. Verkeren (sommige) proefpersonen in een afhankelijkheidssituatie ten opzichte van de onderzoeker of degene die de deelnemers werft? (lees de toelichting voor voorbeelden wanneer er sprake kan zijn van een afhankelijkheidssituatie)

- ( ) ja
- ( ) nee

D11. Waaruit bestaat de vergoeding voor de proefpersonen?

- [ ] geen vergoeding
- [ ] reiskosten
- [ ] financiële vergoeding (in Euro's)
- [ ] andere vergoeding

D12. Is deze vergoeding afhankelijk van bepaalde voorwaarden, bijvoorbeeld het voltooien van (een deel van) het onderzoek?

- ( ) ja (motiveer)
- ( ) nee
- ( ) niet van toepassing

Ga naar boven Opslaan

E. Sectie - Voor- en nadelen

E1. Wordt er bij dit onderzoek een rechtstreeks therapeutisch effect beoogd bij de proefpersonen / patiënten?

- ( ) ja (therapeutisch onderzoek)
- ( ) nee (niet-therapeutisch onderzoek)

E2. Waaruit bestaat de belasting van het onderzoek (en een eventueel daaraan voorafgaande keuring) voor de proefpersonen?

Tijdbeslag	per bezoek
	totaal
	totale duur van de studie voor de individuele proefpersoon

E3. Worden de proefpersonen in verband met het onderzoek in het ziekenhuis opgenomen of wordt een opname verlengd?

- ( ) ja - het verblijf in het ziekenhuis/instituut wordt in verband met het onderzoek verlengd
- ( ) ja - ze worden voor het onderzoek in het ziekenhuis/instituut opgenomen
- ( ) nee

E4. Beschrijf in hoeverre proefpersonen worden onderworpen aan handelingen dan wel een gedragswijze krijgen opgelegd, zoals vragenlijst, interviews, lichamelijk/psychologisch onderzoek, ontzegging, dieet (voor invasieve ingrepen: zie vraag E6)

E5. Worden de proefpersonen getest op bepaalde aandoeningen/condities?

- ( ) ja (motiveer)
- ( ) nee

E6. Welke extra (invasieve) ingrepen (anders dan bij de standaard behandeling) moeten de proefpersonen in het kader van het onderzoek ondergaan:

- [ ] Niet van toepassing
- [ ] venapunctie
- [ ] arteriepunctie
- [ ] intraveneuze injectie
- [ ] intra-arteriële injectie
- [ ] subcutane injectie
- [ ] intramusculaire injectie
- [ ] intra- of periarticulaire injectie

- liquorafname
- scopie
- biopsie
- catheterisatie
- onderzoek met stralenbelasting
- vaginaal/rectaal
- andere ingrepen

E9. Geef aan welke risico's er voor proefpersonen zijn verbonden aan deelname aan het onderzoek.

E9a. Geef op grond van uw eigen afweging aan waarom het uitvoeren van het onderzoek, in het licht van de belasting en/of risico's die voor proefpersonen aan deelname verbonden zijn, gerechtvaardigd is?

E10. Indien het onderzoek bij minderjarige en/of wilsonbekwame proefpersonen wordt uitgevoerd en geen direct therapeutisch effect wordt beoogd: waarom kunnen belasting en risico's als minimaal worden beschouwd? (Verwijs eventueel naar de relevante pagina's in het protocol.)

- niet van toepassing

E11. Kan de eventuele therapie na beëindiging van het onderzoek worden voortgezet?

- ja (motiveer)
- nee (motiveer)
- niet van toepassing

E12. Heeft deelname aan het onderzoek voor de proefpersoon tot gevolg dat van de standaardbehandeling of -diagnostiek kan worden afgeweken of deze kan worden uitgesteld?

- ja
- nee
- niet van toepassing

Ga naar boven Opslaan

F. Sectie - Informatie en privacy

F1. Hoe worden de proefpersonen geworven en door wie (onderzoeker, behandelend arts, andere persoon) wordt de proefpersoon/wettelijke vertegenwoordiger geïnformeerd en om toestemming gevraagd?

F2. Hoeveel bedenktijd krijgen de proefpersonen/wettelijke vertegenwoordigers om te beslissen over deelname?

F3. Wordt de huisarts, behandelend specialist en/of apotheker van de proefpersoon geïnformeerd over diens deelname aan het onderzoek?

- ja (de proefpersoon dient hiervoor toestemming te geven)
- nee

F4. Worden persoonsgegevens gecodeerd?

