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neuGRID

A GRID-BASED e-INFRASTRUCTURE FOR DATA ARCHIVING/ COMMUNICATION AND COMPUTATIONALLY INTENSIVE APPLICATIONS IN THE MEDICAL SCIENCES

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Executive summary

The aim of this deliverable is to review existing European requirements on software used for handling of imaging and clinical data and provide a regulatory framework for evaluating code bases of existing projects and for code development within the context of the neuGRID.

A comprehensive review of regulation sources is presented in brief and an early selection of relevant regulations is carried out. Following is the detailed investigation of their respective relevance and implications within the context of this project. The work is concluded by the discussion of project legal status within the medical arena in foreseeable future.

This document should be the basis for development decisions and will ensure that the development is carried out in accordance with existing regulations.

Introduction

The *5.2 Regulatory guidelines document for code development* deliverable deals with regulations imposed on medical software applications and infrastructures within the European context and their implications on development process of the neuGRID project.

To protect the health and privacy of patients as well as other participants of the healthcare process, the European community established number of directives and standards that pose requirements on various products within the healthcare arena. In order to ensure that the users of neuGRID are able to extract its full potential, it is necessary to establish its context within the legal framework and make sure that it fulfils all relevant quality standards that are required for providing its services.

The aim of this deliverable is thus to make a survey into relevant European legislation and compile the information collected to form a regulatory framework for the neuGRID development. As the neuGRID project aims to incorporate some existing code bases of other projects, this deliverable also aims to evaluate these code bases against the legal requirements.

Methodological approach

The broader picture presented in this research relies on studies published by the European Commission within the Information Society thematic portal accessible at http://ec.europa.eu/information_society [IS]. With particular relevance to this work are the studies presented in the e-Health sector of this portal at http://ec.europa.eu/information_society/activities/health/studies/published [EHEALTHS].

The relevant directives and standards were selected and reviewed. The primary source of information providing for roadmap to official regulatory and explanatory documents was the European Commission web portal dedicated to medical devices at http://ec.europa.eu/enterprise/medical_devices [MDS]. Complementary to this source of information were the explanatory guidelines intended to be used by Notified Bodies[1] available at http://www.meddev.info [MED-DEV]. During the research a number discussions were carried out with competent authorities, namely the Czech Electro-Technical Testing Institute [EZU].

Thus this research was carried out by carefully analyzing the law and discussing the problematic parts with authorized European professionals and drawing conclusions accordingly.

[1] Notified Body denotes an organization authorized to carry out the certification procedures inherent to medical devices

Activity carried out and results

Putting Healthcare Information Technologies in European Legal Context

Nowadays, information systems are fundamental components of almost every organisation, including healthcare facilities. As the state of the art progresses, the functionality provided by information systems transforms from supporting role in the management of various data to truly analytical functionalities. Thus the systems gradually take on new responsibilities, to the level where the lives of people depend directly on correct system behaviour.

A corresponding movement can easily be observed in healthcare arena. As Electronic Health Records are becoming widely implemented and most of the Clinical as well as Imaging or other measurement data is being captured and stored in digital form, new strategies of analyzing and exploiting the data in an automated, computer-aided manner are developed. Thus information technologies in healthcare bear an ever greater responsibility in the healthcare provision process.

As a result of this movement legal frameworks ensuring patient privacy and safety are being developed. The field of medical software systems is legally governed by a set of directives and standards that specify the safety and quality requirements that the manufacturers of medical systems and devices have to meet in order to enter the European market. It is essential for neuGRID to be developed in accordance with these requirements.

Within the scope of current deliverable we have identified significant directives and standards relevant for neuGRID and examined their requirements with respect to existing code bases as well as future code development.

The legal context of technology specific for healthcare (herein referred to as "medical devices") centres on following directives:

- Directive 93/42/EEC concerning medical devices [MDD]
- Directive 98/79/EC concerning in vitro diagnostic medical devices [IVD]
- Directive 2001/83/EC concerning the Community code relating to medicinal products for human use [MPD]
- Directive 90/385/EEC concerning the approximation of the laws of the Member States relating to active implantable medical devices [AID]

Besides the legal context specific to healthcare the basic legal principles still apply such as [EHEALTH]:

- Protection of human privacy with respect to providing healthcare and corresponding data handling (according to Directive 95/46/CE on the protection of individuals with regards to the processing of personal data and on the free movement of such data [DPD], the Directive 2002/58/CE concerning the processing of personal data and the protection of privacy in the electronic communications sector [PPDD] and other relevant legal sources, comprehensive list of which can be found in [EHEALTH])
- Information society in general (according to Directive 1999/93/EC on a Community framework for electronic signatures [ESIGD] and Directive 2000/31/EC on certain legal

aspects of information society services, in particular electronic commerce in the Internal Market [ECD])

- General business and consumer protection (according to Directive 2005/29/EC concerning unfair business-to-consumer commercial practices in the internal market [UFBD], Directive 2001/95/EC on general product safety [GPSD] or Directive 85/374/EEC on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products [LDPD])

The Legal Context of neuGRID Project

The envisioned neuGRID architecture and services neuGRID aims to provide make it very specific from the point of view of the current legislation.

One of the key aspects of the project is its cooperative distributed nature making it possible for multiple centres around the continent to share resources and contribute to the computing and storage power of the system.

The system aims to provide for a distributed clinical data management environment for patient records and for automated analysis of processed imaging data. These functionalities therefore have to be evaluated against existing law and relevant requirements on the system stated.

The information exchanged during the system work contains sensitive personal data of the patients. It is therefore necessary to ensure that privacy rights of the persons involved are not violated and protection of such data is in line with relevant legislation. The ethical, data protection and privacy issues are dealt with other deliverables [D2.1 and D2.3] within the project and thus are considered to be outside of the scope of this deliverable.

The Medical Devices Directive

The regulations concerned specifically with technology and devices in healthcare build upon the directives that were already mentioned earlier in the section "Putting Healthcare Information Technologies in European Legal Context". These directives ensure that only products that are known and verified not to harm the patient or other participants of healthcare process can enter the market and define requirements the products have to fulfil and procedures the manufacturers have to follow in order to be able to put their products to the market.

The one directive specifically relevant to neuGRID project is the Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (Medical Devices Directive) [MDD]. For the aims of this deliverable we examined the Directive in detail, discussed all relevant scenarios and have drawn conclusions accordingly.

The basic logic of the directive is as follows:

- Define the circumstances under which an apparatus, device or system constitutes a medical device
- Define the essential requirements a medical device has to fulfil
- Define the classes of devices and the classification rules to be used when determining the class of a individual device

- Define the procedures by which the conformance with the requirements of the directive can be assessed for a certain class of a product (referred to as Conformance Assessment Procedure or CAP)

Following the logic of current deliverable we sought answers to following questions:

- Is neuGRID a medical device?
- If yes, what requirements will it have to meet?
- How would they translate into guidance and regulation for code base development?

The work underpinning the answers to these questions included evaluation of various envisioned use cases of neuGRID with respect to the directive. Unfortunately, the wording of the directive is not always clear within the specific context of neuGRID, therefore the explanations have to be sought by consulting the official authorities.

The definition of a medical device the directive presents is as follows:

Medical device means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- *diagnosis, prevention, monitoring, treatment or alleviation of disease*
- *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap*
- *investigation, replacement or modification of the anatomy or of a physiological process*
- *control of conception*

From this definition it is obvious that not only the characteristics of the device have to be considered when determining whether it qualifies as a medical device, but also the purpose for which it is intended to be used.

Going deeper into the explanatory materials accompanying the directive, following guidance can be found:

MEDDEV 2.1/1

Medical Devices Guidance Document published by European Commission on definition of Medical Devices [MDEV2.1/1]:

Medical devices are defined as articles which are intended to be used for a medical purpose. The medical purpose is assigned to a product by the manufacturer...

...

In the case of software intended for use with multipurpose informatics equipment a distinction has to be made between software providing for a proper diagnostic or therapeutic tool and software for handling general patient-related data. Only in the first case may a medical purpose be determined. Examples for medical devices:

- *Calculation of anatomical sites of the body*
- *Image enhancing software intended for diagnostic purpose.*

There is no medical purpose in the case of software used for administration of general patient data

NB-MED/2.2/Rec4 - Software and Medical Devices

Recommendation document intended for co-ordination of Notified Bodies within the Medical Devices sector (NB-MED) (note that cosmetic changes were made to the text in order to make the shortened version easily readable. None of the logic was altered in any way) [NB-MED2.2/Rec4]:

Software is regarded as a medical device when one or more of the circumstances given at (a) to (d) apply:

a. ...
b. ...
c. The software is intended for the analysis of patient data generated by a medical device with a view to diagnosis and monitoring. Examples:
    - *SW used for diagnostic image processing.*
    - *SW for long term comparative monitoring of stored images for oncological diagnosis.*
    - *SW for the measurement/calculation of anatomical sites of the body with a view of an irradiation or surgical intervention.*
d. ...

