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Building a Roadmap for Striking Collaboration in Medical R&D for an IT Solution

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The objective of this thesis was to build a roadmap for striking collaboration in medical R&D for an IT solution. This thesis started with analyzing the previous experiences in medical R&D collaboration projects done at the case company and focused on identifying the gaps and improvements that can help to improve the process of setting up an R&D collaboration project in the future. The results of this analysis made it possible to outline some critical elements in the striking of medical R&D cooperation, but also showed the gap that needed to be further explored.

For this end, the thesis focused on search for available knowledge and best practice from other institutions as well as from literature about the practices in striking medical R&D cooperation in similar R&D projects and the best practices suggested by the literature. Based on this knowledge, there was a step-by-step process outlined of the elements and steps that needs to be considered for striking collaboration. Many of the points discussed in literature were also complemented with sample materials (shown in annexes) from the previous projects and can be helpful in future projects. Thus equipped, the thesis proceeded to building a roadmap for striking future medical R&D cooperation projects for the case company.

As inputs for building the proposal, as stressed above, first, there were previous R&D projects analyzed that were carried out between the case company and the Helsinki university hospital (HUS); second, there were also inputs considered from best practice that and literature suggested for medical R&D and other similar research projects from different companies (Freenome and Deepmind) as well as from the European Union level. The proposal suggested the steps and elements to help bridge the gaps in a setup for a collaboration project. The final proposal included a roadmap of 15 steps that can support the process of striking medical R&D cooperation. In this thesis work topics such as patient consent, intellectual property rights, data ownership, data handling, data anonymization, funding management were studied and applied into the proposal as well as the different profiles roles and duties that every member of the project needs to be responsible of. Adding up to the proposal, there are complemented material and sample of the best clinical practices, framework agreement model, patient brochure, that can be used for future collaboration projects.

The results of the Thesis can help in future projects in order to speed up the process of defining the cooperation framework agreement and gathering documents that are required or needed for string a medial R&D collaboration (legal and practical documentation).

Keywords	Medical R&D collaboration, Aarificial intelligence, Machine learning, framework agreement, partners

Contents

Preface

Health technology is a new field in my professional development, Thus, have the opportunity to explore this area with fresh eyes is something that could be considered as an adventure. All my years of experience in IT brings a different vision and most probably also a different thinking of how collaboration research could be strike in medical R&D.

I would like to thank you the university that has gave me the opportunity to explore this new area and in particular to my teachers that have enlighten the path where I have been walking the past years as well as my thesis tutor that has helped me to bring this adventure into a new port where I could continue by myself. Special thanks to my family that has been supporting me to accomplish my personal goals.

Abstract

Strike collaboration refers to how to open up a collaboration project. This includes how to approach the parties and motivate them to collaborate with you.

1 Introduction

Medical diagnostics more and more relies in the use of AI (Artificial Intelligence). To introduce new IT tools for use in medical organizations, a lot of preliminary R&D work is needed. The researcher and developers need to collect and analyze a big amount of patient´s data which will be used to fine-tune the new IT tools. This data collection, or in certain cases, utilization of existing data, requires extensive collaboration with medical organizations that is in itself a significant challenge.

To build collaboration with medical organizations, the IT companies, especially the innovative IT star-ups need careful planning and a clear set of actions how to organize such a collaboration. This presents a challenge also for the case company of this thesis. This thesis is devoted to building a plan for collaboration in the area of Medical R&D for refining a new IT solution that will help doctors to make diagnostics easier, faster and more precise.

1.1 Business Context

The case company in this thesis is Top Data Science (TDS), a company focused on advanced data analytics, Artificial Intelligent (AI) and Machine Learning (ML) solutions. It was stablished in 2004 and acquired in October 2018 by Morpho Inc. TDS has developed an algorithm capable to analyze histopathological images (prostate area) and detect cancerous cells in it. The algorithm has been developed using AI principles.

TDS is one of the first companies in Finland researching the usage of AI to analyze histopathological images (prostatic area). The research has been carry out in collaboration with the Helsinki University Hospital (HUS). TDS as a pioneer in the prostate cancer detection using AI has the challenge of proving that histopathological images (prostate area) can be analyzed using artificial intelligent.

The pre-clinical test has been successfully carried out in collaboration with the Helsinki University Hospital (HUS) with a 95% approx. of accuracy detection. The current challenge for TDS is to find a new partner to deploy the system and carry out the medical trial.

1.2 Business Challenge, Objective and Outcome

The healthcare industry is one of the most difficult market to entry with new products. Before a medical equipment/device or software (medical software) is allowed to be launched to the market, it needs to fulfil several requirements (the requirements are determinated by the classification of the product). One of those requirement is the medical trial. To satisfy this requirement, TDS is seeking collaboration with clinics/hospitals where to validate the usage of artificial intelligent for prostate cancer detection.

According to the Directorate-General of the European commission (Eurostat), the standardized death rates among males (prostate cancer) aged <65 years was 2.6 in Europe (per 100000 inhabitants) and for males >65 was 191 (Eurostat, 2019). This numbers are relatively low compared with other diseases. Thus, there are so far no hospitals or research institutions focused 100% in prostate cancer detection. This is one of the challenges that TDS needs to overcome.

For conducting the required trial, the case company needs, first, to identify the hospitals with a urology department interested to cooperate in this medical trial. Another challenge is to commit the resources (human and equipment) for this trial. TDS is providing the access to the software but the hospital needs to have the urologist and pathologist doctors, a slide-scanner and some other IT infrastructure in order to be eligible for this medical trial. Additionally, the requirements for a collaboration project with hospitals is different depending of the country and/or institution. In other words, striking this type of complex collaboration with a hospital for this medical trial needs to be careful plan based on each case. Therefore, the objective of this thesis is *to propose a roadmap for striking collaboration in medical R&D solution in prostatic cancer.*

The outcome of this thesis is *a roadmap how to strike collaboration in Medical R&D solution*. To reach the objective, two main steps were needed in the study: first, this study needed to propose a strategy to contact a target medical institution/hospital; second, identify and prepare all the documents needed for collaboration (as standard as possible). And finally, to have a clear overall understanding how such collaboration can be established and developed.

1.3 Thesis Outline

The study was conducted using qualitative analysis methods. This means the analysis were built around gathering all the documentation used in previous projects and interviewing their participants, so that to build a roadmap for collaboration. As there is currently one pre-medical study done in collaboration with HUS, this knowledge was used to develop the basis of this thesis.

This Thesis is written is seven sections. Section 1 is the Introduction. Section 2 describes the method and material used to conduct this thesis. This section includes the description of data collation and data analysis methods. Section 3 contains the results of the current state analysis and learnings from the previous collaboration with HUS. The idea is to find common practices and gather all the lessons learnt that can be useful for future cases. Section 4 discusses the most relevant concepts form academic and business literature about building collaboration in medical R&D field for testing IT solutions. Section 5 presents the proposal for the roadmap for collaboration, based on the internal best practice (HUS project), and the experiences gained in previous projects with the best practices offered by the literature. Section 5 contains also a new project plan based on the experiences and best practice gained in previous projects, merged with the best practices suggested by the literature, and also co-created with the key stakeholders in the case company. Section 6 will contain validation of the proposed plan for striking collaboration in medic R&D for testing the new IT solution by the case company. Finally, Section 7 presents the discussion and conclusions form the study.

2 Method and Material

This section describes the research approach, research design, and data collection and analysis methods used in this Thesis.

2.1 Research Approach

The method used for this thesis is applied research and an explanatory approach. The idea is to describe in the best possible manner how to strike a collaboration with a medical institution based on the previous cases. There are some topics and/or areas which cannot be exposed due to a confidential agreement between the parties. However, in those cases the information is given on a high level and/or generic level. The idea is to provide enough level of information to allow a proper understanding of the topic.

The material used in this thesis is the documents and experience gathered along the projects. Some of the projects did end in a successful collaboration between the parties and some other due to external reasons were not able to conclude. However, the documents and information of them is used as a study and support material. It is important to highlight that there is no institution name mentioned when documents and or data are presented.

Another important source of material is the document analysis. Documents are different in numbers and nature, depending on the collaboration scenario with different organizations. Depending on how advanced the collaboration conversation was and/or the project moved forward with the different parties, the documentation is more extensive in the cases where it did end in a collaboration than the one that did not. However, there is some sort of documentation in any case to be analyzed. This led to base the research approach in data that already exist and can be analyzed. Thus, the qualitative research approach is the preferred one.

2.2 Research Design

The research design of this study is shown in Figure 1 below. Research diagram is a construct demonstrating the main steps in the study.

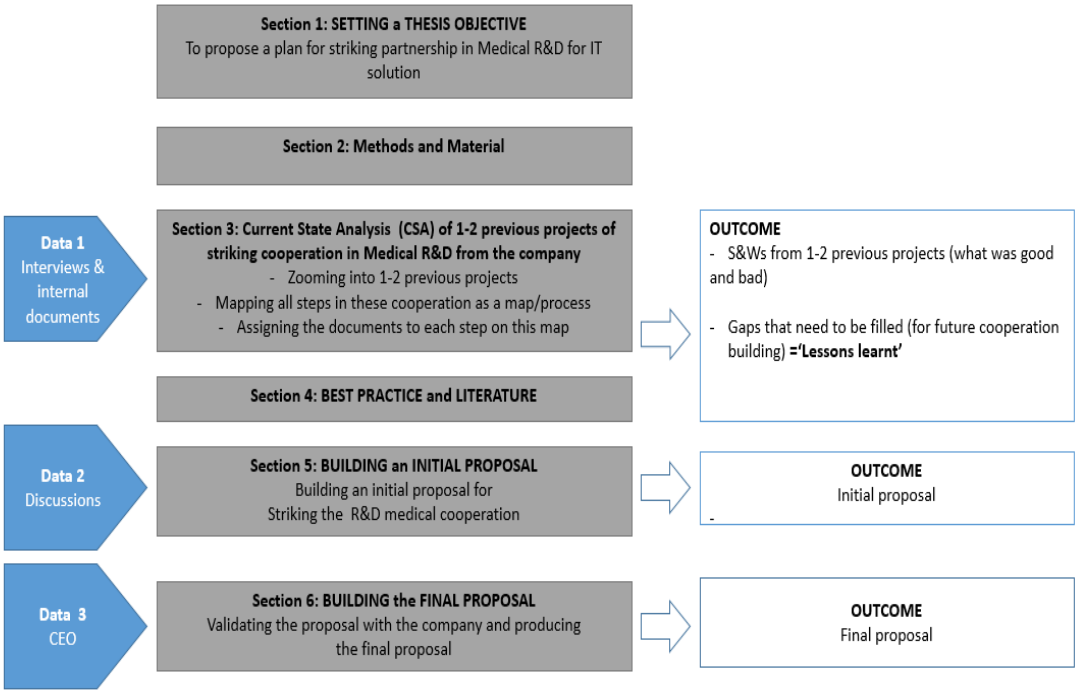

Figure 1. Research design of this study.

2.3 Data Collection and Analysis

There was a variety of data sources used in this study. Some of them are voice recording sessions (interviews), some others are based on documents utilized for the collaboration between the parties, some others are based on the experience and meetings outcomes where the writer of this thesis has participated.

The data has been collected in three different stages of the projects. Some of them are from very early pre-project face that not necessary ended in a collaboration and some of them have been collected after the project has been finalized.

Table 1. Details of interviews, meetings and discussions.

	Participants / role	**Data type**	**Topic, description**	**Date, length**	**Documented as**
	Data 1, for the Current state analysis (Section 3)				
1	Respondent 1: Timo, CEO of the company	5 face-to-face Interviews & discussions	The previous collaboration with HUS; targets for collaboration;	August - December 2018, 5 hours altogether	Field notes

2	Respondent 2: Oguzhan, CO-founder	Face-to-face Interview	The previous collaboration with HUS; targets for collaboration;	Aug. 2018, 45min	Field notes and recording
3	Respondent 3: Francisco, development lead	6 online meetings	How to strive the collaboration and the resources and materials needed	March 2019, 45min each	Meetings memos
4	Respondent 4: Doctor HUS	Face-to-face and online meetings	Participant of the first collaboration done	March 2020, 40min each	Field notes and recording

Table 1 above shows the data sources used for this study.

The sources of the current state analysis are a mix of interviews, face-to-face meetings and also documentation gathered along this project.

In Data collection 1, the current analysis started with face-to-face meetings. The aim of that meeting was to get familiar with TDS and also to have a global view of the artificial intelligent project. It was crucial to understand how the idea of a research in the prostate cancer kept the attention of TDS and how the approach towards HUS was handled. These interviews also inlcuded interviews inside the organization. The idea was to interview two different roles inside the TDS to have different point of views on the same project. One from the technical point of view (interviewing somebody who has participated coding the application) and another from the business side (CEO). Having different views helped to understand how future projects may affect the system. The third part of the current state analysis was to gather documentation created for this project. This included mail communications, agreements between the parties, etc. The aim of this step was to analyze all the project steps (in written form) and find some common standard documentation or any other information which could be useful for future projects.

All textual data was analysed using the Themathic/content analysis.

3 Current State Analysis

The current state analysis focused on exploring how successful collaboration was built with HUS in 2018. This project is used to learn from best practice available internally. The target for this analysis was to identify: (1) the key steps done by the company to approach the hospital; (2) the key documents used for striking collaboration; (3) the key activities by the company for building this collaboration.

3.1 Company Competences and Key Steps in Research Collaboration

TDS is a company of 30 employees from different nationalities. Mainly data scientists at TDS are graduates with their Master´s or PHD degrees in the IT field. TDS´s portfolio also includes others applications and services that are not connected to the topic of this thesis. However, the interviews carried out for this thesis has been done with the people who was connected directly to the HUS´s project research. On the organizational level, TDS structure does not have a very complex hierarchy level. In the top level of the organization, there are the CEO and the two co-cofounders. Right after them comes the data scientists. Due to the small size of the company, many other vital roles of the company are held within the co-founders and the CEO, as well as project workers.

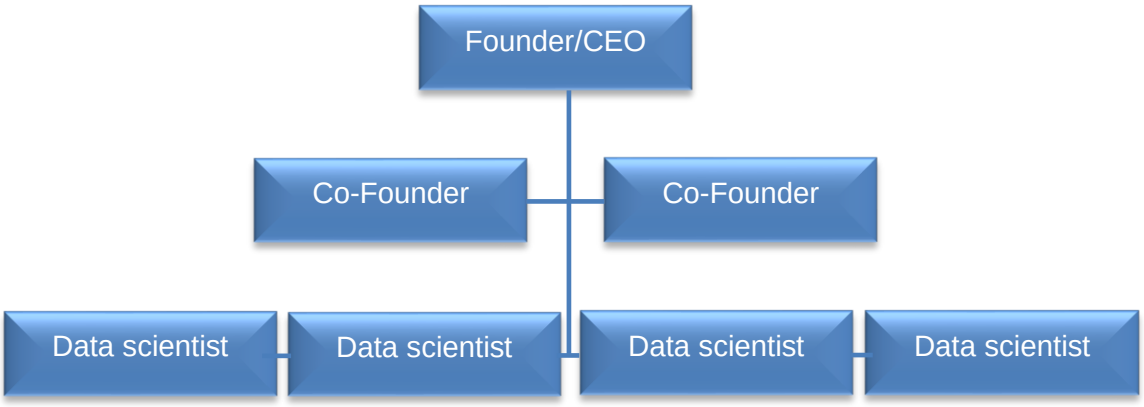

Figure 2. TDS organizational structure 2019.

TDS is one of the first companies (start-up) in Finland focused on image analysis using artificial intelligent. As one of the pioneers in this area, they have developed a system capable to identify and detect differences in pictures. They have applied this technology in different fields including the health care. In this area, they have been able to train an Artificial intelligent system to automatically detect anomalies in the skin´s tissues (the system requires annotated digital images to be train first). Once the system is trained, it is capable to not just identify the areas where possible cancerous cells are, it is also capable to assign a grade depending on how cancerous the cells are. The differences in the tissue cells assess with a grade, it indicates a possible cancer and the stage of it.

> "*TDS has implemented over 20 research and clinical projects by applying cutting-edge Computer Vision, Predictive Analytics and Natural Language Processing technologies* (TDS, 2021)".

The health technology area is a wide area and the image recognition system can be applied in many of them. Unfortunately, the rule of "one method serves all" does not apply in to the cancer cases and artificial intelligent. Thus, TDS focused in one specific body part to be able to achieve the best and most accurate results possible. The body part is the prostate. The main reason why TDS has focused in the prostate area is that at the time when the Artificial intelligent system was in a well advance development phase, the Helsinki university hospital (HUS) oncological research group were looking for a partner to cooperate in this area. The result of the research has been published under the name: *Detection and local histological staging of prostate cancer foci in H&E whole slide images using convolutional neural networks* (C. Stürenberg, 2019)

Cancer is fundamentally a genome disease where genes mutate. Cancer is caused by mutations in normal cells that allow them to bypass normal biological controls and utilise normal cell characteristics in unusual ways. The term "cancer" refers to a group of disorders, all of which share common characteristics such as alterations in normal cell behaviour and a lack of biological regulators (Figure 2). All cancers share the same characteristics: cells divide incessantly, with no natural control on cell proliferation. The new cells invade, disrupt, and destroy surrounding local tissues without respect for biological order or organization. These new cells can travel to the other parts of the body (metastasize) using the blood and lymph vascular system. Figure 3 below summarizes the cancer definition.

Box 1.3 The Defining Characteristics of Cancer

1. *Uncontrolled cell division*
   - Rapid expansion of the cancer cell population
2. *Invasion and destruction of surrounding normal tissues*
   - Disregard for normal tissue architecture
3. *Colonization of distant body sites with repetition of 1 and 2*
   - Metastasis through the blood and lymph systems
   - Survival in a foreign environment
   - Continuation of division and invasion without control

Figure 3. Cancer definition (Compton, 2021).

The time it takes for cancer to progress from initiation to carcinoma in situ (CIS) and then to cancer varies by the nature of the cancer and the part of the body where it locates. The figure below shows the different stages and average time of the cancer progresiong. It is important to highlight that as early as the cell mutation is detected as higger are the probability of clinical intervention and to be cure.

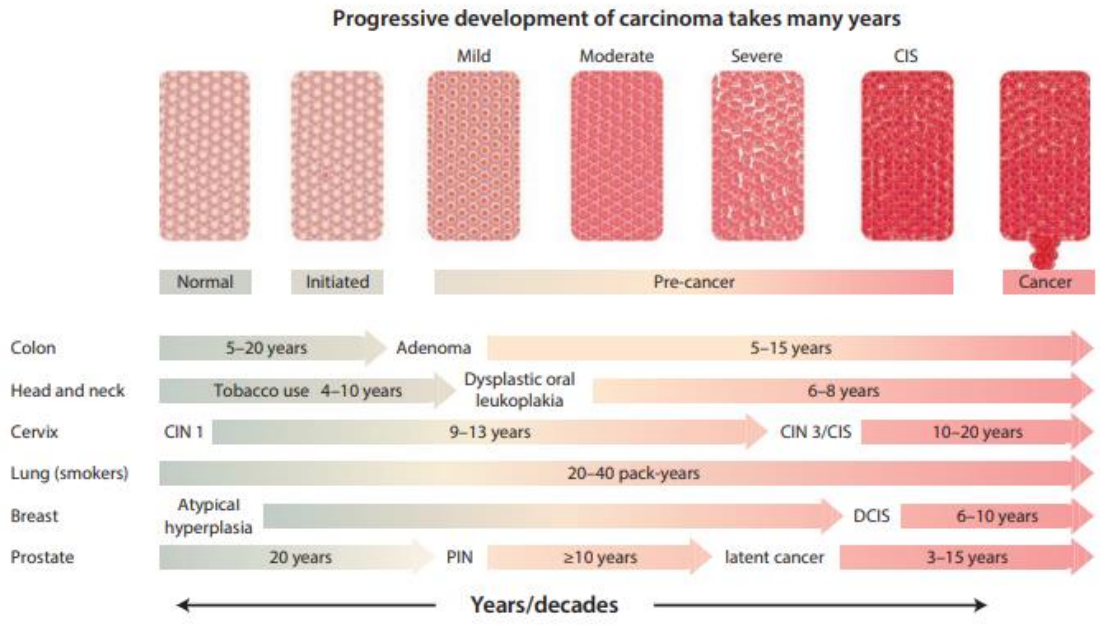

Figure 4. Progressive development of carcinoma in different part of the body.

Prostate cancer is on of the most frequently cancer diagnosed among men in the world. The cause of Prostate cancer is unknown. However, it has been identified that hormones are closly connected to it. There are also some substances that increase the risk of some canceres including prostate cancer like Beta-carotene; vitamin E; selenium and folate.

In 2016, about 65 200 men died from malignant neoplasm of the prostate (prostate cancer) in the EU (Eurostat, 2020). According the international agency for research on cancer, the new cases for prostate cancer estimations for 2020 in the world is 1.414.259 (Cancer, 2020).

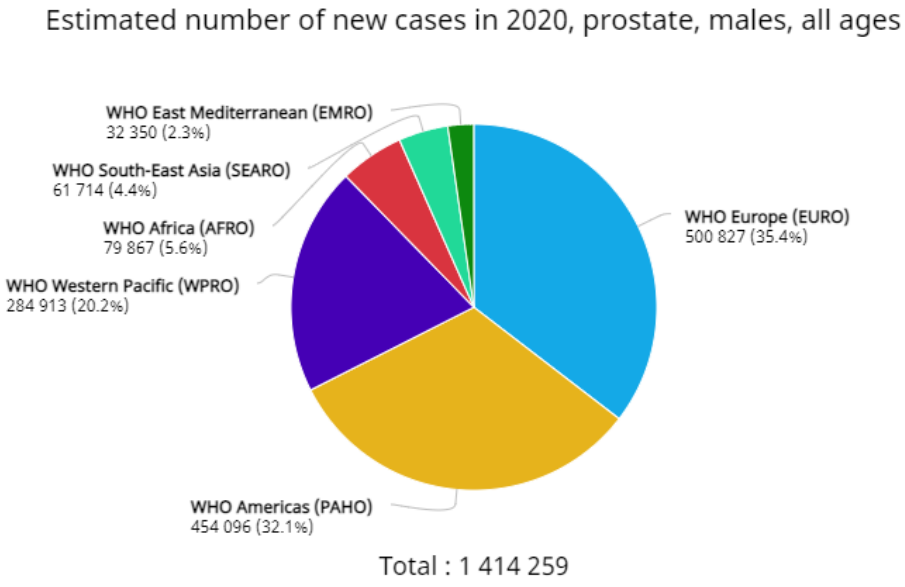

Figure 5. Estimations of the new prostate cancer by region (Cancer, 2020).

The International Agency for Research on Cancer has also estimated the mortality of men due to prostate cancer in the world (Cancer, 2020). Figure 6 below shows the estimation of deaths in 2020 due to Prostate cancer among men.

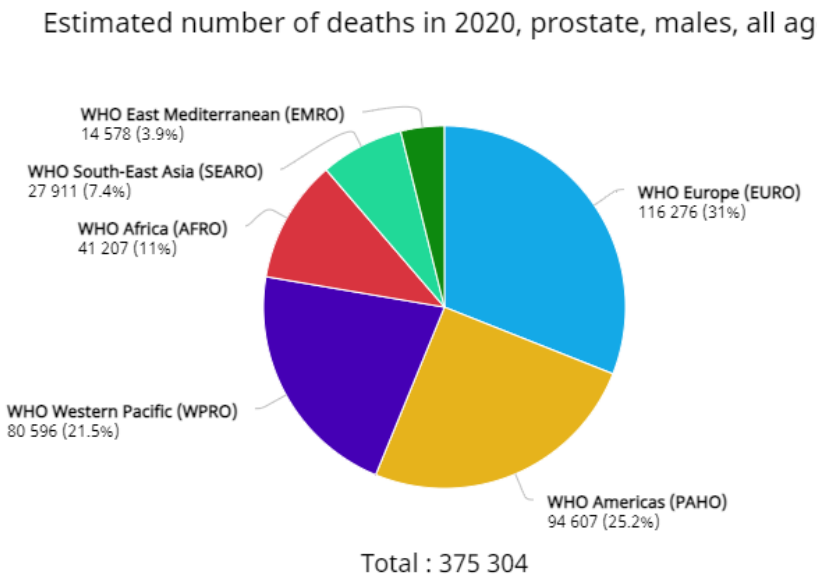

Figure 6. Estimation of deaths in 2020 due to Prostate cancer (Cancer, 2020).

Analyzing the Finnish case of prostatic cancer, the estimation is 5710 cases by 2020 and the death rate is 4.4 %, which is equivalent to 914 cases (Figure 6 and Figure 7).

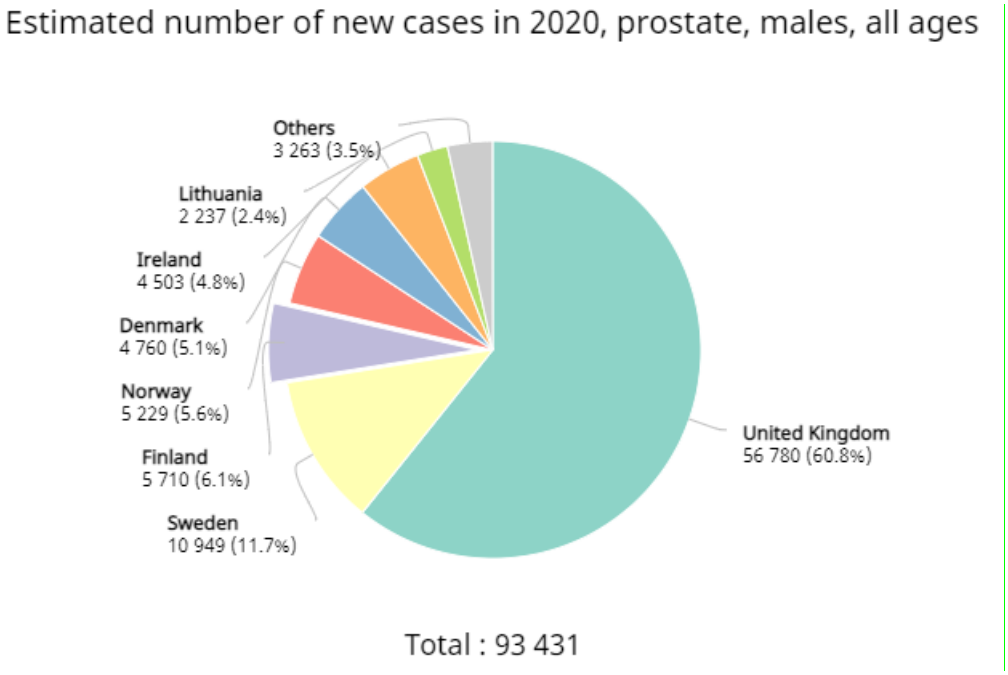

Figure 7. Estimated new prostate cases in 2020 (Cancer, 2020).

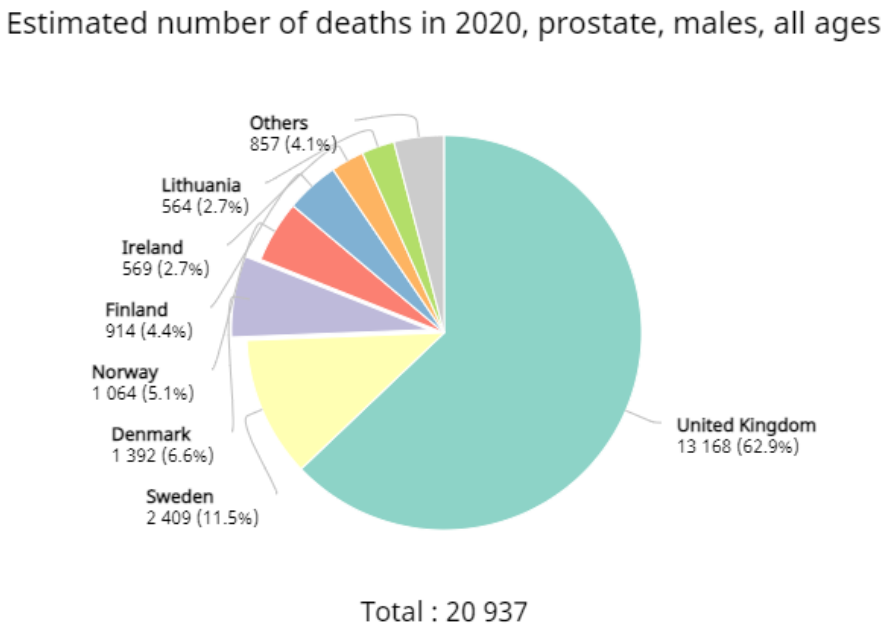

Figure 8. Estimated numbers of deadths due to prostate cancer by 2020 (Cancer, 2020).

As summary, it can identify the prostate cancer is an illness that keeps growing on a yearly basis. New technologies such as Machine learning applied in the healthcare area can speed up the process of cancer detections. TDS has developed and tested a machine learning system capable to support health professionals in the decision making. Machine learning as well as AI is one of their key competences.

3.1.1 AI Technology challenges: Training the system and open resources

One of the key components of any Artificial intelligent system is the capacity to learn from previous cases and use them for self-learning (Machine learning). Therefore, data is the most important component of any Artificial intelligent system, if not, at least it is one of the most crucial one. An artificial intelligent system without data or very limited amount of it, most probably it will not be able to provide reliable results. On the other hand, having a lot of data does not guaranty good results. For example, if we have a good amount of data but it has been manipulated to not be accurate, the artificial intelligent system will learn from it and as result of this, there is a high probability that any conclusion or result provided by the Artificial intelligent system will be wrong. Thus, quality data from a trusted source is a must when developing an Artificial intelligent system.

One of the challenges that TDS had during the project with the University of Helsinki was the access to the data to train the system (images). There is a very strict regulation in Europe regarding data privacy (GDPR). The general data protection regulation (GDPR) state in Article 1.

> "*This Regulation lays down rules relating to the protection of natural persons with regard to the processing of personal data and rules relating to the free movement of personal data"* (Intersoft, 2016).
>
> *"This Regulation protects fundamental rights and freedoms of natural persons and in particular their right to the protection of personal data"* (Intersoft, 2016).
>
> *"The free movement of personal data within the Union shall be neither restricted nor prohibited for reasons connected with the protection of natural persons with regard to the processing of personal data"* (Intersoft, 2016).

Due to this regulation, the datasets from the hospital of Helsinki, could not be just shared with third parties without the consent of the patients. The datasets meant to be used in this research project was historical data (data that has been collected already in the past for the hospital of Helsinki) and new data. It was possible to obtain the patient´s consent for the new data. However, the amount of this dataset was limited. Thus, the usage of historical data to train the artificial intelligent system was required. The research project had certain time line and it was crucial for the project to train the system with any other dataset available.

After some research, TDS found that there are some public datasets available to be use for research purposes. This is how the training of the Artificial intelligent started. As part of the project, the need to allocate more resources with the relevant competences and experience was needed.

> *"When I joined TDS the project was on-going and they have had study the topic for a while. I joined the project. If I am not mistaken this original idea came from the Helsinki hospital. They were interesting to find, detect and classify more precisely cancer in the prostate."* Oguzhan, CO-founder.

For the case company, the usage of the public datasets provided the oportunity to start developing the algoritm with real data. As the datasets where public, there is always a level of uncertenty about the quality of it. However, this datasets provided the first gleams of the potential of the algoritm as well as prove that the concept and technology used for this first development were suitable for the research. The level of accuracy of the system after the first trial with the public dataset was promising enought to keep developing the algoritm with real data. It allowed the case company to start their project in medial AI application.

3.1.2 Data anonymization

Since May 2018 when the GDPR was put in effect,

> *the new regulation imposes obligations onto organizations anywhere, so long as they target or collect data related to people in the EU. The GDPR will levy harsh fines against those who violate its privacy and security standards, with penalties reaching into the tens of millions of euros* (EU, 2021).

In the healthcare sector, images like magnetic resonances images (MRI) or computer tomography (CT scan) contain personal data. Some of this personal data can be: names, social security number, age, etc. along with some other medical information. The GDPR explicitly mention in Article 5 “Principles relating to processing of personal data” (EU, 2018) how the information needs to be handled in order to protect the patients and their private information. If there is any data breach, the patient needs to be informed and possible fines may be applied. There have been cases in Denmark for example where a Danish taxi service has been fine due to the uncompliant of the Art.5 of the GDPR (EU, 2019). Thus, Anonymize the patient data was mandatory in order to be able to share and utilize it for this research project. Figure 2 shows an overall number of fine by month due to GDPR uncompliant.

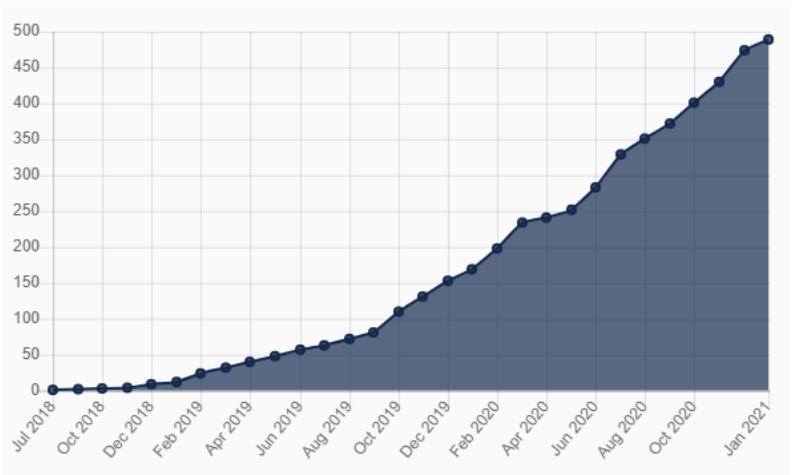

Figure 9. Accumulative numbers of fine in Europe since the GDPR has been in place (tracker, 2021).

The datasets meant to be used for this research project, contained patient information that is protected under the GDPR. Therefore, using a third-party application, the datasets were anonymized in order to be compliant with the GDPR. The datasets anonymization was in the level that it was impossible for TDS to identify from whom the images belonged to.

However, a code was given to each dataset for validation purpose (with this code, HUS was able to track to whom the data belonged to). The validation process consisted in a comparison of the predictions of the system against the annotated data from the pathologists. The validation process with the pathologist was mandatory in order to have some level of confidence on the system as well as adjust it accordingly to achieve the highest accuracy possible.

3.1.3 Images annotation

MRI and CT images is a technology used for create images of the body. There are several differences between MRI and CT images. One of them is the quality of the images. However, both technologies can be use to identify prostate cancer among other pathologies and disease. The result of an MRI or CT scan is basically a picture that can be used for healthcare professional to diagnostic something. Without the interpretation and assessment of a qualified professional, the images do not provide much information in the majority of the cases. Thus, just images without any annotations cannot be used to train an artificial intelligent system.

> *Getting the data has been a long journey. We have to make sure that the annotations are done properly. Even though that is not TDS responsibility we have to support them explaining how we will teach the algorithm so the system can understand the annotation without mistakes. This preparation of data is very complex and we need to ensure that this part goes very smooth. Once we are confident that we have the right data we have the resources and the capabilities to train the system*. Oguzhan, CO-founder.

The project between TDS and the hospital of the university of Helsinki had among the professionals a team of pathologist. They were in charge of annotate the MRI or CT scan pictures to be use to train the system. The Figures 3 and 4 shows a real image used for this study before and after the annotations. It is important the mention that the images are very high resolution. However, the resolution has been adjusted (lowered) for this document. Figure 10 shows an example of a digital image used for the research project without any annotations.

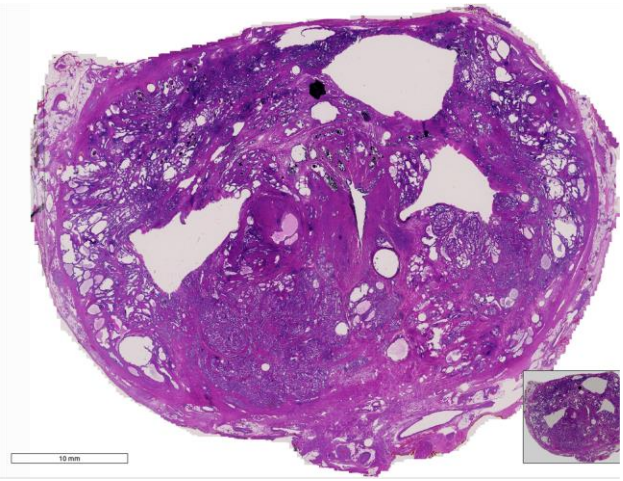

Figure 10. Digital example of an image used for the research project without any annotations.

In contrust, Figure 11 shows an example of a digital image used for the research project with an annotations.

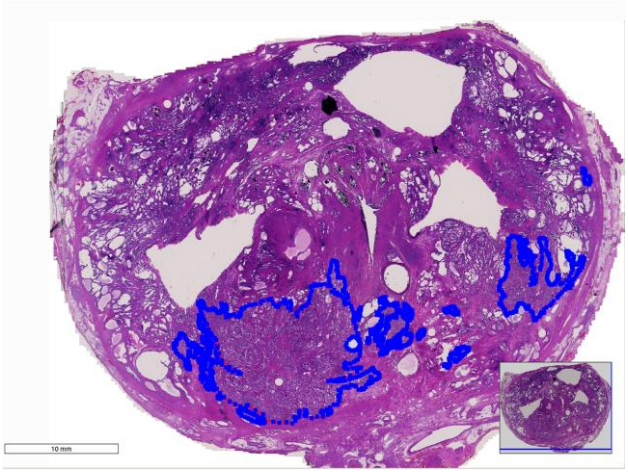

Figure 11. Digital example of an image used for train the artificial intelligent system with annotations.

A well trained artificial intelligent system can have an error rate lower than humans. There have been several studies about the usage of the Artificial intelligent for image recognition and compare those results with the same task performed by a person.

Figure 12 below shows a graph from an article call “A Roadmap for Foundational Research on Artificial Intelligence in Medical Imaging: From the 2018 NIH/RSNA/ACR/The Academy Workshop“ showing the error rates of humans and also the advantages of using image recognition systems, compared to the humar error.

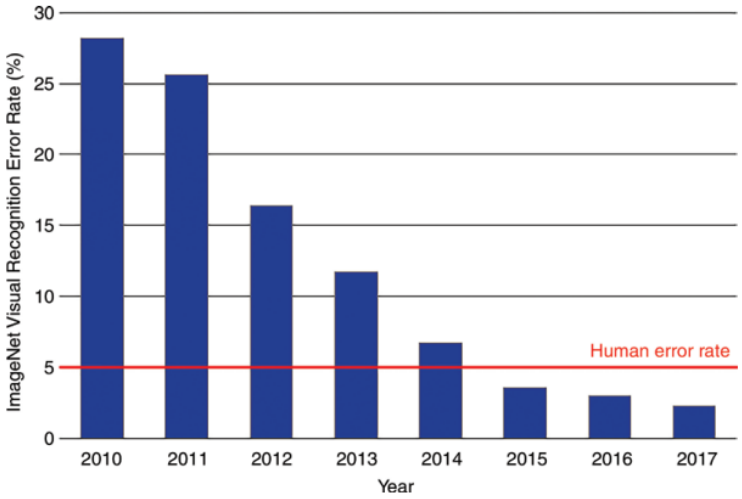

Figure 12. Error rates on the ImageNet Large-Scale Visual Recognition Challenge (C. P Langlotz, 2019).

As can be seen from Figure 12, accuracy dramatically improved with the introduction of deep learning in 2012 and continued to improve thereafter. Humans perform with an error rate of approximately 5%. (C. P Langlotz, 2019)

3.1.4 Key Steps in Striking Research Collaboration

The up-to-date experience of the case company shows that collaboration with health institution for research are not simply to strike. Based on the case company's experience, there could be several reasons for this. One of the reasons is the complexity and the number of requirements that the health institutions demand before any collaboration. In addition to that, there may be some interactions or feedback required from the patient´s side. This also requires some minimum awareness towards the patient about the investigation and what could be the possible impact to him/her in the investigation. In addition to the points mentioned above. There is a general lack of doctors/specialist in the health sector. In Finland the number of doctors per 10.000 habitants is 46,4 (Organization, 2021) the case is more drastically in other European countries like Poland where in 2017 (latest data available) there are 23,79 doctors per 10.000 habitants (Organization, 2021). Figure 13 present a graph with the number of doctors per 10.000 habitants in Europe.