- ja
- nee

F5. Hoe wordt het lichaamsmateriaal gedurende het onderzoek bewaard?

- in tot de proefpersoon herleidbare vorm (gecodeerd)
- in niet tot de proefpersoon herleidbare vorm (volledig geanonimiseerd)
- niet van toepassing

F6. Wordt afgenomen lichaamsmateriaal na afloop van het onderzoek vernietigd?

- ja
- nee (motiveer)
- niet van toepassing

F7. Kunnen proefpersonen na afloop van het onderzoek opnieuw benaderd worden (bijvoorbeeld voor nader onderzoek of follow-up)?

- ja
- nee

Ga naar boven Opslaan

G. Sectie - Financieel

G1. Door welke geldstroom wordt het onderzoek gefinancierd?

- eerste geldstroom (Geld van Ministerie van OC&W aan universiteiten)
- tweede geldstroom (NWO of KNAW), namelijk
- derde geldstroom (anders dan 1e of 2e geldstroom, zoals collectebusfondsen, Europese Unie, vakministeries of bedrijven), namelijk

G2. Wordt het onderzoek (mede) gefinancierd door de industrie/bedrijven?

- ja - door de industrie/bedrijf zoals is opgegeven bij vraag B6/B7 (opdrachtgever van het onderzoek)
- ja - (ook) door andere industrie/bedrijven dan de opdrachtgever
- nee

G3. Wat is de hoogte van de vergoeding die de arts/onderzoeker cq onderzoeksafdeling/maatschap ontvangt voor de uitvoering van het onderzoek?

- Per patiënt of proefpersoon
- Per deelnemend centrum

bedrag afronden op hele euro's: €

G3a. Hoe is de vergoeding opgebouwd?

G4. Heeft/hebben de onderzoeker(s) gedurende de afgelopen vijf jaar op een of andere wijze een persoonlijke financiële relatie (gehad) met de verrichter/sponsor van het huidige onderzoek?

- ja (licht toe)
- nee

Ga naar boven Opslaan

I. Sectie - Indiening en beoordeling

I1. Sla het formulier eerst op en selecteer vervolgens de toetsingscommissie die het oordeel geeft in de zin van de WMO

Opslaan

Commissie

Selecteer Toetsingscommissie

Ga naar boven Opslaan

J. Sectie - Aanvullende opmerkingen

Aanvullende opmerkingen

Ga naar boven Opslaan

K. Sectie - Samenvatting

K1. Nederlandse Samenvatting

Achtergrond van het onderzoek:

Doel van het onderzoek:

Onderzoeksopzet:

Onderzoekspopulatie:

Primaire onderzoeksvariabelen/uitkomstmaten:

Secundaire onderzoeksvariabelen/uitkomstmaten (indien van toepassing):

Omschrijving en inschatting van belasting en risico (indien van toepassing):

K2. Engelse Samenvatting

Background of the study:

Objective of the study:

Study design:

Study population:

Primary study parameters/outcome of the study:

Secundary study parameters/outcome of the study (if applicable):

Nature and extent of the burden and risks associated with participation, benefit and group relatedness (if applicable):

Ga naar boven Opslaan

ONDERTEKENING

De verrichter en indiener verklaren hierbij:

a. het formulier (en samenvatting) volledig en naar waarheid te hebben ingevuld;

b. de antwoorden op de vragen uit het ABR-formulier niet in strijd zijn met het bijbehorende onderzoeksdossier en onderzoekscontract

Naar waarheid getekend, door de verrichter (=opdrachtgever)	door de indiener
datum	datum .....
Handtekening	Handtekening
naam	naam
functie	functie

Ga naar boven Opslaan

Wijzigingsgeschiedenis

29-05-2015 15:35:00 - jksont heeft dit formulier opgeslagen

29-05-2015 15:34:45 - jksont heeft dit ABR-formulier aangemaakt

Ga naar boven

Appendix 6: Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects[40]

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975.
35th WMA General Assembly, Venice, Italy, October 1983.
41st WMA General Assembly, Hong Kong, September 1989.
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996.
52nd WMA General Assembly, Edinburgh, Scotland, October 200 .
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added).
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added).
59th WMA General Assembly, Seoul, Republic of Korea, October 2008.
64th WMA General Assembly, Fortaleza, Brazil, October 2013.

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive,

[40] Declaration of Helsinki – Ethical Principles for Medical Reseach Involving Humab Subjects. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html (Assessed 2015)

diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
- and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
- Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.