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AI ethics and incidental findings policy

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DEC	Websites, patent fillings, videos etc.	
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CO	Confidential (Consortium members including the Commission Services)	
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1 Executive Summary

The aim of this deliverable is to describe the approach that the CAPABLE consortium will have with respect to the ethics issues that might arise during the development and use of the CAPABLE AI-based clinical decision support system. In addition, the document also describes the policy related to incidental findings detection and management.
This is an initial document that provides an overview of the foreseen issues, with specific focus on ethical and legal evaluations about data management, incidental findings, and residual risks. Some specific cases related to the project development are detected and described. The document is structured as follows: after a general introduction on the project and its objectives (Section 2), incidental findings and risks are defined, together with the policy that CAPABLE will adopt to detect and manage them (Section 3). In Section 4 we present how CAPABLE will deal with the communication of such findings and risks to the users of the system. Section 5 details the data protection impact assessment (DPIA).

2 Preliminary and brief description of the purposes of the project

After the primary intervention, most cancer patients are managed at home, facing long-term treatments or sequelae, making the disease comparable to a chronic condition. Despite their benefit, strong therapeutic regimens often cause toxicity, severely impairing quality of life. This may decrease adherence to treatment, thus compromising therapeutic efficacy. Also due to age-related multimorbidity, patients and their caregivers develop emotional, educational and social needs.
CAPABLE is developing a cancer patient coaching system with the objective of facing these needs/issues. It will fully exploit Artificial Intelligence (AI) and Big Data potentialities for cancer care and bring them to patients' homes.
CAPABLE will rely on predictive models based on both retrospective and prospective data (clinical data, data from unobtrusive environmental and wearable sensors, data from social media and questionnaires). Models will be integrated with existing clinical practice guidelines and made available to oncologists.
Thanks to the mobile coaching system for patients, CAPABLE will allow providing patient-specific decision support. This feature, together with the chance of discovering unknown adverse effects of most recent treatments, makes CAPABLE more than a personalised tool for improving life quality, an advance for the whole research community.

The Consortium acknowledges and believes that is it extremely important to manage possible risks in this type of systems. This is the starting point of the following document, which reflects our initial evaluation of the scenarios that CAPABLE may face during its development and use.
It is preliminary to note here that:
1) The risks identified in this Deliverable are subject to an ongoing monitoring process specifically designed for CAPABLE that includes internal and external monitoring processes and bodies.

2) This monitoring is also part of the general risk management strategy.

It is also important to provide some definitions. *Incidental risks* are the risks of misuse of the system caused by internal and external factors. These risks can be mitigated (reduced) using suitable policies. The risks that remain after these policies have been implemented and taken full effect are termed *residual risks*.
To identify possible sources of incidental risks we have reviewed privacy and data protection inquiries and the academic literature on the subject. This investigation has focused particularly on the recent literature and experience following the introduction of new European Data protection regulations, the General Data Protection Regulation (GDPR) in 2016 (enacted on May 25th 2018).

This Deliverable is focused on ethical and legal evaluations about data management, incidental findings, and residual risks, to set a policy for the CAPABLE project.

3 Incidental findings

3.1 Introduction

The notion of incidental findings originated in medical and genetic research. Incidental findings are traditionally defined as results that are outside the original purpose for which a test or procedure was conducted.
According to the literature [1], incidental findings are distinct from *primary findings*, which are the results that are actively sought as the primary target of a test or procedure.
They can be either “anticipatable” or “unanticipatable.” An *anticipatable incidental finding* is one that is known to be associated with a test or procedure. Anticipatable incidental findings need not be common or even likely to occur—their defining characteristic is that the possibility of finding them is known.
Unanticipatable incidental findings include findings that could not have been anticipated given the current state of scientific knowledge. Researchers cannot plan for these types of findings specifically. However, they can consider in advance what they might do if a particular kind of unexpected finding arises, for example, one that could be actionable or lifesaving.
A *secondary finding*, by contrast, is not the primary target of the test or procedure; rather, it is an additional result actively sought by the practitioner. Secondary findings might be sought deliberately when doing so is recommended by an expert body or by a consensus of practitioners. Table 3.1.1 provides examples of each type of finding.