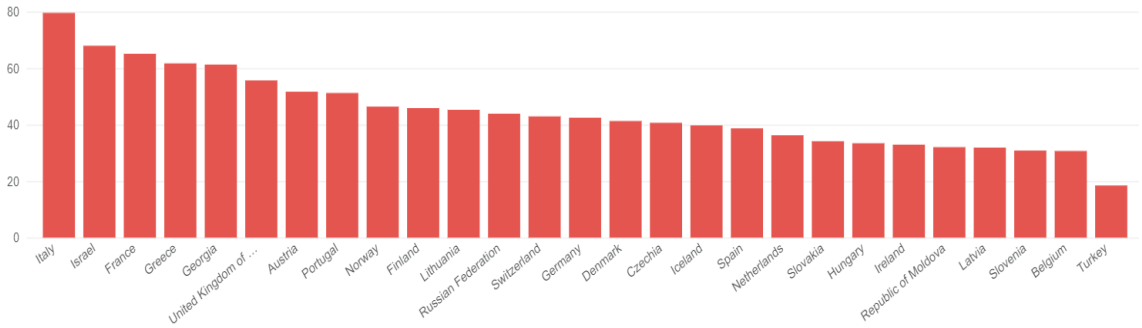

Figure 13. Number of medical doctors in Europe 2017 (per 10.000 habitants) (Organization, 2021).

For this thesis, there has been identified three main scenarios of collaboration that so far were experienced in the case company. All of them were based on own experience and the different approaches that were so far used to strike a collaboration. However, these approaches have not led to the development of actual, long-term collaboration due to different reasons. Based on the experience of the case company over the time span of 1 years (from September 2018 until September 2019), these scenarios include:

Strike collaboration, Scenario A

The first scenario identified is when the research project brings benefits to both parties. This is most likely to happen when the health institution has a research and development interest. This scenario starts with the first contact point that presents the research project as well as the benefits of joining it. Another important fact to have in consideration are the funds. Not all the institutions have a defined fund for researches. Some of them get the funds based on the importance of the project for them. Based on the health institution´s contacted for this trial (6 different institutions), 2 of them had a research area where this project could be suitable for them.

Strike collaboration, Scenario B

Not all of medical institutions have a research area where they investigate new technologies or develop new treatments. Thus, to strike a collaboration with those institutions, it requires to book a meeting directly from a doctor or specialist to present the project. As the project requires resources and time and often doctors do not have the time neither enough human resource, the interest decrease. Thus, they prefer to focus on something more meaningful for them or for the patients (trials not a warranty of any success, especially in complex long-term projects). Therefore, any collaboration with a health institution that does not have a research program or area is very unlikely to happen.

Based on the experience of the case company, 5 different institutions fell into this category (from different part of the world) that were contacted for this research project. As a general summary, the collaboration with health institutions in this scenario failed due to extremely demanding and complex nature of the proposed project and thus, collaboration.

Strike collaboration, Scenario C

The health sector is a very traditional sector where new technologies need to be thoroughly tested before been accepted and approved to be use in the health sector. Machine learning is also something relatively new compared with other technologies but definitely it is something very new in the healthcare sector. This may be seen as something positive and keep the interests of health institutions to strike a collaboration with such an innovative partner.

The challenges identified in this scenario was that the institution was willing to cooperate as well as have a research area and the doctors also interested in the project. However, the minimum equipment needed for the collaboration was missing. However, the funds for the equipment were budgeted and the order was placed few months after. This was the case in 1 institution that the collaboration almost succeeds. Due to external factors (not related to any of the 2 parties), this collaboration could not continue.

Summing up, Figure 14 below represents the step-by-step process of how the collaboration was (almost) successfully stroked with one of health institutions mentioned in Scenario C. The same procedure was attempted to be use for all the three scenarios. However, not all the steps were reached due to different reason or just lack of interest from the health institutions.

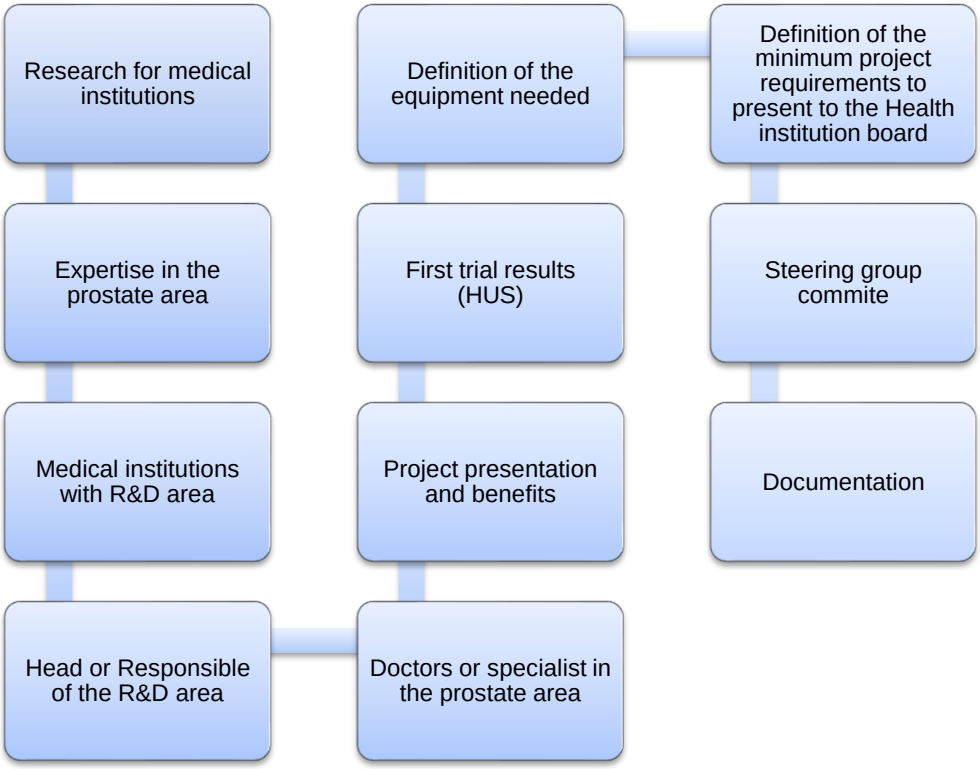

Figure 14. A step-by-step process used to strike a collaboration with a health institution by the case company of this thesis.

The first step was to find a medical institution, after the first step was done, TDS moved onto the particular area where their expertise could be a good match for the collaboration project (prostate cancer). The third step was to investigate if they have an R&D area and look for the person in charge of it as well as engage other professional from the same institution. The company proposal and the result of the first trial (HUS) were presented

in the first meeting. As the party was interested after the presentation, TDS started defining the minimum equipment needed for the collaboration to continue afterwards with the presentation of the project to the health institution board. The Steering group commit and final documentation/result of the collaboration covers all the steps identified.

Next, the documents used for and within collaboration are discussed.

3.2 Key Documents Used for Striking Collaboration

The recommendation or requirements to strike a collaboration with a health institution, are well defined and documented by the European union. However, this recomdations are applicable in Europe and not all over the world. However, Those recommendations can also by utilize as bases for project outside of europe. The key documents used for striking collaboration are mentioned below. This documents cover areas like protocol compliance, quality management, financing, trial design assesment of safty to mention some.

Based on the experience of the case compnay, which used most of these documents recommended by EU in this project, not all of them were actually needed/ required. The types of documents needed for research collaboration are dicussed below.

3.2.1 Research collaboration agreement

A research project in medical R&D requires, first of all, *a collaboration agreement* between the parties to carry out reseerch, observations or tests. This agreement defines the bases, guidelines as well as the accountable parties of the different parts of the research project. There are different elements that need to be consider for a research project. Depending of the nature of it, these requirements maybe simple or complex. Often, in the health care area there is also the need to have the patient consent in order to do researches about specific diseases.

The research collaboration agreement between TDS and the Helsinki university hospital, has in consideration many points that are relevant for any other research collaboration with any health care institution

Parties definition

The party's definition is where the institutions provide the general information about them. Information like: name of the company, address, Company ID, Contact information of the principal investigator of the project, and general terms about the research project.

Background and objects

The background is the part where the parties describe in high level their competences and how those competences are relevant for the research project. The objectives are also defined here in a high level. In the case of the collaboration between TDS and Helsinki university hospital, there are appendixes where the detailed objectives are defined as well as the milestones of the research project.

Definitions

All the key terms that will be use for the project and should be understood for both parties in the same manner. Terms like: Confidential information, direct exploitation, intellectual property rights, personal data, processing of personal data, research purposes, etc. have to have a definition and common understanding for the parties.

Obligations of the parties

Here is where the responsibility for the project is defined, as well as the different activities´ responsible. It is common that in this chapter there is a reference to the appendix where the full project plan is as well as each activity with the name of the responsible (company name). Data storage, data handling and reporting schedules are also defined under the obligations of the parties.

Results and Rights

Any project needs to deliver some results and/or improvements. In the health technology area this is not the exception. In this chapter is where we defined who owns the results (and for how long in case of exclusivity). For what purposes the results can be used for (commercial purposes, investigation purposes, etc.) as well as the Intellectual property rights (IPR) of the system development.

Confidentiality

The parties commonly agree about the confidentially of the project along the different phases of the it as well as the consequences in case of any disclose.

Costs

The total budget for the research project as well as any funding and the period of it.

Termination

Detailed description of in what scenarios the agreement may be terminated before the end of the project. For example, Data breaches, code of conduct, legal issues, etc. The termination noticed period is also consider in this chapter

Patient consent

In the healthcare area as well as other areas, sharing patient information without their consent is not allowed and they are protected under the general data protection regulation. In case of a research or study that may requires some data from them, the patient needs to be informed about what personal data will be use and for what purposes will be used for as well as other details like aims of the research, methods to be utilized, sources of funding (if there is any), 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. There is a guideline published by the world medical association called ”Declaration of Helsinki – Ethical Ethical principles for Medical research involving human subjects” (WMA, 2018). In the preamble of the document it state:

> *The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involcing human subjects, including research on identifiable human material and data.*
> Preamble WMA Declaration of Helsinki

According a research study made by European journal of anesthesiology (From the Department of Anaesthesiology and Pain Medicine, 2015) out of 24 hospitals in Europe, 23 of them had some level of patient consent written or oral.

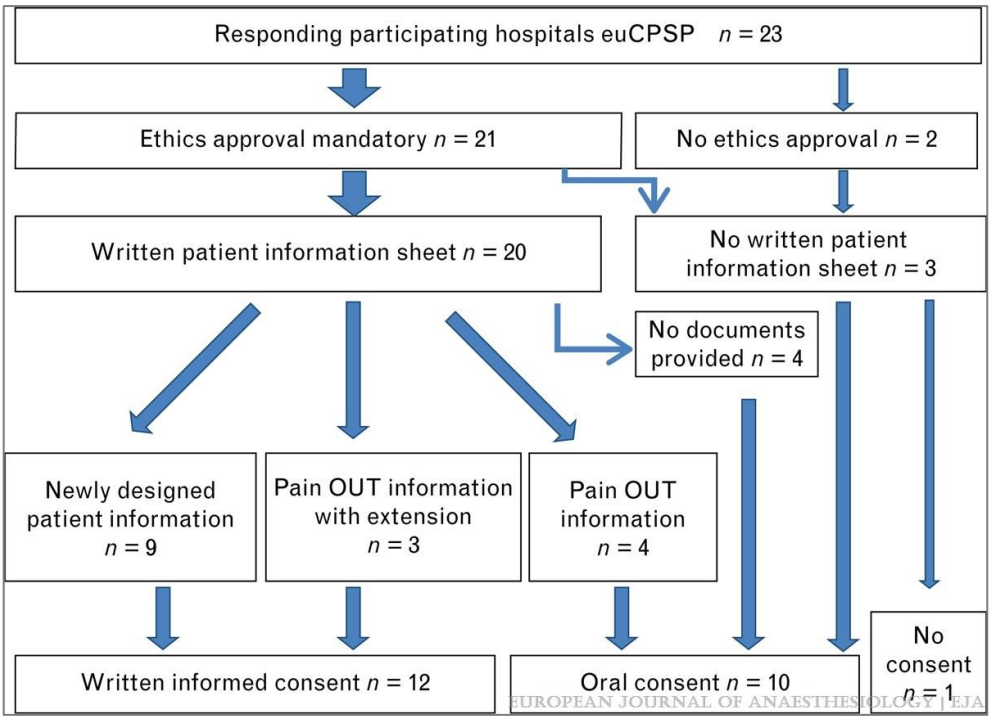

Figure 15. Flow chart of responding hospitals participating in the European observational study on chronic postsurgical pain and their procedures for patient information and consent. (Source: Ethical procedures and patient consent differ in Europe (From the Department of Anaesthesiology and Pain Medicine, 2015).

The Declaration of Helsinki has also a particular segment about Research ethics committees where its states:

> *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.* WMA Declaration of Helsinki

As a good practice, the recommendation of the world medical association (WMA) in the declaration of Helsinki, it is a good document to be study and understood properly before any research investigation collaboration stars. The document provides clear guidance as well as a strong bases of all the different topics that needs to be tackle and covered during a research in the health area that involves human subjects. However, it needs to be adjusted according to every particular research (WMA provides the guidelines). Thus, every project research which involves human subjects should use them as base and merch it with other guidelines from different technologies that maybe involved along the research project to fulfill the project needs.

3.3 Key Factors to Build Collaboration

This section describes the key activities that allowed TDS to have a successful collaboration project with Helsinki university hospital (Scenario C). The key activities may varies depending of the person and the level of engagement for the research project. Thus, the following one are the most relevant and crucial based on my experience and engagement in the project.

3.3.1 Experience and knowledge

Nowadays there is a wide range of companies that have an AI system in their portfolio. Thus, find a partner who can develop or adapt their AI system to fulfill any needs may not be so complicated. However, when the applicable field of this system is in the healthcare sector, the challenges are more complex.

First of all, the amount of healthcare institutions is very limited compared with other sectors. Therefore opportunities to investigate and collect data is also limited. Second, the healthcare sector is a very classic sector were introducing new technologies or methods may not be easily welcomed. Third, depending of the research, manage patient

data and get the permission to use human samples requires many different authorizations from the healthcare institution as well as from the patients.

In the TDS case, the company had already (before the collaboration with the Helsinki university hospital) made some studies about the usage of AI to detect prostate cancer. This was one of the key factors for the collaboration.

3.3.2 Focused area in the usage of AI in different fields

One of the main focus areas of TDS is the image recognition using AI. Different research projects have been carried out in the healthcare sector as well as other sectors. This was a big advantage at the time when the project was presented to HUS. TDS had the experience already of image recognition and also in the healthcare sector.

3.3.3 HUS research field

HUS was interested in a partner who could develop an AI system capable to detect and also classify cancerous cells in the body. One of the main researchers from HUS, was a pathologist interested in prostate cancer the same area where TDS has had already some studies about it.

For example, in the research collaboration project with HUS, all the medical knowledge as well as the medical equipment and healthcare professional were provided by HUS. On the other side, we have TDS providing all the IT infrastructure as well as the algorithm and the data scientist that could make possible to process and analysis of the data (digital images). Commitment and effort are some of the key requirements that may lead into a successful and long-term collaboration. As short summary of what are the minimum requirement for a collaboration we have:

- A commitment to mutual relationships and goals
- A jointly developed structure and shared responsibility
- Mutual authority and accountability for success
- Sharing of resources and rewards.

3.4 Key Findings from the Current State Analysis

Prostate cancer is one of the most common cancers among males. According the World Health Organization the prostate cancer will keep increasing in the upcoming years in Europe (Figure 15).

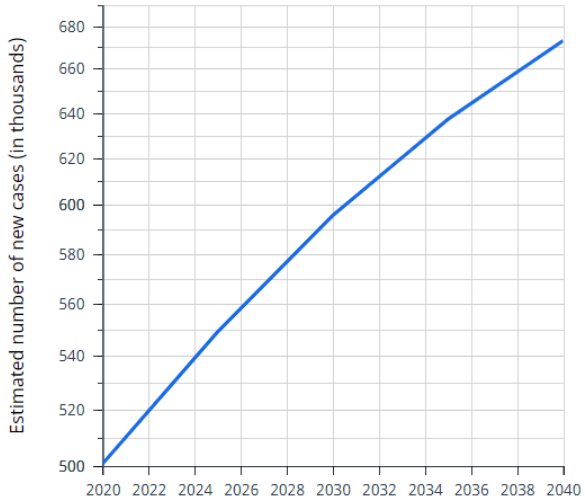

Figure 16. Estimated number of new cases from 2020 to 2040, Males, age [0-85+] (WHO, 2021).

The fact that most of males will have the need to be checked for anomalies in the prostate area proves that an automated and smart system (Machine learning) capable to support doctors or pathologies in the decision making could bring significant new benefits in this area. A machine learning system could potentially speed up the process of image analysis as well as reduce the time of the pathologies to make the annotations in the images and further analysis of them. Another benefit of a machine learning system and one of the most important is that there is unlimited capacity to learn, remember and recognize patterns. Thus, it could be more accurate than a human eye (this assumption is based on high data quality and large amount of data). On the opposite side, we have that the Machine learning requires data to learn. This data is provided by doctors or pathologists (images with annotations). If the data used for train the system is not correct or accurate, the result of the information coming out from the system will not be accurate neither. Therefore, Data verification (annotations in the images) by more than one doctor or pathologist is critical in order to have a machine learning application that could be trusted. It is important to mention that a machine learning application is a support tool for healthcare professionals. It is not an application that is intended to replace doctors or pathologies.

For the case company, the collaboration in this research project with HUS was an opportunity to validate the usage of this technology (Machine learning) into the health sector. The research program and interest from a doctor specialist in this area was a big advantage to make the collaboration to move forward. There were several challenges along the way. Especially in the documents required by HUS to have a common ground to start cooperating. The documentation part took several months before it was ready to start the collaboration.

Another key point is the collaboration with HUS was the definition of the image quality as well as the size of the slices (tissue samples). In order to have a proper research project that protocol was well defined (this definition was mutually agreed with the healthcare professional and the data scientists), the aim of this was to avoid having samples that have been process in a different manner. Thus, reduce the risk of misinformation or lack of it due to not having a protocol to follow.

Importantly, image annotations is fundament in order to succeed training a machine learning system, this needs to be as precise as possible and if it is possible to be reviewed by at least two different doctors or pathologist (ideally). This will secure the data quality that is use to train the system. The procedure for these annotations requires to be independent from each doctor or pathologist. This means at least two different doctors or pathologists (ideally) will make the annotations in two identical copies of the images and then those will be merge into one.

An early development of the machine learning algorithm helped to speed up the development process. The first internal trial was made using open-source datasets. The amount of data contained in those datasets was not big but it was enough to start working in the algorithm that could recognize images and the difference in tissues.

3.4.1 Strengths and Weaknesses of HUS Collaboration, Scenario C

There are several strengths that helped to carry out this research project with HUS. One of the main strengths of this project was the “know how knowledge”. TDS was working in the image recognition as well as Machine learning for some time before this research project with HUS started. Thus, once the project was introduced, the bases were already in place and there was no need to start from the scratches. Another strength was the expertise and experience of the people participating in this project. From the HUS side

a research doctor with a best experience in the research and also clinical field. From the TDS side a PhD professional who has done his doctoral thesis in machine learning and has published many articles about the usage of machine learning in the health sector for cancer detection. Due to the number of resources needed to carry out this project (mainly from the HUS side), having the funds needed for the research was very fundamental for the collaboration. The perseverance and enthusiasm from both parties was also one of the key strengths of this project. The documentation part took very long time before the collaboration could start. However, both parties kept the energy and enthusiasm high to make it happen.

On the opposite side, the weakness that delayed the project was mainly related to the documents required to start the collaboration as well as the legal part for this project, intellectual property rights, ownership of the data and how it needs to be manipulated, how and where the fundings will be used, who can publish the results of the research, among other topics, were some of the questions that needed to be addressed, agreed and stated in formal documents before the collaboration could start. Those documents need to be reviewed and approved by the committee and board of the project as well as legal representants. Although the documents required by HUS where somehow common in the health sector research area, the approval and validation of them was complex, time consuming and overall, a long process.

Figure 17 below summarizes the strengths and weaknesses that played a role in striking collaboration with HUS, Scenario C.

Strengths	Weaknesses
1. Unique AI and IT competences in this area	
2. Successful previous experience in similar projects	1. Legal documentation agreement (1/3) (including ownership of the **data** and how it needs to be manipulated)
3. Resources and R&D program (HUS) secured	2. Legal documentation agreement (2/3) (including **intellectual property rights**, who can publish the results of the research)
4. Funds for the project	3. Legal documentation agreement (3/3) (including how and where **the funding** will be used)

Figure 17. Summary of the strengths and weaknesses identified in the HUS collaboration, Scenario C.

Summing up, the research collaboration with HUS, Scenario C, makes a good example of a collaboration between two parties working in different industries (HUS medical sector and TDS in the IT sector) that joined effort together to develop a trial solution to improve, support and validate the usage of new machine learning in the field of cancer detections.

Nowadays we see more and more IT industries cooperating in the health sector. This collaboration (as first experience) may be very complex and difficult to achieve for companies that are not familiar with the way of health sector works or how research projects are carried out in this area. The complexity of these collaboration comes from all the regulations, global recommendations and internal polices of the health institution. The experience gained with HUS and another health institution in South America have provide us some valuable insights that can be fruitful for future collaboration.

The 3 weaknesses identified based on the experience of the case company in successful Scenario 3 will be targeted next, so that to find best practice and suggestions from existing knowledge and literature in order to tackle them better in the next project collaboration.

4 Existing Knowledge and Best Practice in Healthcare Research Collaboration

This section is focused on how collaboration between multidisciplinary partners and the benefits of having a multidisciplinary team, in order to achieve results in striking medical R/D collaboration. The section is based on academic and business literature, regulatory documents, cases and the best practices in this area. Some examples of successful collaboration are also provided as well as experiences gained throughout the research projects using machine learning to detected anomalies in the prostate area.

4.1 Research Collaboration

The usage of different technologies in various fields has changed the manner of collaborate. Technology used in a specific area is more specific to that area than generic. Due to complexity of different technologies in the IT field as well as in the health sector, the collaborations between these two areas requires some very specific knowledge. Thus, having a multidisciplinary collaboration team that merge both disciplines to carry out a research collaboration project is a must.

The definition for collaboration is ”*working together to create something new in support of a shared vision or objective”* (Hemmens, 2016). There are also other definitions which includes different concepts of collaboration including technology which are more complex like *“social processes whereby human beings pool their experience, knowledge and social skills with the objective of producing new knowledge, including knowledge as embedded in technology*” (B. Bozeman, 2014). This definition covers many other aspects that are fundamental in a collaboration like social skills, experience and knowledge. However, it is very much focused into human interaction as collaboration which may not be necessary the case for a collaboration.

There are also cases where the collaboration is based on the utilization of resources like IT infrastructure, data, etc. A clear example of infrastructure collaboration is the European High-Performance Computing Joint Undertaking (EuroHPC) where a super computer is shared and available to be use for institutions, scientist or research purpose (European commision, 2021).

Another example of collaboration is collaboration between universities that have built a network focused in collaboration among other universities. This is the case of the University of Pennsylvania that in 2014 hosted a meeting to discuss potential mechanisms of collaborations with several universities around the world (Germany, India, Barbados, Jamaica, Trinidad and Tobago, South Africa, Ghana). As conclusion of the meeting, it was established basic guidelines for working together, including a steering committee of 'champions' from each institution and two thematic priorities within the broader field of global health. This collaboration network has three pillars of collaboration: Research, Education and Capacity building. Each of these pillars is dependent on the others (Margaret S. Winchester, 2018)

In the European level, there are also similar initiatives on the European and government levels. The European Commission's Framework Programme (FP) constitutes an important share in R&D expenditures in Europe. For example, the Horizon 2020 is the biggest EU Research and Innovation programme ever launched, making nearly €80 billion of funding available over 7 years (2014 to 2020). In addition to financing science and technology development, one of the main objectives of the FP is to foster international collaboration among research organizations and private firms, both large and small (A. Pesole, 2016).

Research collaborations also varies on the interest of the institution. For example, universities are looking mainly for complementary resources that allow them to advance basic research. They are more motivated by the opportunity to build up new knowledge and technology capabilities and to investigate new research areas than they are by technology commercialisation. In contrast, small and medium enterprises (SME) have explicit goals related to innovation outputs such as developing a prototype, a patentable technology, or a complementary technology that will enhance competitiveness. They focus on projects with an applied orientation and engage only in cooperative agreements that are likely to yield tangible benefits, guaranteeing them immediate survival and growth. Larger companies participate in collaborative R&D projects in order to carry out technology watch, acquire new knowledge and build partnerships (A. Pesole, 2016).

Figure 18 below presents the collaboration in Europe from 2014 to 2020 that have been funded by Horizon 2020 in a graphical manner (EU Research and Innovation programme).

Figure 17: % of innovators by collaboration type and innovation potential category

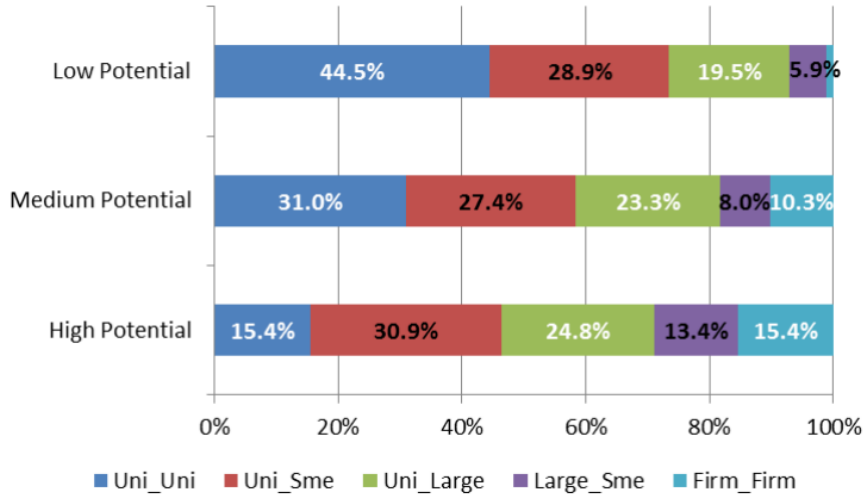

Figure 18. Innovation collaboration between different institutions in Europe from 2014 to 2020. Divided by the level of innovation and potential. (A. Pesole, 2016)

Figure 18 shows that 30,9% of the collaboration between universities and small-medium enterprises have a high potential of innovation. On the opposite side we see that collaboration between universities are having lower percentage of high potential of innovation is 15.4%.

As a summary, a research collaboration is a join effort from different parties that may involve human resources, technical resources, etc that may have a common and/or independent objective that needs each other to achieve their objective.

4.1.1 Cases of Medical R&D Collaboration: Case Examples

Machine learning (ML) is a new technology that has been in trial in the health care sector. (The collaboration between HUS and TDS for prostate cancer detections, discussed in this Thesis, is one example of how this technology could enrich this area). There are other examples where machine learning has been trial to detect other sort of cancer. For example, there is an interesting case of Freenome.

Freenome is an American based company founded in 2014. The main focus is building a multi-disciplinary team with expertise in computational biology and machine learning

techniques to reinvent disease management through early detection and precision intervention (Freenome, 2021).

> "We are programmers, machine learning experts, and computational biologists developing early cancer detection blood tests powered by our multiomics platform." (Freenome, 2021)

Freenonme is a good example of multidisciplinary teams working together to develop a completely new solutions Blood-based detection of early-stage colorectal cancer using multiomics and machine learning (G. Putcha, 2021)

> "We are molecular biologists, clinicians, and sequencing experts working together to ensure the highest quality of scientific research and to develop the infrastructure necessary for next-generation early cancer detection and precision treatments." (Freenome, 2021)

Freenome has published several research about the usage of Machine learning and how this can contribute to the health care institutions. One of those researches is "Blood-based detection of early-stage colorectal cancer using multiomics and machine learning". The following figure describe in a nutshell how Freenome´s process flow is.

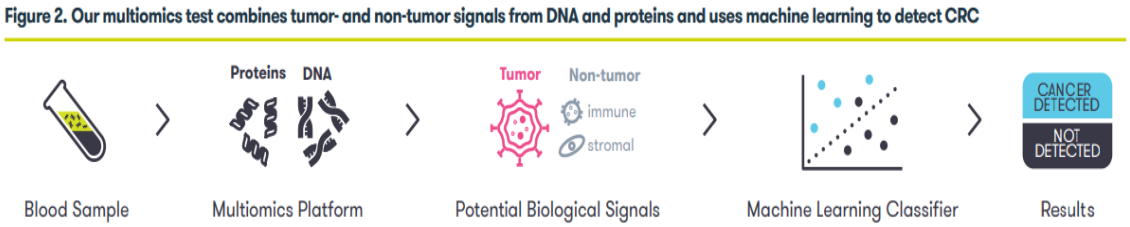

Figure 19. Freenome process flow for Design and Implementation of a Clinical Study to Validate a Multiomics Blood Test for Colorectal Cancer Screening (G. Putcha, 2021).

The research study was done on 817 patients in both genders (male and Female) including people with colorectal cancer (different stages) and without colorectal cancer (Putcha, et al., 2020). The method usage in the research is illustrated in Figure 20.

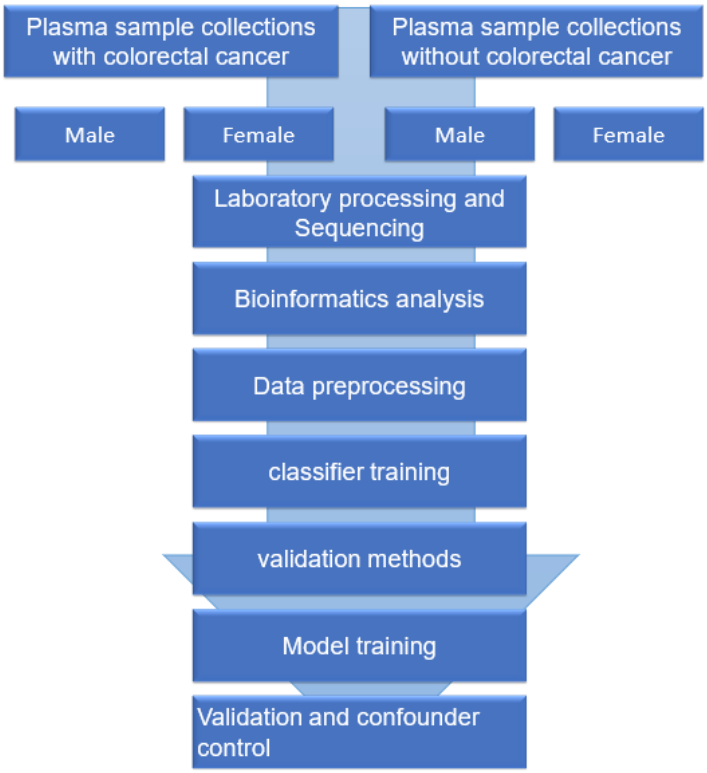

Figure 20. Method used for the research on Machine learning enabling detection of early-stage colorectal cancer by whole-genome sequencing of plasma cell-free DNA (Putcha, et al., 2020).

Freenome in their research verified that A machine learning approach using cfDNA achieved high sensitivity and specificity in a large, predominantly early-stage, colorectal cancer cohort (N. Wan, 2019)

DeepMind is another company that has been focused on the usage of machine learning to help in the health care area. Deepmind founded on 2010 and later acquired by google in 2016 have several researches and medical trials using machine learning to detect or predict illnesses. Acute kidney injures and how Machine learning could help to identify it in an early stage is one of them (A Clinically Applicable Approach to Continuous Prediction of Future Acute Kidney Injury). This collaboration project has been done with the US Department of Veterans Affairs (VA). For the research project DeepMind used datasets of more than 700.000 patients (retrospective data) (Tomašev, et al., 2019). The method used for this project was as following.

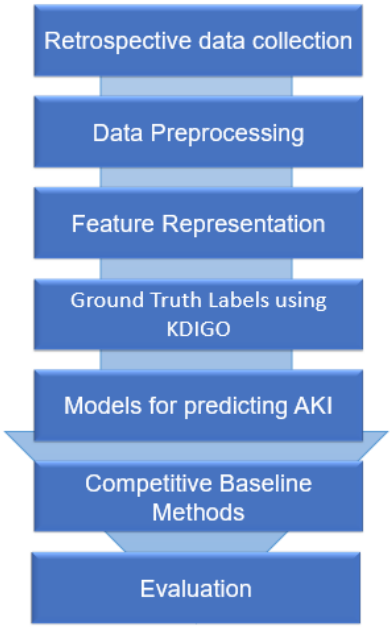

Figure 21. DeepMind method used for the research on the Acute kidney injury (AKI) (Tomašev, et al., 2019).

The collaboration project was able to train a machine learning system capable of identify acute kidney injury (AKI) up to 48 hours in advance for 55,8% of accuracy (Tomašev, et al., 2019).

> "We demonstrate a deep learning approach for the continuous prediction of AKI within a clinically-actionable window of up to 48 hours in advance. We report performance on a clinically diverse population and across a large number of sites to show that our approach may allow for the delivery of potentially preventative treatment, prior to the physiological insult itself in a large number of the cases. Our results open up the possibility for deep learning to guide the prevention of clinically important adverse events. With the possibility of risk predictions delivered in clinically-actionable windows alongside the increasing size and scope of EHR datasets, we now shift to a regime where the role for machine learning in clinical care can grow rapidly, supplying new tools to enhance the patient and clinician experience, and potentially becoming a ubiquitous and integral part of routine clinical pathways." (N. Tomašev, 2019)

Summing up, there has been done similar research and collaboration projects where machine learning has been introduced from Tech companies into the healthcare area as trial to see what benefits could this technology bring to it. So far, it has been proven that

this technology could be a game changer in the health sector. Thus, it becomes more important to guide and simplify the approach from Tech companies into the health sector for striking a research collaboration project.

4.2 EU Guidance that Affects Medical R&D Collaboration

The European medical agency has published a guideline for Good Clinical Practices (GCP). It is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO). (European Medicine Agency, 2017)

Some of the principal of ICH CGP are:

- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s). (European Medicine Agency, 2017)
- The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society. (European Medicine Agency, 2017)
- A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion. (European Medicine Agency, 2017)
- Freely given informed consent should be obtained from every subject prior to clinical trial participation. (European Medicine Agency, 2017)
- The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). (European Medicine Agency, 2017)

4.2.1 Internal Practices Required by EU Guidance: Institutional review board / independent ethics committee (IRB/IEC)

For a medical trial, The European Medicine Agency, recommends to have an Institutional review board or independet ethic commitee. The duties and also responsabilities of the board are define en in the CGP. Some of these are:

- Trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator’s current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities. (European Medicine Agency, 2017)
- The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year. (European Medicine Agency, 2017)
- The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

There is also a recomendation about what the profile of the board members should be like as well as the amount of participants. The board can desice wether a trial is approved or denied.

4.2.2 Procedures

The IRB/IEC is in charge of stablish the documets and procedures needed for the trials as well as stablish the regularity of the followup during the trial. Any procudere modification or deviation of the previously approved procedures, Needs to be assest and aproved by the IRB/IEC before it can be accepted to be use in the trial.

4.2.3 Investigator

Some of the most important recomendations and guidelines about the investigator profile are:

- The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies). (European Medicine Agency, 2017)
- The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties. (European Medicine Agency, 2017)
- The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions. (European Medicine Agency, 2017)
- During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware. (European Medicine Agency, 2017)
- Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects. (European Medicine Agency, 2017)
- The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement. (European Medicine Agency, 2017)
- Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary

of the trial’s outcome, and the regulatory authority(ies) with any reports required. (European Medicine Agency, 2017)

4.2.4 Quality asurance and quality control

The guidance about the quality asurance and quality control specify that the responsibility of implement and mainteining quality controls system, lais on the sponsor of the project, as well as the data data and documents generated during the trial. The responsibility of meet the protocols previously defined as well as keep compliant with the local´s regulatory requirements is also part the sponsor.

- Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly (European Medicine Agency, 2017)

4.2.5 Trial management, data handling, and record keeping

The GCP suggest to have an independent data-monitorig committee to follow the progress of the clincial trials, including the safety data and the critical efficacy endpoints at intevals. If the data is in electronic format, the good practices recommend.

- Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail). (European Medicine Agency, 2017)
- Maintain a security system that prevents unauthorized access to the data. (European Medicine Agency, 2017)
- Maintain a list of the individuals who are authorized to make data changes. (European Medicine Agency, 2017)
- Maintain adequate backup of the data. (European Medicine Agency, 2017)
- If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

- Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s). (European Medicine Agency, 2017)

The guidelines for good clinical practice is a full documet (adopeted by the European Union on 14th of Jun 2017) were all the points which needs to be taken in considretation before, during and after a clinical trial were human samples are involved are covered. The document has a definition of all the different participants (Institutional review board, Investigator, Sponsor) as well as documents and protocols recommended for a research project (Clinical trial protocol and protocol amendments, Investigator´s brochure and Essentials documents for the conduct of a clinical trial). There is a very clear definition of them as well as all the different participants. The points mentioned above are not all what the guidelines contains. However, they were relevant for the the collaboration done for my thesis project. The full guidelines can be found in the European Medical agency website (European Medicine Agency, 2017).

4.3 Specific Weaknesses in Striking Research Collaboration

Next, the weaknesses are discussed that may need to be considered in a collaboration project in the healthcare area. They may not be related to all the possible collaboration research project but most probably they will need to be consider when it involves and information technology application

4.3.1 Data, Its Ownership and How to Share Data (related to the legal side and reflected in the legal agreement)

Patient data and who owns it is a complex area to deal with and analysed. It may differ depending on what angle are your looking it from. Before going into the different angles that data ownership may consider, let´s define what is consider as *patient health data:*

- any and all data generated, created, or collected and retained in any form or medium by the National Health Service (NHS) relating to an individual patient in, during, or as part of a clinical or clinical research encounter (Kathleen Liddell, 2021).

Patient health data is collected using clinical register or electronic medical records. Clinical registries (CRG) are a good proxy for large patient data sets. They use observational methods to gather patient data in order to assess medical outcomes and processes at population levels. They cover a large healthcare domain, extending from clinical quality improvement, safety monitoring and cohort studies, to clinical research and policy evaluation (Mouton Dorey, 2018). Furthermore, clinical records may contain different information depending of the health institution as well as the country where they have been taken from.

On a European level, there is no set guidance dictating the format of clinical notes. Funded by the health programme of the European Union, an overview of national laws on electronic health records in the member states was published in July 2014. This stated that, to date, all countries used one or several electronic health record systems (Mathioudakis, 2016).

Structured information which needs to be included in clinical records

Clinical notes should include
Patient demographics
Reasons for the current visit
The scope of examination
Positive exam findings
Pertinent negative exam findings
Key abnormal test findings
Diagnosis or impression
Clear management plan and agreed actions
Treatment details and future treatment recommendations
Medication administered, prescribed or renewed and any drug allergies
Written (or oral) instructions and/or educational information given to the patient
Clear documentation and justification for resuscitation status and ceiling of care (if inpatient)
Documentation of communications with patient and family/friends (level of awareness of the situation and acceptance of the plans)
Recommended return visit date

Figure 22. Example of clinical records information (Mathioudakis, 2016).

Considering the amount of data that a clinical record may content as well as the criticality of it, we need to think about possible harms. According the Dr. Angela Ballantyne data

harms can include: *Privacy breaches* (unjustified or unauthorised intrusions into a patients' personal sphere), *discrimination and stigma* (data may be used to characterise individuals or groups in ways that confer disadvantages), *disenfranchisement* (a lack of transparency and engagement regarding secondary data use), *disempowerment* (a loss of control and agency over secondary uses of data); and/or *exploitation* (patients or data producers do not benefit sufficiently from secondary uses of clinical data) (Ballantyne, 2020).

Considering the previous points in support for the discussion, *data ownership* could be understood from the following angles: *Private ownership, Patients as data traders, Co-creation of clinical data, Collective ownership claims, non-property relationships* with data (Ballantyne, 2020). Private ownership would think that health data as being the product of their bodies and actions, which in different ways (with antecedents in the philosophy of property) they see as therefore belonging to them (Montgomery, 2017). Also, it is individuals who should not only control their own data but also have the right to make decisions about access to their data, and be informed about how they will be used (Riso B, 2017). Accepting those two statements, from the private point of view, the data (clinical records) always belongs to the patient and should not be used without their concern.

This leads to the point that data belongs to patients and they even may have the right to trade their data (patients as data traders). Personal health and medical data are a valuable commodity for a number of sectors from public health agencies to academic researchers to pharmaceutical companies (Hunter, 2016). Some commentators are concerned that patients are potentially exploited and unfairly excluded from the benefits of the new data economy. This concern drives the development of platforms to let patients participate as traders of health data (Ballantyne, 2020).

Health information usually is not generated solely or predominantly by the patient; rather, it is constructed by number of different parties and devices (co-creation data). Consider an innocuous trip to the clinician. A presenting patient might describe symptoms of wound that will not heal. The clinician's subsequent investigation of these data by, for example, examining the patient and ordering laboratory tests. It creates more data, which is processed and interpreted before being documented or reported to the patient (Kathleen Liddell, 2021). In national health systems (such as in the Britain, Australia, Singapore and New Zealand), doctors who co-produce clinical data are paid (directly or indirectly) as public servants, and the resources to store and manage data are provided

by taxpayers. Arguably, the results of these professionals' labour are ethically co-owned by the state and should be used for public benefit and/or kept in the public domain (Collective ownership claims) (Ballantyne, 2020).

Summing up this discussion, sharing of clinical trial data has great potential to accelerate scientific progress and ultimately improve public health by generating better evidence on the safety and effectiveness of therapies for patients (Committee on Strategies for Responsible Sharing of Clinical Trial Data; Board on Health Sciences Policy; Institute of Medicine, 2015). At the same time, sharing individual-level data from clinical studies remains extremely challenging. The *status quo* often requires scientists to establish a formal collaboration and execute extensive data usage agreements before sharing such data. Thus, (1) established criteria for sharing clinical trial data, (2) procedures for fairly adjudicating requests for data against those criteria, and (3) accountability for both data holders and requesters in adhering to those standards are critically necessary. Clear, transparent, and accountable processes for data sharing must also include (4) protection of participant privacy and respectful handling of individual participant data (B. K. Beaulieu-Jones, 2019).

4.3.2 Intellectual Property Rights, Including Publishing the Results (related to the legal side and reflected in the legal agreement)

Broadly speaking, the term *Intellectual Property* ('IP') refers to unique, value-adding creations of the human intellect that results from human ingenuity, creativity and inventiveness. An IP right is thus a legal right, which is based on the relevant national law encompassing that particular type of intellectual property right. Such a legal right comes into existence only when the requirements of the relevant IP law are met and, if required, it is granted or registered after following the prescribed procedure under that law (Kalanje, 2005).

Intellectual properties rights are a term wildly use in the technology industry as well as others industries that involves several other key concepts that needs to be well understood. Some of these concepts are: copyright, patent rights, rights in a trademark, utility model rights, design copyright, rights to a commercial name, protection of integrated circuits and layout designs, and plant variety rights (World Intellectual Property Organization, 2016).

In R&D alliances in particular, intellectual property (IP) rights (IPR) allocation and protection are more critical than for other forms of partnership. The patent is therefore the most frequently used IP protection mechanism to safeguard foreground knowledge (the technology created during the alliance) in R&D alliances. However, when the collaborative process ends, the division of IPR may lead to either of three situations: individual IP ownership (sole patent), joint IP ownership (joint patent), or no patent at all (Delerue, 2018). Small and medium enterprises (SMEs) often neglect using them (patents). Research indicates that IP protection through patents is positively related to performance in terms of commercialization success (Brem, 2017)

What comes to the publication rights, it is little is known about publication agreements between industry and academic investigators in trial protocols and the consistency of these agreements with corresponding statements in publications (Kasenda, 2016). However, a research study made during 2000 until 2003 concluded that. Of 647 eligible randomized clinical trials (RCTs), 456 (70.5%) mentioned an agreement regarding publication of results. Out of these 456, 393 (86.2%) documented an industry partner's right to disapprove or at least review proposed manuscripts; 39 (8.6%) agreements were without constraints of publication. The remaining 24 (5.3%) protocols referred to separate agreement documents not accessible by the study. Of those 432 protocols with an accessible publication agreement, 268 (62.0%) trials were published. Most agreements documented in the protocol were not reported in the subsequent publication (197/268 [73.5%]). Out of 71 agreements reported in publications, 52 (73.2%) were concordant with those documented in the protocol. In 14 of 37 (37.8%) publications in which statements suggested unrestricted publication rights, at least one co-author was an industry employee. In 25 protocol-publication pairs, author statements in publications suggested no constraints, but 18 corresponding protocols documented restricting agreements (Kasenda, 2016).

To conclude this discussion, Intellectual property rights may take a form of patents (technology related) and those intellectual property rights maybe have three different forms: (1) sole patent, (2) joint patent, or (3) no patent. In regards to (4) the publications rights, the literature explored suggest that the topic is not always considered in agreement level or there is a lack of evidence of such a documentation or existence of an agreement between the parties.

4.3.3 Funding and How to Use It (reflected in the legal agreement)

Investments in research and development (R&D) are commonly considered a fundamental determinant of the firm´s competitiveness, economic growth and development. Despite their importance and effectiveness, R&D projects are considered harder to finance than traditional investments in physical capital. This is, first of all, a consequence of the fact they are perceived as riskier, both in terms of maturity and probability of success. Second, the assessment of these risk is complicated by the information asymmetries which frequently permeate the relationships between inside investors (or entrepreneurs) and outside investors (or financiers). Third, such information asymmetries are exacerbated as a result of the intrinsic nature of these projects and their serendipity, which largely make them unsuited to serve as collateral (irelli, 2021). Unlike small enterprises, large firms are more likely to be less reactive to changes in external R&D financing sources as they have less difficulty in financing their R&D activities, and because they have a lot of collateral and available funds (Kou, 2020).

On the EU level, Horizon 2020 is the European Union's Framework Programme for Research and Innovation (2014-2020). With its dedicated budget of around EUR 77 billion over seven years, it is the biggest EU Research and Innovation programme ever (Commission, 2018). By 2021 there has been 637 grants assigned for the health area (including heath technology) (European Commission, 2021)

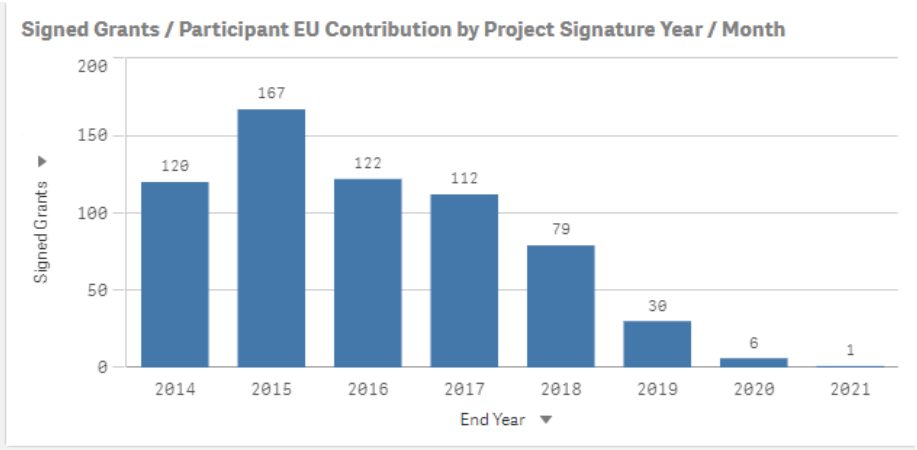

Figure 23. Amount of grants signed by year under the EU program Horizon 2020 (European Commission, 2021).

About the usage of the funds, there is not a rule of thumb of how to use them. This will depend on the project needs as well as the amount of the fund. If we considered clinical

trials (Average clinical trials for new drugs last on average 12 years in Europe (EFPIA, 2022)) as reference on how the funds are consumed in overall, we can see that 50% of the funds is spent on the different stages of medical trials. 30% is spent on the preclinical phase and 20% in the regulatory phase (Stefan Harrer, 2019) in the USA (Figure 21). In the European side, numbers are not much different according the European Federation of Pharmaceutical industries and association (EFPIA). 58,6% of the time and investment goes into the different stages of the medical trials and the other 41,4% goes to the pre-clinical phase and regulation work (EFPIA, 2022).

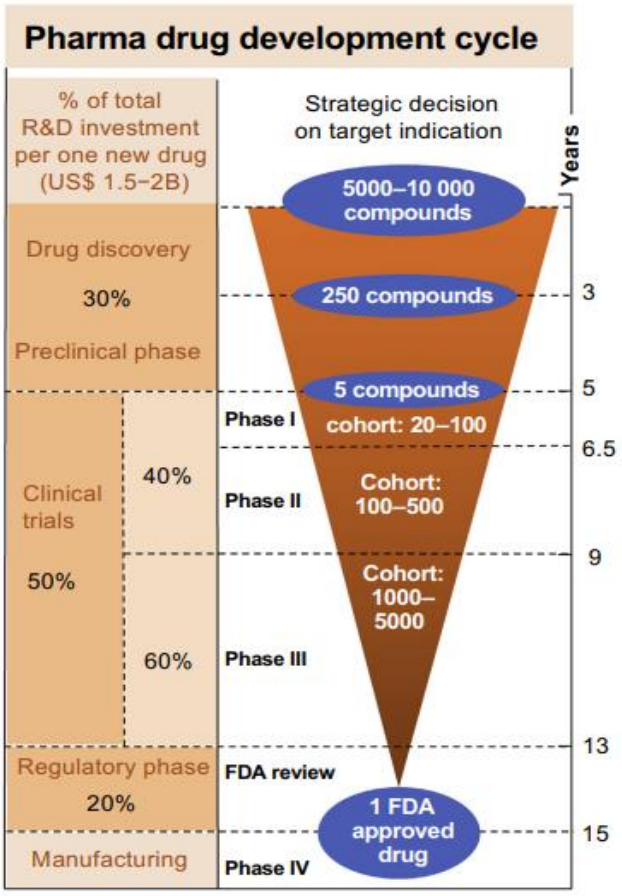

Figure 24. Overall funds spending for medical trials in the USA (new drugs for different treatments).

4.4 Conceptual Framework of This Thesis

The following table represent the conceptual framework of the thesis as well as the key points that should be taken into consideration for striking a medical R&D collaboration.

The Conceptual framework consists of two elements. First, it is **the map** "how to strike collaboration in medical R&D" which is pulled together based on available literature and best practice discussed in Section 4 above. This map is shown in Figure 25 below.

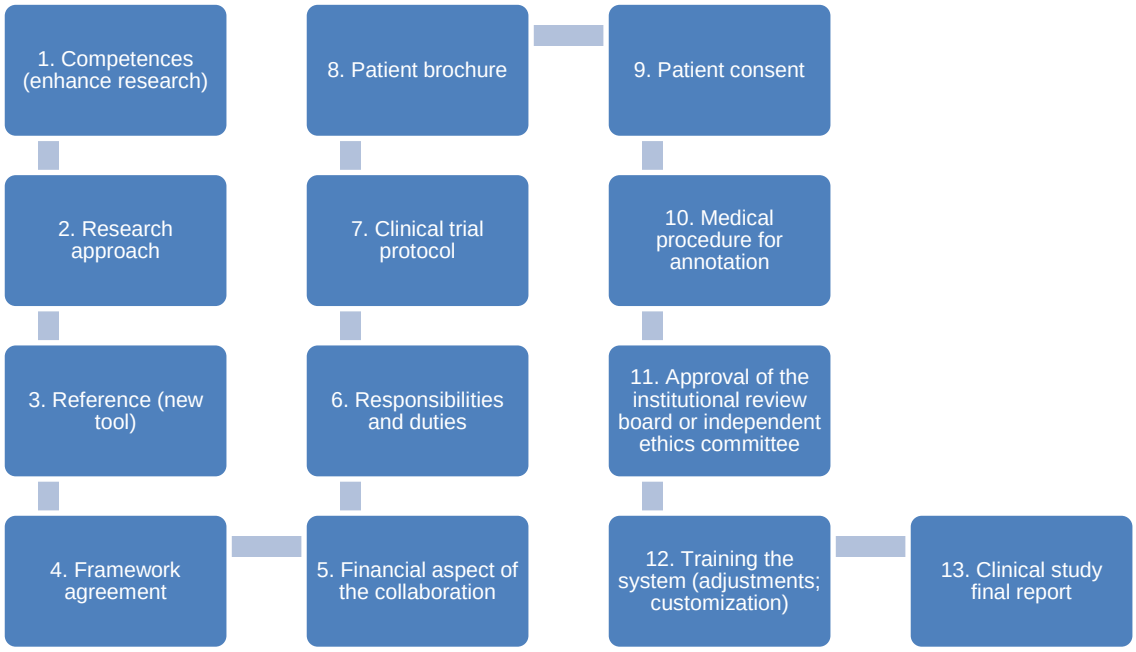

Figure 25. Map with the key steps that need to be considered for striking a Medical R&D collaboration.

As illustrated in Figure 25, literature suggests the following to be considered as important for similar R&D projects in the healthcare area:

Collaboration could be defined as *social processes whereby human beings pool their experience, knowledge and social skills with the objective of producing new knowledge, including knowledge as embedded in technology*" (B. Bozeman, 2014). Thus, it is important to fine the right partner to collaborate. A right partner is someone who could complement the knowledge, infrastructure, data or technology for the research purposes as well as share the interest of research in the same area (1.enhance research). Once the right partner has been found, it is important to have an agreement where both parties agrees in the bases of the collaboration (2.framework agreement). Research and developments collaboration also requires funding that needs to be applied for or as alternative, a common budget (3.financial aspect of the collaboration). The good practices for R&D

in clinical trials also suggest that there has to be a clear structure of the different participants of the project. Every participant of the project has a profile with certain responsibilities that needs to be acknowledge (4.responsibilities and duties). A description of the objectives, design, methodology, statistical considerations and aspects related to the organization of clinical trials also needs to be included (5.clinical trial protocol). In order to inform and motivate the patients to participate in the project (6.patient consent), it is important to inform them about the project, benefits, risk, data privacy and any other important matter that may concern them in a summarized manner (7.patient brochure). As the clinical trial in this case involves annotations for the images. This requires the attention of pathologist and/or doctors to mark the areas for machine learning purpose. Thus a protocol that describe this procedure is also important to have (8.medical procedure for annotation). From the IT point of view, there has to be a similar protocol to import/teach the system (9.training the system). All the previous points mentioned needs to be reviewed, accepted as well as approved by healthcare institution or the committee responsible of the research (10.approval of the institutional review board or independent ethics committee). To close up the research, a final report is also needed (11.clinical study final report)

Second, the other element of the Conceptual framework points to the key considerations that need be taken into consideration for striking a medical R&D collaboration. These considerations originated as the key concerns from the current state analysis, and responses to these concerns were pulled together based on available literature and best practice discussed in Section 4 above. They are summarized in Figure 26 below.

Research Collaboration (general concerns)	• A commitment to mutual relationships and goals • A jointly developed structure and shared responsibility • Mutual authority and accountability for success • Sharing of resources and rewards
EU Guidance that Affects Medical R&D Collaboration (general guidance and legal concerns)	• Trial protocol(s)/amendment(s) • Procedures • Quality assurance and quality control • Trial management, data handling, and record keeping

1.Data, Its Ownership and How to Share Data (related to the legal side and reflected in the legal agreement)	• New data generated (After annotations) • Further usage of the data (data usage for other projects)
2.Intellectual Property Rights, Including Publishing the Results (related to the legal side and reflected in the legal agreement	• Copyright • Patent rights • Utility model rights
3.Funding and How to Use It (reflected in the legal agreement and reflected in the legal agreement)	• Project funds • Individual funds

Figure 26. Conceptual framework for the key point that need to be considered for striking a Medical R&D collaboration.

Guided by these suggestions identified from available knowledge and best practice in Section 4, next, Section 5 moves on to developing the Proposal for the case company.

5 Building Proposal for the Company

This section merges the results of the current state analysis, suggestions from the conceptual framework and inputs from the key stakeholder towards the building of the Proposal.

5.1 Overview of the Proposal Building Stage

In this thesis, the Proposal is built based on (a) selected relevant suggestions from the available knowledge and best practice reviewed in Section 4, as well as (b) the results of the current state analysis, and (c) inputs from the key stakeholder. These key inputs are summarized below.

First, the current state analysis, Section 3, described and analyzed how the only successful research collaboration project was carried out by the case company in collaboration with the Helsinki University Hospital (HUS). As the result of that collaboration, it was proven that machine learning has a high level of accuracy detecting mutation in the tissues in the prostate area that may lead into prostate cancer as well as categorize them in the different stages of it (after training). As the first project of this nature curried out in practice, there were some lessons learnt and gaps identified that should be developed further.

This successful project between HUS and TDS means an important step further in terms of collaboration projects in the prostate cancer area. The project has demonstrated the competences and expertise in the area of machine learning that TDS has as well as the willingness of TDS to move forward in researching of advance capabilities of machine learning to support and contribute in the health care area. These key elements (1.competences and 2.research approach) were identified as fundamental for any other research project in the future, and it gave TDS a backup of their capabilities with proven results from the past project as well as future reference for new collaboration projects (3.reference).

Another important element of success is that, after the collaboration project with HUS, TDS has a machine learning algorithm (4.new tools) with a high level of training that has been feed with dataset from different sources (public available datasets as well as from

a well know and recognize source) capable to detect with a high level of accuracy prostate cancer and their different stages, that can be re-use for other research projects in other cancer areas or in a similar one.

One important internal learning (5.data anonymization) was identified along the way of the project. Considering the current laws in Europe and in the world (there is not such a world police about this, instead it depends of the local regulations) about the data privacy and the usage of, it is important to have this point well defined as part of the protocol of the project (6.reliable protocol). This definition should cover the minimum information needed from the patient (if any) and what would be the method to anonymize the data.

Thus, the results and “lessons learnt” from the collaboration project with HUS and TDS was that it would be good to have *a clear roadmap* as a basis for any future collaboration projects to speed up the process and do not start building one form the scratch. At this point, literature and best practice search started to identify useful suggestions from available knowledge.

Second, literature suggests the following to be considered as important for similar R&D projects in the healthcare area. As any project or work where two or more different institutions are participating, there has to be defined a legal framework of the collaboration based on legal terms (7.framework agreement) this are the legal bases definitions of the collaboration where terns like: *Parties definition, background and objects, obligations of the parties, results and rights, confidentiality, costs, termination, patient consent* are considered. A research collaboration project, is not an exception. Thus, this also needs to be part of the minimum required documentation while setting up the collaboration project (8.minimum required documentation).

As some of the terms previously mentioned are more or less applicable for any project/collaboration, it is important to make them *tailor-made* based on the objectives of the both parties (9.adjustments; customization). Based on the experience collaboration with HUS, this customization was well defined and commonly agreed based on the targets of each participant. However, this process took some time due to the legal part is open for interpretations and they are different depending on individuals.

Third, the key stakeholder of TDS, its CEO, made valuable inputs into the Proposal building which are discussed in the section below. Altogether, these 3 key inputs have lead

to building the proposal for *a roadmap for striking medical R&D collaboration in the IT area.*

5.2 Inputs into the Proposal: Suggestions from Available Knowledge and Best Practice, Results from Earlier Practices with HUS, and inputs from the Key Stakeholder (Data 2)

The inputs into the proposal are based on (a) the available knowledge and selected best practice recommended in literature reviewed in Section 4, as well as (b) the results from the current state analysis, and (c) inputs for the proposal building from the key stakeholder, TDS´s CEO.

The initial framework was taken from literature that suggests the 13 steps which were discussed in the Conceptual framework as important for similar R&D projects in the healthcare area. These steps were extended with the results from the current state analysis, and inputs for the proposal building from the key stakeholder. The proposal is described below.

Step 1, Competences.

It is important to look for a partner that would enhance the research topic with their knowledge and/or experience. The partner should have the competences to provide the minimum requirements in order to kick off the collaboration project. The competences required will depend on the focus of the research project.

> *"It is difficult to strike collaboration because the research institution/hospital need to get some benefits. In this case, this AI tool is a benefit for them, as well as the training in the AI area around this new tool. For us, the benefit is access to their data, images".* (Heikkinen, 2021)

The first point to consider for Striking Collaboration in Medical R&D for an IT solution is to look for *the right competences* of *the partner*. Such competences would enhance the research and help to achieve the ultimate goal of the collaboration (it could be a common or individual goal). Although a health institution may have the right competences for a collaboration, they may not always have a relevant research and development area (R&D). Thus, having the competences only does not warranty a partnership.

Step 2, Research approach

The research approach is something almost mandatory for a collaboration project. We have seen cases where the medical institution is interested in the project but as there is not research area, there are not resources available to engage in the project.

Step 3, Reference

Next, for Striking Collaboration in Medical R&D is important to keep track of *the previous projects or experiences* as well as *the references* from them. This is valuable information to be presented towards the partner to motivate a future collaboration. References is the manner that an organization can demonstrate what has been done in previous collaboration projects and how successful the collaboration was. References are some sort of validation between parties that can be share for future projects.

Step 4, Framework agreement

A framework agreement is one of the difficult parts to accomplish if the collaboration project is between a big healthcare center and a small startup. The reason is that small companies may not have the knowledge neither the expertise to create one. Without such a document, health center may not be willing to collaborate. Thus, having a framework agreement model would be beneficial for speed up a collaboration project. Within the framework agreement topics like *Intellectual property rights* are considered.

Step 5, Financial aspect of the collaboration

It is important to define by the parties how the collaboration project will be fund. This may be via public fundings or private. Regardless the funding (public or private) they need to be well defined and commonly agreed.

> *"Without any financial support, it may be difficult to start a project, this is true. On the other hand, in some cases, there is no money involved. We are not selling anything to these institutions, no buying, so there may be no financial element. Or the financial support can come from other parties, for example, from Business Finland".* (Heikkinen, 2021)

Step 6, Responsibilities and duties

As medical R&D trial requires to define several roles as well as the duties of each of them. The definition of the role and the responsibilities is also a recommendation from the good clinical practices. Defining these roles and duties help to keep the project in a structure manner as well as provide a clear vision of the responsibility of each team member.

Step 7, Clinical trial protocol

The clinical trial protocol is where all the procedures and activities related to the collaboration project are defined. This protocol needs to be created in collaboration with the different stake holders that are participating in the project (doctors, specialists, pathologist, data scientists, etc.) A good definition of this protocols provides a structured manner of repeat all the procedures in the same manner to be analyzed further.

Step 8, Patient brochure

Patient brochure summarized the most important data and questions that a patient could have. This brochure is critical to engage the patient into the project (as data provider). The literature suggest that many people may not be interested in participating in medical trials because of the lack of knowledge on how the trial could potentially affect them.

> *"Lack of benefit for participants/patients may hinder getting a patient concept, yes, it is true."* (Heikkinen, 2021)

Step 9, Patient consent

Once the patient has been informed about the trial (using the brochure), The patient needs to consent for their data usage. This is done via a document called patient consent. The patient consent documents should have more extensive description of the trial (in comparison with the brochure) as well as the explicit consent of the user. The document needs to be signed by the patient. There are two alternatives that may have an influence in the patient consent document: (1) the research is done with prospective data, (2) the research is done using retrospective data. For prospective data, having brochure

or some short of document where the patient could gain knowledge about what the research project is, how he would benefit of participating in the research and by whom and how his information (data) will be use, it could be beneficial for patient to acknowledge and sign up for the research study. Although, if the data is based on retrospective data, the patient consent may not be needed instead, an authorization and consent from the healthcare center to use the data is required.

> *"For getting the patient consent, the institution should actively ask patients for it. Alternatively, they can use the existing research datasets, where the patient consents were already given earlier."* (Heikkinen, 2021)

Step 10, Medical procedure for annotation

As the images needs to be transferred to the Machine learning system. There has to be a well define procedure for the doctors to annotate the images in certain manner. This operation needs to be done in a consistently throughout the project.

Step 11, Approval of the institutional reviewed board or independent committee

All the steps mentioned above needs to be reviewed and approved by an independent committee. Without that approval the project cannot be started.

Step 12, Training the system

Training the system is critical in order to succeed in the project, The annotations in the step 10 plays a fundamental role on this part. If the images are not annotated correctly, the machine learning system will also learn "wrongly" providing inaccurate information as result of this. The training and adjustments may take some time.

Step 14, Clinical study final report

The final report can be done commonly with the collaboration partner o it could also be done indecently. The idea of the report is to validate the thesis question.

5.3 Proposal Draft

Figure 27 summarizes the key steps that needs to be address for strike a collaboration in Medical R&D for an IT Solution.

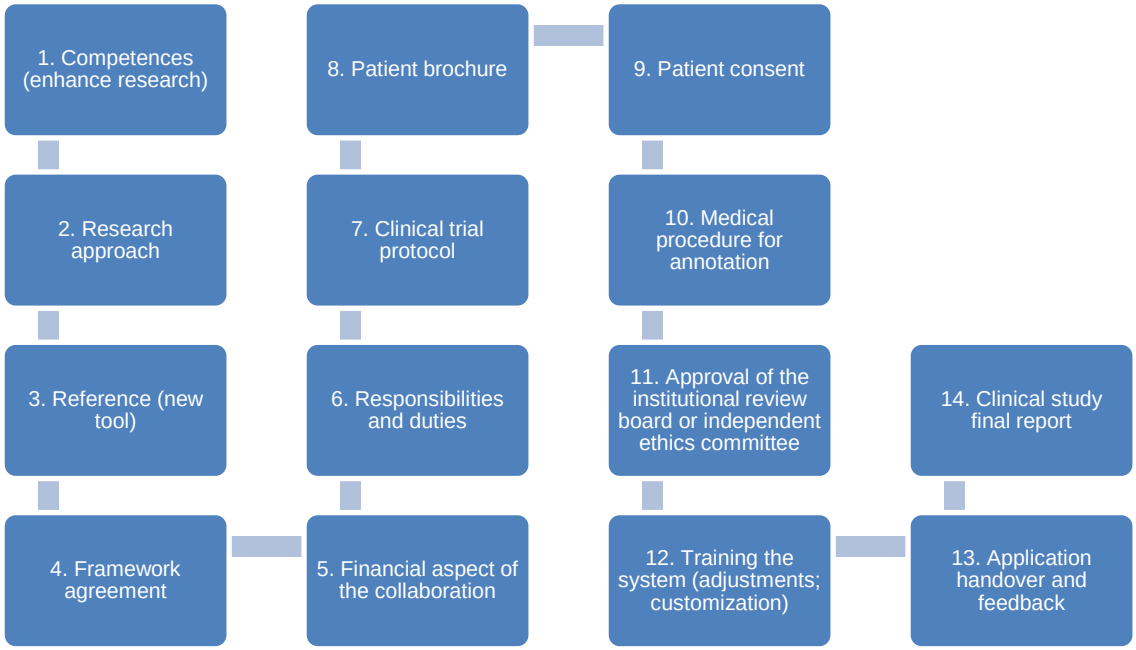

Figure 27. Key steps that need to be address for strike a collaboration in Medical R&D for an IT Solution (A proposal draft).

Figure 27 pulls together the key points based on the findings from the current state analysis, suggestions from best practice and literature, and inputs from the key stakeholder for striking a Medical R&D collaboration in AI/ML projects.

It is important to highlight that in the conceptual framework and the draft proposal there is one extra step (draft propposal). This extra 13th step is *"Application handover and feedback".* This has been added in order to involve the doctors or specialist for future improvements as well as get reall insights from the end users.

The next seccions is where the proposal is validated with different professional on the health technology fields.

6 Validation of the Proposal

This section reports on the results of the validation stage and points to further developments to the initial Proposal. At the end of this section, the Final proposal is presented.

6.1 Overview of the Validation Stage

Validation is one of the key points of any thesis work. Since the thesis is based on the analysis of the past projects, as well as available knowledge and best practice, and also guidance by the key stakeholder, validation is required to make sure that the proposal is valid, accurate as well as bring value projects in Medical R&D in the IT area.

In this thesis, validation of this thesis work was done with 3 experts who were consulted and introduced the proposal as well as the thesis work before seeking their professional opinion. Their feedback was taken in consideration to improve the initial proposal.

The proposal was presented to three different professionals that are currently working in the IT Health Technology area. The profile of this professionals were different as well as their professional experience. However, two of them are part of academia and research in the IT Health Tech research projects. The third professional involved into the discussion was the CEO of Top data science, i.e. a practitioner in this field.

With all 3 experts, the presentation of the proposal was done virtually using the platform google meet. The first presentation was made to the CEO of top data science. Few days letter, the same proposal was introduced to the two university professors using the same platform as before and both professors participating in the same meeting. After the first session with the CEO of Top Data Science, some requests for development were made, for example, (1). documentation was suggested to be added to the initial proposal to enrich the content of the thesis (appendixes). The second validation stage carried out with the professors, it did include the documents suggested after the first proposal. During the second validation session, the proposal did not receive any additional requests for development that could be interpreted or have an impact that ends up in a significant change to the proposal, instead the proposal was approved as well as the appendixes that could also bring some extra value in similar projects. A more detailed report on the contents of validation feedback is presented below.

6.2 Developments to the Proposal

Based on the feedback by Top Data Science CEO, as well as the feedback from the second session with the professor, their consolidated feedback from both stages can be summarized as follows.

As for Step 1, the proposal draft was presented to a well experience professional in the healthcare area, many of the mentioned points in the conceptual framework were recognized as points to be address for future collaborations. Despite of some of those were coming from past experiences, see them in a visual representation helped to identify them easily. Some of the main concerns like data privacy as well intellectual property rights were also comment during the first session. One of the main takeaways of the first session was that sample documents could bring some extra benefits to have included in this thesis work (annexes). Regarding Step 2, the draft proposal included the improvements/changes suggested in the first session making the proposal completer and more robust. Particulary the annexes were very much appreciated and potentially use internall in other projects.

> *“Really valuable documents (EIT Model Framework Partner Agreement, Guideline for good clinical practice E6(R2)) It could also be use internally at the university for the Innovation Center for future projects"* (Lukkarinen, 2021)

> *"Other small companies have had similar challenges while making a Framework Partner agreement with big entities. This document could help them to improve that area"* (Lukkarinen, 2021)

Along the past years, TDS has had several successful research projects using artificial intelligent with different institutions around the world. “Use of machine learning in prediction of granule particle size distribution and tablet tensile strength in commercial pharmaceutical manufacturing” was done in collaboration with Orion Pharma and the University of Helsinki. TDS has also developed a new testing solution (using artificial intelligent) that can find an infected sample from PCR testing when the patient’s viral load is still low for COVID-19. This collaboration was done with Vietnam Military Medical University (VMMU) and Ampharco USA

> *“By now, TDS had increased the number of successful collaboration projects stricken outside Finland to 3-5. So, we have more extensive experience now is this area.”* (Heikkinen, 2021)

The proposal has been presented to the respective stakeholders as well as discussed in order to complement the proposal based on their feedback. As conclusion of the discussion and feedback, it was concluded that the proposal covers the main points for Striking Collaboration in Medical R&D for IT Solution

> *“It covers the topic and contents well”.* (Heikkinen, 2021)

Thus, the validation sessions gave general approval to the proposal and stress its value for the researchers in similar projects as it give not only the roadmap for striking medical &D cooperation in the area of Health Tech, but also provides examples of concreate documents that could help the researchers to carry out the initial stages of their projects, namely to help in striking cooperation.

6.3 Final Proposal

The final proposal has been revised taking in consideration the initial proposal as well as the comments and feedback provided in the two stages of validation.

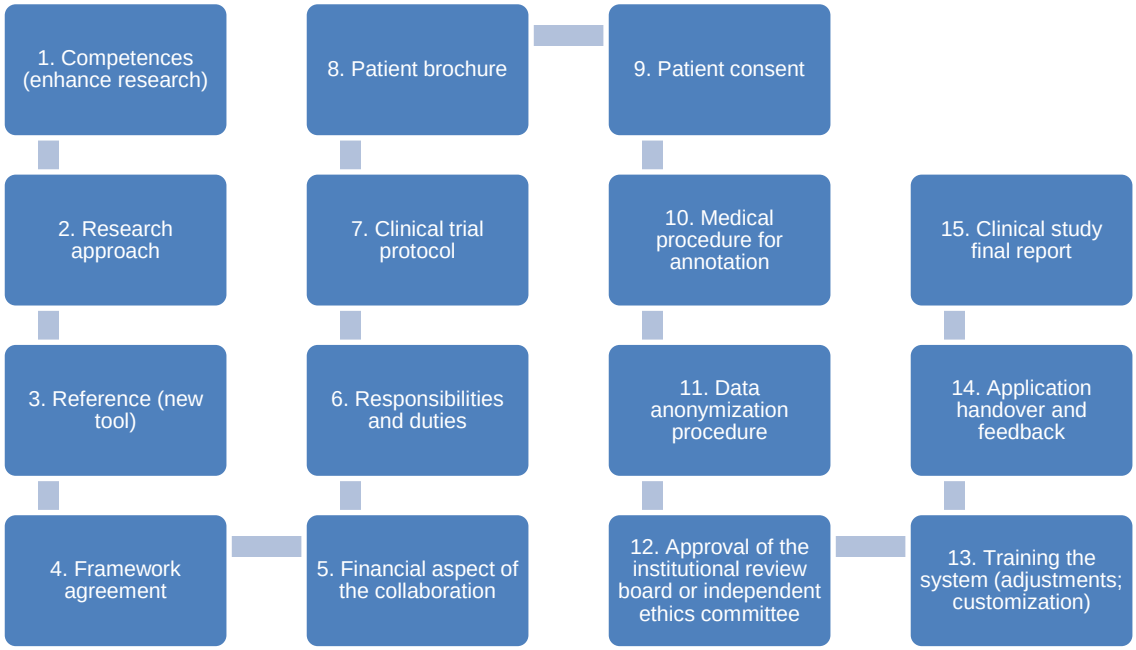

Figure 28. Final proposal: the roadmap for Striking Collaboration in Medical R&D for building an IT Solution.

The first 3 stages of the proposal have been accepted as part of the pre-collaboration work to find a proper collaboration partner. The Model Framework Partnership Agreement by the European Institute of Innovation and Technology (EIT) presented in the annexes provides a wide range of alternatives and topics that need to be covered while setting up the collaboration project. Topics like Rights and Obligations under the framework partnership, Termination of the Framework agreement, Ownership of the investigations result, IPR, confidentiality, Processing of personal data among others. It is important to also have a particular attention in the intellectual property in the framework agreement. This part needs to be fully understood by all the parties.

The financial aspect of the collaboration is also covered in the Model Framework Partnership Agreement included in the annexes. In regards of the responsibilities and duties as well as clinical trial protocol, are covered by the guideline for good clinical practice (annexes). Examples of the Patient brochure as well as patient consent are also topics that help to inform and gain the authorization of the patient to participate in the collaboration (examples of this documents has been added in the annexes). Medical procedure for annotation as well as data anonymization procedure needs to be well defined. The

reminding boxed of the final proposal could be defined mutually while the collaboration is ongoing but they do not have a direct impact on the topic of this thesis work (Plan for Striking Collaboration in Medical R&D for IT Solution).

The final proposal has one more step which is related to data anonymization. This was one of the highlights of both session with the different experts. There has been identified that data anonymization plays a big role while doing collaboration projects in medical R&D. Thus, to have a dedicate step to have a particular attention on that was discussed and added to the final proposal.

7 Conclusion

This section includes the Executive summary, thesis self-evaluation and managerial implications that the next researchers should consider before implementing the results of this thesis into practice.

7.1 Executive Summary

The objective of this thesis was to build a roadmap for striking collaboration in medical R&D for an IT solution.

This thesis started with analyzing the previous TDS experiences in medical R&D collaboration projects done at the case company focused on identifying the gaps and improvements that can help to improve the process of setting up an R&D collaboration project in the future. The results of this analysis made it possible to outline some critical elements in the striking of medical R&D cooperation, but also showed the gap that needed to be further explored.

For this end, the thesis focused on search for available knowledge and best practice from other institutions as well as from literature about the practices in striking medical R&D cooperation in similar R&D projects and the best practices suggested by the literature. Based on this knowledge, there was a step-by-step process outlined of the elements and steps that needs to be considered for striking collaboration. Many of the points discussed in literature were also complemented with sample materials (shown in annexes) from the previous projects and can be helpful in future projects. Thus equipped, the thesis proceeded to building a roadmap for striking future medical R&D cooperation projects for the case company.

As inputs for building the proposal, as stressed above, first, there were previous R&D projects analyzed that were carried out between the case company and the Helsinki university hospital (HUS); second, there were also inputs considered from best practice that and literature suggested for medical R&D and other similar research projects from different companies (Freenome and Deepmind) as well as from the European Union level. The proposal suggested the steps and elements to help bridge the gaps in a setup for a collaboration project. The final proposal included 15 steps that can support the process

of striking medical R&D cooperation, namely: (1) Competences, (2) Research approach, (3) References, (4) Framework agreement, (5) Financial aspect of the collaboration, (6) Responsibilities and duties, (7) Clinical trial protocol, (8) Patient brochure, (9) Patient consent, (10) Medical procedure for annotation, (11) Data anonymization procedure, (12) Approval of the institutional review board or independent committee, (13) Training the system, (14) Application handover, (15) Clinical study final report. In this thesis work topics such as patient consent, intellectual property rights, data ownership, data handling, data anonymization, funding management were studied and applied into the proposal as well as the different profiles roles and duties that every member of the project needs to be responsible of. Adding up to the proposal, there are complemented material and sample of the best clinical practices, framework agreement model, patient brochure, that can be used for future collaboration projects.

The results of the Thesis can help in future projects in order to speed up the process of defining the cooperation framework agreement and gathering documents that are required or needed for string a medial R&D collaboration (legal and practical documentation).

7.2 Managerial Implications (Next Steps and Recommendations toward Implementation)

Nowadays, we see more and more IT applications or new technology as fundamental part in the health care area. This systems or application takes years of testing and validation before they are recognized and accepted to be use in a medical environment. Thus, new technologies like machine learning or Artificial intelligent are such a new technology that is it is even harder to anticipate the potential that this could bring into the health area. Therefore, strike a collaboration R&D project may be more difficult than other technologies.

As shown in this thesis, striking a collaboration with a party may depend on several factors that are not always connected to the quality or idea of the collaboration research, instead it may be more related to the interests and motivation of each party to collaborate. When we refer to medical R&D, the situation is a bit more complex due to all the regulations and necessary documentation that this R&D requires as well as some more specific documents if the research involves patients or patients' data.

Machine learning and image recognition has been one of the key competences of TDS since several years. All that expertise and experience has been channeled to develop a machine learning system capable to detect cancer and the level of it in the prostate area. As result of this years of development and effort, TDS had the opportunity to carry out the first real R&D project of the system in cooperation with Helsinki university (HUS). As result, the system was capable to identify with more than 90% of accuracy the areas where the tissues where mutated ending up in a prostate cancer. Due to this project, it was identified that there are some areas to be improve specially in what relates to how to strike a collaboration R&D project with other health center/ hospitals and what could be the minimum requirements needed to setup such a collaboration.

There are not standards when it comes to medical R&D collaboration projects in contract matters or documentation required for such a collaboration. Different institutions may be more open and flexible while setting up an R&D collaboration projects and some others may require more formal documents. It will also depend very much on the nature of the R&D as well as if it is involving patient and/or patient data. However, there are certain documents that are a must in order to make this collaboration smooth as well as successful as possible. Documents like Framework agreement, patient consent (if the research involves patient data), patient brochure, etc. There are also good practices and recommendations that are recommended to be revised as well as followed as much as possible for an R&D project in the healthcare area. The good practices/recommendations can be implemented before or while the collaboration is ongoing but, in any case, they need to be documented and approved by the committee steering group.

Regarding this Thesis and its Proposal, the level of implementation of this proposal will depend very much on the nature of the next R&D project as well as the institution with whom this R&D project will be. However, based on the experiences as well as the literature studied for this thesis, the proposal will be useful to be use (if not completely, it will be partially) for any upcoming project. It is recommended to adjust the proposal according the need and the nature of the next project. The following points need to be taken into account for successfully striking cooperation:

First, the company needs to test the final proposal in a real project. This will give the opportunity to identify any missing or extra step as well as verify if the proposal helps to improve the time of signing a collaboration project. Second, the company should try to approach the collaboration research always using the same minimum documents (final

proposal) this will help to have a standardized manner of doing collaboration projects as well as give the advantaje of have a proven process for documents requirements. Third, the other researchers can investigate if the final proposal could we implemented in other health technology areas where machine learning is not part of the investigation.

Health technology and machine learning are evolving quickly. Thus, the traditional and document orientated process for medical R&D may be different in the near future (simplier). Thus, part of the proposal could be obsolete if the regulation and recommendations change. Therefore, a constant review and update could be required in order to adapt the proposal with the latest recommendations.

7.3 Thesis Evaluation / Research Quality Criteria for This Thesis

The initial objective of this thesis was to identify possible gaps that the case company experienced in the past projects and how those can be tackled and covered better in future projects. Ideally as end result of the thesis, the company would have a set of documents that can be use as base line to start new collaboration projects with other institutions. Due to the different nature of the R&D project that may involve artificial intelligent/machine learning, it has turned out to be challenging to have a set of specific documents that can be use “as it is”. However, throughout the thesis work, there has been some help given to identify certain key documents that will help in future collaborations. Although, some adjustment may be need to be done according each project.