TYPE OF RESULT DISCOVERED	DESCRIPTION	EXAMPLE
Primary Finding	Practitioner aims to discover A, and result is relevant to A	In a child with unknown vaccine history, a test done to determine a child's immunity status before the chickenpox vaccine is administered
Incidental Finding: *Anticipatable*	Practitioner aims to discover A, but learns B, a result known to be associated with the test or procedure at the time it takes place	Discovering misattributed paternity when assessing a living kidney donor and potential recipient who believe they are biologically related
Incidental Finding: *Unanticipatable*	Practitioner aims to discover A, but learns C, a result not known to be associated with the test or procedure at the time it takes place	When a DTC genetic testing company identifies a health risk based on a newly discovered genetic association not knowable at the time a previous sample was submitted
Secondary Finding	Practitioner aims to discover A, and also actively seeks D per expert recommendation	ACMG recommends that laboratories conducting large-scale genetic sequencing for any purpose should actively look for variants underlying 24 phenotypic traits

Table 3.1.1 - Description and examples of research results. Source: [2].

The most pressing ethical questions in the debate on the management of incidental findings as it pertains to medical research are often summarised as follows [3]:
• should the physician be obligated to report all such findings back to the patients, or just some findings—in that case, which ones, or none?
• should the patients have a right to demand such results to be delivered to them under all circumstances, or should they be allowed to refuse to receive any such information?
• should a patient with a genetic variant implicated in the development of serious, but preventable/treatable clinical condition be allowed to refuse to know such information and consequently withhold it from family members that can also be carriers of that same genetic variant?
• should some genetic variants that can cause preventable/treatable clinical conditions that come up as incidental results in genome-scale screening testing be actively sought in such testing, becoming thus a secondary instead of incidental finding, or, in fact, a regular finding of the clinical screening?
Detection and feedback of incidental findings can be a "double edged sword", as they may allow for timely treatment (thus leading to medical benefit) but may also harm research participants because of the burdens of costs of follow-up testing and (possible) over- treatment [4].

The ethical path we have elaborated includes:

(i) Thinking about anticipatable incidental findings
(ii) Preparing a set of information provisions for the informed consent of the research participants (research participants will be given the opportunity either to opt out of receiving information about incidental findings or to withdraw from the study);
(iii) communication of the incidental finding policies to the research participant should align with national regulations and customs;
(iv) definition of the person/institution who will take responsibility for the clinical follow-up of the research participant.

The project, also thanks to the incidental findings policy, states its:

(i) compliance with laws, regulations and court assessments,
(ii) technological conformance with existing standards,
(iii) congruence with ethical principles, could be better achieved if based on empirical knowledge and reasonable estimation.

According to the literature, it should be considered carefully whether to allocate time and resources to seeking secondary findings, or to interpreting, assessing, and disclosing incidental findings, especially when these decisions might benefit individuals in the research study but stall broader societal benefits of the research activity. Researchers do not have an ethical duty to seek secondary findings. However, researchers must determine how their incidental findings management policy will affect participants as individuals, and how it will affect their ability to contribute to generalizable knowledge.
The Consortium takes the responsibility to make choices according to the principles listed in Table 3.1.2.

Principle	*Definition*	*Application*
Respect for Persons	This principle recognizes the fundamental human capacity for rational self- determination.	Researchers must communicate the fundamental aspects of their research – including the possibility of discovering incidental or secondary findings and the plan for their disclosure or management – so that participants can make informed decisions about whether to enrol.
Beneficence	This principle calls on professionals to take action to ensure the wellbeing of others. Its corollary, non-maleficence, requires not imposing harm on others.	This principle supports returning findings when disclosure might help forestall or prevent harm. By contrast, disclosing an incidental finding for which no preventive or positive action can be taken has the potential to cause anxiety and distress with no corresponding medical benefit.
Justice and Fairness	This principle requires fair and equitable distribution of the potential benefits and burdens across society.	The principle of justice and fairness calls upon researchers to take into account how policies for returning incidental and secondary findings could benefit or burden some participants or, alternatively, could burden the research enterprise and the ability to contribute to generalizable knowledge.

Intellectual Freedom and Responsibility	This principle protects sustained and dedicated creative intellectual exploration that furthers scientific progress, while requiring that researchers take responsibility for their actions.	This principle supports affording wide latitude to researchers in pursuing their scientific goals and engaging in intellectual exploration for the good of society, while also expecting that researchers uphold and respect the trust placed in them by participants. Ethical conduct of research with human participants includes acknowledgment and planning for incidental and secondary findings.