The areas that could have done differently is to have more Finnish cases of Machine learning in the health technology area (different companies). If I would have had the opportunity to find more companies that have had similar collaboration projects, it could have provided a comparison point of view for similar realities in a similar field. Another point that it could have been interesting to test is if the proposal could suit the need of a different company in a similar area. This could have provided the validation of how standard the minimum documents and contract requirements are.

7.4 Closing Words

Overall, the area of heath technology is something that is evolving towards technology more and more. Thus, simplify the process of introduce new technology should also evolve to be easier and more approachable for IT solutions. It is visible that due to all the current procedures in the healthcare sector, requirements and complicated R&D processes make it difficult to an IT company to enter into this sector. To add on top of the previous mentioned points, the process of validation a medical software or equipment also takes a long time (it may take even more than a year before it is validated). Before this validation process, the software or equipment cannot be advertised as medical equipment. Thus, cannot be commercialized as such. All these barriers make the health technology area a difficult market to enter. The difficulties become a really showstopper for small companies that their revenue stream needs to be in short terms and not in long terms.

8 Reference s

A. Pesole, D. N., 2016. *Universities and Collaborative Innovation in EC-funded Research Projects: An Analysis based on Innovation Radar Data,* s.l.: European Commission.
B. Bozeman, C. B., 2014. *Research Collaboration and Team Science.* s.l.:Springer Cham Heidelberg.

B. K. Beaulieu-Jones, P. Z. S. W. P. C. W. R. L. M. S. P. B. M. J. B. B. M. M. a. C. S. G. P., 2019. Privacy-Preserving Generative Deep Neural Networks Support Clinical Data Sharing. *Circulation: Cardiovascular Quality and Outcomes.*

Ballantyne, A., 2020. How should we think about clinical data ownership?. *Journal of medical ethics*.

Brem, A. N. P. &. H., 2017. Open innovation and intellectual property rights: How do SMEs benefit from patents, industrial designs, trademarks and copyrights?. *Management Decision.*

C. P Langlotz, B. E. M. L. J. K.-C., 2019. A Roadmap for Foundational Research on Artificial Intelligence in Medical. Issue 2019, p. 12.

C. Stürenberg, U. K. K. S. O. G. A. M. A. E. T. H. A. R. a. T. M., 2019. Detection and local histological staging of prostate cancer foci in H&E whole slide images using convolutional neural networks.

Cancer, I. A. f. R. o., 2020. *International Agency for Research on Cancer.* [Online] Available at: https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=population&mode_population=who&population=900&populations=900&key=total&sex=1&cancer=27&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_ca [Accessed 11 October 2021].

commission, E., 2014. *HORIZON 2020 in Brief.* [Online] Available at: https://ec.europa.eu/programmes/horizon2020/sites/default/files/H2020_inBrief_EN_Fi

nalBAT.pdf
[Accessed 01 November 2021].

Commission, E., 2018. *HORIZON 2020 in full swing Three years on KEY FACTS AND FIGURES 2014-2016.* [Online] Available at: https://ec.europa.eu/programmes/horizon2020/sites/default/files/h2020_threeyearson_a4_horizontal_2018_web.pdf
[Accessed 1 November 2021].

Committee on Strategies for Responsible Sharing of Clinical Trial Data; Board on Health Sciences Policy; Institute of Medicine, 2015. Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk.. *National Academies Press (US).*

Compton, C., 2021. *A Comprehensive Textbook of Cancer's Causes, Complexities and Consequences.* 1st ed. Arizona: Springer.

Delerue, H., 2018. Shadow of joint patents: Intellectual property rights sharing by SMEs in contractual R&D alliances. *Journal of Business Research.*

EFPIA, 2022. Clinical trials. *European federation of pharmaceutical industries and association*, 22 October, pp. https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/clinical-trials/.

EFPIA, 2022. *European federation of pharmaceutical industries and association.* [Online] Available at: https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/clinical-trials/
[Accessed 22 October 2022].

EU, 2018. *Principles relating to processing of personal data.* [Online] Available at: https://gdpr.eu/article-5-how-to-process-personal-data/
[Accessed 24 January 2021].

EU, 2019. *The Danish taxi service Taxa 4×35 faces a 1.2 million kroner fine (roughly €160,000) for not deleting or anonymizing its users' data. Studying this example sheds light on how data protection agencies are enforcing GDPR requirements for data*

anonymization.. [Online]
Available at: https://gdpr.eu/data-anonymization-taxa-4x35/
[Accessed 24 January 2021].

EU, 2021. *What is GDPR, THe EU´s new data protection law.* [Online]
Available at: https://gdpr.eu/what-is-gdpr/
[Accessed 24 January 2021].

European commision, 2021. *European High-Performance Computing Joint Undertaking.* [Online]
Available at: https://eurohpc-ju.europa.eu/sites/default/files/2021-03/Decision%2006.2021%20-%20Access%20policy.pdf
[Accessed 30 October 2021].

European Commission, 2021. *FP7 project details.* [Online]
Available at: https://webgate.ec.europa.eu/dashboard/sense/app/eaf1621c-67ce-4972-a07b-dddba31815c1/sheet/076eedee-e14d-4554-a8a0-5545d89da416/state/analysis
[Accessed 1 November 2021].

European Medicine Agency, 2017. *Guideline for good clinical practices E6 (R2).* [Online]
Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf
[Accessed 20 Februry 2021].

Eurostat, 2019. *Cancer statistics - specific cancer.* [Online]
Available at: https://ec.europa.eu/eurostat/statistics-explained/pdfscache/39738.pdf
Eurostat, 2020. *Deaths from prostate cancer in EU regions.* [Online]
Available at: https://ec.europa.eu/eurostat/en/web/products-eurostat-news/-/edn-20201119-1
[Accessed 23 January 2021].

Freenome, 2021. *Freenome.* [Online]
Available at: https://www.freenome.com/about-f
[Accessed 30 October 2021].

From the Department of Anaesthesiology and Pain Medicine, I. a. D. o. C. R. (. N. F. U. f. C. E. I. U. o. B. B. S. (. C. T. N. E. S. o. A., 2015. Ethical procedures and patient consent differ in Europe. *European journal of anaesthesiology,* Volume 32, pp. 126-231.

G. Putcha, J. G. C. X. A. S. a. T. R. L., 2021. *Freenome design-and-implementation-of-a-clinical-study.* [Online]
Available at: https://static1.squarespace.com/static/54e4c4c4e4b06b5b9b5b6e2c/t/615a1bf801f50853aa03ccc8/1633295352782/Putcha+et+al.%2C+AAFP_2021_final.pdf
[Accessed 30 October 2021].

G. Putcha, T.-Y. L. E. A. M. B. A. D. M. D. G. H. S. K.-H. J. L. K. L. S. M., 2021. *Freenome bloodbased-detection-of-earlystage.* [Online]
Available at: https://static1.squarespace.com/static/54e4c4c4e4b06b5b9b5b6e2c/t/5ea7ee51ce8ddf535f9a5c17/1588063830347/2020_ASCO%2BGI_Poster.pdf
[Accessed 30 October 2021].

Heikkinen, T., 2021. *Proposal validation* [Interview] (11 Novemebr 2021).

Hemmens, B., 2016. *Conscious collaboration Re-think the way we work together for good.* United Kingdom: Springer Nature.

Hunter, P., 2016. The big health data sale: As the trade of personal health and medical data expands, it becomes necessary to improve legal frameworks for protecting patient anonymity, handling consent and ensuring the quality of data.. *EMBO Rep.*

Intersoft, C., 2016. *GDPR.* [Online]
Available at: https://gdpr-info.eu/
[Accessed 24 January 2021].

irelli, M. &. S., 2021. R&D financing and growth. Economics of innovation and new technology. *Economics of Innovation and New Technology.*

Jiang F, J. Y. Z. H., 2017. *Artificial intelligence in.* [Online]
Available at: https://svn.bmj.com/content/svnbmj/2/4/230.full.pdf
[Accessed 11 02 2019].

Kalanje, C. M., 2005. *Role of Intellectual Property in Innovation and New Product.* [Online]
Available at: https://www.wipo.int/export/sites/www/sme/en/documents/pdf/ip_innovation_development.pdf
[Accessed 31 October 2021].

Kasenda, B. v. E. E. Y. J. J. B. A. T. Y. S. R. .. .. .. B. M., 2016. Agreements between Industry and Academia on Publication Rights: A Retrospective Study of Protocols and Publications of Randomized Clinical Trials.

Kathleen Liddell, D. A. S. a. A. L., 2021. Patient data ownership: who owns your health?. *Jurnal of law and the biosciences*, 1 October.

Kou, M. Y. Y. &. C. K., 2020. The impact of external R&D financing on innovation process from a supply-demand perspective. *Economic modelling.*

Lukkarinen, S., 2021. *Senior Lecturer* [Interview] (23 November 2021).

Margaret S. Winchester, C. A. K. R. B., 2018. *Global Health Collaboration Challenges and Lessons.* s.l.:Springer International.

Mathioudakis, A. R. I. G. A. A. S. N. &. H., 2016. How to keep good clinical records. *Breathe (Lausanne, Switzerland)*.
Montgomery, J., 2017. Data Sharing and the idea of ownership.

Mouton Dorey, C. B. H. &. B.-A., 2018. Patient data and patient rights: Swiss healthcare stakeholders' ethical awareness regarding large patient data sets - a qualitative study. *BMC medical ethics*.

N. Tomašev, X. G. J. W. R. M. Z. H. A. A. S. A. M. C. M. S. R. I. P. A. C. C. O. H. A. K. J. C. H. M., 2019. *NCBI.* [Online]
Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6722431/
[Accessed 18 October 2021].

N. Wan, D. W. T.-Y. L. K. N. E. A. A. D. D. A. K. B. W. M. B. M. B. N. B. D. B. J. C. A. M. D. R. E. S. F. E. G. L. H., 2019. *Machine learning enables detection of early-stage colorectal cancer by whole-genome sequencing of plasma cell-free DNA.* [Online] Available at: https://bmccancer.biomedcentral.com/articles/10.1186/s12885-019-6003-8#MOESM1
[Accessed 18 Octuber 2021].

Organization, W. H., 2021. *World Health Organization (WHO).* [Online] Available at: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/medical-doctors-(per-10-000-population)
[Accessed 12th October 2021].

Putcha, G. et al., 2020. Blood-based detection of early-stage colorectal cancer using multiomics and machine learning. *Journal of clinical oncology*, 1 February.

Riso B, T. A. V. D. F. H. C. J. L. M. K. N. Z. S. R. V., 2017. Ethical sharing of health data in online platforms – which values should be considered?. *Life Sci Soc Policy.*

Stefan Harrer, P. S. B. A. H., 2019. Artificial Intelligence for Clinical Trial Desig. *CELPRESS,* p. 15.

TDS, 2021. *TopData science.* [Online] Available at: https://topdatascience.com/health-tech/
[Accessed 23 January 2021].

Tomašev, N. et al., 2019. A clinically applicable approach to continuous prediction of future acute kidney injury. *Nature (London)*, August.

tracker, E., 2021. *Enforcement tracker.* [Online] Available at: https://www.enforcementtracker.com/?insights
[Accessed 24 January 2021].

WHO, 2021. *International Agency for Research on Cancer.* [Online] Available at: https://gco.iarc.fr/tomorrow/en/dataviz/trends?types=0&sexes=1&mode=population&group_populations=0&multiple_populations=1&multiple_cancers=1&cancers=27&populat

ions=994&group_cancers=1
[Accessed 13th October 2021].

WHO, 2021. *World health organization.* [Online]
Available at: https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-clinical-trials-by-year-country-who-region-and-income-group
[Accessed 13th October 2021].

WMA, 2018. *WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS.* [Online]
Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
[Accessed 2 February 2021].

World Intellectual Property Organization, 2016. *World intellectual Property Organization.* [Online]
Available at: https://www.wipo.int/edocs/pubdocs/en/wipo_pub_895_2016.pdf
[Accessed 31 October 2021].

Appendix 1

European Institute of Innovation & Technology

Model

Framework Partnership Agreement

European Institute of Innovation and Technology (EIT)

December 2015

www.eit.europa.eu

The EIT is a body of the European Union

Disclaimer

Appendix 1

This document aims to support applicants for the EIT's Call for Knowledge and Innovation Communities (KIC) Proposals under Horizon 2020, the EU Framework Programme for Research and Innovation (2014-2020). It shows the full range of provisions that may be applied to this type of agreement, and is provided for information purposes only. The legally binding agreement will be that which is signed by the parties.

EIT KIC logo

Ref. EIT.2015.I

8.1.1 Version 10.11.2015

FRAMEWORK PARTNERSHIP AGREEMENT

NUMBER [insert number] — [insert acronym]

This 'Framework Partnership Agreement' is between the following parties:on the

one part,

The European Institute of Innovation and Technology ('the EIT')
represented for the purposes of signature of this Framework Partnership Agreement by [[function], [forename and surname],

and

on the other part,

1. The Knowledge and Innovation Community Legal Entity ('the KIC LE'):

[full official name (short name)][legal form] [official registration No] established in [official address in full] [VAT number], represented for the purposes of signing the Framework Partnership Agreement by [function, forename and surname]

2. and the other Knowledge and Innovation Community ('KIC') Partners listed in Annex 2, ifthey have signed their 'Accession Form' (see Annex 4 and Article 62),

Unless otherwise specified, references to 'KIC Partner' or 'KIC Partners' include the KIC LE.

The parties referred to above have agreed to enter into the Framework Partnership Agreement under the terms and conditions below.

The Framework Partnership Agreement is composed of:

Terms and Conditions

Annex 1 Strategic Agenda of the KIC

Annex 2 List of KIC Partners

Annex 3 Model Specific Agreement

Annex 1 Description of the specific action

Annex 2 Estimated budget

Annex 3 Model for the financial statements

Annex 4 Model for the certificate on the financial statementsAnnex 4 Accession Forms

Annex 5 List of linked third parties

Annex 6 Model for the certificate on the methodology

TERMS AND CONDITIONS

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CHAPTER 1 GENERAL

ARTICLE 1 — SUBJECT MATTER OF THE AGREEMENT

This Agreement establishes a long term cooperation ('framework partnership') and sets out its terms and conditions and the general terms and conditions and rights and obligations applicable to the specific grants that may be awarded by the EIT for specific actions under theframework partnership.

CHAPTER 2 FRAMEWORK PARTNERSHIP

ARTICLE 2 — STRATEGIC AGENDA — AWARD OF SPECIFIC GRANTS — SPECIFIC AGREEMENTS –MAXIMUM EIT FINANCIAL CONTRIBUTION

2.1 Strategic Agenda

The strategy, objectives, expected impact and activities under the framework partnership areset out in the 'Strategic Agenda' in Annex 1.

2.2 Award of specific grants for specific actions — Specific Agreements

The EIT may award 'specific grants' for ‘specific actions’ to be implemented under the framework partnership.

The specific action consists of ‘KIC added value activities’ under a Business Plan for a given time period. In accordance with Article 2(11) of the EIT Regulation, ‘KIC added-value activities’ means activities carried out by KIC Partners, contributing to the integration of the knowledge triangle of higher education, research and innovation, including the establishment, administrative and coordination activities of the KICs, and contributing to the overall objectives of the EIT.

In order to obtain proposals for specific grants, the EIT will consult the KIC LE on the basis of an invitation to submit a proposal that sets out the award criteria it will apply.

The EIT will decide on the award of the specific grants following an evaluation of the proposaland a competitive review across KICs. The proposal consists of a Business Plan, including short, mid and long-term objectives and targets, key performance indicators, and describing the KIC activities which consist of KIC added value activities to be supported by the specific grant and KIC complementary activities having a clear link with at least one KIC added value activity and not financed from the EIT contribution.

If the EIT decides to award a specific grant, it will propose the KIC LE to conclude a 'Specific Agreement (SGA)' (see Annex 3).

By the signature of the Specific Agreement by the KIC LE and by the signature of the Accession Form by the KIC Partners, the KIC Partners accept the specific grant and agree to implement the specific action under their own responsibility, without prejudice to and in

accordance with Article 47.1, and in accordance with the Framework Partnership Agreement and this Specific Agreement, with all the obligations and conditions they set out.

Specific Agreements must be concluded before the end of the framework partnership (see Article 3).

After the end of the framework partnership or its termination, the Framework Partnership Agreement continues to apply to specific actions that are implemented under Specific Agreements which have entered into force before end of the duration.

2.3 Maximum EIT financial contribution

The sum of the final amounts of the grants (see Article 10.3) under the specific grant agreements signed under this Framework Partnership Agreement until 31 December 2022 may not exceed 25% of the KIC overall funding.

The KIC overall funding consists of the costs incurred by the KIC Partners, their linked third parties (see Article 19) and/or third parties receiving financial support (see Article 20) in implementing the KIC activities (KIC added value activities and KIC complementary activities) as described in the Business Plans (see Annex 1 SGA).

The costs of KIC complementary activities shall be

- proportionate to the cost of KIC added value activities and/or to the expected impact in furthering the mission of a framework partnership (i.e. the relative weight of KIC complementary activities within KIC activities must be suitable and reasonable to achieve the objectives of the activity);
- incurred after the designation date of the framework partnership;
- identifiable and verifiable.

If the sum of the final amount of the grants exceeds 25% of the KIC overall funding, the EIT will recover the difference at the time of the last payment of the balance of a grant awarded under this Framework Partnership Agreement until 31 December 2022 (see Article 50).

ARTICLE 3 — DURATION AND STARTING DATE OF THE FRAMEWORK PARTNERSHIP

The Framework Partnership Agreement is concluded for a period of 7 years as of its entry into force (see Article 64). This period may be extended.

ARTICLE 4 — RIGHTS AND OBLIGATIONS UNDER THE FRAMEWORK PARTNERSHIP

4.1 General obligation to properly implement the framework partnership

Without prejudice to and in accordance with Article 47.1, the KIC Partners must respect the objectives of the framework partnership and implement it as described in Annex 1 andendeavour to achieve those objectives also in the specific actions.

The KIC Partners must maintain relations of mutual co-operation and regular and transparentexchanges of information with the EIT on:

- the implementation and follow-up of the Strategic Agenda, the Business Plans andthe specific grants and

- other matters of common interest related to the Framework Partnership Agreement.

The KIC Partners must implement the framework partnership in compliance with Articles 39, 40, 41, 42, 44, 45, 52 — *mutatis mutandis.*

4.2 KIC Internal Agreement

The KIC Partners must have internal arrangements regarding their operation and co- ordination to ensure that the framework partnership and the specific actions are implemented properly. These internal arrangements must be set out in writing and may cover:

- internal organisation of the KIC, notably governance arrangements reflecting the knowledge triangle of higher education, research and innovation, and openness to new KIC Partners if they add value to the KIC;

- the principles of good governance;

- distribution of EIT funding;

- additional rules on rights and obligations related to background and results (including whether access rights remain or not, if a KIC Partner is in breach of its obligations) (see Subsection 3 of Chapter 3);

- settlement of internal disputes;

- liability, indemnification and confidentiality arrangements between the KIC Partners.

These internal arrangements shall be included in the 'Internal Agreements' between the KIC LE and other KIC Partners or shall be included in the statutes or by-laws of the KIC LE.

The internal arrangements must not contain any provision contrary to the Framework Partnership Agreement and the Specific Agreements.

4.3 EIT Labelled degrees and diplomas

4.3.1 Degrees and diplomas relating to the KIC education and training activities awarded by Higher Education Institutions participating in the KIC may be labelled as EIT degrees and diplomas, provided they fulfil the following quality criteria:

a. Robust entrepreneurship education

b. Highly integrated, innovative "learning by doing" curricula

c. Mobility, European dimension and openness to the world

d. Outreach strategy and access policy

4.3.2 The EIT, in close cooperation with the KIC LE, must define the modalities for assessment, labelling and follow up review and governance of EIT labelled degrees anddiplomas. EIT labelled degrees and diplomas must build on the experience gained in the context of the European Higher Education Area.

4.3.3 Education and training activities not being awarded with the EIT label must not use the EIT label. Such activities must use the KIC brand adopted by the EIT.

ARTICLE 5 — SUSPENSION OF FRAMEWORK PARTNERSHIP IMPLEMENTATION

The parties may suspend the implementation of the framework partnership on the grounds and according to the procedure — *mutatis mutandis* — set out in Article 55.

If the EIT suspends the framework partnership implementation, the implementation of the specific actions is also deemed suspended (see Article 55), from the date of suspension of theframework partnership.

ARTICLE 6 — TERMINATION OF THE FRAMEWORK PARTNERSHIP AGREEMENT OR OF THE PARTICIPATION OF ONE OR MORE KIC PARTNERS

6.1 Termination of the Agreement

The parties signing the Framework Partnership Agreement may terminate the Framework Partnership Agreement at any time.

The party terminating the Framework Partnership Agreement must formally notify termination to the other party, stating the date the termination will take effect. This date must be after the notification.

Without prejudice to and in accordance with Article 47.1, termination of the Framework Partnership Agreement does not release the parties from their obligations under Specific Agreements which have entered into force before the date on which the termination takes effect, unless they have been terminated.

Neither party may claim damages due to termination by the other party.

6.2 Termination of the participation of one or more KIC Partners

The parties may terminate participation of one or more KIC Partners in the frameworkpartnership on the grounds and according to the procedures – *mutatis mutandis* – set out in Article 56.2.1, 56.3.1 and 56.3.2.

The KIC LE must submit a request for amendment (see Article 61) to adapt Annex 1 and, if necessary, the addition of one or more new KIC Partners (see Article 62).

If the request for amendment is rejected by the EIT, the Framework Partnership Agreement may be terminated (see above).

Without prejudice to and in accordance with Article 47.1, termination of participation in the framework partnership does not release the KIC Partner concerned from its obligations underSpecific Agreements. It cannot however participate in specific actions for which specificgrants are awarded after the date on which the termination takes effect.

CHAPTER 3 SPECIFIC GRANTS

SECTION 1 SPECIFIC ACTIONS

ARTICLE 7 — SPECIFIC ACTIONS TO BE IMPLEMENTED – BUSINESS PLANS

The specific actions to be implemented are set out in the Specific Agreements (see Article 2 and Annex 1 SGA).

The Business Plan containing the specific action to be implemented as well as the KIC complementary activities are set out in the Specific Agreement (see Annex 1 SGA).

ARTICLE 8 — DURATION OF THE SPECIFIC ACTIONS

The duration of the specific actions is set out in the Specific Agreements (see Article 3 SGA).

ARTICLE 9 — ESTIMATED BUDGET AND BUDGET TRANSFERS

9.1 Estimated budget

The estimated budget for the specific action is set out in Annex 2 to the Specific Agreement.

It contains the estimated eligible costs, broken down by KIC Partners and linked third party and budget category. It also contains the estimated costs of the KIC Partners not receiving EITfunding, if applicable (see Article 6 SGA).

9.2 Budget transfers

The estimated budget breakdown indicated in Annex 2 to the Specific Agreement may be adjusted by transfers of amounts between KIC Partners or budget categories. This does not

require an amendment according to Article 61, if the specific action is implemented asdescribed in Annex 1 to the Specific Agreement.

However the KIC Partners may not add costs relating to subcontracts not provided for in Annex 1 to the Specific Agreement, unless such additional subcontracts are approved in accordance with Article 18.

Lump sums set out in Annex 1 to the Specific Agreement can never be adjusted.

SECTION 2 SPECIFIC GRANTS

ARTICLE 10 — GRANT AMOUNT, FORM OF GRANT, REIMBURSEMENT RATES AND FORMS OF COSTS

10.1 Maximum grant amount

The maximum grant amount for the specific grants is set out in the Specific Agreements (see Article 4 SGA).

10.2 Form of grant, reimbursement rates and form(s) of costs

The form of the grant, reimbursement rate(s), estimated eligible costs and the form(s) of costs of the specific grants are set out in the Specific Agreements (see Article 4 SGA).

10.3 Final grant amount — Calculation

The final grant amount of a specific grant depends on the actual extent to which the specific action is implemented in accordance with the terms and conditions of the Framework Partnership Agreement and the Specific Agreement concerned.

This amount is calculated by the EIT — when the payment of the balance is made (see Article 17 SGA) — in the following steps:

Step 1 – Application of the reimbursement rates to the eligible costsStep 2

– Limit to the maximum grant amount

Step 3 – Reduction due to the no-profit rule

Step 4 – Reduction due to improper implementation or breach of other obligations

10.3.1 Step 1 — Application of the reimbursement rates to the eligible costs

The reimbursement rate (see Article 4 SGA) is applied to the eligible costs (actual costs, unit costs, flat-rate costs and lump sum costs; see Article 5 SGA) declared by the KIC Partners and the linked third parties (see Article 16 SGA) and approved by the EIT (see Article 17 SGA).

10.3.2 Step 2 — Limit to the maximum grant amount

If the amount obtained following Step 1 is higher than the maximum grant amount (seeArticle 4 SGA), it will be limited to the latter.

10.3.3 Step 3 — Reduction due to the no-profit

rule The specific grant must not produce a

profit.

'Profit' means the surplus of the amount obtained following Steps 1 and 2 plus the specificaction's total receipts, over the specific action's total eligible costs.

The 'specific action's total eligible costs' are the consolidated total eligible costs approved bythe EIT.

The 'specific action's total receipts' are the consolidated total receipts generated during itsduration (see Article 3 SGA).

The following are considered receipts:

a) income generated by the specific action; if the income is generated from selling equipment or other assets purchased for the specific action under the SpecificAgreement, the receipt is up to the amount declared as eligible under the Specific Agreement;

b) financial contributions given by third parties to the KIC Partner or to a linked thirdparty specifically to be used for the specific action, and

c) in-kind contributions provided by third parties free of charge specifically to be usedfor the specific action, if they have been declared as eligible costs.

The following are however not considered receipts:

(a) income generated by exploiting the specific action's results (see Article 34);

(b) financial contributions by third parties, if they may be used to cover costs other thanthe eligible costs (see Article 5 SGA);

(c) financial contributions by third parties with no obligation to repay any amount unused at the end of the period set out in Article 3 of the Specific Agreement.

If there is a profit, it will be deducted from the amount obtained following Steps 1 and 2.

10.3.4 Step 4 — Reduction due to improper implementation or breach of other obligations —Reduced grant amount — Calculation

If the specific grant is reduced (see Article 49), the EIT will calculate the reduced grantamount by deducting the amount of the reduction (calculated in proportion to the improper implementation of the specific action or to the seriousness of the breach of obligations in accordance with Article 49.2) from the maximum grant amount (see Article 4 SGA).

The final grant amount will be the lower of the following two:

- the amount obtained following Steps 1 to 3 or
- the reduced grant amount following Step 4.

10.4 Revised final grant amount — Calculation

If — after the payment of the balance (in particular, after checks, reviews, audits or investigations; see Article 28) — the EIT rejects costs (see Article 48) or reduces the specific grant (see Article 49), it will calculate the 'revised final grant amount' for the KIC Partner concerned by the findings.

This amount is calculated by the EIT on the basis of the findings, as follows:

- in case of rejection of costs: by applying the reimbursement rate to the revised eligiblecosts approved by the EIT for the KIC Partner concerned;
- in case of reduction of the specific grant: by calculating the concerned KIC Partner's share in the grant amount reduced in proportion to its improper implementation of the specific action or to the seriousness of its breach of obligations (see Article 49.2).

In case of rejection of costs and reduction of the specific grant: the revised final grant amountfor the KIC Partner concerned will be the lower of the two amounts above.

ARTICLE 11 — ELIGIBLE AND INELIGIBLE COSTS

11.1 Eligible costs

The general and specific conditions for costs to be eligible under the specific grants are set out in the Specific Agreements (see Article 5 SGA).

11.2 Ineligible costs

The conditions under which costs are considered ineligible under the specific grants are set out in the Specific Agreements (see Article 5 SGA).

11.3 Consequences of declaration of ineligible costs

Declared costs that are ineligible will be rejected (see Article 48).

This may also lead to any of the other measures described in Section 5.

SECTION 3 RIGHTS AND OBLIGATIONS OF THE PARTIES UNDER THE SPECIFIC GRANTS

SUBSECTION 1 RIGHTS AND OBLIGATIONS RELATED TO IMPLEMENTING THE SPECIFIC

ACTIONSARTICLE 12 — GENERAL OBLIGATION TO PROPERLY IMPLEMENT THE SPECIFIC

ACTIONS

12.1 General obligation to properly implement the specific actions

Without prejudice to and in accordance with Article 47.1, the KIC Partners must implement the specific actions as described in Annex 1 to the Specific Agreements and in compliance with the provisions of the Framework Partnership Agreement and the Specific Agreements and all legal obligations applicable under EU, international and national law.

Annex 1 of the Specific Agreement indicates the KIC Partners participating in theimplementation of each KIC added value activity.

12.2 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the specific grants may be reduced (see Article 49).

Such breaches may also lead to any of the other measures described in Section 5.

ARTICLE 13 — RESOURCES TO IMPLEMENT THE SPECIFIC ACTIONS – THIRD PARTIES INVOLVEDIN THE SPECIFIC ACTIONS

The rules on the resources to implement the specific actions and involvement of third parties in the action are set out in the Specific Agreements (see Article 6 SGA).

ARTICLE 14 — IMPLEMENTATION OF ACTION TASKS BY KIC PARTNERS NOT RECEIVING EITFUNDING

The Specific Agreements may provide for rules for the implementation of tasks forming part of the specific actions by KIC Partners not receiving EIT funding (see Article 7 SGA).

ARTICLE 15 — PURCHASE OF GOODS, WORKS OR SERVICES

The Specific Agreements may provide for rules for the purchase of goods works and services (see Article 8 SGA).

ARTICLE 16 — USE OF IN-KIND CONTRIBUTIONS PROVIDED BY THIRD PARTIES AGAINST PAYMENT

The Specific Agreements may provide for rules for the use of in-kind contributions provided by third parties against payment (see Article 9 SGA).

ARTICLE 17 — USE OF IN-KIND CONTRIBUTIONS PROVIDED BY THIRD PARTIES FREE OF CHARGE

The Specific Agreements may provide for rules for the use of in-kind contributions provided by third parties free of charge (see Article 10 SGA).

ARTICLE 18 — IMPLEMENTATION OF ACTION TASKS BY SUBCONTRACTORS

The Specific Agreements may provide for rules for subcontracting action tasks (see Article 11 SGA).

ARTICLE 19 — IMPLEMENTATION OF ACTION TASKS BY LINKED THIRD PARTIES

The affiliated entities and third parties with a legal link to a KIC Partner ('linked third parties') listed in Annex 5 may implement action tasks attributed to them in Annex 1 to a Specific Agreement.

The rules for calling on linked third parties are set out in the Specific Agreements (see Article 12 SGA).

ARTICLE 20 — FINANCIAL SUPPORT TO THIRD PARTIES

The Specific Agreements may provide for rules for providing financial support to third parties (see Article 13 SGA).

ARTICLE 21 — SUPPORT TO OR IMPLEMENTATION OF TRANS-NATIONAL PROJECTS

Not applicable

ARTICLE 22 — PROVISION OF TRANS-NATIONAL OR VIRTUAL ACCESS TO RESEARCH INFRASTRUCTURES

Not applicable

SUBSECTION 2 RIGHTS AND OBLIGATIONS RELATED TO THE GRANT

ADMINISTRATIONARTICLE 23 – GENERAL OBLIGATION TO INFORM

23.1 General obligation to provide information upon request

The KIC Partners must provide — during implementation of the specific actions or afterwards and in accordance with Article 47.1— any information requested in order to verify eligibilityof the costs, proper implementation of the specific actions and compliance with any other obligations under the Framework Partnership Agreement and the Specific Agreements.

23.2 Obligation to keep information up to date and to inform about events and circumstances likely to affect the Agreements

Each KIC Partner must immediately inform the KIC LE — which must immediately inform theEIT and the other KIC Partners — of any of the following:

(a) events which are likely to affect significantly or delay the implementation of a specificaction or the EIT's financial interests, in particular:

(i) changes in its legal, financial, technical, organisational or ownership situation orthose of its linked third parties and

(ii) changes in the name, address, legal form, organisation type of its linked thirdparties;

(b) circumstances affecting:

(i) the decision to award a specific grant and the Framework Partnership Agreement, or

(ii) compliance with requirements under the Framework Partnership Agreement orthe Specific Agreements.

23.3 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the specific grant may bereduced (see Article 49).

Such breaches may also lead to any of the other measures described in Section 5.

ARTICLE 24 — KEEPING RECORDS — SUPPORTING DOCUMENTATION

24.1 Obligation to keep records and other supporting documentation

For each specific grant, the KIC Partners must — for a period of five years after the payment of the balance — keep records and other supporting documentation in order to prove the proper implementation of the specific action and the costs they declare as eligible.

They must make them available upon request (see Article 23) or in the context of checks, reviews, audits or investigations (see Article 28).

If there are on-going checks, reviews, audits, investigations, litigation or other pursuits of claims under a Specific Agreement (including the extension of findings; see Article 28), theKIC Partners must keep the records and other supporting documentation until the end of these procedures.

The KIC Partners must keep the original documents. Digital and digitalised documents are considered originals if they are authorised by the applicable national law. The EIT may accept non-original documents if it considers that they offer a comparable level of assurance.

24.1.1 Records and other supporting documentation on the scientific and technical implementation

The KIC Partners must keep records and other supporting documentation on the implementation of the specific action in line with the accepted standards in the respective field.

24.1.2 Records and other documentation to support the eligible costs declared

The KIC Partners must keep the records and documentation supporting the eligible costs declared, in particular the following:

(a) for actual costs: adequate records and other supporting documentation to prove the eligible costs declared, such as contracts, subcontracts, invoices and accounting records. In addition, the KIC LE or KIC Partners' usual cost accounting practices and internal control procedures must enable direct reconciliation between the amounts declared, the amounts recorded in their accounts and the amounts stated in the supporting documentation;

(b) for unit costs: adequate records and other supporting documentation to prove the number of units declared. KIC Partners do not need to identify the actual eligible costs covered or to keep or provide supporting documentation (such as accounting statements) to prove the amount per unit.

In addition, for direct personnel costs declared as unit costs calculated in accordance with the KIC Partner's usual cost accounting practices, the KIC Partners must keep adequate records and documentation to prove that the cost accounting practices used comply with the eligibility conditions set out in the Specific Agreements (see Point A of Article 5 SGA).

The KIC Partners and their linked third parties may submit to the EIT, for approval by the Commission, a certificate (drawn up in accordance with Annex 6) stating that their usual cost accounting practices comply with these conditions ('certificate on the methodology'). If the certificate is approved, costs declared in line with this methodology will not be challenged subsequently, unless the KIC Partners have concealed information for the purpose of the approval.

(c) for flat-rate costs: adequate records and other supporting documentation to prove the eligibility of the costs to which the flat-rate is applied. The KIC Partners do not need to identify the costs covered or provide supporting documentation (such as accounting statements) to prove the amount declared at a flat-rate.

(d) for lump sum costs: adequate records and other supporting documentation to prove that the corresponding tasks or part of the specific action as described in Annex 1 to the Specific Agreement concerned were implemented properly. The KIC Partners do not need to identify the actual eligible costs covered or provide supporting

documentation (such as accounting statements) to prove the amount declared as alump sum.

In addition, for personnel costs (declared as actual costs or on the basis of unit costs), the KIC Partners must keep time records for the number of hours declared. The time records must bein writing and approved by the persons working on the specific action and their supervisors,at least monthly. In the absence of reliable time records of the hours worked on the specific action, the EIT may accept alternative evidence supporting the number of hours declared, if itconsiders that it offers an adequate level of assurance.

As an exception, for persons working exclusively on the specific action, there is no need to keep time records, if the KIC Partner signs a declaration confirming that the persons concerned have worked exclusively on the specific action.

For costs declared by linked third parties (see Article 19), it is the KIC Partner that must keep the originals of the financial statements and the certificates on the financial statements ofthe linked third parties.

24.2 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, costs of the specific action insufficiently substantiated will be ineligible (see Article 5 SGA) and will be rejected (see Article 48), and the specific grant may be reduced (see Article 49).

Such breaches may also lead to any of the other measures described in Section 5.

ARTICLE 25 — SUBMISSION OF DELIVERABLES

The provisions on submission of deliverables for the specific grants are set out in the Specific Agreements (see Article 15 SGA).

ARTICLE 26 — REPORTING — PAYMENT REQUESTS

The provisions on reporting and payment requests for the specific grants are set out in the Specific Agreements (see Article 16 SGA).

ARTICLE 27 — PAYMENTS AND PAYMENT ARRANGEMENTS

The provisions on payments and payment arrangements for the specific grants are set out in the Specific Agreements (see Article 17 SGA).

ARTICLE 28 — CHECKS, REVIEWS, AUDITS AND INVESTIGATIONS — EXTENSION OF FINDINGS

28.1 Checks, reviews and audits by the EIT and the Commission

28.1.1 Right to carry out checks

The EIT will — during the implementation of a specific action or afterwards — check the proper implementation of the specific action and compliance with the obligations under the Framework Partnership Agreement and the Specific Agreement, including assessing deliverables and reports.

For this purpose the EIT may be assisted by external persons or bodies.

The EIT may also request additional information in accordance with Article 23. The EIT may request KIC Partners to provide such information to it directly.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

28.1.2 Right to carry out reviews

The EIT may — during the implementation of a specific action or afterwards — carry out reviews on the proper implementation of the specific action (including assessment of deliverables and reports), compliance with the obligations under the Framework Partnership Agreement and the Specific Agreement.

Reviews may be started up to two years after the payment of the balance. They will be formally notified to the KIC LE or KIC Partner concerned and will be considered to havestarted on the date of the formal notification.

If the review is carried out on a third party (see Articles 15 to 22), the KIC Partner concerned must inform the third party.

The EIT may carry out reviews directly (using its own staff) or indirectly (using external persons or bodies appointed to do so). It will inform the KIC LE or the KIC Partner concerned of the identity of the external persons or bodies. They have the right to object to theappointment on grounds of commercial confidentiality.

The KIC LE or KIC Partner concerned must provide — within the deadline requested — any information and data in addition to deliverables and reports already submitted (including information on the use of resources).

The KIC LE or KIC Partner concerned may be requested to participate in meetings, including with external experts.

For on-the-spot reviews, the KIC Partners must allow access to their sites and premises, including to external persons or bodies, and must ensure that information requested isreadily available.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

On the basis of the review findings, a 'review report' will be drawn up.

The EIT will formally notify the review report to the KIC LE or KIC Partner concerned, which has 30 days to formally notify observations ('contradictory review procedure').

Reviews (including review reports) are in English.

28.1.3 Right to carry out audits

The EIT or the Commission may — during the implementation of a specific action or afterwards — carry out audits on the proper implementation of the specific action and compliance with the obligations under the Framework Partnership Agreement and the Specific Agreement.

Audits may be started up to two years after the payment of the balance. They will be formallynotified to the KIC LE or KIC Partner concerned and will be considered to have started on the date of the formal notification.

If the audit is carried out on a third party (see Articles 15 to 22), the KIC Partner concerned must inform the third party.

The EIT or the Commission may carry out audits directly (using its own staff) or indirectly (using external persons or bodies appointed to do so). It will inform the KIC LE or the KIC Partner concerned of the identity of the external persons or bodies. They have the right to object to the appointment on grounds of commercial confidentiality.

The KIC LE or the KIC Partner concerned must provide — within the deadline requested — any information (including complete accounts, individual salary statements or other personal data) to verify compliance with the Framework Partnership Agreement and Specific Agreements. The EIT or the Commission may request KIC Partners to provide such information to it directly.

For on-the-spot audits, the KIC Partners must allow access to their sites and premises, including to external persons or bodies, and must ensure that information requested isreadily available.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

On the basis of the audit findings, a 'draft audit report' will be drawn up.

The EIT or the Commission will formally notify the draft audit report to the KIC LE or the KIC Partner concerned, which has 30 days to formally notify observations ('contradictory audit procedure'). This period may be extended by the EIT or the Commission in justified cases.

The 'final audit report' will take into account observations by the KIC LE or KIC Partner concerned. The report will be formally notified to it.

Audits (including audit reports) are in English.

The EIT or the Commission may also access the KIC Partners' statutory records for theperiodical assessment of unit costs, flat-rate amounts or lump sums.

28.2 Investigations by the European Anti-Fraud Office (OLAF)

Under Regulations No 883/2013[1] and No 2185/96[2] (and in accordance with their provisions and procedures), the European Anti-Fraud Office (OLAF) may — at any moment duringimplementation of a specific action or afterwards — carry out investigations, including on- the-spot checks and inspections, to establish whether there has been fraud, corruption orany other illegal activity under the Framework Partnership Agreement or Specific Agreement affecting the financial interests of the EU.

28.3 Checks and audits by the European Court of Auditors (ECA)

Under Article 287 of the Treaty on the Functioning of the European Union (TFEU) and Article 111 of the EIT Financial Regulation[3], the European Court of Auditors (ECA) may — at any moment during implementation of a specific action or afterwards — carry out audits.

The ECA has the right of access for the purpose of checks and audits.

28.4 Checks, reviews, audits and investigations for international organisationsNot applicable

28.5 Consequences of findings in checks, reviews, audits and investigations —Extension offindings

28.5.1 Findings in a specific grant

Findings in checks, reviews, audits or investigations carried out in the context of a specific grant may lead to the rejection of ineligible costs (see Article 48), reduction of the specific grant (see Article 49), recovery of undue amounts (see Article 50) or to any of the other measures described in Section 5.

Rejection of costs or reduction of the specific grant after the payment of the balance will leadto a revised final grant amount (see Article 4 SGA).

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[1] Regulation (EU, Euratom) No 883/2013 of the European Parliament and of the Council of 11 September 2013 concerning investigations conducted by the European Anti-Fraud Office (OLAF) and repealing Regulation (EC) No 1073/1999 of the European Parliament and of the Council and Council Regulation (Euratom) No 1074/1999(OJ L 248, 18.09.2013, p. 1).

[2] Council Regulation (Euratom, EC) No 2185/1996 of 11 November 1996 concerning on-the-spot checks and inspections carried out by the Commission in order to protect the European Communities' financial interests against fraud and other irregularities (OJ L 292, 15.11.1996, p. 2).

[3] Decision of the Governing Board of the European Institute of Innovation and Technology (EIT) of 27 December 2013 on adopting the financial regulation for the European Institute of Innovation and Technology

Findings in checks, reviews, audits or investigations may lead to a request for amendment for the modification of Annex 1 to the Specific Agreement (see Article 61).

Checks, reviews, audits or investigations that find systemic or recurrent errors, irregularities, fraud or breach of obligations may also lead to consequences in other EIT, EU or Euratom grants awarded under similar conditions ('extension of findings from the specific grant to other grants').

Moreover, findings arising from an OLAF investigation may lead to criminal prosecution under national law.

28.5.2 Findings in other grants

The EIT or the Commission may extend findings from other grants to a specific grant ('extension of findings from other grants to a specific grant'), if:

(a) the KIC Partner concerned is found, in other EIT, EU or Euratom grants awarded under similar conditions, to have committed systemic or recurrent errors, irregularities, fraud or breach of obligations that have a material impact on the specific grant and

(b) those findings are formally notified to the KIC Partner concerned — together with the list of grants affected by the findings — no later than two years after the payment of the balance of the specific grant.

The extension of findings may lead to the rejection of costs (see Article 48) reduction of the specific grant (see Article 49), recovery of undue amounts (see Article 50), suspension of the action implementation (see Article 55) or termination of the specific grant (see Article 56).

28.5.3 Procedure

The EIT or the Commission will formally notify the KIC Partner concerned the systemic or recurrent errors, and its intention to extend these audit findings together with the list of grants affected.

28.5.3.1 If the findings concern eligibility of costs: the formal notification will include:

(a) an invitation to submit observations on the list of grants affected by the findings;

(b) the request to submit revised financial statements for all grants affected;

(c) the correction rate for extrapolation established by the EIT or the Commission on the basis of the systemic or recurrent errors, to calculate the amounts to be rejected if the KIC Partner concerned:

(i) considers that the submission of revised financial statements is not possible orpracticable or

(ii) does not submit revised financial statements.

The KIC Partner concerned has 90 days from receiving notification to submit observations, revised financial statements or to propose a duly substantiated alternative correction method. This period may be extended by the EIT or the Commission in justified cases.

The amounts to be rejected will be determined on the basis of the revised financial statements, subject to their approval.

If the EIT or the Commission does not receive any observations or revised financial statements, does not accept the observations or the proposed alternative correction method or does not approve the revised financial statements, it will formally notify to the KIC Partner concerned the application of the initially notified correction rate for extrapolation.

If the EIT or the Commission accepts the alternative correction method proposed by the KIC Partner concerned, it will formally notify to the KIC Partner concerned the application of the accepted alternative correction method.

28.5.3.2 If the findings concern improper implementation or breach of other obligations, theformal notification will include:

(a) an invitation to submit observations on the list of grants affected by the findingsand

(b) the flat-rate the EIT or the Commission intends to apply according to the principleof proportionality.

The KIC Partner concerned has 90 days from receiving notification to submit observations or to propose a duly substantiated alternative flat-rate.

If the EIT or the Commission does not receive any observations or does not accept the observations or the proposed alternative flat-rate, it will formally notify to the KIC Partner concerned the application of the initially notified flat-rate.

If the EIT or the Commission accepts the alternative flat-rate proposed by the KIC Partner, it will formally notify the KIC Partner concerned the application of the accepted alternative flat- rate.

28.6 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, any insufficiently substantiated costs of specific actions will be ineligible (see Article 5 SGA) and will be rejected(see Article 48).

Such breaches may also lead to any of the other measures described in Section 5.

ARTICLE 29 —MONITORING AND EXTERNAL EVALUATION OF THE KIC

29.1 Right to monitor and evaluate the KIC

The EIT or the Commission may carry out interim and final evaluations of the output, resultsand impact of the KIC.

Evaluations may be started during implementation of a specific action and up to a period of five years after the payment of the balance. The evaluation is considered to start on the date of the formal notification to the KIC LE or KIC Partners.

The EIT or the Commission may make these evaluations directly (using its own staff) or indirectly (using external bodies or persons it has authorised to do so).

The KIC LE and KIC Partners must provide any information requested to evaluate its impact, including information in electronic format.

29.2 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the EIT may apply the measures described in Section 5.

SUBSECTION 3 RIGHTS AND OBLIGATIONS RELATED TO BACKGROUND AND RESULTS OF THESPECIFIC ACTIONS

SUBSUBSECTION 1 GENERAL

ARTICLE 29a — MANAGEMENT OF INTELLECTUAL PROPERTY

29a.1 Obligation to take measures to implement the Commission Recommendation on the management of intellectual property in knowledge transfer activities

KIC Partners that are universities or other public research organisations must take measures to implement the principles set out in Points 1 and 2 of the Code of Practice annexed to the Commission Recommendation on the management of intellectual property in knowledge transfer activities.

This does not change the obligations set out in Subsubsections 2 and 3 of this Subsection.

The KIC Partners must ensure that researchers and third parties involved in the specific actions are aware of them.

29a.2 Consequences of non-compliance

If a KIC Partner breaches its obligations under this Article, the EIT may apply any of the measures described in Section 5.

SUBSUBSECTION 2 RIGHTS AND OBLIGATIONS RELATED TO BACKGROUND

ARTICLE 30 — AGREEMENT ON BACKGROUND

30.1 Agreement on background

'Background' means any data, know-how or information held by any KIC Partner — whatever its form or nature (tangible or intangible), including any rights such as intellectual property rights — that:

(a) is held by the KIC Partners before they entered into the Specific Agreement concerned or no later than before the commencement of the particular KIC added value activity and

(b) is needed to implement the KIC added-value activities in which they participate under the specific action or exploit the results thereof.

The KIC Partners must identify and agree (in writing) on the background for the KIC added value activities in which they participate under the specific action ('agreement onbackground').

30.2 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the grant may be reduced(see Article 49).

Such breaches may also lead to any of the other measures described in Section 5.

ARTICLE 31 — ACCESS RIGHTS TO BACKGROUND

31.1 Exercise of access rights — Waiving of access rights — No sub-licensing

To exercise access rights, this must first be requested in writing ('request for access').

'Access rights' means rights to use results or background under the terms and conditions laiddown in this Agreement.

Waivers of access rights are not valid unless in writing.

Unless agreed otherwise, access rights do not include the right to sub-license.

31.2 Access rights for other KIC Partners, for implementing their own tasks under thespecific action

The KIC Partners participating in the same KIC added value activity under the specific action must give each other access — on a royalty-free basis — to background needed to implement their own tasks under the particular KIC added value activity, unless the KIC Partner that holds the background has — no later than before the commencement of the particular KIC added value activity —:

(a) informed the other KIC Partners participating in the same KIC added value activity that access to its background is subject to legal restrictions or limits, including those imposed by the rights of third parties (including personnel), or

(b) agreed with the other KIC Partners participating in the same KIC added value activity that access would not be on a royalty-free basis.

31.3 Access rights for other KIC Partners, for exploiting their own results of the specific action

The KIC Partners participating in the same KIC added value activity must give each other access — under fair and reasonable conditions— to background needed for exploiting their own results of the same KIC added value activity, unless the KIC Partner that holds the background has — no later than before the commencement of the particular KIC added value activity — informed the other KIC Partners participating in the same KIC added value activity that access to its background is subject to legal restrictions or limits, including those imposed by the rights of third parties (including personnel).

'Fair and reasonable conditions' means appropriate conditions, including possible financial terms or royalty-free conditions, taking into account the specific circumstances of the request for access, for example the actual or potential value of the results or background to which access is requested and/or the scope, duration or other characteristics of the exploitation envisaged.

Request for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3 of the Specific Agreement.

31.4 Access rights for other KIC Partners, for other KIC added value activities under the specific action

The Specific Agreement may provide for access rights to background for other KIC Partners for other KIC added value activities under the specific action (under the framework partnership) (see Article 18 SGA).

31.5 Access rights for affiliated entities

Unless otherwise agreed in the Internal Agreement, access to background must also be given — under fair and reasonable conditions (see above Article 31.3) and unless it is subject to legal restrictions or limits, including those imposed by the rights of third parties (including

personnel) — to affiliated entities[4] established in an EU Member State or 'associated country'[5], if this is needed to exploit the results generated by the KIC Partners to which they are affiliated.

Unless agreed otherwise (see above, Article 31.1), the affiliated entity concerned must make the request directly to the KIC Partner that holds the background.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3 of the Specific Agreement.

31.6 Access rights for third parties

The Specific Agreement may provide for access rights for third parties to background (see Article 18 SGA).

31.7 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the specific grant may be reduced (see Article 49).

Such breaches may also lead to any of the other measures described in Section 5.

SUBSUBSECTION 3 RIGHTS AND OBLIGATIONS RELATED TO RESULTS

ARTICLE 32 — OWNERSHIP OF RESULTS

32.1 Ownership by the KIC Partner that generates the results

Results of the specific action are owned by the KIC Partner that generates them.

'Results' means any (tangible or intangible) output of the specific action such as data, knowledge or information — whatever its form or nature, whether it can be protected or not — that is generated in the specific action, as well as any rights attached to it, including intellectual property rights.

32.2 Joint ownership by the several KIC

PartnersTwo or more KIC Partners own results jointly if:

(a) they have jointly generated them and

(b) it is not possible to:

(i) establish the respective contribution of each KIC Partner, or

[4] As defined in the Article 2.1(2) of the Horizon 2020 Rules for Participation, Regulation (EU) No 1290/2013.

[5] As defined in the Article 2.1(3) of the Horizon 2020 Rules for Participation, Regulation (EU) No 1290/2013.

(ii) separate them for the purpose of applying for, obtaining or maintaining theirprotection (see Article 33).

The joint owners must agree (in writing) on the allocation and terms of exercise of their joint ownership ('joint ownership agreement'), to ensure compliance with their obligations under the Framework Partnership Agreement and the Specific Agreement.

Unless otherwise agreed in the joint ownership agreement, each joint owner may grant non- exclusive licences to third parties to exploit jointly-owned results (without any right to sub- license), if the other joint owners are given:

(a) at least 45 days advance notice and

(b) fair and reasonable compensation.

Once the results have been generated, joint owners may agree (in writing) to apply another regime than joint ownership (such as, for instance, transfer to a single owner (see Article 36) with access rights for the others).

32.3 Rights of third parties (including personnel)

If third parties (including personnel) may claim rights to the results, the KIC Partner concerned must ensure that it complies with its obligations under the Framework PartnershipAgreement and the Specific Agreement.

If a third party generates results, the KIC Partner concerned must obtain all necessary rights (transfer, licences or other) from the third party, in order to be able to respect its obligations as if those results were generated by the KIC Partner itself.

If obtaining the rights is impossible, the KIC Partner must refrain from using the third party to generate the results.

32.4 EIT ownership, to protect results

32.4.1 The EIT may — with the consent of the KIC Partner concerned — assume ownership ofthe results of a specific action to protect them, if a KIC Partner intends — up to four years after the period set out in Article 3 of the Specific Agreement — to disseminate its results without protecting them, except in any of the following cases:

(a) the lack of protection is because protecting the results is not possible, reasonable orjustified (given the circumstances);

(b) the lack of protection is because there is a lack of potential for commercial orindustrial exploitation, or

(c) the KIC Partner intends to transfer the results to another KIC Partner or third partyestablished in an EU Member State or associated country, which will protect them.

Before the results are disseminated and unless any of the cases above under Points (a), (b) or (c) applies, the KIC Partner must formally notify the EIT and at the same time inform it of any reasons by the KIC Partner for refusing consent. The KIC Partner may refuse consent only if it can show that its legitimate interests would suffer significant harm.

If the EIT decides to assume ownership, it will formally notify the KIC Partner within 45 daysof receiving notification.

No dissemination relating to these results may take place before the end of this period or, if the EIT takes a positive decision, until it has taken the necessary steps to protect the results.

32.4.2 The EIT may — with the consent of the KIC Partner concerned — assume ownership ofthe results of a specific action to protect them, if a KIC Partner intends — up to four years after the period set out in Article 3 of the Specific Agreement— to stop protecting them or not to seek an extension of protection, except in any of the following cases:

(a) the protection is stopped because of a lack of potential for commercial or industrialexploitation;

(b) an extension would not be justified given the circumstances.

A KIC Partner that intends to stop protecting results or not seek an extension must — unless any of the cases above under Points (a) or (b) applies — formally notify the EIT at least 60 days before the protection lapses or its extension is no longer possible and at the same time inform it of any reasons for refusing consent. The KIC Partner may refuse consent only if it can show that its legitimate interests would suffer significant harm.

If the EIT decides to assume ownership, it will formally notify the KIC Partner concerned within 45 days of receiving notification.

32.5 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the specific grant may bereduced (see Article 49).

Such breaches may also lead to the any of the other measures described in Section 5.

ARTICLE 33 — PROTECTION OF RESULTS — VISIBILITY OF EU FUNDING

33.1 Obligation to protect the results

Each KIC Partner must examine the possibility of protecting its results of the specific action and must adequately protect them — for an appropriate period and with appropriate territorial coverage — if:

(a) the results can reasonably be expected to be commercially or industrially exploitedand

(b) protecting them is possible, reasonable and justified (given the circumstances).

When deciding on protection, the KIC Partner must consider its own legitimate interests and the legitimate interests (especially commercial) of the other KIC Partners.

33.2 EIT ownership, to protect the results

If a KIC Partner intends not to protect its results, to stop protecting them or not seek an extension of protection, the EIT may — under certain conditions (see Article 32.4) — assume ownership to ensure their (continued) protection.

33.3 Information on EIT and EU funding

Applications for protection of results (including patent applications) filed by or on behalf of a KIC Partner must — unless the EIT requests or agrees otherwise or unless it is impossible — include the following:

> "The activity leading to this application has received funding from the European Institute of Innovation and Technology (EIT) under grant agreement No [number]. ThisEuropean body receives support from the European Union's the Horizon 2020 research and innovation programme".

33.4 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the specific grant may bereduced (see Article 49).

Such a breach may also lead to any of the other measures described in Section 5.

ARTICLE 34 — EXPLOITATION OF RESULTS

34.1 Obligation to exploit the results

Each KIC Partner must — up to four years after the period set out in Article 3 of the Specific Agreement — take measures aiming to ensure 'exploitation' of its results of the specific action (either directly or indirectly, in particular through transfer or licensing; see Article 36) by:

(a) using them in further research activities (outside the specific action);

(b) developing, creating or marketing a product or process;

(c) creating and providing a service;

(d) using them in standardisation activities, or

(e) using them in further knowledge triangle activities.

The Specific Agreement may provide for additional exploitation obligations (see Article 18SGA).

This does not change the security obligations in Article 43, which still apply.

34.2 Results that could contribute to European or international standards — Information on EIT and EU Funding

The Specific Agreement may provide for additional exploitation provisions (see Article 18SGA).

If results are incorporated in a standard, the KIC Partner concerned must — unless the EIT requests or agrees otherwise or unless it is impossible — ask the standardisation body to include the following statement in (information related to) the standard:

> "Results incorporated in this standard received funding from the European Institute of Innovation and Technology (EIT) under grant agreement No [Number]. This European body receives support from the European Union's Horizon 2020 research and innovation programme".

34.3 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the specific grant may be reduced in accordance with Article 49.

Such a breach may also lead to any of the other measures described in Section 5.

ARTICLE 35 — DISSEMINATION OF RESULTS — OPEN ACCESS — VISIBILITY OF EIT AND EUFUNDING

35.1 Obligation to disseminate results

Unless it goes against their legitimate interests, each KIC Partner must — as soon as possible — 'disseminate' its results of the specific action by disclosing them to the public by appropriate means (other than those resulting from protecting or exploiting the results), including in scientific publications (in any medium).

The Specific Agreement may provide for additional dissemination obligations (see Article 18 SGA).

This does not change the obligation to protect results in Article 33, the confidentiality obligations in Article 42, the security obligations in Article 43 or the obligations to protect personal data in Article 45, all of which still apply.

A KIC Partner that intends to disseminate its results must give advance notice to the other KICPartners of — unless agreed otherwise — at least 45 days, together with sufficient information on the results it will disseminate.

Any other KIC Partner may object within — unless agreed otherwise — 30 days of receiving notification, if it can show that its legitimate interests in relation to the results or background would be significantly harmed. In such cases, the dissemination may not take place unless appropriate steps are taken to safeguard these legitimate interests.

If a KIC Partner intends not to protect its results, it may — under certain conditions (see Article 32.4.1) — need to formally notify the EIT before dissemination takes place.

35.2 Open access to scientific publications

Each KIC Partner must ensure open access (free of charge, online access for any user) to all peer-reviewed scientific publications relating to its results.

In particular, it must:

(a) as soon as possible and at the latest on publication, deposit a machine-readable electronic copy of the published version or final peer-reviewed manuscript accepted for publication in a repository for scientific publications;

Moreover, the KIC Partner must aim to deposit at the same time the research dataneeded to validate the results presented in the deposited scientific publications.

(b) ensure open access to the deposited publication — via the repository — at thelatest:

(i) on publication, if an electronic version is available for free via the publisher, or

(ii) within six months of publication (twelve months for publications in the socialsciences and humanities) in any other case.

(c) ensure open access — via the repository — to the bibliographic metadata that identify the deposited publication.

The bibliographic metadata must be in a standard format and must include all of thefollowing:

- the terms "EIT", "European Union (EU)" and "Horizon 2020";
- the name of the specific action, acronym and grant number;

- the publication date, and length of embargo period if applicable, and
- a persistent identifier.

35.3 Open access to research data

The Specific Agreement may provide for additional dissemination obligations concerningopen access to research data (see Article 18 SGA).

35.4 Information on EIT and EU funding — Obligation and right to use the EIT KIC logo andEU emblem

Unless the EIT requests or agrees otherwise or unless it is impossible, any dissemination ofresults (in any form, including electronic) must:

(a) display the EIT KIC logo as adopted by the EIT (hereafter referred to as "EIT KIClogo");

(b) display the EU emblem and

(c) include the following text:

"This activity has received funding from the European Institute of Innovation and Technology (EIT) under grant agreement No [Number]. This European body receives support from the Horizon 2020 research and innovation programme".

When displayed together with another logo, the EIT KIC logo and EU emblem must have appropriate prominence.

For the purposes of their obligations under this Article, the KIC Partners may use the EIT KIClogo and the EU emblem without first obtaining approval from the EIT or the Commission.

This does not however give them the right to exclusive use.

Moreover, they may not appropriate the EIT KIC logo and the EU emblem (or any similar trademark or logo), either by registration or by any other means.

35.5 Disclaimer excluding EIT responsibility

Any dissemination of results must indicate that it reflects only the author's view and that theEIT is not responsible for any use that may be made of the information it contains.

35.6 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the specific grant may bereduced (see Article 49).

Such a breach may also lead to any of the other measures described in Section 5.

ARTICLE 36 — TRANSFER AND LICENSING OF RESULTS

36.1 Transfer of ownership

Each KIC Partner may transfer ownership of its results of the specific action.

It must however ensure that its obligations under Articles 32.2, 32.4, 33, 34, 35, 36 and 37 also apply to the new owner and that this owner has the obligation to pass them on in any subsequent transfer.

This does not change the security obligations in Article 43, which still apply.

Unless agreed otherwise (in writing) for specifically-identified third parties or unless impossible under applicable laws on mergers and acquisitions, a KIC Partner that intends to transfer ownership of results must give at least 45 days advance notice (or less if agreed in writing) to the other KIC Partners that still have (or still may request) access rights to the results. This notification must include sufficient information on the new owner to enable any KIC Partner concerned to assess the effects on its access rights.

Unless agreed otherwise (in writing) for specifically-identified third parties, any other KIC Partner may object within 30 days of receiving notification (or less if agreed in writing), if it can show that the transfer would adversely affect its access rights. In this case, the transfer may not take place until agreement has been reached between the KIC Partners concerned.

36.2 Granting licenses

Each KIC Partner may grant licences to its results of the specific action (or otherwise give the right to exploit them), if:

(a) this does not impede access rights (see Article 37) and

(b) the KIC Partner complies with its additional exploitation obligations (if any) (see Article 34.1).

In addition to Points (a) and (b), exclusive licences for results may be granted only if all the other KIC Partners concerned have waived their access rights (see Article 37.1).

This does not change the dissemination obligations in Article 35 or security obligations in Article 43, which still apply.

36.3 EIT right to object to transfers or licensing

The Specific Agreement may provide for the right of the EIT to object to a transfer ofownership or the licencing of results (see Article 18 SGA).

36.4 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the specific grant may bereduced (see Article 49).

Such a breach may also lead to any of the other measures described in Section 5.

ARTICLE 37 — ACCESS RIGHTS TO RESULTS

37.1 Exercise of access rights — Waiving of access rights — No sub-licensingThe conditions set out in Article 31.1 apply.

The obligations set out in this Article do not change the security obligations in Article 43,which still apply.

37.2 Access rights for the other KIC Partners, for implementing their own tasks under thespecific action

The KIC Partners participating in the same KIC added value activity must give each other access — on a royalty-free basis — to results needed for implementing their own tasks in the same KIC added value activity under the specific action.

37.3 Access rights for the other KIC Partners, for exploiting their own results

For each specific action, the KIC Partners participating in the same KIC added value activity must give each other — under fair and reasonable conditions (see Article 31.3) — access to results needed for exploiting their own results from the same KIC added value activity.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3 of the Specific Agreement.

37.4 Access rights for the other KIC Partners, for other KIC added value activities under thespecific action

The Specific Agreement may provide for access rights to results for the other KIC Partners for other KIC added value activities under the specific action (under the framework partnership) (see Article 18 SGA).

37.5 Access rights of affiliated entities

Unless agreed otherwise in the Internal Agreement, access to results must also be given — under fair and reasonable conditions (see Article 31.3) — to affiliated entities established in an EU Member State or associated country, if this is needed for those entities to exploit the results generated by the KIC Partners to which they are affiliated.

Unless agreed otherwise (see Article 37.1), the affiliated entity concerned must make anysuch request directly to the KIC Partner that owns the results.

Requests for access may be made — unless agreed otherwise — up to one year after theperiod set out in Article 3 of the Specific Agreement.

37.6 Access rights for the EU institutions and bodies and EU Member States

The Specific Agreement may provide for access rights for EU institutions and bodies and EUMember States to results (see Article 18 SGA).

37.7 Access rights for third parties

The Specific Agreement may provide for access rights for third parties to results (see Article18 SGA).

37.8 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the specific grant may be reduced (see Article 49).

Such breaches may also lead to any of the other measures described in Section 5.

SUBSECTION 4 OTHER RIGHTS AND OBLIGATIONS

ARTICLE 38 — RECRUITMENT AND WORKING CONDITIONS FOR RESEARCHERS

38.1 Obligation to take measures to implement the European Charter for Researchers andCode of Conduct for the Recruitment of Researchers

The KIC Partners must take all measures to implement the principles set out in the Commission Recommendation on the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers[6], in particular regarding:

- working conditions;
- transparent recruitment processes based on merit, and
- career development.

The KIC Partners must ensure that researchers and third parties involved in the specificaction are aware of them.

38.2 Consequences of non-compliance

[6] Commission Recommendation 2005/251/EC of 11 March 2005 on the European Charter for Researchers andon a Code of Conduct for the Recruitment of Researchers (OJ L 75, 22.3.2005, p. 67).

If a KIC Partner breaches its obligations under this Article, the EIT may apply any of the measures described in Section 5.

ARTICLE 39 — GENDER EQUALITY

39.1 Obligation to aim for gender equality

The KIC Partners must take all measures to promote equal opportunities between men and women in the implementation of the specific actions. They must aim, to the extent possible, for a gender balance at all levels of personnel assigned to the specific actions, including at supervisory and managerial level.

39.2 Consequences of non-compliance

If a KIC Partner breaches its obligations under this Article, the EIT may apply any of the measures described in Section 5.

ARTICLE 40 — ETHICS

40.1 Obligation to comply with ethical principles

The KIC Partners must carry out the specific actions in compliance with:

(a) ethical principles (including the highest standards of research integrity — as set out, for instance, in the European Code of Conduct for Research Integrity[7] — and including, in particular, avoiding fabrication, falsification, plagiarism or other research misconduct) and

(b) applicable international, EU and national law.

Funding will not be granted for activities carried out outside the EU if they are prohibited inall Member States.

The KIC Partners must ensure that the activities under the specific actions have an exclusive focus on civil applications.

The KIC Partners must ensure that the activities under the specific actions do not:

(a) aim at human cloning for reproductive purposes;

[7] The European Code of Conduct for Research Integrity of ALLEA (All European Academies) and ESF (European Science Foundation) of March 2011. http://www.esf.org/fileadmin/Public_documents/Publications/Code_Conduct_ResearchIntegrity.pdf

(b) intend to modify the genetic heritage of human beings which could make such changes heritable (with the exception of research relating to cancer treatment of the gonads, which may be financed), or

(c) intend to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer.

40.2 Activities raising ethical issues

Activities raising ethical issues must comply with the 'ethics requirements' set out in Annex 1 to the Specific Agreements (if applicable).

Before the beginning of an activity raising an ethical issue, the KIC LE must submit (see Article58) to the EIT a copy of:

(a) any ethics committee opinion required under national law, and

(b) any notification or authorisation for activities raising ethical issues required under national law.

If these documents are not in English, the KIC LE must also submit an English summary of the submitted opinions, notifications and authorisations (containing, if available, the conclusions of the committee or authority concerned).

If these documents are specifically requested for a specific action, they must contain an explicit reference to the action title. The KIC LE must submit a declaration by each KIC Partnerconcerned that these documents specifically cover the action tasks.

40.3 Activities involving human embryos or human embryonic stem cells

Activities involving research on human embryos or human embryonic stem cells may be carried out, only if:

- they are set out in Annex 1 to the Specific Agreements or
- if the KIC LE has obtained explicit approval (in writing) from the EIT (see Article 58).

40.4 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the specific grant may be reduced (see Article 49) and the Specific Agreement concerned or participation of the KIC Partner may be terminated (see Article 56).

Such breaches may also lead to any of the other measures described in Section 5.

ARTICLE 41 — CONFLICT OF INTERESTS

41.1 Obligation to avoid a conflict of interests

The KIC Partners must take all measures to prevent any situation where the impartial and objective implementation of the specific actions is compromised for reasons involving economic interest, political or national affinity, family or emotional ties or any other shared interest (‘conflict of interests’).

They must formally notify to the EIT without delay any situation constituting or likely to lead to a conflict of interests and immediately take all the necessary steps to rectify this situation.

The EIT may verify that the measures taken are appropriate and may require additional measures to be taken by a specified deadline.

41.2 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the grant may be reduced (see Article 49) and the Specific Agreement or participation of the KIC Partner may beterminated (see Article 56).

Such breaches may also lead to any of the other measures described in Section 5.

ARTICLE 42 — CONFIDENTIALITY

42.1 General obligation to maintain confidentiality

During implementation of the specific action and for four years after the period set out in Article 3 of the Specific Agreement, the parties must keep confidential any data, documents or other material (in any form) that is identified as confidential at the time it is disclosed (‘confidential information’).

If a KIC Partner requests, the EIT may agree to keep such information confidential for an additional period beyond the initial four years.

If information has been identified as confidential only orally, it will be considered to be confidential only if this is confirmed in writing within 15 days of the oral disclosure.

Unless otherwise agreed between the parties, they may use confidential information only to implement the Framework Partnership Agreement or Specific Agreement.

The KIC Partners may disclose confidential information to their personnel or third parties involved in the specific action only if they:

(a) need to know to implement the Framework Partnership Agreement or SpecificAgreements and

(b) are bound by an obligation of confidentiality.

This does not change the security obligations in Article 43, which still apply.

The EIT may disclose confidential information to its staff, other EU institutions and bodies orthird parties, if:

(a) this is necessary to implement the Framework Partnership Agreement or Specific Agreement or safeguard the EIT's financial interests and

(b) the recipients of the information are bound by an obligation of confidentiality.

The confidentiality obligations no longer apply if:

(a) the disclosing party agrees to release the other party;

(b) the information was already known by the recipient or is given to him without obligation of confidentiality by a third party that was not bound by any obligation of confidentiality;

(c) the recipient proves that the information was developed without the use of confidential information;

(d) the information becomes generally and publicly available, without breaching any confidentiality obligation, or

(e) the disclosure of the information is required by EU or national law.

42.2 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the specific grant may bereduced (see Article 49).

Such breaches may also lead to any of the other measures described in Section 5.

ARTICLE 43 — SECURITY-RELATED OBLIGATIONS

43.1 Results with a security recommendation

Before disclosing 'results with a security recommendation' to a third party (including linked third parties, such as affiliated entities), a KIC Partner must inform the KIC LE — which must request written approval from the EIT.

43.2 Classified results

Activities related to 'classified results' (see Annex 1 to the Specific Agreement) must comply with the 'security requirements' (Security Aspect Letter (SAL) and the Security Classification

Guide (SCG) (if applicable), set out in Annex 1 to the Specific Agreement until they are declassified.

Action tasks related to classified results may not be subcontracted without prior explicit written approval from the EIT.

The KIC Partners must inform the KIC LE — which must immediately inform the EIT — of any changes in the security context and — if necessary —request for Annex 1 to the Specific Agreement to be amended (see Article 61).

43.3 Activities involving dual-use goods or dangerous materials and substances

Activities involving dual-use goods or dangerous materials and substances must comply with applicable EU, national and international law.

Before the beginning of the activity, the KIC LE must submit to the EIT (see Article 58) a copy of any export or transfer licences required under EU, national or international law.

43.4 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the specific grant may be reduced (see Article 49).

Such breaches may also lead to any of the other measures described in Section 5.

ARTICLE 44 — PROMOTING THE KIC — VISIBILITY OF THE EIT AND EU FUNDING

44.1 Communication activities by the KIC Partners

44.1.1 Obligation to promote the specific action and its results

The KIC Partners must promote the specific action and its results by providing targeted information to multiple audiences (including the media and the public) in a strategic and effective manner.

This does not change the specific dissemination obligations in Article 35, the confidentiality obligations in Article 42 or the security obligations in Article 43, all of which still apply.

Before engaging in a communication activity expected to have a major media impact, the KIC Partners must inform the EIT (see Article 58).

44.1.2 Information on EIT and EU funding — Obligation and right to use the EIT KIC logo andthe EU emblem

Unless the EIT requests or agrees otherwise or unless it is impossible, any communication activity related to the specific action (including in electronic form, via social media, etc.) as well as any infrastructure, equipment and major results funded by the specific grants must:

(a) display the EIT KIC logo as adopted by the EIT;

(b) display the EU emblem;

(c) follow the brand guidelines outlined in the EIT Community Brand Book as adopted by the EIT; and

(d) include the following text:

> For communication activities: 'This activity has received funding from the European Institute of Innovation and Technology (EIT). This body of the European Union receives support from the European Union's Horizon 2020 research and innovation programme.'
>
> For infrastructure, equipment and major results: 'This *[infrastructure] [equipment] [insert type of result]* is part of an activity that has received funding from the European Institute of Innovation and Technology (EIT). This body of the European Union receives support from the European Union's Horizon 2020 research and innovation programme.'.

When displayed together with another logo, the EIT KIC logo and the EU emblem must have appropriate prominence.

For the purposes of their obligations under this Article, the KIC Partners may use the EIT KIC logo and the EU emblem without prior approval from the EIT.

This does not, however, give them the right to exclusive use.

Moreover, they may not appropriate the EIT KIC logo or the EU emblem (or any similar trademark or logo), either by registration or by any other means.

44.1.3 Disclaimer excluding EIT responsibility

Any communication activity related to the specific action must indicate that it reflects only the author's view and that the EIT is not responsible for any use that may be made of the information it contains.

44.2 Communication activities by the EIT

44.2.1 Right to use KIC's materials, documents or information

The EIT may use, for its communication and dissemination activities, information relating to the specific action, documents notably summaries for publication and public deliverables as well as any other material, such as pictures or audio-visual material that it receives from any KIC Partner (including in electronic form).

This does not change the confidentiality obligations in Article 42 and the security obligations in Article 43, all of which still apply.

However, if the EIT's use of these materials, documents or information would risk compromising legitimate interests, the KIC Partner concerned may request the EIT not to use it (see Article 58).

The right to use a KIC Partner's materials, documents and information includes:

(a) use for its own purposes (in particular, making them available to persons working forthe EIT or any other EU institution, agency or body, or institutions in EU Member States; and copying or reproducing them in whole or in part, in unlimited numbers);

(b) distribution to the public (in particular, publication as hard copies and in electronic ordigital format, publication on the internet, as a downloadable or non-downloadable file, broadcasting by any channel, public display or presentation, communicating through press information services, or inclusion in widely accessible databases or indexes);

(c) editing or redrafting for communication and publicising activities (including shortening, summarising, inserting other elements (such as meta-data, legends, other graphic, visual, audio or text elements), extracting parts (e.g. audio or video files), dividing into parts, use in a compilation);

(d) translation;

(e) giving access in response to individual requests under Regulation No 1049/2001 , without the right to reproduce or exploit;

(f) storage in paper, electronic or other form;

(g) archiving, in line with applicable document-management rules, and

(h) the right to authorise third parties to act on its behalf or sub-license the modes of useset out in Points (b),(c),(d) and (f) to third parties, if needed for the communication and publicising activities of the EIT.

If the right of use is subject to rights of a third party (including personnel of the KIC Partner), the KIC Partner must ensure that it complies with its obligations under the FrameworkPartnership Agreement and the Specific Agreement (in particular, by obtaining the necessary approval from the third parties concerned).

Where applicable (and if provided by the KIC Partners), the EIT will insert the following information:

"© - [year] - [name of the copyright owner]. All rights reserved. Licensed to theEuropean Institute of Innovation and Technology (EIT) under conditions."

44.3 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under this Article, the specific grant may be reduced (see Article 49).

Such breaches may also lead to any of the other measures described in Section 5.

ARTICLE 45 — PROCESSING OF PERSONAL DATA

45.1 Processing of personal data by the EIT and the Commission

Any personal data under the Framework Partnership Agreement and the Specific Agreementswill be processed by the EIT or the Commission under Regulation No 45/2001[8] and according to the 'notifications of the processing operations' to the Data Protection Officer (DPO) of the EIT or of the Commission (publicly accessible in the DPO register).

Such data will be processed by the 'data controller' of the EIT or of the Commission for the purposes of implementing, managing and monitoring of those agreements or protecting the financial interests of the EIT, the EU or Euratom (including checks, reviews, audits and investigations; see Article 28).

The persons whose personal data are processed have the right to access and correct their own personal data. For this purpose, they must send any queries about the processing of their personal data to the data controller, via the contact point indicated in the 'service specific privacy statement' on the EIT's and the Commission's website.

They also have the right to have recourse at any time to the European Data Protection Supervisor (EDPS).

45.2 Processing of personal data by the KIC Partners

The KIC Partners must process personal data under the Framework Partnership Agreement and Specific Agreements in compliance with the applicable EU and national law on data protection (including authorisations or notification requirements).

The KIC Partners may grant their personnel access only to data that is strictly necessary for implementing, managing and monitoring of those agreements.

The KIC Partners must inform the personnel whose personal data are collected and processed by the EIT or the Commission. For this purpose, they must provide them with the service specific privacy statement (see above), before transmitting their data to the EIT or theCommission.

[8] Regulation (EC) No 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, 12.01.2001, p. 1).

45.3 Consequences of non-compliance

If a KIC Partner breaches any of its obligations under Article 45.2, the EIT may apply any ofthe measures described in Section 5.

ARTICLE 46 — ASSIGNMENTS OF CLAIMS FOR PAYMENT AGAINST THE EIT

The KIC Partners may not assign any of their claims for payment against the EIT to any third party, except if approved by the EIT on the basis of a reasoned, written request by the KIC LE (on behalf of the KIC Partner concerned).

If the EIT has not accepted the assignment or the terms of it are not observed, the assignment will have no effect on it.

In no circumstances will an assignment release the KIC Partners from their obligations towards the EIT.

SECTION 4 DIVISION OF KIC PARTNERS' ROLES AND RESPONSIBILITIES

ARTICLE 47 — DIVISION OF KIC PARTNERS' ROLES AND RESPONSIBILITIES

47.1 Roles and responsibilities towards the EIT

The KIC Partners have full responsibility for implementing the action ("action" in the context of this article means the particular KIC added value activity in which the KIC Partner participates) as described in Annex 1 to the Specific Agreement and complying with the Framework Partnership Agreement and the Specific Agreement.

The KIC Partners are jointly and severally liable for the technical implementation of the action as described in Annex 1 to the Specific Agreement. If a KIC Partner fails to implement its part of the action, the other KIC Partners become responsible for implementing this part (without being entitled to any additional EIT funding for doing so), unless the EIT expressly relieves them of this obligation.

The financial responsibility of each KIC Partner is governed by Articles 50, 51 and 52.

47.2 Internal division of roles and responsibilities

The internal roles and responsibilities of the KIC Partners are divided as follows:

(a) Each KIC Partner must:

(i) not applicable;

(ii) inform the KIC LE immediately of any events and circumstances likely to affect significantly or delay the implementation of a specific action (see Article 23);

(iii) submit to the KIC LE in good time:

- individual financial statements for itself and its linked third parties and, if required, certificates on the financial statements (see Article 16 SGA);
- the data needed to draw up the technical report (see Article 16 SGA);
- ethics committee opinions and notifications or authorisations for activities raising ethical issues (see Article 40);
- any other documents or information required by the EIT under the Framework Partnership Agreement or the Specific Agreement, unless those agreements require the KIC Partner to submit this information directly to the EIT.

(b) The KIC LE must:

(i) monitor that the specific action is implemented properly (see Article 12);

(ii) act as the intermediary for all communications between the KIC Partners andthe EIT (in particular, providing the EIT with the information described in Article 23), unless the Framework Partnership Agreement or the Specific Agreement specify otherwise;

(iii) request and review any documents or information required by the EIT and verifytheir completeness and correctness and consolidate them before passing it on to the EIT;

(iv) submit the deliverables and reports to the EIT (see Articles 25 and Article 16 SGA);

(v) ensure that all payments are made to the other KIC Partners without unjustified delay (see Article 17 SGA);

(vi) inform the EIT of the amounts paid to each KIC Partner, when required under the Framework Partnership Agreement (see Articles 50 and 56) or requested by the EIT.

The KIC LE may not delegate the above-mentioned tasks to any other KIC Partner orsubcontract them to any third party.

47.3 Internal arrangements

The KIC Partners must have internal arrangements regarding their operation and co-ordination to ensure that the specific actions are implemented properly (see Article 4).

47.4 Relationship with complementary beneficiaries — Collaboration

agreementNot applicable

47.5 Relationship with participants of a joint action — Coordination

agreementNot applicable

SECTION 5 REJECTION OF COSTS — REDUCTION OF THE GRANT — RECOVERY — PENALTIES
— DAMAGES — SUSPENSION — TERMINATION — FORCE MAJEURE

SUBSECTION 1 REJECTION OF COSTS — REDUCTION OF THE GRANT — RECOVERY — PENALTIESARTICLE 48 — REJECTION OF INELIGIBLE COSTS

48.1 Conditions

48.1.1 The EIT will — at the time of the payment of the balance or afterwards — reject any costs for a specific action which are ineligible (see Article 5 SGA), in particular, following checks, reviews, audits or investigations (see Article 28).