Table 3.1.2 - Principles that constitute the foundation of the CAPABLE incidental findings policy. Source: [2].

These principles are explicitly recognized and promoted also by important European documents, such as:

- the Declaration of Helsinki, Ethical Principles for medical research involving human subjects;
- the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Oviedo, 4 April 1997) (Oviedo Bioethics Convention)- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use as well as the requirements for authorization of the manufacturing or importation of such products (OJ L 91, 9.4.2005, p. 13).
- The Regulation No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC (OJ L158, 27/5/2014).

3.2 Events

Tables 3.2.1 and 3.2.2 represent possible cases of Incidental Findings and Clinical Incidental Risks in the CAPABLE project. They will be periodically updated during the development of the project, and especially during the clinical trial phase.

Incidental findings	Management	Subject involved
From collected data, physicians discover a new disease	The patient will be informed about the possibility of anticipatable or unanticipatable cases in the informed consent. The physician who is taking care of the patient will inform him/her about the disease, offering all possible information	Physicians

	about treatment and contacts of specialized physicians	
From collected data, the decision support system reveals a risk of diseases linked to the cancer (e.g. cardiovascular risk)	The patient will be informed about the possibility of the discovery of new risks in the informed consent. The physician who is taking care of the patient will inform him/her about the increased risk, proposing the patient the useful/necessary actions to take.	Physicians

Table 3.2.1 - examples of incidental findings within the CAPABLE project. For each finding, we provide a possible management strategy, and we identify the subjects that are involved in the management.

Incidental Risks	**Management**	**Subject/component involved**
Malfunction of the system that delivers wrong/missing recommendation to the patient (e.g. nutrition advice)	Human periodical check and immediate information to the patient about how to change behaviour	Physicians who take care of the patient; Software engineers
Malfunction of the system that delivers wrong medical indication to the patient (e.g. which pills to take)	Human frequent periodical check and immediate information to the patient about how to change behaviour	Physicians who take care of the patient; Software engineers
Patients' misbehaviours such as taking supplements or substances (herbals, etc) that have not been reported.	Informing initially and periodically the patient about the necessity to report all new supplements or substances taken during the trial period	Physicians and app notifications
Patients' misbehaviours such as not being compliant with the therapeutic contract (drugs combined with physical and mental activity)	A clear statement in the Informed Consent about the terms of the therapeutic contracts and delivering periodical recommendations about the compliance to it	Physicians and app notifications.
Patient does not report his data	Both patients and healthcare professionals will be reminded of the importance of providing complete data. In case the system detects a persistent abstention from the use by the	Physicians and app notifications.

	patient, an alert will be sent to the patient and the healthcare provider.	

Table 3.2.2 - examples of incidental risks within the CAPABLE project. For each case, we provide a possible management strategy, and we identify the subjects or system components involved.

Monitoring of incidental findings and risks

During the clinical study, when real users will test the system, we will implement a monitoring strategy to detect possible events that generate a potential risk or an incidental finding.
Both the users and the technical partners will take part in the monitoring process.
Each time a potentially risky behaviour of the system or incidental finding is detected, it should be reported. In particular, the following information are needed:

- who detected the event
- date of the event
- type of event (incidental finding -anticipatable or not- or incidental risk)
- description of the event
- patient(s) involved
- user and component involved
- was the event detected at the same time it happened?
- was the event managed? how? when?
- was there any consequence of the event?

Some of the information will be reported by the user who experienced the event, some others will be completed by the CAPABLE research team. In general, the system users will notify the first level support at the clinical center, who will be responsible to report the event to the CAPABLE research team, who will meet periodically to analyze the cases.

Managing the risks of wrong or unethical decisions

Explainability and traceability

In order to support explainability and interpretability of decision models, we promote formal and symbolic representation of the domain knowledge. In particular we employ the PROforma language [5] to represent broadly understood clinical rules and workflows, such as clinical practice guidelines, clinical pathways and other algorithms employed by the CAPABLE system (for example, algorithms for recommending the so-called “well-being capsules” to a patient, which are non-pharmacological interventions to improve the mental well-being and managing stress). PROforma requires explicit specification of considered data items and conditions imposed on these items that are associated with specific decisions, which contributes to *intrinsic* interpretability of applied models. In order words, a model can be relatively easily verified and tested before it is deployed to practical use. A sample

guideline modeled in PROforma is presented in Figure 3.2.1.