48.1.2 The rejection may also be based on the extension of findings from other grants to aspecific grant, under the conditions set out in Article 28.5.2.

48.2 Ineligible costs to be rejected — Calculation — Procedure

Ineligible costs will be rejected in full, except for lump sum costs, which will be rejected proportionally to the tasks or parts of the specific action not implemented.

If the EIT rejects costs without reduction of the specific grant (see Article 49) or recovery of undue amounts (see Article 50), it will formally notify the KIC LE or the KIC Partner concerned the rejection of costs, the amounts and the reasons why (if applicable, together with the notification of amounts due; see Article 27). The KIC LE or the KIC Partner concerned may — within 30 days of receiving notification — formally notify the EIT of its disagreement and the reasons why.

If the EIT rejects costs with reduction of the specific grant or recovery of undue amounts, it will formally notify the rejection in the 'pre-information letter' on reduction or recovery set out in Articles 49 and 50.

48.3 Effects

If the EIT rejects costs at the time of the payment of the balance, it will deduct them from thetotal eligible costs declared, for the specific action, in the financial statement (see Article 16 SGA). It will then calculate the payment of the balance (see Article 17 SGA).

If the EIT rejects costs after the payment of the balance, it will deduct the amount rejected from the total eligible costs declared, by the KIC Partner, in the financial statement. It will then calculate the revised final grant amount as set out in Article 10.4.

ARTICLE 49 — REDUCTION OF THE GRANT

49.1 Conditions

49.1.1 The EIT may — at the payment of the balance or afterwards — reduce the maximum grant amount (see Article 4 SGA), if a specific action has not been implemented properly as described in Annex 1 to the Specific Agreement concerned or another obligation under the Framework Partnership Agreement or that Specific Agreement has been breached.

49.1.2 The EIT may also reduce the maximum grant amount on the basis of the extension of findings from other grants to a specific grant, under the conditions set out in Article 28.5.2.

49.2 Amount to be reduced — Calculation — Procedure

The amount of the reduction will be proportionate to the improper implementation of the specific action or to the seriousness of the breach.

Before reduction of the specific grant, the EIT will formally notify a 'pre-information letter' to the KIC LE or the KIC Partner concerned:

- informing it of its intention to reduce the grant, the amount it intends to reduce andthe reasons why and
- inviting it to submit observations within 30 days of receiving notification.

If the EIT does not receive any observations or decides to pursue reduction despite the observations it has received, it will formally notify confirmation of the reduction (if applicable, together with the notification of amounts due; see Article 17 SGA).

49.3 Effects

If the EIT reduces the specific grant at the time of the payment of the balance, it will calculatethe reduced grant amount for the specific action and then determine the amount due as payment of the balance (see Article 10.3.4 and Article 17 SGA).

If the EIT reduces the specific grant after the payment of the balance, it will calculate the revised final grant amount for the KIC Partner concerned (see Article 10.4). If the revised finalgrant amount for the KIC Partner concerned is lower than its share of the final grant amount, the EIT will recover the difference (see Article 50).

ARTICLE 50 — RECOVERY OF UNDUE AMOUNTS

50.1 Amount to be recovered — Calculation — Procedure

The EIT will — after termination of the participation of a KIC Partner, at the payment of the balance or afterwards — claim back any amount that was paid but is not due for a specific grant under the Framework Partnership Agreement and the Specific Agreement concerned.

Each KIC Partner's financial responsibility in case of recovery is limited to its own debtincluding undue amounts paid by the EIT for costs declared by its linked third parties, except for the amount retained for the Guarantee Fund (see Article 17 SGA).

50.1.1 Recovery after termination of a KIC Partner's participation

If recovery takes place after termination of a KIC Partner's participation (including the KIC LE),the EIT will claim back the undue amount from the KIC Partner concerned by formallynotifying it a debit note (see Article 56.2 and 56.3). This note will specify the amount to be recovered, the terms and the date for payment.

If payment is not made by the date specified in the debit note, the EIT will recover the amount as follows:

(a) by 'offsetting' it — without the KIC Partner's consent — against any amounts owedto the KIC Partner concerned by the EIT.

In exceptional circumstances, to safeguard the EU's financial interests, the EIT mayoffset before the payment date specified in the debit note;

(b) not applicable;

(c) taking legal action (see Article 63).

If payment is not made by the date specified in the debit note, the amount to be recovered (see above) will be increased by late-payment interest at the rate set out in Article 17 of the Specific Agreement, from the day following the payment date in the debit note, up to and including the date the EIT receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the KIC Partner, unless Directive 2007/64/EC[9] applies.

[9] Directive 2007/64/EC of the European Parliament and of the Council of 13 November 2007 on payment services in the internal market amending Directives 97/7/EC, 2002/65/EC, 2005/60/EC and 2006/48/EC and repealing Directive 97/5/EC (OJ L 319, 05.12.2007, p. 1).

50.1.2 Recovery at payment of the balance

If the payment of the balance takes the form of a recovery (see Article 17 SGA), the EIT will formally notify a 'pre-information letter' to the KIC LE:

- informing it of its intention to recover, the amount due as the balance and the reasons why;
- specifying that it intends to deduct the amount to be recovered from the amount retained for the Guarantee Fund;
- requesting the KIC LE to submit a report on the distribution of payments to the KIC Partners within 30 days of receiving notification, and
- inviting the KIC LE to submit observations within 30 days of receiving notification.

If no observations are submitted or the EIT decides to pursue recovery despite the observations it has received, it will confirm recovery (together with the notification of amounts due; see Article 17 SGA) and:

- pay the difference between the amount to be recovered and the amount retained for the Guarantee Fund, if the difference is positive or
- formally notify to the KIC LE a debit note for the difference between the amount to be recovered and the amount retained for the Guarantee Fund, if the difference is negative. This note will also specify the terms and the date for payment.

If the KIC LE does not repay the EIT by the date in the debit note and has not submitted the report on the distribution of payments: the EIT will recover the amount set out in the debit note from the KIC LE (see below).

If the KIC LE does not repay the EIT by the date in the debit note, but has submitted the report on the distribution of payments: the EIT will

a) identify the KIC Partners for which the amount calculated as follows is negative:

{{{{KIC Partner's costs declared in the final summary financial statement and approved by the EIT multiplied by the reimbursement rate set out in Article 4 of the Specific Agreement for the KIC Partner concerned

[plus

its linked third parties' costs declared in the final summary financial statement and approved by the EIT multiplied by the reimbursement rate set out in Article 4 of the Specific Agreement for each linked third party concerned]}

divided by

the EU contribution for the specific action calculated according to Article 10.3.1}

multiplied by

the final grant amount (see Article 10.3)},

minus

{pre-financing payment received by the KIC Partner}}.

b) formally notify to each KIC Partner identified according to point (a) a debit note specifying the terms and date for payment. The amount of the debit note is calculated as follows:

{{amount calculated according to point (a) for the KIC Partner concerned
divided by

the sum of the amounts calculated according to point (a) for all the KIC Partners identified according to point (a)}

multiplied by

the amount set out in the debit note formally notified to the KIC LE}.

If payment is not made by the date specified in the debit note, the EIT will recover the amount:

(a) by offsetting it — without the KIC Partner's consent — against any amounts owed to the KIC Partner concerned by the EIT.

In exceptional circumstances, to safeguard the EU's financial interests, the EIT mayoffset before the payment date specified in the debit note;

(b) by drawing on the Guarantee Fund. The EIT will formally notify the KIC Partner concerned the debit note on behalf of the Guarantee Fund and recover the amount by taking legal action (see Article 63).

If payment is not made by the date in the debit note, the amount to be recovered (seeabove) will be increased by late-payment interest at the rate set out in Article 17 of the Specific Agreement, from the day following the payment date in the debit note, up to and including the date the EIT receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the KIC Partner, unless Directive 2007/64/EC applies.

50.1.3 Recovery of amounts after payment of the balance

If for a KIC Partner, the revised final grant amount (see Article 10.4) is lower than its share of the final grant amount, it must repay the difference to the EIT.

The KIC Partner's share of the final grant amount is calculated as follows:

{{{KIC Partner's costs declared in the final summary financial statement and approved by the EIT multiplied by the reimbursement rate set out in Article 4 of the Specific Agreement for the KIC Partner concerned

[plus

its linked third parties' costs declared in the final summary financial statement andapproved by the EIT multiplied by the reimbursement rate set out in Article 4 of the Specific Agreement for each linked third party concerned]}

divided by

the EIT contribution for the action calculated according to Article 10.3.1}

multiplied by

the final grant amount (see Article 10.3)}.

If the KIC LE has not distributed amounts received (see Article 17 SGA), the EIT will also recover these amounts.

The EIT will formally notify a pre-information letter to the KIC Partner concerned:

- informing it of its intention to recover, the due amount and the reasons why and
- inviting it to submit observations within 30 days of receiving notification.

If no observations are submitted or the EIT decides to pursue recovery despite the observations it has received, it will confirm the amount to be recovered and formally notify tothe KIC Partner concerned a debit note. This note will also specify the terms and the date for payment.

If payment is not made by the date specified in the debit note, the EIT will recover the amount:

(a) by offsetting — without the KIC Partner's consent — it against any amounts owed tothe KIC Partner concerned by the EIT.

In exceptional circumstances, to safeguard the EU's financial interests, the EIT mayoffset before the payment date specified in the debit note;

(b) by drawing on the Guarantee Fund. The EIT will formally notify the KIC Partner concerned the debit note on behalf of the Guarantee Fund and recover the amount by taking legal action (see Article 63).

If payment is not made by the date in the debit note, the amount to be recovered (seeabove) will be increased by late-payment interest at the rate set out in Article 17 SGA, from the day following the date for payment in the debit note, up to and including the date the EITreceives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the KIC Partner, unlessDirective 2007/64/EC applies.

ARTICLE 51 — ADMINISTRATIVE AND FINANCIAL PENALTIES

51.1 Conditions

Under Articles 109 and 131(4) of the Financial Regulation No 966/2012, the EIT may impose administrative and financial penalties if a KIC Partner:

(a) has committed substantial errors, irregularities or fraud or is in serious breach of its obligations under the Framework Partnership Agreement or a Specific Agreement or

(b) has made false declarations about information required under those agreements or for the submission of a proposal (or has not supplied such information).

Each KIC Partner is responsible for paying the financial penalties imposed on it.

Under Article 109(3) of the Financial Regulation No 966/2012, the EIT may — under certain conditions and limits — publish decisions imposing administrative or financial penalties.

51.2 Duration — Amount of penalty — Calculation

Administrative penalties exclude the KIC Partner from all EIT contracts and grants for a maximum of five years from the date the infringement is established by the EIT.

If the KIC Partner commits another infringement within five years of the date the first infringement is established, the EIT may extend the exclusion period up to 10 years.

Financial penalties will be between 2% and 10% of the maximum EIT contribution indicated, for the KIC Partner concerned, in the estimated budget (see Annex 2 SGA).

If the KIC Partner commits another infringement within five years of the date the first infringement is established, the EIT may increase the rate of financial penalties to between4% and 20%.

51.3 Procedure

Before applying a penalty, the EIT will formally notify the KIC Partner concerned:

- informing it of its intention to impose a penalty, its duration or amount and thereasons why and

- inviting it to submit observations within 30 days.

If the EIT does not receive any observations or decides to impose the penalty despite of observations it has received, it will formally notify confirmation of the penalty to the KIC Partner concerned and — in case of financial penalties — deduct the penalty from the payment of the balance or formally notify a debit note, specifying the amount to be recovered, the terms and the date for payment.

The EIT will inform the Commission of any penalty imposed.

If payment is not made by the date specified in the debit note, the EIT may recover the amount:

(a) by offsetting it— without the KIC Partner's consent — against any amounts owed tothe KIC Partner concerned by the EIT.

In exceptional circumstances, to safeguard the EU's financial interests, the EIT mayoffset before the payment date in the debit note;

(c) by taking legal action (see Article 63).

If payment is not made by the date in the debit note, the amount to be recovered (seeabove) will be increased by late-payment interest at the rate set out in Article 17 of the Specific Agreement, from the day following the payment date in the debit note, up to and including the date the EIT receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the KIC Partner, unless Directive 2007/64/EC applies.

SUBSECTION 2 LIABILITY FOR DAMAGES

ARTICLE 52 — LIABILITY FOR DAMAGES

52.1 Liability of the EIT

The EIT cannot be held liable for any damage caused to the KIC Partners or to third parties as a consequence of implementing the Framework Partnership Agreement or a Specific Agreement, including for gross negligence.

The EIT cannot be held liable for any damage caused by any of the KIC Partners or third parties involved in the specific action, as a consequence of implementing the Framework Partnership Agreement or a Specific Agreement.

52.2 Liability of the KIC Partners

52.2.1 Conditions

Except in case of force majeure (see Article 57), the KIC Partners must compensate the EITfor any damage the EIT sustains as a result of the implementation of a specific action or because a specific action was not implemented in full compliance with the Framework Partnership Agreement or a Specific Agreement.

Each KIC Partner is responsible for paying the damages claimed from it.

52.2.2 Amount of damages - Calculation

The amount the EIT can claim from a KIC Partner will correspond to the damage caused by that KIC Partner.

52.2.3 Procedure

Before claiming damages, the EIT will formally notify the KIC Partner concerned:

- informing it of its intention to claim damages, the amount and the reasons why and
- inviting it to submit observations within 30 days.

If the EIT does not receive any observations or decides to claim damages despite the observations it has received, it will formally notify confirmation of the claim for damages and a debit note, specifying the amount to be recovered, the terms and the date for payment.

If payment is not made by the date specified in the debit note, the EIT may recover the amount:

(a) by offsetting it — without the KIC Partner's consent — against any amounts owed tothe KIC Partner concerned by the EIT.

In exceptional circumstances, to safeguard its financial interests, the EIT may offsetbefore the payment date in the debit note;

(b) by taking legal action (see Article 63).

If payment is not made by the date in the debit note, the amount to be recovered (seeabove) will be increased by late-payment interest at the rate set out in Article 17 SGA, from the day following the payment date in the debit note, up to and including the date the EIT receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interestand then against the principal.

Bank charges incurred in the recovery process will be borne by the KIC Partner, unlessDirective 2007/64/EC applies.

SUBSECTION 3 SUSPENSION AND TERMINATION

ARTICLE 53 — SUSPENSION OF PAYMENT DEADLINE

53.1 Conditions

The EIT may — at any moment — suspend the payment deadline in a specific grant (seeArticle 17 SGA) if a request for payment (see Article 16 SGA) cannot be approved because:

(a) it does not comply with the provisions of the Specific Agreement (see Article 16SGA);

(b) the final report has not been submitted or is not complete or additional informationis needed, or

(c) there is doubt about the eligibility of the costs declared in the financial statementsand additional checks, reviews, audits or investigations are necessary.

53.2 Procedure

The EIT will formally notify the KIC LE of the suspension and the reasons why.

The suspension will take effect the day notification is sent by the EIT (see Article 58).

If the conditions for suspending the payment deadline are no longer met, the suspension willbe lifted — and the remaining period will resume.

If the suspension exceeds two months, the KIC LE may request the EIT if the suspension will continue.

If the payment deadline has been suspended due to the non-compliance of the final report (see Article 16 SGA) and the revised report or statement is not submitted or was submitted but is also rejected, the EIT may also terminate the Specific Agreement concerned or the participation of the KIC Partner (see Article 56.3.1(j)).

ARTICLE 54 — SUSPENSION OF PAYMENTS

54.1 Conditions

The EIT may — at any moment — suspend for a specific grant, in whole or in part, the pre- financing payment for one or more KIC Partners or the payment of the balance for all KIC Partners, if a KIC Partner:

a) has committed or is suspected of having committed substantial errors, irregularities, fraud or serious breach of obligations in the award procedure or under the Framework Agreement or a Specific Agreement or

b) has committed — in other EIT, EU or Euratom grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on the specific grant (extension of findings from other grants to the specific grant; see Article 28.5.2).

54.2 Procedure

Before suspending payments, the EIT will formally notify the KIC LE:

- informing it of its intention to suspend payments and the reasons why and
- inviting it to submit observations within 30 days of receiving notification.

If the EIT does not receive observations or decides to pursue the procedure despite the observations it has received, it will formally notify confirmation of the suspension. Otherwise,it will formally notify that the suspension procedure is not continued.

The suspension will take effect the day the confirmation notification is sent by the EIT.

If the conditions for resuming payments are met, the suspension will be lifted. The EIT will formally notify the KIC LE.

The KIC Partners may suspend implementation of the specific action (see Article 55.1) or terminate the Specific Agreement concerned or the participation of the KIC Partner concerned (see Articles 56.1 and 56.2).

ARTICLE 55 — SUSPENSION OF THE IMPLEMENTATION OF THE SPECIFIC ACTION

55.1 Suspension of the implementation of the specific action, by the KIC Partners

55.1.1 Conditions

The KIC Partners may suspend implementation of a specific action or any part of it, if exceptional circumstances — in particular *force majeure* (see Article 57) — make implementation impossible or excessively difficult.

55.1.2 Procedure

The KIC LE must immediately formally notify to the EIT of the suspension (see Article 58), stating:

- the reasons why and
- the expected date of resumption.

The suspension will take effect the day this notification is received by the EIT.

Once circumstances allow for implementation to resume, the KIC LE must immediately formally notify the EIT and request an amendment of the Specific Agreement concerned to set the date on which the specific action will be resumed, extend the duration of the specific action and make other changes necessary to adapt the specific action to the new situation (see Article 61) — unless the Specific Agreement or the participation of a KIC Partner has been terminated (see Article 56).

The suspension will be lifted with effect from the resumption date set out in the amendment. This date may be before the date on which the amendment enters into force.

Costs incurred during suspension of the implementation of the specific action are not eligible (see Article 5 SGA).

55.2 Suspension of the implementation of the specific action, by the EIT

55.2.1 Conditions

The EIT may suspend implementation of a specific action or any part of it:

(a) if a KIC Partner has committed or is suspected of having committed substantial errors, irregularities, fraud or serious breach of obligations in the award procedure or under the Framework Partnership Agreement or a Specific Agreement;

(b) if a KIC Partner has committed — in other EIT, EU or Euratom grants awarded to itunder similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on the specific grant (extension of findings from other grants to the specific grant; see Article 28.5.2).

(c) not applicable.

55.2.2 Procedure

Before suspending implementation of the specific action, the EIT will formally notify the KIC LE:

- informing it of its intention to suspend the implementation and the reasons why and
- inviting it to submit observations within 30 days of receiving notification.

If the EIT does not receive observations or decides to pursue the procedure despite the observations it has received, it will formally notify confirmation of the suspension. Otherwise,it will formally notify that the procedure is not continued.

The suspension will take effect five days after the confirmation notification is received by the KIC LE (or on a later date specified in the notification).

It will be lifted if the conditions for resuming implementation of the specific action are met. The KIC LE will be formally notified of the lifting and the Specific Agreement concerned will beamended to set the date on which the specific action will be resumed, extend the duration ofthe specific action and make other changes necessary to adapt the specific action to the new situation (see Article 61) — unless the Agreement has already been terminated (see Article 56).

The suspension will be lifted with effect from the resumption date set out in the amendment.This date may be before the date on which the amendment enters into force.

Costs incurred during suspension are not eligible (see Article 5 SGA).

The KIC Partners may not claim damages due to suspension by the EIT (see Article 52).

Suspension of the implementation of the specific action does not affect the EIT's right to terminate the Agreement or participation of a KIC Partner (see Article 56), reduce the grant or recover amounts unduly paid (see Articles 49 and 50).

ARTICLE 56 — TERMINATION OF THE SPECIFIC AGREEMENT OR OF THE PARTICIPATION OF ONEOR MORE KIC PARTNERS

56.1 Termination of the Specific Agreement, by the KIC Partners

56.1.1 Conditions and procedure

The KIC Partners may terminate a Specific Agreement.

The KIC LE must formally notify termination to the EIT (see Article 58), stating:

- the reasons why and

- the date the termination will take effect. This date must be after the notification.

If no reasons are given or if the EIT considers the reasons do not justify termination, the Specific Agreement concerned will be considered to have been 'terminated improperly'.

The termination will take effect on the day specified in the notification.

56.1.2 Effects

The KIC LE must — within 60 days from when termination takes effect — submit a final report(see Article 16 SGA).

If the EIT does not receive the report within the deadline (see above), no costs are considered as eligible.

The EIT will calculate the final grant amount (see Article 10.3) and the balance (see Article 17 SGA) on the basis of the report submitted. Only costs incurred until termination are eligible. Costs relating to contracts due for execution only after termination are not eligible.

Improper termination may lead to a reduction of the grant (see Article 49).

After termination, the KIC Partners' obligations (in particular Articles 26, 28, 29, Subsection 3 of Section 3 of Chapter 3, 42, 43, 44, 46) continue to apply.

56.2 Termination of the participation of one or more KIC Partners, by the KIC Partners

56.2.1 Conditions and procedure

The participation of one or more KIC Partners in a specific action may be terminated by the KIC LE, on request of the KIC Partner concerned or on behalf of the other KIC Partners; such a request shall be made in compliance with the KIC's governance rules.

The KIC LE must formally notify termination to the EIT (see Article 58) and inform the KIC Partner concerned.

If the KIC LE's participation is terminated, the formal notification must be done by another KIC Partner (acting on behalf of all the other KIC Partners).

The notification must include:

- the reasons why;
- the opinion of the KIC Partner concerned (or proof that this opinion has beenrequested in writing);
- the date the termination takes effect. This date must be after the notification;

- a request for amendment (see Article 61), with a proposal for reallocation of the tasks and the estimated budget of the KIC Partner concerned (see Annexes 1 and 2 SGA) and, if necessary, the addition of one or more new KIC Partners (see Article62). If termination takes effect after the period set out in Article 3 of the Specific Agreement, no request for amendment must be included unless the KIC Partner concerned is the KIC LE. In this case, the request for amendment must propose a new KIC LE.

If this information is not given or if the EIT considers that the reasons do not justify termination, the participation will be considered to have been terminated improperly.

The termination will take effect on the day specified in the notification.

56.2.2 Effects

The KIC LE must — within 30 days from when termination takes effect — submit:

(i) a report on the distribution of payments to the KIC Partner concerned and

(ii) if termination takes effect during the period set out in Article 3 of the Specific Agreement, a 'termination report' from the KIC Partner concerned, containing an overview of the progress of the work until termination, an overview of the use of resources, the individual financial statement and, if applicable, the certificate on the financial statement (see Article 16 SGA).

The information in the termination report must also be included in the final report (seeArticle 16 SGA).

If the request for amendment is rejected by the EIT (because it calls into question thedecision awarding the specific grant or breaches the principle of equal treatment of applicants or the KICs), the Specific Agreement concerned may be terminated according to Article 56.3.1(c).

If the request for amendment is accepted by the EIT, the Specific Agreement concerned is amended to introduce the necessary changes (see Article 61).

The EIT will calculate — on the basis of the termination report and the report on thedistribution of payments — if the pre-financing payment received by the KIC Partner concerned exceed the KIC Partner's EIT contribution (calculated by applying the reimbursement rate(s) to the eligible costs declared by the KIC Partner and its linked third parties and approved by the EIT. Only costs incurred by the KIC Partner concerned until termination takes effect are eligible (see Article 5 SGA). Costs relating to contracts due for execution only after termination are not eligible.

- If the payments received exceed the amounts due:

- if termination takes effect during the period set out in Article 3 of the Specific Agreement and the request for amendment is accepted, the KIC Partner concerned must repay to the KIC LE the amount unduly received. The EIT will formally notify the amount unduly received and request the KIC Partner concerned to repay it to the KIC LE within 30 days of receiving notification. If it does not repay the KIC LE, the EIT will draw upon the Guarantee Fund to pay the KIC LE and then notify a debit note on behalf of the Guarantee Fund to the KIC Partner concerned (see Article 50);

- in all other cases (in particular if termination takes effect after the period setout in Article 3 of the Specific Agreement), the EIT will formally notify a debit note to the KIC Partner concerned. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the EIT the amount due and the EIT will notify a debit note on behalf of the Guarantee Fund to the KIC Partner concerned (see Article 50);

- if the KIC Partner concerned is the former KIC LE, it must repay the new KIC LE the amount unduly received;

  In this case, the EIT will formally notify a debit note to the former KIC LE. If payment is not made by the date in the debit note, the Guarantee Fund will pay to EIT the amount due. The EIT will then pay the new KIC LE and notify a debit note on behalf of the Guarantee Fund to the former KIC LE (see Article 50).

• If the payments received do not exceed the amounts due: amounts owed to the KIC Partner concerned will be included in the payment of the balance.

If the EIT does not receive the termination report within the deadline (see above), the EIT willnot consider any cost as eligible.

If the EIT does not receive the report on the distribution of payments within the deadline (seeabove), it will consider that:

- the KIC LE did not distribute any payment to the KIC Partner concerned, and that

- the KIC Partner concerned must not repay any amount to the KIC LE.

Improper termination may lead to a reduction of the specific grant (see Article 49) ortermination of the Specific Agreement concerned (see Article 56).

After termination, the concerned KIC Partner's obligations (in particular Articles 26, 28, 29, Subsection 3 of Section 3 of Chapter 3, 42, 43, 44, 46) continue to apply.

56.3 Termination of the Specific Agreement or participation for one or more KIC Partners, bythe EIT

56.3.1 Conditions

The EIT may terminate a Specific Agreement or the participation of one or more KIC Partnersin a specific action, if:

(a) one or more KIC Partner do not accede to the Framework Partnership Agreement

(b) a change to their legal, financial, technical, organisational or ownership situation (or those of its linked third parties) is likely to substantially affect or delay the implementation of the specific action or calls into question the decision to award thespecific grant;

(c) following termination of participation for one or more KIC Partners (see above), the necessary changes to the Specific Agreement would call into question the decision awarding the specific grant or breach the principle of equal treatment of applicants or the KICs (see Article 61);

(d) implementation of the specific action is prevented by force majeure (see Article 57) or suspended by the KIC LE (see Article 55.1) and either:

(i) resumption is impossible, or

(ii) the necessary changes to the Specific Agreement would call into question the decision awarding the specific grant or breach the principle of equal treatment of applicants or the KICs;

(e) a KIC Partner is declared bankrupt, being wound up, having its affairs administered by the courts, has entered into an arrangement with creditors, has suspended business activities, or is subject to any other similar proceedings or procedures under national law;

(f) a KIC Partner (or a natural person who has the power to represent or take decisions on its behalf) has been found guilty of professional misconduct, proven by anymeans;

(g) a KIC Partner does not comply with the applicable national law on taxes and social security;

(h) not applicable;

(i) a KIC Partner (or a natural person who has the power to represent or take decisions on its behalf) has committed fraud, corruption, or is involved in a criminal organisation, money laundering or any other illegal activity affecting the EU's financial interests;

(j) a KIC Partner (or a natural person who has the power to represent or take decisions on its behalf) has — in the award procedure or under the Framework Partnership Agreement or the Specific Agreement — committed:

(i) substantial errors, irregularities, fraud or

(ii) serious breach of obligations, including improper implementation of the specificaction, submission of false information, failure to provide required information, breach of ethical principles;

(k) a KIC Partner has committed — in other EIT, EU or Euratom grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on the specific grant(‘extension of findings from other grants to the specific grant’);

The Specific Agreements may provide for additional grounds for termination (see Article 20 SGA).

56.3.2 Procedure

Before terminating the Specific Agreement or participation of one or more KIC Partners, the EIT will formally notify the KIC LE:

- informing it of its intention to terminate and the reasons why and
- inviting it, within 30 days of receiving notification, to submit observations and — in case of Point (j.ii) above — to inform the EIT of the measures to ensure compliance with the obligations under the Framework Partnership Agreement and the Specific Agreement concerned.

If the EIT does not receive observations or decides to pursue the procedure despite the observations it has received, it will formally notify to the KIC LE confirmation of the termination and the date it will take effect. Otherwise, it will formally notify that the procedure is not continued.

The termination will take effect:

- for terminations under Points (b), (c), (e), (g), (h) and (j.ii) above: on the day specified in the notification of the confirmation (see above);
- for terminations under Points (a), (d), (f), (i), (j.i) and (k) above: on the day after the notification of the confirmation is received by the KIC LE.

56.3.3 Effects

(a) for termination of the Agreement:

The KIC LE must — within 60 days from when termination takes effect — submit the final report (see Article 16 SGA).

If the Specific Agreement is terminated for breach of the obligation to submit the final report (see Article 52.3.1(j) and Article 16 SGA) the KIC LE may not submit any reports after termination.

If the EIT does not receive the report within the deadline (see above), the EIT will notconsider any cost as eligible for the specific action.

The EIT will calculate the final grant amount (see Article 10.3) and the balance (see Article 17 SGA) on the basis of the report submitted. Only costs incurred until termination takes effect are eligible (see Article 5 SGA). Costs relating to contracts due for execution only aftertermination are not eligible.

This does not affect the EIT's right to reduce the specific grant (see Article 49) or to impose administrative and financial penalties (Article 51).

The KIC Partners may not claim damages due to termination by the EIT (see Article 52).

After termination, the KIC Partners' obligations (in particular Articles 26, 28, 29, Subsection 3 of Section 3 of Chapter 3, 42, 43, 44, 46) continue to apply.

(b) for termination of the participation of one or more KIC Partners:

The KIC LE must — within 60 days from when termination takes effect — submit:

(i) a report on the distribution of payments to the KIC Partner concerned;

(ii) a request for amendment (see Article 61), with a proposal for reallocation of the tasks and the estimated budget of the KIC Partner concerned (see Annexes 1 and 2 SGA) and, if necessary, the addition of one or more new KIC Partners (see Article62). If termination takes effect after the period set out in Article 3 of the Specific Agreement, no request for amendment must be included unless the KIC Partner concerned is the KIC LE. In this case, the request for amendment must propose a new KIC LE, and

(iii) if termination takes effect during the period set out in Article 3 of the Specific Agreement, a termination report from the KIC Partner concerned, containing an overview of the progress of the work until termination, an overview of the use of resources, the individual financial statement and, if applicable, the certificate on the financial statement (see Article 16 SGA);

The information in the termination report must also be included in the final report (seeArticle 16 SGA).

If the request for amendment is rejected by the EIT (because it calls into question thedecision awarding the grant or breaches the principle of equal treatment of applicants or the KICs), the Specific Agreement may be terminated according to Article 56.3.1(c).

If the request for amendment is accepted by the EIT, the Specific Agreement is amended tointroduce the necessary changes (see Article 61).

The EIT will calculate — on the basis of the termination report and the report on thedistribution of payments — if the pre-financing payment received by the KIC Partner concerned exceed the KIC Partner's EU contribution (calculated by applying the reimbursement rate(s) to the eligible costs declared by the KIC Partner and its linked third parties and approved by the EIT). Only costs incurred by the KIC Partner concerned until termination takes effect are eligible (see Article 5 SGA). Costs relating to contracts due for execution only after termination are not eligible.

- If the payments received exceed the amounts due:
  - if termination takes effect during the period set out in Article 3 of the Specific Agreement and the request for amendment is accepted, the KIC Partner concerned must repay to the KIC LE the amount unduly received. The EIT will formally notify the amount unduly received and request the KIC Partner concerned to repay it to the KIC LE within 30 days of receiving notification. If it does not repay the KIC LE, the EIT will draw upon the Guarantee Fund to pay the KIC LE and then notify a debit note on behalf of the Guarantee Fund to the KIC Partner concerned (see Article 50);
  - in all other cases, in particular if termination takes effect after the period set out in Article 3 of the Specific Agreement, the EIT will formally notify a debit note to the KIC Partner concerned. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the EIT the amount due and the EIT will notify a debit note on behalf of the Guarantee Fund to the KIC Partner concerned (see Article 50) ;
  - if the KIC Partner concerned is the former KIC LE, it must repay the new KIC LE the amount unduly received.

    In this case, the EIT will formally notify a debit note to the former KIC LE. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the EIT the amount due. The EIT will then pay the new KIC LE and notify a debit note on behalf of the Guarantee Fund to the former KIC LE (see Article50).
- If the payments received do not exceed the amounts due: amounts owed to the KIC Partner concerned will be included in the payment of the balance.

If the EIT does not receive the termination report within the deadline (see above), the EIT willnot consider any cost as eligible.

If the EIT does not receive the report on the distribution of payments within the deadline (see above), it will consider that:

- the KIC LE did not distribute any payment to the KIC Partner concerned, and that
- the KIC Partner concerned must not repay any amount to the KIC LE.

After termination, the concerned KIC Partner's obligations (in particular Articles 26, 28, 29, Subsection 3 of Section 3 of Chapter 3, 42, 43, 44, 46) continue to apply.

SUBSECTION 4 FORCE

MAJEUREARTICLE 57 —

FORCE MAJEURE

'Force majeure' means any situation or event that:

- prevents either party from fulfilling their obligations under the Agreement,
- was unforeseeable, exceptional situation and beyond the parties' control,
- was not due to error or negligence on their part (or on the part of third partiesinvolved in the action), and
- proves to be inevitable in spite of exercising all due diligence.

The following cannot be invoked as force majeure:

- any default of a service, defect in equipment or material or delays in making themavailable, unless they stem directly from a relevant case of force majeure,
- labour disputes or strikes, or
- financial difficulties.

Any situation constituting force majeure must be formally notified to the other party withoutdelay, stating the nature, likely duration and foreseeable effects.

The parties must immediately take all the necessary steps to limit any damage due to forcemajeure and do their best to resume implementation of the action as soon as possible.

The party prevented by force majeure from fulfilling its obligations under the Framework Partnership Agreement or a Specific Agreement cannot be considered in breach of them.

CHAPTER 4 FINAL PROVISIONS

ARTICLE 58 — COMMUNICATIONS BETWEEN THE PARTIES SIGNING THE FRAMEWORK PARTNERSHIP AGREEMENT

58.1 Form and means of communications

Communication under the Framework Partnership Agreement and the Specific Agreements (information, requests, submissions, formal notifications, etc.) must:

- be made in writing and
- bear the number of the Framework Partnership Agreement and the Specific Agreement concerned;
- be submitted to the addresses listed in Article 58.3.

Communication may be made either:

- through the EIT dedicated electronic exchange platform and using the forms and templates provided there;
- electronically in the form of e-mail; or
- by registered post with proof of delivery ('formal notification on paper').

If the electronic exchange system is temporarily unavailable, instructions will be provided by the EIT.

Formal notifications must be made by registered post with proof of delivery.

Electronic communications must be confirmed by an original signed paper version of that communication, if requested by any of the parties signing the Framework Partnership Agreement, provided that this request is submitted without unjustified delay. The sender shall send the original signed paper version without unjustified delay.

Communications from the other KIC Partners shall be channelled via the KIC LE.

58.2 Date of communications

Communications are considered to have been made when they are received by the receiving party, unless the Framework Partnership Agreement or the Specific Agreement refers to the date when the communication was sent.

Electronic communications are considered to have been made on the day of successful dispatch of the communication, provided that it is sent to the addressees listed in Article 58.3. Dispatch is considered unsuccessful if the sending party receives a message of non- delivery. In this case, the sending party must immediately send again such communication to any of the other addresses listed in Article 58.3. In case of unsuccessful dispatch, the sending party will not be held in breach of its obligation to send such communication within a specified deadline.

Formal notifications on paper sent by registered post with proof of delivery are considered tohave been made on either:

- the delivery date registered by the postal service or
- the deadline for collection at the post office.

Formal notifications through the EIT dedicated electronic exchange platform are considered tohave been made when they are received by the receiving party (i.e. on the date and time of acceptance by the receiving party). A formal notification that has not been accepted within30 days after sending is considered to have been accepted.

58.3 Addresses for communication

Communications addressed to the EIT must be sent to the following address:

Director
European Institute of Innovation and Technology - EIT
Infopark, Building E, 1 Neumann Janos Street
1117 Budapest
Hungary

E-mail address:

EIT-director@eit.europa.eu

Communications from the EIT to the KIC Partners must be sent to the KIC LE's legal addressor e-mail address as specified in the preamble.

The electronic exchange platform can be accessed via the following URL:

https://duna.eit.europa.eu

The EIT will formally notify the KIC LE in advance of any changes to this platform.

ARTICLE 59 — INTERPRETATION OF THE FRAMEWORK PARTNERSHIP AGREEMENT AND THE SPECIFIC AGREEMENTS

59.1 Precedence of the Terms and Conditions over the Annexes

The provisions in the Terms and Conditions of the Framework Partnership Agreement andthe Specific Agreements take precedence over their Annexes.

The provisions in Annex 2 to the Specific Agreement take precedence over its Annex 1.

59.2 Precedence of the Terms and Conditions of the Specific Agreements over theFramework Partnership Agreement

The provisions in the 'Terms and Conditions' of the Specific Agreements take precedence over the Framework Partnership Agreement.

ARTICLE 60 — CALCULATION OF PERIODS, DATES AND DEADLINES

In accordance with Regulation No 1182/71[10], periods expressed in days, months or years are calculated from the moment the triggering event occurs.

The day during which that event occurs is not considered as falling within the period.

ARTICLE 61 — AMENDMENTS TO THE FRAMEWORK PARTNERSHIP AGREEMENT AND THE SPECIFIC AGREEMENTS

61.1 Conditions

The Framework Partnership Agreement and the Specific Agreements may be amended, unless the amendment entails changes to those agreements which would call into question the decisions awarding the framework partnership or specific grants concerned or breach theprinciple of equal treatment of the applicants or KICs.

Amendments may be requested by any of the parties signing the Framework Partnership Agreement.

61.2 Procedure

The party requesting an amendment must submit a request for amendment (see Article 58).

The KIC LE submits and receives requests for amendment on behalf of the KIC Partners (see Annex 4).

If a change of the KIC LE is requested, the submission must be done by another KIC Partner (acting on behalf of the other KIC Partners).

The request for amendment must include:

- the reasons why;
- the appropriate supporting documents, and
- for a change of the KIC LE: the opinion of the KIC LE (or proof that this opinion hasbeen requested in writing).

The EIT may request additional information.

[10] Regulation (EEC, Euratom) No 1182/71 of the Council of 3 June 1971 determining the rules applicable toperiods, dates and time-limits (OJ L 124, 8.6.1971, p. 1).

If the party receiving the request agrees, it must sign the amendment within 45 days of receiving notification (or any additional information the EIT has requested). If it does not agree, it must formally notify its disagreement within the same deadline. The deadline may be extended, if necessary for the assessment of the request. If no notification is received within the deadline, the request is considered to have been rejected.

An amendment enters into force on the day of the signature of the receiving party.

An amendment takes effect on the date agreed by the parties or, in the absence of such an agreement, on the date on which the amendment enters into force.

ARTICLE 62 — ACCESSION TO THE FRAMEWORK PARTNERSHIP AGREEMENT AND THE SPECIFICAGREEMENTS

62.1 Accession of the KIC Partners mentioned in Annex 2

The other KIC Partners must accede to the Framework Partnership Agreement by signing the Accession Form (see Annex 4), within 120 days after its entry into force (see Article 64).

All KIC Partners having acceded to the Framework Partnership Agreement must be part of the Specific Agreements. The KIC Partners will accede to the Specific Agreement by signature of the KIC LE (mandate in Annex 4).

They will assume the rights and obligations under the agreements with effect from the dateof their entry into force (see Article 64 and Article 21 SGA).

If a KIC Partner does not accede to the Framework Partnership Agreement within the above deadline, the KIC LE must — within 30 days — request an amendment to make any changes necessary to ensure proper implementation of the Strategic Agenda. This does not affect the EIT's right to terminate the agreements (see Articles 6 and 56).

62.2 Addition of new KIC Partners

In justified cases, the KIC Partners may request the addition of a new KIC Partner.

For this purpose, the KIC LE must submit a request for amendment of the Framework Partnership Agreement and the ongoing Specific Agreement in accordance with Article 61. The request must include an Accession Form (see Annex 4) signed by the new KIC Partner.

New KIC Partners must assume the rights and obligations under the agreements with effect from the date of their accession specified in the Accession Form (see Annex 4).

ARTICLE 63 — APPLICABLE LAW AND SETTLEMENT OF DISPUTES

63.1 Applicable law

The Framework Partnership Agreement and the Specific Agreements are governed by the applicable EU law, supplemented if necessary by the law of Belgium.

63.2 Dispute settlement

If a dispute concerning the interpretation, application or validity of the Framework Partnership Agreement or a Specific Agreement cannot be settled amicably, the General Court — or, on appeal, the Court of Justice of the European Union — has sole jurisdiction. Such actions must be brought under Article 272 of the Treaty on the Functioning of the EU (TFEU).

As an exception, if such a dispute is between the EIT and non-EU KIC Partner(s) (except KIC Partners established in an associated country with an association agreement to Horizon 2020 that stipulates sole jurisdiction of the European Court of Justice), the competent Belgian courts have sole jurisdiction.

For KIC Partners not receiving EIT funding under a Specific Agreement, such disputes must — if they cannot be settled amicably — be referred to arbitration.

The Permanent Court of Arbitration Optional Rules for Arbitration Involving International Organisations and States in force at the date of entry into force of the Agreement will apply.

The appointing authority will be the Secretary-General of the Permanent Court of Arbitration following a written request submitted by either party signing the Framework Partnership Agreement.

The arbitration proceedings must take place in Brussels and the language used in the arbitral proceedings will be English.

The arbitral award will be binding on all parties and will not be subject to appeal.

If a dispute concerns administrative or financial penalties or offsetting (see Articles 50, 51 and 52), the KIC Partners must bring action before the General Court — or, on appeal, the Court of Justice of the European Union — under Article 263 TFEU.

ARTICLE 64 — ENTRY INTO FORCE OF THE FRAMEWORK PARTNERSHIP AGREEMENT

The Framework Partnership Agreement will enter into force on the day of signature by theEIT or the KIC LE, depending on which is later.

SIGNATURES

For the KIC LE

[function/forename/surname]
[signature]

For the EIT

[forename/surname]
[signature]

Done in [English] at [place] on [date]

Done in [English] at [place] on [date]

List of KIC part-

KIC Partner	Short name	Legal form	SME[1]	AREA[2]	Website (if available)	Official address in full	VAT number	Eligibility period (start)	Eligibility period (end)	CODE

[1] Please refer to the definition of the EC: http://ec.europa.eu/enterprise/policies/sme/facts-figures-analysis/sme-definition/index_en.htm

[2] Either "Business", "Cities, Regions, NGOs", "Research","Higher Education"

8.1.1.1 ACCESSION FORM FOR KIC PARTNERS

[Full official name of the KIC Partner/new KIC Partner/new KIC LE (short name)][legal form], [KIC PartnerNo], established in [official address in full] [VAT number], (*['the KIC Partner'][‘the KIC LE’]*), represented for the purpose of signing this Accession Form by [forename and surname, function],

hereby agrees

to become *[KIC partner][KIC LE]* No [insert KIC Partner no] in Framework Partnership Agreement (FPA) No [insert agreement number] (‘Agreement’) signed between [full official name of the KIC LE] and the European Institute of Innovation and Technology ('the EIT'),

[OPTION for KIC partners/new KIC partners: and

empowers

the KIC LE:

- *to submit any proposals for the award of Specific Grants;*
- *to sign in its name and on its behalf all the Specific Agreements that may be awarded (seeArticles 2 and 62 of the FPA);*
- *to submit and sign in its name and on its behalf any amendments to the Framework Partnership Agreement and Specific Agreements (see Article 61 of the FPA),*

subject to the fulfilment of the KIC’s governance rules.

By signing this Accession Form, the KIC Partner accepts the grant and agrees to *[OPTION: for new KIC LEs: take on the obligations and role of KIC LE and to]* implement the grant in accordance with the Agreement, with all the obligations and conditions it sets out *[OPTION for new KIC Partners:, as from [insert date][the date of signature of the Accession Form][the date of entry into force of the amendment] (‘accession date’) — if the EIT agrees with the request for amendment]*.

SIGNATURE

For the KIC Partner/new KIC Partner/new KIC LE:

[function/forename/surname]

[signature]

Done in [English] at [place] on [date]

Countersigned by KIC LE:

[fully official name of KIC LE] [function/forename/sur-name]

[signature]

Done in [English] at [place] on [date]

8.1.1.2 *List of linked third parties to the KIC LE and/or KIC Partnersin accordance with Article 19 of the FPA*

Full official name ofthe linked third party	Short name	Status of theentity (Affiliated entity or linked third party)	Nature of affiliation [1]Or nature of legal link with the third party	Legal form	SME[2]	AREA[3]	Website (if available)	Official addressin full	VAT number	KIC Partner	Eligibility period (start)	Eligibility period (end)

[1] For the definition see Article 2.1(2) Rules for Participation Regulation No 1290/2013: 'affiliated entity' means any legal entity that is:

- under the direct or indirect control of a participant, or
- under the same direct or indirect control as the participant, or
- directly or indirectly controlling a participant.'Control' may take any of the following forms:

(a) the direct or indirect holding of more than 50% of the nominal value of the issued share capital in the legal entity concerned, or of a majority of the voting rights of the shareholders or associates ofthat entity;
(b) the direct or indirect holding, in fact or in law, of decision-making powers in the legal entity concerned.
However, the following relationships between legal entities shall not in themselves constitute controlling relationships:
(a) the same public investment corporation, institutional investor or venture-capital company has a direct or indirect holding of more than 50% of the nominal value of the issued share capital or a majority of voting rights of the shareholders or associates;
(b) the legal entities concerned are owned or supervised by the same public body.
'Third party with a legal link to a beneficiary' is any legal entity which has a legal link to the beneficiary implying collaboration that is not limited to the action.

[2] Please refer to the definition of the EC: http://ec.europa.eu/enterprise/policies/sme/facts-figures-analysis/sme-definition/index_en.htm

[3] Either "Business", "Cities, Regions, NGOs", "Research","Higher Education"

8.1.1.3 MODEL FOR THE CERTIFICATE ON THE METHODOLOGY

TABLE OF CONTENTS

Terms of reference for an audit engagement for a methodology certificate in connection with one or more grant agreements financed under the Horizon 2020 Research and Innovation Framework Programme

This document sets out the 'Terms of Reference (ToR)' under which

[OPTION 1: [insert name of the partner] ('the Partner)] [OPTION 2: [insert name of the linked third party] ('the Linked Third Party'), third party linked to the Partner [insert name of the partner] ('the Partner')]

agrees to engage

[insert legal name of the auditor] ('the Auditor')

to produce an independent report of factual findings ('the Report') concerning the *[Partner's] [Linked Third Party's]* usual accounting practices for calculating and claiming direct personnel costs declared as unit costs ('the Methodology') in connection with grant agreements financed under the Horizon 2020 Research and Innovation Framework Programme.

The procedures to be carried out for the assessment of the methodology will be based on the grant agreement(s) detailed below:

[title and number of the grant agreement(s)] ('the Agreement(s)')

The Agreement(s) has(have) been concluded between the KIC LE on behalf of the Partner *and the EIT.*

The *EIT* is mentioned as a signatory of the Agreement with the KIC LE on behalf of the Partner only. The *European Union* is not a party to this engagement.

1.1 Subject of the engagement

According to Article 24 of the Framework Partnership Agreement, partners *[and linked third parties]* that declare direct personnel costs as unit costs calculated in accordance with their usual cost accounting practices may submit to the *EIT*, for approval, a certificate on the methodology ('CoMUC') stating that there are adequate records and documentation to prove that their cost accounting practices used comply with the conditions set out in Point A of Article 5.2 of the Specific Agreement.

The subject of this engagement is the CoMUC which is composed of two separate documents:

- the Terms of Reference ('the ToR') to be signed by the *[Partner] [Linked Third Party]* and the Auditor;

- the Auditor's Independent Report of Factual Findings ('the Report') issued on the Auditor's letterhead, dated, stamped and signed by the Auditor which includes; the standard statements ('the Statements') evaluated and signed by the *[Partner] [Linked Third Party]*, the agreed-upon procedures ('the Procedures') performed by the Auditor and the standard factual findings ('the Findings') assessed by the Auditor. The Statements, Procedures and Findings are summarised in the table that forms part of the Report.

The information provided through the Statements, the Procedures and the Findings will enable the EITto draw conclusions regarding the existence of the *[Partner's] [Linked Third Party's]* usual cost accounting practice and its suitability to ensure that direct personnel costs claimed on that basis comply with the provisions of the Agreement. The EIT draws its own conclusions from the Report and any additional information it may require.

1.2 Responsibilities

The parties to this agreement are the *[Partner] [Linked Third Party]* and the

Auditor.The *[Partner] [Linked Third Party]:*

- is responsible for preparing financial statements for the Agreement(s) ('the Financial Statements') in compliance with those Agreements;
- is responsible for providing the Financial Statement(s) to the Auditor and enabling the Auditor to reconcile them with the *[Partner's] [Linked Third Party's]* accounting and bookkeeping system and the underlying accounts and records. The Financial Statement(s) will be used as a basis for the procedures which the Auditor will carry out under this ToR;
- is responsible for its Methodology and liable for the accuracy of the Financial Statement(s);
- is responsible for endorsing or refuting the Statements indicated under the heading 'Statements to be made by the Partner / Linked Third Party' in the first column of the table that forms part of the Report;
- must provide the Auditor with a signed and dated representation letter;
- accepts that the ability of the Auditor to carry out the Procedures effectively depends uponthe *[Partner] [Linked Third Party]* providing full and free access to the *[Partner] [Linked Third Party's]* staff and to its accounting and other relevant records.

The Auditor:

- *[Option 1 by default: is qualified to carry out statutory audits of accounting documents in accordance with Directive 2006/43/EC of the European Parliament and of the Council of 17 May 2006 on statutory audits of annual accounts and consolidated accounts, amending Council Directives 78/660/EEC and 83/349/EEC and repealing Council Directive 84/253/EEC or similar national regulations]*.
- *[Option 2 if the Partner or Linked Third Party has an independent Public Officer: is a competent and independent Public Officer for which the relevant national authorities have established the legal capacity to audit the Partner]*.
- *[Option 3 if the Partner or Linked Third Party is an international organisation: is an [internal] [external] auditor in accordance with the internal financial regulations and procedures of the international organisation]*.

The Auditor:

- must be independent from the Partner *[and the Linked Third Party]*, in particular, it must not have been involved in preparing the Partner's *[and Linked Third Party's]* Financial Statement(s);
- must plan work so that the Procedures may be carried out and the Findings may be assessed;

- must adhere to the Procedures laid down and the compulsory report format;

- must carry out the engagement in accordance with these ToR;
- must document matters which are important to support the Report;
- must base its Report on the evidence gathered;
- must submit the Report to the *[Partner] [Linked Third Party]*.

The EIT sets out the Procedures to be carried out and the Findings to be endorsed by the Auditor. The Auditor is not responsible for their suitability or pertinence. As this engagement is not an assurance engagement the Auditor does not provide an audit opinion or a statement of assurance.

1.3 Applicable Standards

The Auditor must comply with these Terms of Reference and with[1]:

- the International Standard on Related Services ('ISRS') 4400 *Engagements to perform Agreed- upon Procedures regarding Financial Information* as issued by the International Auditing and Assurance Standards Board (IAASB);
- the *Code of Ethics for Professional Accountants* issued by the International Ethics Standards Board for Accountants (IESBA). Although ISRS 4400 states that independence is not a requirement for engagements to carry out agreed-upon procedures, the EIT requires that the Auditor also complies with the Code's independence requirements.

The Auditor's Report must state that there was no conflict of interests in establishing this Report between the Auditor and the Partner *[and the Linked Third Party]* that could have a bearing on the Report, and must specify – if the service is invoiced - the total fee paid to the Auditor for providing the Report.

1.4 Reporting

The Report must be written in the language of the Agreement (see Article 20.7 of the Agreement).

Under Article 28 of the Framework Partnership Agreement, the Commission, *the EIT*, the European Anti-Fraud Office and the Court of Auditors have the right to audit any work that is carried out under the action and for which costs are claimed from *the European Union*. This includes work related to this engagement. The Auditor must provide access to all working papers related to this assignment if the Commission*, the EIT*, the European Anti-Fraud Office or the European Court of Auditors requests them.

1.5 Timing

The Report must be provided by [dd Month yyyy].

1.6 Other Terms

[1] Supreme Audit Institutions applying INTOSAI-standards may carry out the Procedures according to the corresponding International Standards of Supreme Audit Institutions and code of ethics issued by INTOSAI instead of the International Standard on Related Services ('ISRS') 4400 and the Code of Ethics for Professional Accountants issued by the IAASB and the IESBA.

[The [Partner] [Linked Third Party] and the Auditor can use this section to agree other specific terms, such as the Auditor's fees, liability, applicable law, etc. Those specific terms must not contradict the terms specified above.]

[legal name of the Auditor]	[legal name of the [Partner] [Linked Third Party]]
[name & title of authorised representative]	[name & title of authorised representative]
[dd Month yyyy]	[dd Month yyyy]
Signature of the Auditor	Signature of the *[Partner][Linked Third Party]*

Independent report of factual findings on the methodology concerning grant agreements financed under the Horizon 2020 Research and Innovation Framework Programme

(To be printed on letterhead paper of the auditor)

To
[name of contact person(s)], [Position] [[Partner's] [Linked Third Party's] name][Address]
[dd Month yyyy]

Dear [Name of contact person(s)],

As agreed under the terms of reference dated [dd Month yyyy]

with *[OPTION 1: [insert name of the Partner] ('the Partner')] [OPTION 2: [insert name of the linked thirdparty] ('the Linked Third Party'), third party linked to the Partner [insert name of the Partner] ('the Partner')]*,

we established at [name of the auditor] ('the Auditor'), represented by [full address/city/state/province/country], [name and function of an authorised representative],

have carried out the agreed-upon procedures ('the Procedures') and provide hereby our Independent Report of Factual Findings ('the Report'), concerning the *[Partner's] [Linked Third Party's]* usual accounting practices for calculating and declaring direct personnel costs declared as unit costs ('the Methodology').

You requested certain procedures to be carried out in connection with the grant(s) [title and number of the grant agreement(s)] ('the Agreement(s)').

The Report

Our engagement was carried out in accordance with the terms of reference ('the ToR') appended to this Report. The Report includes the standard statements ('the Statements') made by the *[Partner] [Linked Third Party]*, the agreed-upon procedures ('the Procedures') carried out and the standard factual findings ('the Findings') confirmed by us.

The engagement involved carrying out the Procedures and assessing the Findings and the documentation requested appended to this Report, the results of which the EIT uses to draw conclusions regarding the acceptability of the Methodology applied by the *[Partner] [Linked Third Party]*.

The Report covers the methodology used from [dd Month yyyy]. In the event that the *[Partner] [LinkedThird Party]* changes this methodology, the Report will not be applicable to any Financial Statement[2] submitted thereafter.

The scope of the Procedures and the definition of the standard statements and findings were determined solely by the EIT. Therefore, the Auditor is not responsible for their suitability or pertinence.

Since the Procedures carried out constitute neither an audit nor a review made in accordance with International Standards on Auditing or International Standards on Review Engagements, we do notgive a statement of assurance on the costs declared on the basis of the *[Partner's] [Linked Third Party's]* Methodology. Had we carried out additional procedures or had we performed an audit or review in accordance with these standards, other matters might have come to its attention and would have been included in the Report.

Exceptions

Apart from the exceptions listed below, the *[Partner] [Linked Third Party]* agreed with the standard Statements and provided the Auditor all the documentation and accounting information needed bythe Auditor to carry out the requested Procedures and corroborate the standard Findings.

List here any exception and add any information on the cause and possible consequences of eachexception, if known. If the exception is quantifiable, also indicate the corresponding amount.

Explanation of possible exceptions in the form of examples (to be removed from the Re-

i. the [Partner] [Linked Third Party] did not agree with the standard Statement number … because…;

ii. the Auditor could not carry out the procedure … established because …. (e.g. due to the inabilityto reconcile key information or the unavailability or inconsistency of data);

Remarks

We would like to add the following remarks relevant for the proper understanding of the Methodology applied by the [Partner] [Linked Third Party] or the results reported.

Example (to be removed from the Report):

Regarding the methodology applied to calculate hourly rates …Regarding standard Finding 15 it has to be noted that …
The [Partner] [Linked Third Party] explained the deviation from the benchmark statement …

[2] Financial Statement in this context refers solely to Annex 3 of the Specific Agreement by which the Partner declares costs under the Agreement.

Annexes

Please provide the following documents to the auditor and annex them to the report when submittingthis CoMUC to the EIT:

1. Brief description of the methodology for calculating personnel costs, productive hours andhourly rates;
2. Brief description of the time recording system in place;
3. An example of the time records used by the [*Partner] [Linked Third Party*];
4. Description of any budgeted or estimated elements applied together with an explanation as towhy they are relevant for calculating the personnel costs and how they are based on objectiveand verifiable information;
5. A summary sheet with the hourly rate for direct personnel declared by the [*Partner*] [*Linked Third Party*] and recalculated by the Auditor for each staff member included in the sample (thenames do not need to be reported);
6. A comparative table summarising for each person selected in the sample a) the time claimed by the [*Partner*] [*Linked Third Party*] in the Financial Statement(s) and b) the time according to the time record verified by the Auditor;
7. A copy of the letter of representation provided to the Auditor.

Use of this Report

This Report has been drawn up solely for the purpose given under Point 1.1 Reasons for the engagement.

The Report:

- is confidential and is intended to be submitted to the EIT by the [*Partner*] [*Linked Third Party*]in connection with Article 24 of the Framework Partnership Agreement;
- may not be used by the [*Partner*] [*Linked Third Party*] or by the EIT for any other purpose, nordistributed to any other parties;
- may be disclosed by the EIT only to authorised parties, in particular the European Anti-FraudOffice (OLAF) and the European Court of Auditors.
- relates only to the usual cost accounting practices specified above and does not constitute areport on the Financial Statements of the [*Partner*] [*Linked Third Party*].

No conflict of interest[3] exists between the Auditor and the Partner *[and the Linked Third Party*] that could have a bearing on the Report. The total fee paid to the Auditor for producing the Report wasEUR_____(including EUR__of deductible VAT).

[3] A conflict of interest arises when the Auditor's objectivity to establish the certificate is compromised in fact or in appearance when the Auditor for instance:

- was involved in the preparation of the Financial Statements;
- stands to benefit directly should the certificate be accepted;
- has a close relationship with any person representing the Partner;

- is a director, trustee or partner of the Partner; or
- is in any other situation that compromises his or her independence or ability to establish the certificate impartially.

We look forward to discussing our Report with you and would be pleased to provide any further information or assistance which may be required.

Yours sincerely

[legal name of the Auditor]
[name and title of the authorised representative][dd Month yyyy]
Signature of the Auditor

Statements to be made by the Partner/Linked Third Party ('the Statements') and Procedures to be carried out by the Auditor ('the Procedures') and standard factual findings ('the Findings') to be confirmed by the Auditor

The EIT reserves the right to provide the auditor with guidance regarding the Statements to be made, the Procedures to be carried out or the Findings to be ascertained and the way in which to present them. The EIT reserves the right to vary the Statements, Procedures or Findings by written notification to the Partner/Linked Third Party to adapt the procedures to changes in the grant agreement(s) or to any other circumstances.

If this methodology certificate relates to the Linked Third Party's usual accounting practices for calculating and claiming direct personnel costs declared as unit costs any reference here below to 'the Partner' is to be considered as a reference to 'the Linked Third Party'.

Please explain any discrepancies in the body of the Report.	
Statements to be made by Partner	Procedures to be carried out and Findings to be confirmed by the Auditor
A. Use of the Methodology I. The cost accounting practice described below has been in use since *[*dd Month yyyy*].* II. The next planned alteration to the methodology used by the Partner will be from [dd Month yyyy*].*	Procedure: ✓ The Auditor checked these dates against the documentation the Partner has provided. Factual finding: 1. The dates provided by the Partner were consistent with the documentation.

B. Description of the Methodology III. The methodology to calculate unit costs is being used in a consistent manner and is reflected in the relevant procedures. *[Please describe the methodology your entity uses to calculate personnel costs, productive hours and hourly rates, present your description to the Auditor and annex it to this certificate]* *[If the statement of section "B. Description of the methodology" cannot be endorsed by the Partner or there is no written methodology to calculate unit costs it should be listed here below and reported as exception by the Auditor in the main Report of Factual Findings:* - *…]*	Procedure: ✓ The Auditor reviewed the description, the relevant manuals and/or internal guidance documents describing the methodology. Factual finding: 2. The brief description was consistent with the relevant manuals, internal guidance and/or other documentary evidence the Auditor has reviewed. 3. The methodology was generally applied by the Partner as part of its usual costs accounting practices.
C. Personnel costsGeneral IV. The unit costs (hourly rates) are limited to	Procedure: *The Auditor draws a sample of employees tocarry out the procedures indicated in this section*

Please explain any discrepancies in the body of the Report.	
Statements to be made by Partner	Procedures to be carried out and Findings to be confirmed by the Auditor
salaries including during parental leave, social security contributions, taxes and other costs included in the remuneration required under national law and the employment contract or equivalent appointing act; V. Employees are hired directly by the Partner in accordance with national law, and work under its sole supervision and responsibility; VI. The Partner remunerates its employees in accordance with its usual practices. This means that personnel costs are charged in line with the Partner's usual payroll policy (e.g. salary policy, overtime policy, variable pay) and no special conditions exist for employees assigned to tasks relating to the European Union or Euratom, unless explicitly provided for in the grant agreement(s); VII. The Partner allocates its employees to the relevant group/category/cost centre for the purpose of the unit cost calculation in line with the usual cost accounting practice; VIII. Personnel costs are based on the payroll system and accounting system. IX. Any exceptional adjustments of actual personnel costs resulted from relevant budgeted or estimated elements and were based on objective and verifiable information. *[Please describe the 'budgeted or estimated elements' and their relevance to personnel costs, and explain how they were reasonable and based on objective and verifiable information, present your explanation to the Auditor and annex it to this certificate].* X. Personnel costs claimed do not contain any of the following ineligible costs: costs related to return on capital; debt and debt service charges; provisions for future losses or debts; interest owed; doubtful debts; currency exchange losses; bank costs charged by the Partner's bank	*C and the following sections D to F.* *[The Auditor has drawn a random sample of 10 full-time equivalents made up of employees assigned to the action(s). If fewer than 10 full- time equivalents are assigned to the action(s), the Auditor has selected a sample of 10 full-time equivalents consisting of all employees assigned to the action(s), complemented by other employees irrespective of their assignments.].* For this sample: ✓ the Auditor reviewed all documents relating to personnel costs such as employment contracts, payslips, payroll policy (e.g. salary policy, overtime policy, variable pay policy), accounting and payroll records, applicable national tax , labour and social security law and any other documents corroborating the personnel costs claimed; ✓ in particular, the Auditor reviewed the employment contracts of the employees in the sample to verify that: i. they were employed directly by the Partner in accordance with applicable national legislation; ii. they were working under the sole technical supervision and responsibility of the latter; iii. they were remunerated in accordance with the Partner's usual practices; iv. they were allocated to the correct group/category/cost centre for the purposes of calculating the unit cost in line with the Partner's usual cost accounting practices; ✓ the Auditor verified that any ineligible items or any costs claimed under other costs categories or costs covered by other types of grant or by other grants financed from the European Union budget have not been taken into account when

for	calculating the personnel

Please explain any discrepancies in the body of the Report.	
Statements to be made by Partner	Procedures to be carried out and Findings to be confirmed by the Auditor
transfers from the EIT; excessive or reckless expenditure; deductible VAT or costs incurred during suspension of the implementation of the action. XI. Personnel costs were not declared under another EU or Euratom grant (including grants awarded by a Member State and financed by the EU budget and grants awarded by bodies other than the EIT for the purpose of implementing the EU budget). <u>If additional remuneration as referred to in the grant agreement(s) is paid</u> XII. The Partneris a non-profit legal entity; XIII. The additional remuneration is part of the Partner's usual remuneration practices and paid consistently whenever the relevant work or expertise is required; XIV. The criteria used to calculate the additional remuneration are objective and generally applied regardless of the source of funding; XV. The additional remuneration included in the personnel costs used to calculate the hourly rates for the grant agreement(s) is capped at EUR 8 000 per full-time equivalent (reduced proportionately if the employee is not assigned exclusively to the action). *[If certain statement(s) of section "C. Personnel costs" cannot be endorsed by the Partner they should be listed here below and reported as exception by the Auditor in the main Report of Factual Findings:* *- …]*	costs; ✓ the Auditor numerically reconciled the total amount of personnel costs used to calculate the unit cost with the total amount of personnel costs recorded in the statutory accounts and the payroll system. ✓ to the extent that actual personnel costs were adjusted on the basis of budgeted or estimated elements, the Auditor carefully examined those elements and checked the information source to confirm that they correspond to objective and verifiable information; ✓ if additional remuneration has been claimed, the Auditor verified that the Partner was a non-profit legal entity, that the amount was capped at EUR 8000 per full-time equivalent and that it was reduced proportionately for employees not assigned exclusively to the action(s). ✓ the Auditor recalculated the personnel costs for the employees in the sample. Factual finding: 4. All the components of the remuneration that have been claimed as personnel costs are supported by underlying documentation. 5. The employees in the sample were employed directly by the Partner in accordance with applicable national law and were working under its sole supervision and responsibility. 6. Their employment contracts were in line with the Partner's usual policy; 7. Personnel costs were duly documented and consisted solely of salaries, social security contributions (pension contributions, health insurance, unemployment fund contributions, etc.), taxes and other

	statutory costs

Please explain any discrepancies in the body of the Report.	
Statements to be made by Partner	Procedures to be carried out and Findings to be confirmed by the Auditor
	included in the remuneration (holiday pay, thirteenth month's pay, etc.); 8. The totals used to calculate the personnel unit costs are consistent with those registered in the payroll and accounting records; 9. To the extent that actual personnel costs were adjusted on the basis of budgeted or estimated elements, those elements were relevant for calculating the personnel costs and correspond to objective and verifiable information. The budgeted or estimated elements used are: — (indicate the elements and their values). 10. Personnel costs contained no ineligible elements; 11. Specific conditions for eligibility were fulfilled when additional remuneration was paid: a) the Partner is registered in the grant agreements as a non-profit legal entity; b) it was paid according to objective criteria generally applied regardless of the source of funding used and c) remuneration was capped at EUR 8000 per full-time equivalent (or up to up to the equivalent pro-rata amount if the person did not work on the action full-time during the year or did not work exclusively on the action).
D. Productive hours XVI. The number of productive hours per full- time employee applied is *[delete as appropriate]*: A. 1720 productive hours per year for a person working full-time (corresponding pro-rata for persons not working full time). B. the total number of hours worked in the year by a person for the Partner C. the standard number of annual hours generally applied by the	Procedure (same sample basis as for Section C: Personnel costs): ✓ The Auditor verified that the number of productive hours applied is in accordance with method A, B or C. ✓ The Auditor checked that the number of productive hours per full-time employee is correct and that it is reduced proportionately for employees not exclusively assigned to the action(s). ✓ If method B is applied the Auditor verified i) the manner in which the

Partner for	total

Please explain any discrepancies in the body of the Report.	
Statements to be made by Partner	Procedures to be carried out and Findings to be confirmed by the Auditor
its personnel in accordance with its usual cost accounting practices. This number must be at least 90% of the standard annual workable hours. <u>If method B is applied</u> XVII. The calculation of the total number of hours worked was done as follows: annual workable hours of the person according to the employment contract, applicable labour agreement or national law plus overtime worked minus absences (such as sick leave and special leave). XVIII. 'Annual workable hours' are hours during which the personnel must be working, at the employer's disposal and carrying out his/her activity or duties under the employment contract, applicable collective labour agreement or national working time legislation. XIX. The contract (applicable collective labour agreement or national working time legislation) do specify the working time enabling to calculate the annual workable hours. <u>If method C is applied</u> XX. The standard number of productive hours per year is that of a full-time equivalent; for employees not assigned exclusively to the action(s) this number is reduced proportionately. XXI. The number of productive hours per year on which the hourly rate is based i) corresponds to the Partner's usual accounting practices; ii) is at least 90 % of the standard number of workable (working) hours per year. XXII. Standard workable (working) hours are hours during which personnel are at the Partner's disposal preforming the duties described in the relevant employment contract, collective labour	number of hours worked was done and ii) that the contract specified the annual workable hours by inspecting all the relevant documents, national legislation, labour agreements and contracts. ✓ If method C is applied the Auditor reviewed the manner in which the standard number of working hours per year has been calculated by inspecting all the relevant documents, national legislation, labour agreements and contracts and verified that the number of productive hours per year used for these calculations was at least 90 % of the standard number of working hours per year. Factual finding: <u>General</u> 12. The Partner applied a number of productive hours consistent with method A, B or C detailed in the left-hand column. 13. The number of productive hours per year per full-time employee was accurate and was proportionately reduced for employees not working full- time or exclusively for the action. <u>If method B is applied</u> 14. The number of 'annual workable hours', overtime and absences was verifiable based on the documents provided by the Partner and the calculation of the total number of hours worked was accurate. 15. The contract specified the working time enabling to calculate the annual workable hours. <u>If method C is applied</u> 16. The calculation of the number of productive hours per year corresponded to the usual costs

agreement or national labour legislation. The number of	accounting practice of

Please explain any discrepancies in the body of the Report.	
Statements to be made by Partner	Procedures to be carried out and Findings to be confirmed by the Auditor
standard annual workable (working) hours that the Partner claims is supported by labour contracts, national legislation and other documentary evidence. *[If certain statement(s) of section "D. Productive hours" cannot be endorsed by the Partner they should be listed here below and reported as exception by the Auditor:* *- …]*	the Partner. 17. The calculation of the standard number of workable (working) hours per year was corroborated by the documents presented by the Partner. 18. The number of productive hours per year used for the calculation of the hourly rate was at least 90 % of the number of workable (working) hours per year.
E. Hourly rates The hourly rates are correct because: XXIII. Hourly rates are correctly calculated since they result from dividing annual personnel costs by the productive hours of a given year and group (e.g. staff category or department or cost centre depending on the methodology applied) and they are in line with the statements made in section C. and D. above. *[If the statement of section 'E. Hourly rates' cannot be endorsed by the Partner they should be listed here below and reported as exception by the Auditor:* *- …]*	Procedure ✓ The Auditor has obtained a list of all personnel rates calculated by the Partner in accordance with the methodology used. ✓ The Auditor has obtained a list of all the relevant employees, based on which the personnel rate(s) are calculated. For 10 full-time equivalent employees selected at random (same sample basis as Section C: Personnel costs): ✓ The Auditor recalculated the hourly rates. ✓ The Auditor verified that the methodology applied corresponds to the usual accounting practices of the organisation and is applied consistently for all activities of the organisation on the basis of objective criteria irrespective of the source of funding. Factual finding: 19. No differences arose from the recalculation of the hourly rate for the employees included in the sample.
F. Time recording XXIV. Time recording is in place for all persons with no exclusive dedication to one Horizon 2020 action. At least all	Procedure ✓ The Auditor reviewed the brief description, all relevant manuals and/or internal guidance describing

hours	the

Please explain any discrepancies in the body of the Report.	
Statements to be made by Partner	Procedures to be carried out and Findings to be confirmed by the Auditor
worked in connection with the grant agreement(s) are registered on a daily/weekly/monthly basis *[delete as appropriate]* using a paper/computer-based system *[delete as appropriate]*; XXV. For persons exclusively assigned to one Horizon 2020 activity the Partner has either signed a declaration to that effect or has put arrangements in place to record their working time; XXVI. Records of time worked have been signed by the person concerned (on paper or electronically) and approved by the action manager or line manager at least monthly; XXVII. Measures are in place to prevent staff from: i. recording the same hours twice, ii. recording working hours during absence periods (e.g. holidays, sick leave), iii. recording more than the number of productive hours per year used to calculate the hourly rates, and iv. recording hours worked outside the action period. XXVIII. No working time was recorded outside the action period; XXIX. No more hours were claimed than the productive hours used to calculate the hourly personnel rates. *[Please provide a brief description of the time recording system in place together with the measures applied to ensure its reliability to the Auditor and annex it to the present certificate[4]].*	methodology used to record time. The Auditor reviewed the time records of the random sample of 10 full-time equivalents referred to under Section C: Personnel costs, and verified in particular: ✓ that time records were available for all persons with not exclusive assignment to the action; ✓ that time records were available for persons working exclusively for a Horizon 2020 action, or, alternatively, that a declaration signed by the Partner was available for them certifying that they were working exclusively for a Horizon 2020 action; ✓ that time records were signed and approved in due time and that all minimum requirements were fulfilled; ✓ that the persons worked for the action in the periods claimed; ✓ that no more hours were claimed than the productive hours used to calculate the hourly personnel rates; ✓ that internal controls were in place to prevent that time is recorded twice, during absences for holidays or sick leave; that more hours are claimed per person per year for Horizon 2020 actions than the number of productive hours per year used to calculate the hourly rates; that working time is recorded outside the action period; ✓ the Auditor cross-checked the information with human-resources records to verify consistency and to

[4] The description of the time recording system must state among others information on the content of the time records, its coverage (full or action time-recording, for all personnel or only for personnel involved in H2020

actions), its degree of detail (whether there is a reference to the particular tasks accomplished), its form, periodicity of the time registration and authorisation (paper or a computer-based system; on a daily, weeklyor monthly basis; signed and countersigned by whom), controls applied to prevent double-charging of time or

Please explain any discrepancies in the body of the Report.	
Statements to be made by Partner	Procedures to be carried out and Findings to be confirmed by the Auditor
[If certain statement(s) of section "F. Time recording" cannot be endorsed by the Partner they should be listed here below and reported as exception by the Auditor: - *…]*	ensure that the internal controls have been effective. In addition, the Auditor has verified that no more hours were charged to Horizon 2020 actions per person per year than the number of productive hours per year used to calculate the hourly rates, and verified that no time worked outside the action period was charged to the action. Factual finding: 20. The brief description, manuals and/or internal guidance on time recording provided by the Partner were consistent with management reports/records and other documents reviewed and were generally applied by the Partner to produce the financial statements. 21. For the random sample time was recorded or, in the case of employees working exclusively for the action, either a signed declaration or time records were available; 22. For the random sample the time records were signed by the employee and the action manager/line manager, at least monthly. 23. Working time claimed for the action occurred in the periods claimed; 24. No more hours were claimed than the number productive hours used to calculate the hourly personnel rates; 25. There is proof that the Partner has checked that working time has not been claimed twice, that it is consistent with absence records and the number of productive hours per year, and that no working time has been claimed outside the action period. 26. Working time claimed is consistent with that on record at the human-resources

ensure consistency with HR-records such as absences and travels as well as it information flow up to its usefor the preparation of the Financial Statements.

Please explain any discrepancies in the body of the Report.	
Statements to be made by Partner	Procedures to be carried out and Findings to be confirmed by the Auditor
	department.

[official name of the [Partner] [Linked Third Party]]
[name and title of authorised representative]

[dd Month yyyy]
<Signature of the [Partner] [Linked Third Party]>

[official name of the Auditor]
[name and title of authorised represent
[dd Month yyyy]
<Signature of the Auditor>

SIGNATURE

For the KIC Partner/new KIC Partner/new KIC LE:[function/forename/surname]

[signature]

Done in [English] at [place] on [date]

1 December 2016
EMA/CHMP/ICH/135/1995
Committee for Human Medicinal Products

8.1.2 Guideline for good clinical practice E6(R2)

Step 5

Adopted by CHMP for release for consultation	23 July 2015
Start of public consultation	4 August 2015
End of consultation (deadline for comments)	3 February 2016
Final adoption by CHMP	15 December 2016
Date for coming into effect	14 June 2017

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Document History

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***Step 5* corrected version**

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Current E6(R2) Addendum *Step 5* version

Code	History	Date
E6	Adoption by the Regulatory Members of the ICH Assembly under Step 4. Integrated Addendum to ICH E6(R1) document. Changes are integrated directly into the following sections of the parental Guideline: Introduction, 1.63, 1.64, 1.65, 2.10, 2.13, 4.2.5, 4.2.6, 4.9.0, 5.0, 5.0.1, 5.0.2, 5.0.3, 5.0.4, 5.0.5, 5.0.6, 5.0.7, 5.2.2, 5.5.3 (a), 5.5.3 (b), 5.5.3 (h), 5.18.3, 5.18.6 (e), 5.18.7, 5.20.1, 8.1	9 November 2016

8.1.3 Guideline for good clinical practice E6(R2)

8.1.3.1.1 Table of contents

Introduction

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

ADDENDUM

Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. When the original ICH E6(R1) text was prepared, clinical trials were performed in a largely paper-based process. Advances in use of electronic data recording and reporting facilitate implementation of other approaches. For example, centralized monitoring can now offer a greater advantage, to a broader range of trials than is suggested in the original text. Therefore, this guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting whilecontinuing to ensure human subject protection and reliability of trial results. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency havealso been updated.

This guideline should be read in conjunction with other ICH guidelines relevant to the conduct of clinical trials (e.g., E2A (clinical safety data management), E3 (clinical study reporting), E7 (geriatric populations), E8 (general considerations for clinical trials), E9 (statistical principles), and E11 (pediatricpopulations)).

This ICH GCP Guideline Integrated Addendum provides a unified standard for the European Union, Japan, the United States, Canada, and Switzerland to facilitate the mutual acceptance of data from clinical trials by the regulatory authorities in these jurisdictions. In the event of any conflict between the E6(R1) text and the E6(R2) addendum text, the E6(R2) addendum text should take priority.

1. Glossary

1.1. Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2. Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormallaboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3. Amendment (to the protocol)

See Protocol Amendment.

1.4. Applicable regulatory requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

1.5. Approval (in relation to institutional review boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.6. Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.7. Audit certificate

A declaration of confirmation by the auditor that an audit has taken place.

1.8. Audit report

A written evaluation by the sponsor's auditor of the results of the audit.

1.9. Audit trail

Documentation that allows reconstruction of the course of events.

1.10. Blinding/masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11. Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

1.12. Clinical trial/study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. Theterms clinical trial and clinical study are synonymous.

1.13. Clinical trial/study report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

1.14. Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

1.15. Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP)requirements, and the applicable regulatory requirements.

1.16. Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

1.17. Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financialmatters. The protocol may serve as the basis of a contract.

1.18. Coordinating committee

A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

1.19. Coordinating investigator

An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

1.20. Contract Research Organization (CRO)

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

1.21. Direct access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor’s proprietary information.

1.22. Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23. Essential documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

1.24. Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25. Independent Data-Monitoring Committee (IDMC) (data and safety monitoring board, monitoring committee, data monitoring committee)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26. Impartial witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27. Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial andto provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent EthicsCommittee to act in agreement with GCP as described in this guideline.

1.28. Informed consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

1.29. Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30. Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31. Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review oftrial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32. Interim clinical trial/study report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33. Investigational product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, orwhen used to gain further information about an approved use.

1.34. Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

1.35. Investigator / institution

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

1.36. Investigator's brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see 7. Investigator’s Brochure).

1.37. Legally acceptable representative

An individual or juridical or other body authorized under applicable law to consent, on behalf of aprospective subject, to the subject's participation in the clinical trial.

1.38. Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.39. Monitoring report

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor’s SOPs.

1.40. Multicentre trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

1.41. Nonclinical study

Biomedical studies not performed on human subjects.

1.42. Opinion (in relation to independent ethics committee)

The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

1.43. Original medical record

See Source Documents.

1.44. Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

1.45. Protocol amendment

A written description of a change(s) to or formal clarification of a protocol.

1.46. Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

1.47. Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48. Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49. Regulatory authorities

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50. Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

(see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.51. Source data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of thetrial. Source data are contained in source documents (original records or certified copies).

1.52. Source documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accuratecopies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

1.53. Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54. Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.55. Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56. Subinvestigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

1.57. Subject/trial subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58. Subject identification code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

1.59. Trial site

The location(s) where trial-related activities are actually conducted.

1.60. Unexpected adverse drug reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for ClinicalSafety Data Management: Definitions and Standards for Expedited Reporting).

1.61. Vulnerable subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members ofthe armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and thoseincapable of giving consent.

1.62. Well-being (of the trial subjects)

The physical and mental integrity of the subjects participating in a clinical trial.

ADDENDUM

1.63. Certified Copy

A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

1.64. Monitoring Plan

A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

1.65. Validation of Computerized Systems

A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration

the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

2. The principles of ICH GCP

2.1.

Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2.

Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continuedonly if the anticipated benefits justify the risks.

2.3.

The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4.

The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5.

Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6.

A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7.

The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8.

Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9.

Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10.

All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

ADDENDUM

This principle applies to all records referenced in this guideline, irrespective of the type of media used.

2.11.

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12.

Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13.

Systems with procedures that assure the quality of every aspect of the trial should be implemented.

ADDENDUM

Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

3. Institutional Review Board / Independent EthicsCommittee (IRB/IEC)

3.1. Responsibilities

3.1.1.

An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2.

The IRB/IEC should obtain the following documents:

- trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects,the investigator’s current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.