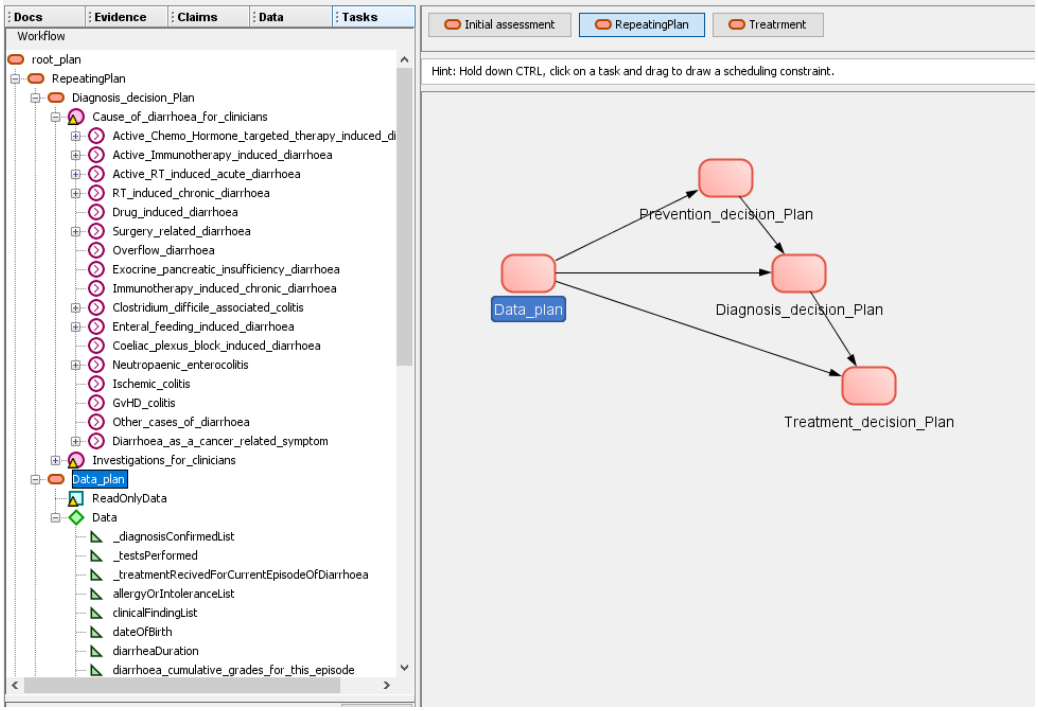

Figure 3.2.1 - Example of a guideline modeled using the PROforma language.

Moreover, PROforma modeling and execution tools allow for associating relevant parts of evidence-based documents, such as guidelines or systematic reviews. These parts can be presented to a decision maker (physician) when considering possible options for a given decision. This further enhances the *post-hoc* interpretability of the models -- the decision maker is not only able to trace the "path" in the model followed for a specific patient, but is also offered sound justification behind specific choices. This is illustrated in Figure 3.2.2, where the upper part presents possible treatment options (candidates), and the bottom part brings relevant parts of the guideline.

We should also note that decision models in PROforma are meant to be used as assistants to human decision makers (physicians and patients) in order to ensure the required level of human autonomy. Thus, physicians and patients are provided by decision recommendations established by CAPABLE, and they can either accept or discard them and freely choose options that are not among the ones suggested by the system.

During later stages of the system development we plan to employ "blackbox" models, such as convolutional neural networks, for personalization of capsules. These models will rely on sensor data, such as blood volume pulse or other biomarkers that may be related to stress. Since such models are not directly interpretable, we will combine them with explainable AI methods, e.g., LIME, to provide better insight into operations and reasoning of these models. In any case, no critical decision will be taken by the system without the intervention of the healthcare personnel.

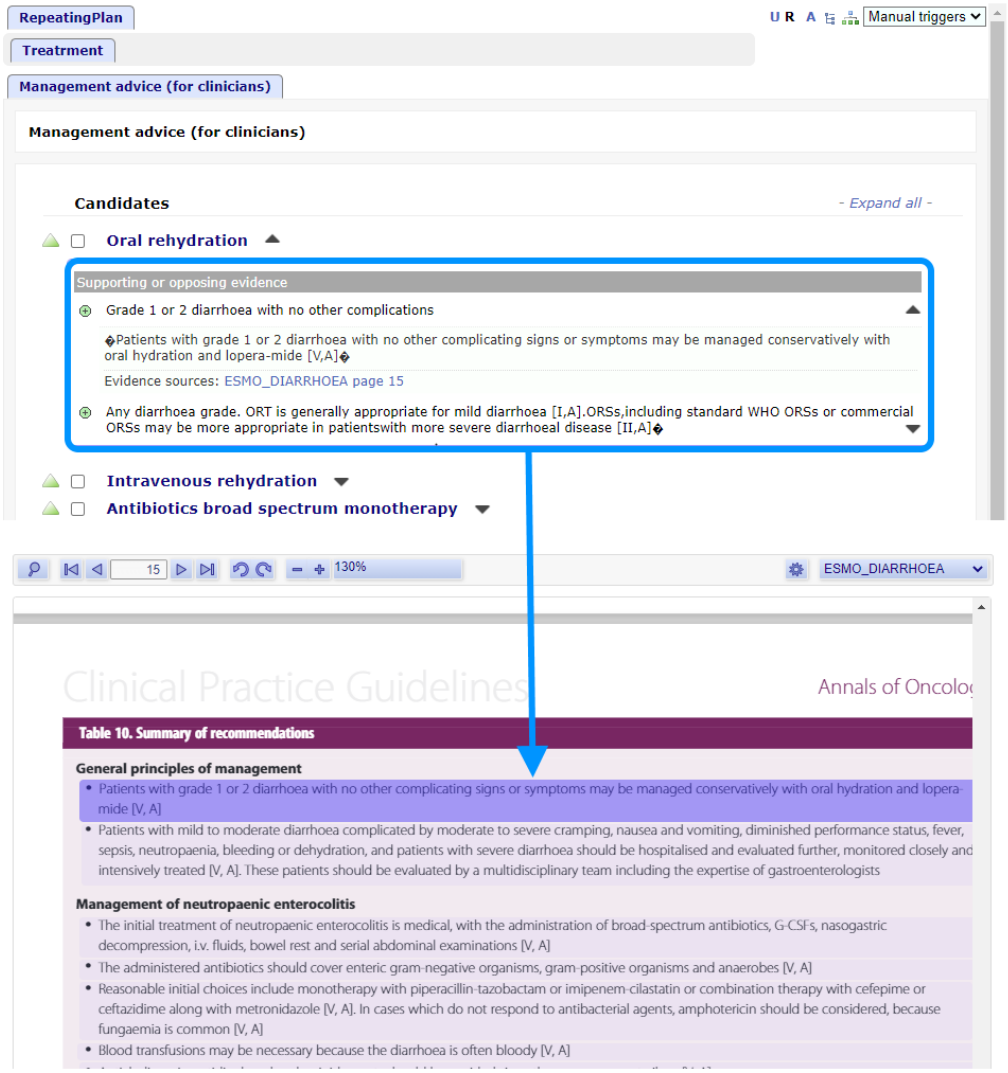

Figure 3.2.2 - Explanation of evidence in PROforma.

Avoidance of unfair bias

CAPABLE will employ two types of data-driven predictive models -- personal and population-based. Personal models have been already mentioned above in the context of capsule personalization. We plan to build a separate model for each patient managed by the system, thus bias should have negligible impact on models' operations. However, the bias, related for example, to age, gender, or specific type of therapy, may influence population-based models. We plan to identify possible biases during the data preprocessing stage by applying exploratory data analysis methods and address them by applying appropriate resampling techniques to make data sets more "representative" for considered problems. This step will be conducted through cooperation of technical and clinical teams.

4 Communication to participants

Possible incidental findings and risks will be communicated to participants during the informed consent process.
This allows individuals to choose not to participate in research if they are uncomfortable with the project's management plan. The consent materials will include information about the following elements:

- Secondary findings that will be actively sought and returned to participants should be conveyed in the informed consent process, and there should be a specific plan for their return.

- A plan for anticipatable incidental findings (e.g., that researchers will or will not return some or all potential findings)

The plan for managing incidental findings detailed in the informed consent will include also a description of the research team's responsibilities following disclosure of such a finding, also providing:

- basic educational information about the nature of the finding;
- advice regarding how to seek care from a clinician or specialist;
- guidance about obtaining health insurance to secure treatment; and/or
- a referral to a clinical specialist, if one is required.