- The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

- approval/favourable opinion;
- modifications required prior to its approval/favourable opinion;
- disapproval / negative opinion; and
- termination/suspension of any prior approval/favourable opinion.

3.1.3.

The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4.

The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5.

The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgement of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

3.1.6.

When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7.

Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e. in emergency situations).

3.1.8.

The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9.

The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form

and any other written information to be provided to subjects. The way payment will be prorated should be specified.

3.2. Composition, Functions and Operations

3.2.1.

The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of theproposed trial. It is recommended that the IRB/IEC should include:

a) At least five members.

b) At least one member whose primary area of interest is in a nonscientific area.

c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2.

The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3.

An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4.

Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5.

The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6.

An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

3.3. Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1.

Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2.

Scheduling, notifying its members of, and conducting its meetings.

3.3.3.

Conducting initial and continuing review of trials.

3.3.4.

Determining the frequency of continuing review, as appropriate.

3.3.5.

Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourableopinion of the IRB/IEC.

3.3.6.

Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.

3.3.7.

Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8.

Specifying that the investigator should promptly report to the IRB/IEC:

a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).

b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).

c) All adverse drug reactions (ADRs) that are both serious and unexpected.

d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9.

Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

a) Its trial-related decisions/opinions.

b) The reasons for its decisions/opinions.

c) Procedures for appeal of its decisions/opinions.

3.4. Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request fromthe regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

4. Investigator

4.1. Investigator's Qualifications and Agreements

4.1.1.

The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2.

The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3.

The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4.

The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5.

The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2. Adequate Resources

4.2.1.

The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2.

The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3.

The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4.

The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

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4.2.5.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

4.2.6.

If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

4.3. Medical Care of Trial Subjects

4.3.1.

A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2.

During and following a subject's participation in a trial, the investigator/institution should ensurethat adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3.

It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4.

Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4. Communication with IRB/IEC

4.4.1.

Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2.

As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3.

During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

4.5. Compliance with Protocol

4.5.1.

The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

4.5.3.

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

a) to the IRB/IEC for review and approval/favourable opinion,

b) to the sponsor for agreement and, if required,

c) to the regulatory authority(ies).

4.6. Investigational Product(s)

4.6.1.

Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2.

Where allowed/required, the investigator/institution may/should assign some or all of the

investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3.

The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4.

The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5.

The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6.

The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7. Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8. Informed Consent of Trial Subjects

4.8.1.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their originin the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2.

The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject’s consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject’s legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject’s willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3.

Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4.

None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to releasethe investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5.

The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all

pertinent aspects of the trial including the written information and the approval/ favourable opinion by the IRB/IEC.

4.8.6.

The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7.

Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9.

If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

a) That the trial involves research.

b) The purpose of the trial.

c) The trial treatment(s) and the probability for random assignment to each treatment.

d) The trial procedures to be followed, including all invasive procedures.

e) The subject's responsibilities.

f) Those aspects of the trial that are experimental.

g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

j) The compensation and/or treatment available to the subject in the event of trial-related injury.

k) The anticipated prorated payment, if any, to the subject for participating in the trial.

l) The anticipated expenses, if any, to the subject for participating in the trial.

m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which thesubject is otherwise entitled.

n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject’s identity will remain confidential.

p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

s) The expected duration of the subject's participation in the trial.

t) The approximate number of subjects involved in the trial.

4.8.11.

Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject’s participation in the trial, the subject or the subject’s legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12.

When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject’s legally acceptable representative (e.g., minors, or patients with

severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13.

Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14.

Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

b) The foreseeable risks to the subjects are low.

c) The negative impact on the subject's well-being is minimized and low. (d) The trial is not prohibited by law.

d) The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15.

In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9. Records and Reports

ADDENDUM

4.9.0.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be

traceable, should not obscure the original entry, and should be explained if necessary (e.g., *via* an audit trail).

4.9.1.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2.

Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3.

Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections.
Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s).
The investigator/institution should take measures to prevent accidental or premature destruction ofthese documents.

4.9.5.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6.

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7.

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10. Progress Reports

4.10.1.

The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2.

The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11. Safety Reporting

4.11.1.

All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports.The immediate and follow-up reports should identify subjects by unique code numbers assigned to thetrial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2.

Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within thetime periods specified by the sponsor in the protocol.

4.11.3.

For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12. Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1.

If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should

promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2.

If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3.

If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13. Final Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and theregulatory authority(ies) with any reports required.

5. Sponsor

ADDENDUM

5.0. Quality management

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols andtools and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent.

The quality management system should use a risk-based approach as described below.

5.0.1. Critical process and data identification

During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

5.0.2. Risk identification

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

5.0.3. Risk evaluation

The sponsor should evaluate the identified risks, against existing risk controls by considering:

a) The likelihood of errors occurring.

b) The extent to which such errors would be detectable.

c) The impact of such errors on human subject protection and reliability of trial results.

5.0.4. Risk control

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviationsfrom the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

5.0.5. Risk communication

The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

5.0.6. Risk review

The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

5.0.7. Risk reporting

The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actionstaken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

5.1. Quality assurance and quality control

5.1.1.

The sponsor is responsible for implementing and maintaining quality assurance and quality controlsystems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2.

The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents , and reports for the purpose of monitoringand auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3.

Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4.

Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2. Contract Research Organization (CRO)

5.2.1.

A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2.

Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

ADDENDUM

The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

5.2.3.

Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4.

All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

5.3. Medical expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4. Trial design

5.4.1.

The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol andCRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

5.4.2.

For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct.

5.5. Trial management, data handling, and record keeping

5.5.1.

The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trialreports.

5.5.2.

The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3.

When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

ADDENDUM

The sponsor should base their approach to validation of such systems on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

b) Maintains SOPs for using these systems.

ADDENDUM

The SOPs should cover system setup, installation, and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system securitymeasures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities

of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use.

c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).

d) Maintain a security system that prevents unauthorized access to the data.

e) Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).

f) Maintain adequate backup of the data.

g) Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

ADDENDUM

h) Ensure the integrity of the data including any data that describe the context, content, and structure. This is particularly important when making changes to the computerized systems, suchas software upgrades or migration of data.

5.5.4.

If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5.

The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

5.5.6.

The sponsor, or other owners of the data, should retain all of the sponsor- specific essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

5.5.7.

The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8.

If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9.

If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

5.5.10.

Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11.

The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12.

The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

5.6. Investigator selection

5.6.1.

The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their organization and/or selection are the sponsor's responsibility.

5.6.2.

Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3.

The sponsor should obtain the investigator's/institution's agreement:

a) to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC (see 4.5.1);

b) to comply with procedures for data recording/reporting;

c) to permit monitoring, auditing and inspection (see 4.1.4) and

d) to retain the trial related essential documents until the sponsor informs the investigator/institution

these documents are no longer needed (see 4.9.4 and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7. Allocation of responsibilities

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial- related duties and functions.

5.8. Compensation to subjects and investigators

5.8.1.

If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2.

The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3.

When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9. Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10. Notification/submission to regulatory authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11. Confirmation of review by IRB/IEC

5.11.1.

The sponsor should obtain from the investigator/institution:

a) The name and address of the investigator's/institution’s IRB/IEC.

b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

c) Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2.

If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from theinvestigator/institution a copy of the modification(s) made and the date approval/favourable opinion was given by the IRB/IEC.

5.11.3.

The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion.

5.12. Information on investigational product(s)

5.12.1.

When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2.

The sponsor should update the Investigator's Brochure as significant new information becomes available (see 7. Investigator's Brochure).

5.13. Manufacturing, packaging, labelling, and coding investigational product(s)

5.13.1.

The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.13.2.

The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and

devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3.

The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4.

In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5.

If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14. Supplying and handling investigational product(s)

5.14.1.

The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2.

The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favourable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3.

The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4.

The sponsor should:

a) Ensure timely delivery of investigational product(s) to the investigator(s).

b) Maintain records that document shipment, receipt, disposition, return, and destruction of the

investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).

c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).

d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5.

The sponsor should:

a) Take steps to ensure that the investigational product(s) are stable over the period of use.

b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analysesof the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15. Record access

5.15.1.

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2.

The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16. Safety information

5.16.1.

The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2.

The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

5.17. Adverse drug reaction reporting

5.17.1.

The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2.

Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3.

The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18. Monitoring

5.18.1. Purpose

The purposes of trial monitoring are to verify that:

a) The rights and well-being of human subjects are protected.

b) The reported trial data are accurate, complete, and verifiable from source documents.

c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

5.18.2. Selection and qualifications of monitors

a) Monitors should be appointed by the sponsor.

b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

5.18.3. Extent and nature of monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

ADDENDUM

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized

monitoring. The sponsor should document the rationale for the chosen monitoring strategy(e.g., in the monitoring plan).

On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).

Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.

Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.

b) examine data trends such as the range, consistency, and variability of data within and across sites.

c) evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.

d) analyze site characteristics and performance metrics.

e) select sites and/or processes for targeted on-site monitoring.

5.18.4. Monitor's responsibilities

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

a) Acting as the main line of communication between the sponsor and the investigator.

b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

c) Verifying, for the investigational product(s):

   i. That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

   ii. That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

   iii. That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

   iv. That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

   v. That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

e) Verifying that written informed consent was obtained before each subject's participation in the trial.

f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

i) Verifying that the investigator is enroling only eligible subjects.

j) Reporting the subject recruitment rate.

k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

m) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:

   i. The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

   ii. Any dose and/or therapy modifications are well documented for each of the trial subjects.

   iii. Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

   iv. Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

   v. All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

n) Informing the investigator of any CRF entry error, omission, or illegibility.The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who isauthorized to initial CRF changes for the investigator. This authorization should be documented.

o) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

p) Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial).

q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5. Monitoring procedures

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6. Monitoring report

a) The monitor should submit a written report to the sponsor after each trial- site visit or trial-related communication.

b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

ADDENDUM

e) Reports of on-site and/or centralized monitoring should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan. Reporting of centralized monitoring activities should be regular and may be independent from site visits.

ADDENDUM

5.18.7. Monitoring plan

The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.

5.19. Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1. Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2. Selection and qualification of auditors

a) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3. Auditing procedures

a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

c) The observations and findings of the auditor(s) should be documented.

d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20. Noncompliance

5.20.1.

Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

ADDENDUM

If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

5.20.2.

If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21. Premature termination or suspension of a trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and thereason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and

provided the reason(s) for the termination or suspension by the sponsor or by the investigator / institution, as specified by the applicable regulatory requirement(s).

5.22. Clinical trial/study reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

5.23. Multicentre trials

For multicentre trials, the sponsor should ensure that:

5.23.1.

All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favourable opinion by the IRB/IEC.

5.23.2.

The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

5.23.3.

The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4.

All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

5.23.5.

Communication between investigators is facilitated.

6. Clinical trial protocol and protocol amendment(s)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1. General Information

6.1.1.

Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2.

Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3.

Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4.

Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5.

Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6.

Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7.

Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2. Background Information

6.2.1.

Name and description of the investigational product(s).

6.2.2.

A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3.

Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4.

Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5.

A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

6.2.6.

Description of the population to be studied.

6.2.7.

References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3. Trial objectives and purpose

A detailed description of the objectives and the purpose of the trial.

6.4. Trial design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

6.4.1.

A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2.

A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

6.4.3.

A description of the measures taken to minimize/avoid bias, including:

- Randomization.

- Blinding.

6.4.4.

A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5.

The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6.

A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

6.4.7.

Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8.

Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9.

The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

6.5. Selection and withdrawal of subjects

6.5.1.

Subject inclusion criteria.

6.5.2.

Subject exclusion criteria.

6.5.3.

Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

a) When and how to withdraw subjects from the trial/ investigational product treatment.

b) The type and timing of the data to be collected for withdrawn subjects.

c) Whether and how subjects are to be replaced.

d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6. Treatment of Subjects

6.6.1.

The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm ofthe trial.

6.6.2.

Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3.

Procedures for monitoring subject compliance.

6.7. Assessment of Efficacy

6.7.1.

Specification of the efficacy parameters.

6.7.2.

Methods and timing for assessing, recording, and analysing of efficacy parameters.

6.8. Assessment of Safety

6.8.1.

Specification of safety parameters.

6.8.2.

The methods and timing for assessing, recording, and analysing safety parameters.

6.8.3.

Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4.

The type and duration of the follow-up of subjects after adverse events.

6.9. Statistics

6.9.1.

A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2.

The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3.

The level of significance to be used.

6.9.4.

Criteria for the termination of the trial.

6.9.5.

Procedure for accounting for missing, unused, and spurious data.

6.9.6.

Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

6.9.7.

The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10. Direct access to source data/documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatoryinspection(s), providing direct access to source data/documents.

6.11. Quality control and quality assurance

6.12. Ethics

Description of ethical considerations relating to the trial.

6.13. Data handling and record keeping

6.14. Financing and insurance

Financing and insurance if not addressed in a separate agreement.

6.15. Publication policy

Publication policy, if not addressed in a separate agreement.

6.16. Supplements

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

7. Investigator's brochure

7.1. Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitatetheir understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the describeddata.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary withthe stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information.
However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor- investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2. General considerations

The IB should include:

7.2.1. Title page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired

by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2. Confidentiality statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3. Contents of the investigator's brochure

The IB should contain the following sections, each with literature references where appropriate:

7.3.1. Table of contents

An example of the Table of Contents is given in Appendix 2

7.3.2. Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3. Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4. Physical, chemical, and pharmaceutical properties and formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5. Nonclinical studies

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the

methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

- The information provided may include the following, as appropriate, if known/available:
- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:
  - Nature and frequency of pharmacological or toxic effects
  - Severity or intensity of pharmacological or toxic effects
  - Time to onset of effects
  - Reversibility of effects
  - Duration of effects
  - Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

a) Nonclinical pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actionsother than the intended therapeutic effect(s)).

b) Pharmacokinetics and product metabolism in animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites,and their relationship to the pharmacological and toxicological findings in animal species.

c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g. irritancy and sensitisation)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

7.3.6. Effects in humans

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

a) Pharmacokinetics and product metabolism in humans

- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

b) Safety and efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

c) Marketing experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7. Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinicalinformation on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drugreactions that is based on previous human experience and on the pharmacology of the investigational product.

7.4. Appendix 1:

TITLE PAGE *(Example)*

SPONSOR'S NAME

Product:

Research Number:

Name(s): Chemical, Generic (if approved)

Trade Name(s) (if legally permissible and desired by the sponsor)

INVESTIGATOR'S BROCHURE

Edition Number:

Release Date:

Replaces Previous Edition Number: Date:

7.5. Appendix 2:

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE *(Example)*

NB: References on 1. Publications

2. Reports

These references should be found at the end of each chapterAppendices (if any)

8. Essential documents for the conduct of a clinical trial

8.1. Introduction

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones whichare usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution’s site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor’s auditor and inspection by the regulatory authority(ies).

ADDENDUM

The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial.

The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data.

When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.

8.2. Before the clinical phase of the trial commences

During this planning stage the following documents should be generated and should be on file before the trial formally start

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.2.1	**INVESTIGATOR'S BROCHURE**	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	**SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)**	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	**INFORMATION GIVEN TO TRIAL SUBJECT - INFORMED CONSENT FORM (including all applicable translations)**	To document the informed consent	X	X
	- ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	**FINANCIAL ASPECTS OF THE TRIAL**	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.2.5	**INSURANCE STATEMENT** (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	**SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.:** - investigator/institution and sponsor - investigator/institution and CRO - sponsor and CRO - investigator/institution and authority(ies) (where required)	To document agreements	 X X X	 X X (where required) X X
8.2.7	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:** - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - subject compensation (if any) - any other documents given approval/ favourable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.2.8	**INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION**	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	**REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL** (where required)	To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
8.2.10	**CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)**	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	**NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and/or ranges of the tests	X	X
8.2.12	**MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.2.13	**SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)**	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14	**INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS** (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
8.2.15	**SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS**	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
8.2.16	**CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED**	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17	**DECODING PROCEDURES FOR BLINDED TRIALS**	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
8.2.18	**MASTER RANDOMISATION LIST**	To document method for randomisation of trial population		X (third party if applicable)
8.2.19	**PRE-TRIAL MONITORING REPORT**	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	**TRIAL INITIATION MONITORING REPORT**	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X

8.3. During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	**Sponsor**
8.3.1	**INVESTIGATOR'S BROCHURE UPDATES**	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	**ANY REVISION TO:** - protocol/amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X
8.3.3	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:** - protocol amendment(s) - revision(s) of: informed consent form any other written information to be provided to the subject advertisement for subject recruitment (if used) - any other documents given approval/favourable	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X

	opinion - continuing review of trial (where required)			
	Title of Document	**Purpose**	**Located in Files of**	
			Investigator /Institution	**Sponsor**
8.3.4	**REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:** - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	**CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)**	(see 8.2.10)	X	X
8.3.6	**UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7	**UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT**	(see 8.2.15.)	X	X
8.3.9	**CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS**	(see 8.2.16)		X

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.3.10	**MONITORING VISIT REPORTS**	To document site visits by, and findings of, the monitor		X
8.3.11	**RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS** - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
8.3.12	**SIGNED INFORMED CONSENT FORMS**	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13	**SOURCE DOCUMENTS**	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
8.3.14	**SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)**	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15	**DOCUMENTATION OF CRF CORRECTIONS**	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16	**NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS**	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.3.17	**NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION**	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2	X (where required)	X
8.3.18	**NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION**	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	**INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)**	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
8.3.20	**SUBJECT SCREENING LOG**	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21	**SUBJECT IDENTIFICATION CODE LIST**	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
8.3.22	**SUBJECT ENROLMENT LOG**	To document chronological enrolment of subjects by trial number	X	
8.3.23	**INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE**	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	**SIGNATURE SHEET**	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
8.3.25	**RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)**	To document location and identification of retained samples if assays need to be repeated	X	X

8.4. After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	**Sponsor**
8.4.1	**INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE**	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION**	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	**COMPLETED SUBJECT IDENTIFICATION CODE LIST**	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	**AUDIT CERTIFICATE** (if available)	To document that audit was performed		X
8.4.5	**FINAL TRIAL CLOSE-OUT MONITORING REPORT**	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6	**TREATMENT ALLOCATION AND DECODING DOCUMENTATION**	Returned to sponsor to document any decoding that may have occurred		X
8.4.7	**FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)**	To document completion of the trial	X	
8.4.8	**CLINICAL STUDY REPORT**	To document results and interpretation of trial	X (if applicable)	X

Medical Informatics Initiative

Support Structure – Coordination Office of the National Steering Committee

Consent Working Group Patient Consent Form Template

(German original version: Last updated 16 April 2020)

(English translation: Last updated 10 November 2020

Version 1.6d

Comprising information and consent forms for patients

8.2 Patient information

*8.2.1.1 on the use of patient data [**where applicable:**, health insurance dataand biosamples (tissues and body fluids)] for medical research purposes*

Dear patient,

You are currently receiving medical care for the purpose of diagnosis and/or treatment at [*name of the institution providing healthcare*]. Within the scope of your healthcare/treatment, patient data [*where applicable*: and biosamples (tissues and body fluids), e.g. obtained via blood samples, biopsies or operations/surgical interventions] may be collected. These patient data [*where applicable:* and biosamples] could have significant value for medical research.

Medical research is essential to the continuous improvement of the early diagnosis, treatment and prevention of disease; the insights we may gain from your patient data and biosamples could potentially make an important contribution to these efforts. We therefore request that you consent to make your patient data [*where applicable:* and biosamples] available to us for the purpose of medical research. With your consent, your patient data will be collected in a database operated by [*name of the database owner/operator*]. [*Where applicable:* The biosamples you provide will be long-term stored in a quality-controlled manner in the biobank(s) and/or archives of [*biobank and/or archive owner/operator*]].

Your consent is entirely voluntary. If you do not wish to participate, or if at a later time you wish to withdraw your consent, you will not suffer from any reprisal.

If you do not fully agree with the type and long-term nature of use described below, or if your questions have not all been answered to your satisfaction, then you should not give your consent.

1. Collection, processing and scientific use of your patient data

1.1 What are our goals?

Your patient data are to be made available for medical research. The sole aim of medical research is to improve the diagnosis, treatment and prevention of disease; your patient data will not be used for the development of biological weapons or for any discriminatory research. **Moreover, it is not the purpose of this research to provide you with a diagnosis or to influence your specific medical treatment.**

Your patient data will be used for a wide variety of medical research purposes to the benefit of society as a whole. At this point in time, it is not possible to describe all future medical research topics that might be applicable; these may range from the study of specific disease areas (e.g. cancer/oncology, cardiovascular diseases, brain diseases) to individual diseases and genetic disorders that we may currently be unaware of. It is therefore possible that your patient data will be used for research activities that we at this time cannot anticipate. Against this background, your patient data [*where applicable:* and biosamples] will be **stored for 30 years from the time your consent is given**, unless you withdraw your consent before this period has elapsed. In special cases, data [*where applicable:* and biosamples] may be of significant value to science beyond this period. In these instances, we would consult the corresponding data protection supervisory authority and an independent ethics committee to determine whether further use of your data [*where applicable:* and biosamples] is possible.

Patient data

Patient data comprise all information about your person used during your medical examination(s) and treatment(s). Examples of patient data include, but are not limited to: data from doctor's letters/notes, your health records, and results, findings and data from medical examinations, such as blood pressure measurements or X-ray images; also included are the results of laboratory tests, including tests of genetic material (e.g. for congenital or acquired genetic disorders, including tumours).

1.2 How will your patient data be used for scientific research?

Your patient data can, upon request, be made available to universities, research institutions, and companies conducting medical research. The recipient may only use these data for the predetermined research purpose for which they submitted their request, and may not use them or make them available for other purposes. Your patient data [*where applicable:* and donated biosamples] will be used solely for scientific purposes; they will not be sold. However, [*name of the institution providing healthcare*] may request reasonable cost reimbursement from the respective user for the provision of quality-controlled data.

The use of your patient data [*where applicable:* and biosamples] for a specific research project requires prior review and approval by an independent ethics committee.

Results published in scientific titles/media are entirely **anonymised**, i.e. are provided in a form that does not allow them to be traced back to you. [*where genetic studies are proposed:* This also applies in particular to genetic information. However, it is possible that your genetic data, up to and including your complete genetic material, i.e. entire genome, may be included in specially protected scientific databases that are not accessible to the general public].

Anonymisation

When your data are anonymised, they are altered in a manner that they can no longer be traced back to your person, or only with disproportionate technical effort.

Your patient data [*where applicable:* and data from the analysis of your biosamples] may also be merged with your data from databases of other research partners (e.g. other hospitals, institutions or registers).A prerequisite is that you have also allowed the research partners to support such a merge.

1.3 Who has access to your patient data, and how are they protected?

All data that directly identify your person (name, date of birth, address, etc.) are replaced by a combination of characters (i.e. they are encoded). This internal identifier and your associated patient data [*where applicable:* and biosamples] can no longer be directly traced back to you. The connection between this internal identifier and the data that directly identifies you will be managed by an independent internal body or, in particular where data is combined across multiple institutions, by an independent external trust centre [*refer reader to the website(s) of this/these entity/entities*]. Without the assistance of this body/trust centre, the patient data provided for medical research cannot be attributed to you, or can only be traced back to you with disproportionate technical effort. Before your data [*where applicable:* and biosamples] are transferred to researchers external to the institution providing you with healthcare, the internal identifier will be replaced by a new code (combination of characters).

Encoding

When your patient data are collected, information such as your name and date of birth are also recorded. This information can easily be used to identify your person. Upon encoding, this information is replaced by a combination of characters. This prevents the information from being easily traced back to you. You will only be identified if and when your patient data are to be supplemented by additional information on you or to renew contact with you (see Section 4).

Data that identifies you will never be passed on to researchers or other third parties, in particular to insurance companies or employers, except where explicitly permitted by you or where governed by law.

Your consent also applies to the possible transfer of your patient data [*where applicable:* and bio- samples] for the purposes described to recipients in countries within the European Union or the Euro- pean Economic Area, or in other countries where the European Commission has determined there is an adequate level of data protection. **Transfer of your patient data to countries where an adequatelevel of data protection has not been established is hereby expressly excluded.**

You can view the studies using your or others' patient data [*where applicable:* and biosamples] at any time at www.medizininformatik-initiative.de/datennutzung. In addition, you can register at this address for an e-mail distribution list to receive information via e-mail of all new studies at least one week before the data are used.

1.4 What risks are associated with the use of your patient data?

Whenever patient data [*where applicable:* and data from the analysis of your biosamples] are collected, stored and transferred within the scope of research projects, there is a residual risk that these data can be traced back to you through additional information, e.g. from the Internet or social media. This is particularly the case if you publish your genetic or other health data, e.g. for genealogical research, on the Internet.

The risk of personal traceability is greater for genetic patient data. Genetic information typically relates to a specific individual, i.e. yourself. Additionally, in some cases, conclusions on genetic characteristics among your relatives could be drawn from your genetic data.

Should, despite comprehensive technical and organisational protection mechanisms, your data be accessed by unauthorised persons and then, despite the absence of your name, be traced back to you, it is no longer possible to rule out discriminatory or other data use of a type potentially harmful to you or your close relatives.

1.5 How do you personally benefit?

Generally, you cannot personally expect any direct health benefit or advantage from the scientific use of your patient data [*where applicable:* and biosamples]. Your consent will have no impact on your current medical treatment. If any commercial benefit is derived from the research, e.g. through the development of new drugs or diagnostic procedures, you will not share in this benefit.

However, it is possible that in individual cases a result of analysis could be of such significant importance to your health that a physician or researcher considers it urgently necessary to contact you. This is in particular the case where there is strong suspicion of a serious, possibly previously undetected disease that could be treated or whose onset could be prevented.

In addition, there may be further results (additional findings) that might be relevant to your health and of which we would wish to inform you. You may decide whether we are permitted to contact you in these situations. Please note that you may be required to disclose health information received through such feedback to other parties (e.g. before taking out health or life insurance) and could suffer disadvantages as a result. Where information from your genetic material is used for medical research, this may include

your genetic predisposition on your part to certain diseases. You can find further information on genetic data at www.vernetzen-forschen-heilen.de/genetische-daten.

Information from your genetic material may also be important for your family members and for family planning. You can reverse your decision in favour of or against us providing such feedback at any time by informing us.

1.6 What are the benefits to society?

Medical/scientific research projects aim to improve our understanding of the cause of diseases and diagnosis and, on this basis, to improve prevention, care and treatment. Further information on our activities can be found at [*website address*].

[*Where applicable*:

2. Transfer and scientific use of health insurance data

Health insurance data

During your treatment [at/by institution providing healthcare] only data that are required in the direct context of the treatment are collected. For many scientific questions, however, these "snapshots" are generally insufficient. In order to obtain a more comprehensive picture of your state of health, we would, for example, like to also use your data from outpatient care. Your health insurer has this information

We therefore ask for your consent that we may also request your data relating to previous and future contacts with general practitioners and specialist physicians providing outpatient care and, where applicable, relating to further inpatient treatments (hospital stays) and medication prescriptions, and that we may use this data for scientific purposes. In Section 2 of the consent form, you can authorise us to request the relevant data from your health insurer. However, we do not provide the health insurer with any research data that could be traced back to you. You will therefore not suffer any disadvantage through the use of your health insurance data.

***End of health insurer data module*].**

[*Where applicable*:

3. Collection, storage and scientific use of biosamples (tissues and body fluids)

3.1 What are biosamples?

Biosamples

Biosamples are tissue specimen and/or body fluids that have been taken from you for diagnosis or treatment and which, after the conclusion of treatment/examination, are no longer needed (residual materials). Biosamples can be blood, urine, stool, saliva, cerebrospinal fluid, or, for example, tissue removed during an operation or biopsy. These residual materials can be useful for medical research and would be stored in biobanks or hospital or research institution archives. [Where applicable: *Moreover, you can also donate additional samples (e.g. a limited additional amount of blood) for medical research purposes to be collected when a routine blood sample is being taken or a planned puncture is being performed (see Section 3.2 below).*]

3.2 How are your biosamples used scientifically and protected against misuse?

The same rules and principles, as well as the associated goals and risks, apply to your biosamples and the data obtained from them as described above for patient data. Details are given in Sections 1.1 – 1.6 of the patient information. Biosamples may contain your inherited genetic information. In this regard, we draw attention in particular to the risks for genetic data described in Section 1.4. This includes an increased risk of these data being traced back to you.

The intention is to make your biosamples available for a variety of medical research purposes. To this end, they will be stored in a [*name of the biobank or archive owner/operator*] biobank or an institutional archive and may be made available to other research partners upon request.

Research projects using your biosamples may also include analysis of your genetic material, e.g. for congenital or acquired genetic disorders, including tumours. Under certain circumstances, this may also include examination of your entire genetic material (genome).

[*Where applicable:* For research purposes, it can be very useful to extract slightly more biosample when taking a routine blood sample or performing a puncture than is necessary for your treatment. This additional sample will only be collected if you agree to it specifically on the informed consent form. For your protection, there are limits placed on the quantity of additional sample. [According to the instructions of the physician overseeing your treatment, no more than [*locally agreed maximum*] of blood or puncture fluid (approx. [*locally agreed value*] teaspoons) may be taken for research purposes, or in the case of cerebrospinal fluid up to [*locally agreed maximum*] (approx. [*locally agreed value*] teaspoons) [*Either:* within [*locally agreed time period*] *or:* for each sample]. Quantities above these limits require separate, dedicated patient information and consent.]

3.3 Who has ownership of your biosamples?

By providing your consent to the collection, storage and scientific use of your biosamples, ownership of your biosamples is transferred to [*biobank or archive owner/operator*]. Your samples will not be sold, but the owner/operator may request reasonable cost reimbursement from the user for providing quality-controlled biosamples. Transfer of ownership does not affect your right to determine how your personal data are processed. Despite transfer of ownership, you can withdraw your consent to data processing at any time (see Section 6) and request the destruction of your biosamples.

***End of biosamples module*]**

4. Will you be contacted again?

To request additional information [*where applicable:* or biosamples] from you, it may be useful to contact you again at a later date. In addition, renewed contact may be made, for example, for the following purposes:

4.1

To **ask** you, with your consent, for **additional information relevant to scientific questions**, to inform you of new research projects/studies and/or to obtain your consent to combine your patient data with medical information from other databases, or

4.2

to **inform** you of **additional research findings** (see Section 1.5 above).

You can decline the forms of contact described in 4.1 and 4.2 in the declaration of consent ("right not to know").

4.3

Moreover, irrespective of the above, contact can be made in order **to give you feedback via the physician overseeing your treatment or your general practitioner** on analysis results that could be of significant relevance to you personally (see Section 1.5 above).

5. How long is your consent valid?

Your consent to the collection of patient data [*where applicable:* and of biosamples] is valid for **five years** from the date you give consent, unless you withdraw it before this period has elapsed (see below).

This means that during this five year-period [*institution providing healthcare*] may, with prior notice, collect further data [*where applicable:* and biosamples] without you having to sign a new consent form. If you return to [*name of institution providing healthcare*] after five years, we will ask you to give your consent again (renewal of your consent).

Your consent to the processing and use of the data [*where applicable:* and biosamples] collected until now remains valid beyond this period (see Section 1.1).

6. What does your right of withdrawal include?

Your consent is entirely voluntary.

You can withdraw your consent in whole or in part to the further collection and scientific use of your patient data [where applicable: and biosamples] at any time without giving reasons and without any reprisal.

Your withdrawal of consent always only applies to the future use of your patient data [*where applicable:* and biosamples]. Data from analyses already performed cannot be subsequently removed.

In case of withdrawal, [*where applicable:* the biosamples provided by you for research will be destroyed and] your patient data stored on the basis of your consent will be deleted or anonymised, where this is legally permissible. If deletion is not possible or only possible with unreasonable technical effort, your patient data will be anonymised by deleting the identification code assigned to you. However, anonymisation of your patient data cannot entirely exclude the possibility of subsequent tracing of information, in particular genetic information, to you via other sources.

You can also withdraw individual parts of the consent declaration, for example, if you wish to continue to make the patient data available for research, but have no interest in renewed contact for the purposes of subsequent collection of further data or participation in other studies.

If you wish to withdraw your consent, please contact us at:

[*Address/tel./fax/e-mail of body/institution that manages consent withdrawal*]

7. Further information and rights

The legal basis for processing your personal data is your consent (Article 9 (2) (a) and Article 6 (1) (a)of the EU General Data Protection Regulation).

The data controller (institution(s) responsible for data processing) for your patient data is [*insert name(s)of corresponding institution and contact details*].

The data protection officer at this institution can be contacted at [*give contact details*].

It is possible for you to lodge a complaint with any data protection supervisory authority. The supervisory authority for this institution is [*name of the data protection supervisory authority*].

In addition, you have the right to access your patient data (including, upon request, the provision of a copy of the data free of charge) and, where applicable, to require that these data be rectified, or deleted, or that processing be restricted.

You also have the right to receive your personal data which you have provided in a standardised electronic format or to have it transmitted to another data controller (body) designated by you (right to data portability).

8.3 Patient declaration of consent

*8.3.1.1 Consent to the use of patient data [**where applicable:** health insurance data and biosamples (tissues and body fluids)] for medical research purposes*

1. Collection, processing and scientific use of my patient data as described in the patient information; this includes

1.1

the processing and use of my patient data for medical research exclusively as described in the patient information, in conjunction with separate management of my name and other directly identifying data (encoding). I can register at http://www.medizininformatik-initiative.de/datennutzung for an e-mail distribution list, which will inform me by e-mail in advance of all new studies to be conducted with patient data (see Sections 1.1, 1.2 and 1.3 of patient information).

1.2

the scientific analysis and use of my encoded patient data by third parties, such as other universities/institutions/companies conducting research; this may include transfer to other countries for research projects if European data protection legislation applies in these countries or if the European Commission has confirmed an adequate level of data protection in these countries. I will not share in any commercial benefit gained from research. Prior to transfer to researchers outside the institution providing me with healthcare, the internal identifier (code) will be replaced by a new code (combination of characters).

1.3

the possibility of merging my patient data with data in databases of other research partners. **A prerequisite is that I have also allowed the research partners to support such a merge.**

I consent to the collection, processing, storage and scientific use of my **patient data** as described in Sections 1.1 to 1.3 of the declaration of consent and Section 1 of the patient information.

[*Where applicable*:

2. Transfer and scientific use of my health insurance data

I hereby authorise my health insurer, where requested by [*corresponding institution/body*] to transfer data on outpatient and inpatient medical care I have received, on prescribed medications and aids, as well as information on long-term nursing care provided to [*name of institution providing healthcare*] as described in the patient information, namely

2.1

once only **retrospectively for data of the past 5 calendar years**. I agree to the transfer of my health insurance number to [*corresponding institution/body*] for this purpose

2.2

For data **from the five years following the date of my signature**. I agree to the transfer of my health insurance number to [*corresponding institution/body*] for this purpose

***End of health insurer data module*]**.

[*Where applicable*:

3. Collection, storage and scientific use of my biosamples (tissues and body fluids) as described in the patient information; this includes

3.1

the storage and processing of my biosamples at [*biobank or archive owner/operator*] for medical research purposes exclusively as described in the patient information in conjunction with separate management of my name and other directly identifying data (encoding, see Sections 3.1 to 3.3).

3.2

the scientific analysis of my encoded biosamples as well as their transfer and use by third parties, e.g. universities/ institutes/companies that conduct research, for medical research purposes that have been precisely defined and requested; this may also include transfer for research projects in other countries if the European data protection legislation applies in these countries, or where the European Commission has confirmed an adequate level of data protection in these countries. Prior to transfer to researchers outside the institution providing me with healthcare, the internal identifier (code) will be replaced by a new code (combination of characters).

I also agree to the possibility of merging analysis data of my biosamples with analysis data in databases of other research partners. **A prerequisite is that I have also allowed the research partners to support such a merge.**

3.3

I hereby transfer ownership of my biosamples to [*biobank or archive owner/operator*]. Transfer of ownership does not affect my right to determine how my personal data derived from biosamples are processed (see Section 3.3 of patient information).

I consent to the collection, storage and scientific use of my **biosamples** (tissues and body fluids) as described in Section 3.1 to 3.3 of the declaration of consent and Section 3 of the patient information.

☐ Yes ☐ No

[*Where applicable:* My consent also applies to the collection of small additional amount of biosamples during the routine taking of blood samples or performance of punctures, within the limits described in Section 3.2 of the patient information.

***End of biosample module*]**

4. Possibility of renewed contact

4.1

I agree that I may be contacted again by [*name of institution providing healthcare*] to provide additional information [*where applicable:* or biosamples] relevant to scientific questions, to be informed of new research/studies and/or to seek my consent to merge my patient data with medical information from other databases (see Section 4.1 of the patient information).

4.2

I agree that I may be contacted again by [*name of institution providing healthcare*] to be informed of additional research findings (see Section 4.2 of the patient information).

5. Validity period of my consent

My consent to the collection of patient data [*where applicable:* and of biosamples] during care at [*name of institution providing healthcare*] is valid for a **period of five years,** from my declaration of consent. If I return to [*name of institution providing healthcare*] after five years, I can renew my consent. The use of data [*where applicable:* and biosamples] already collected remains permissible beyond this period (Section 5 of the patient information).

6. Right of withdrawal

Your consent is entirely **voluntary.**

You may withdraw your consent in whole or in part at any time without giving reasons to [*name of institution providing healthcare*] without any reprisal.

Upon withdrawal of your consent, [*where applicable:* the biosamples stored for research and] the data stored on the basis of this consent will be [*where applicable:* destroyed, or respectively,] deleted or anonymised, insofar as this is legally permissible. Data from analyses already performed cannot be removed (Section 6 of the patient information).

I have been informed about the use of my patient data [where applicable:, health insurance data and biosamples] and the associated risks, and give my consent within the framework described above. I have had sufficient time to properly consider the matter and all my questions have been answered to my satisfaction.

I have been informed that I will receive a copy of the patient information and a copy of the signed consent form.

Place, date

First and last name of patient
(block capitals)

Signature of patient

I, in person, provided the patient with information and guidance.

First and last name of employee
(block capitals)

Signature of employee

Survivorship Care Planning for Prostate Cancer

8.4 NRG Oncology Clinical Trial:NRG-CC007CD

Increasing the dose of survivorship care planning in prostate cancer survivors who receive androgen deprivation therapy

NRG ONCOLOGY

Advancing Research. Improving Lives.™

9 About the trial

NRG-CC007CD studies how well increasing the dose of survivorship care planning improves care and outcomes in prostate cancer survivors receiving radiation therapy and androgen deprivation therapy. After patients finish prostate cancer treatment, monitoring byboth the cancer specialist (i.e. radiation oncologist) and the primary care provider or cardiologist is needed. This study is trying to improvethe use of the survivorship care plan to help patients improve the monitoring patients need.

ClinicalTrials.gov Identifier: NCT03860961

10 About NRG NCORP

The NRG Oncology National Cancer Institute (NCI) Community Oncology Research Program (NCORP) Research Base provides scientific and statistical leadership for developing, implementing, and analyzing multi-institutional clinical trials of cancer prevention, control, screening, and post-treatment surveillance, as well as cancer care delivery research.

To contact NRG Oncology,

call 215-854-0716 or email info@nrgoncology.org.

10.1 Frequently Asked Questions

What is a clinical trial?

Clinical trials are research studies that look to find better ways to prevent, diagnose, or treat disease.

10.1.1.1.1.1 Who can join this study?

Men who are currently receiving prostate cancer treatment at a clinic.

10.1.1.1.1.2 Am I required to be in this study?

No. Taking part in this study is voluntary. You are free to choose to participate or not to participate. If you choose to participate in thisstudy, you are able to leave the study at any time. If you decide not to take part in this study, your doctor will discuss other treatmentoptions with you.

10.1.1.1.1.3 What will happen if I decide to take part in this study?

As part of this study, you will be receiving a survivorship care plan at the end of radiation treatment. You may receive a treatment plan from your radiation oncology team at the beginning of treatment and additional survivorship care planning. You will also be asked to meet with your primary care provider to discuss the survivorship care plan. Two years after radiation treatment is finished, you will havea blood test to check your blood sugar and cholesterol levels.

Your radiation oncology team will review the recommendations on these care plans with you each time, and each plan will be sent toyour primary care provider. You can help the researchers understand your care and satisfaction with care after finishing radiation treatment by completing questionnaires.

10.1.1.1.1.4 What risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that you may feel uncomfortable being asked about your satisfaction of care. Youwill need to spend more time in the hospital or doctor's office and will be asked sensitive or private questions about things you may notnormally discuss. The most common risks related to drawing blood from your arm are brief pain and possibly bruise. Rarely, an infection can occur.

10.2 More Information

Visit the National Cancer Institute website at https://www.cancer.gov for more information about studies or general information aboutcancer. You may also call: 1-(800)-4-CANCER (1-800-422-6237)