The contact details of the support in case of malfunctioning or unexpected behaviour will also be included in the user manuals of the system. In this way, if during the pilot study one of the users experienced some problems, he/she is informed on how to proceed to report the issue.

5 Data Protection Impact Assessment

The first step is to assess the necessity and proportionality of the intended data processing, which the Article 29 Working Party (WP29) has advised to be done, considering: a) the specified, explicit and legitimate purpose of the processing; b) the lawfulness of processing, and c) the principle of minimization, which requires the data to be adequate, relevant and limited to what is necessary for the objective.

As already detailed in the Deliverable D1.2 (Data Management Plan), the overall objective of CAPABLE is to combine the most advanced technologies for data and knowledge management with a sound socio-psychological approach in order to develop a coaching system for improving the quality of life of cancer patients.
The system aims at early detecting and managing cancer-related issues and at satisfying the needs of patients and their home caregivers.

Ultimately, CAPABLE will exploit several different datasets using AI techniques to effectively monitor individual patients, with the final goal to improve quality of life after cancer treatment. More specifically, the data collection and analysis activities in the CAPABLE project will help achieve the following objectives:

- Identifying, classifying and ranking new cancer patients' and their home caregivers' needs, mostly leveraging on data provided by the AIMAC patients' association, interviews and questionnaires to be administered in the requirements elicitation work package (WP2).
- Improving patients' compliance to treatment by acquiring Patient Reported Outcomes (PROs) and Patient Reported Experiences (PREs).
- Collecting data for early identification of deterioration in quality of life or emotional issues.
- Improving healthcare professional workflows by promptly identifying priority patients and shortening the duration of control visits due to a better understanding of the patient conditions, thanks to data collected in-between visits at the patient home.
- Identifying adverse events of (relatively) new therapies or unknown long-term effects of cancer treatment.
- Developing new, data-driven AI models for the course of cancer, which could drive more personalized interventions.

The system will rely on both data already available to partners at the beginning of the project and on data that will be collected during the clinical study, which will last the entire fourth year of the project. The clinical study, that will take place at the two clinical partner organizations ICSM and NKI, will enroll kidney cancer (ICSM) and melanoma patients (NKI). Thus, the data collected by the project pilot will be focused on these two cancer patient populations, but many of the findings intend to be generalizable to other cancer domains. Table 1 provides a summary of the data that CAPABLE will collect. All the data collected by the project during the pilot studies will be stored in a centralized data repository based on the OMOP CDM [1], in order to improve standardization and promote reusability. Every action will be taken according to the principle of minimization, including only data that have been evaluated useful for the project.

The lawfulness of the processing is granted by the Informed Consent that will be signed by users and participants.

5.1 Risk Assessment

The initial risk-related scenarios that we envisage are summarized in Table 5.1.1.

Data protection risks	Management
Sharing patient's data with the caregiver (both at home, e.g. for not self sufficient patients, and at nursing institutions)	The caregiver is the data processor and thus legitimate to manage data, according to the recommendations that will be delivered and signed.
Data breach: theft of the	The access to the patient's data is protected by a password

smartphone or the tracker	The Capable app can be deactivated remotely (as long as data connection is on) by the technical team/hospital IT. This will prevent any further attempt to login and use the Capable patient app. Also, clinical and personal data stored locally in the patient phone by the Capable app will be encrypted. If the patient reports the phone was lost or stolen, the deactivation will also cause a full data wipe-out from the smartphone local storage. Data will be kept in the centralized Capable Data Platform.
Data breach; a third party access the patient's data on the smartphone or Hacking activity	The access to the app is protected by a password In case of hacking, there will be an immediate notification to the national Data Protection Authority as provided by the GDPR. The access to the patient's data is protected by a password The Capable app can be deactivated remotely (as long as data connection is on) by the technical team/hospital IT. This will prevent any further attempt to login and use the Capable patient app. Also, clinical and personal data stored locally in the patient phone by the Capable app will be encrypted. If the patient reports the phone was lost or stolen, the deactivation will also cause a full data wipe-out from the smartphone local storage. Data will be kept in the centralized Capable Data Platform.
From collected data, patient's habits can be inferred	All people professionally involved in the project shall be compliant with the data protection regulations and will be entitled to use inferred information only for project-related uses.

Table 5.1.1- Description of data protection risks and their management.

While any DPIA must be carried out before the processing of personal data begins, it should be considered a 'live' document. This means this document will be subject to regular review or re-assessment during the development of the project.

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