The information above unfortunately doesn't make it possible to draw final conclusion about whether or not neuGRID actually qualifies as a medical device. It is obvious that some of the systems functionality is clearly outside of scope of the directive – such as the clinical data management and collaboration functionality – while the classification of others – such as the image processing functionality – is not clear. The key question is whether a medical purpose or a view of diagnosis of treatment can be identified in any of the services the system aims to provide.

A comprehensive list of possible and technically feasible envisioned use cases of neuGRID was thus composed to be evaluated. There were two questions being asked about each individual use case:

- Does it correspond to current aspirations of the project?
- Does it qualify neuGRID as a medical device?

The identified use cases are based upon the original proposal submitted to European Commission ([NGWP] – Section 3.2.1 Plan of the use and dissemination of foreground) as well as on communication with senior neuGRID representatives.

Use case 1: Evaluation of correlation of biological marker to measured progression of AD

This is a shortened derivation of the first use case presented in the proposal ("A future neuGRID story in Clinical Neuroscience"):

A neuroscientist believes that a biological marker X that can be assayed in blood might be in a good correlation with the progression of Alzheimer's disease (AD). He obtains the blood samples from AddNeuroMed and US ADNI consortia of patients with various stages of AD. The clinical and imaging data of these patients are stored within neuGRID. By running a correlative analysis matching the presence of the marker X with cortical thickness calculated using the image processing capabilities of neuGRID he is able to verify his suspicion.

Discussion of use case 1:

This use case is the fundamental use case for which neuGRID is being developed, so there can be little doubt about it being relevant.

When trying to determine the medical purpose we can note that one of the steps the system performs is the "calculation of anatomical sites of the body" as mentioned in citation of the MEDDEV 2.1/1 [MDEV2.1/1] explanatory document, however there is no direct view of this information being used for diagnosis or treatment of an individual patient as suggested by the citations of NB-MED/2.2/Rec4 [NB-MED2.2/Rec4] above. The whole process thus remains in the realm of science and does not qualify neuGRID to be a medical device within the scope of the directive.

These thoughts are supported by the opinion of the Notified Body representative to whom this use case was presented for evaluation.

Use case 2: Evaluation of a new image processing algorithm

This is a shortened derivation of the second use case presented in the proposal ("A future neuGRID story in Computational Neuroscience"):

An image processing algorithm developer has developed a new algorithm that provides a new interesting metric that could prove useful in early detection of some neurodegenerative disease. To ensure that the results of this algorithm are stable and relevant and hold well when compared to similar algorithms already deployed in neuGRID he deploys the algorithm to neuGRID infrastructure[2] and evaluates its results on the datasets available within neuGRID and thus obtains evidence on the quality of his algorithm.

Discussion of use case 2:

This use case is very similar to the first use case presented above in that the purpose of systems usage is strictly scientific with no medical purpose or direct view of diagnosis or treatment. Thus the same conclusions apply.

[2] The actual procedure inherent to "deploying a new algorithm" is something that is not clearly defined in current stages of development. However one of the general aims of the system is to provide generic environment under which image analysis pipelines could be deployed with realistic effort.

Use case 3: Evaluation of a clinical trial results by pharmaceutical industry company

Company X has developed a new compound that they would like to test in a human population. A placebo-controlled clinical trial is set up to get measurements relevant to the effect of the drug, which involves brain imaging data acquisition of affected patients. Company X organizes a multi-centre study and the acquired imaging data are subsequently uploaded into neuGRID. By analyzing the data using neuGRIDs image processing capabilities the company is able to determine if a significant difference between the data of drug (active) and placebo populations exists.

Discussion of use case 3:

This use case stands on the border of currently imaginable usage of neuGRID. Thus this use case has to be taken in account and the system legal status should provide for such use case to be performed.

The results of thus conducted study might affect the decision of the company about the effects of the drug and thus possibly affect the health of the patients treated by this substance in the future. However the information provided within the written guidance materials was not sufficient to make a clear decision in this case. Therefore we discussed the case with competent authorities to and with this assistance we arrived to following conclusions.

The process of organizing a multi-centre study, applying either placebo or examined substance, acquiring relevant clinical and imaging data, storing and managing it falls within the medical scope of the process. In this part of the study however neuGRID plays the role of rather a general clinical and imaging data managing tool – such as which was clearly stated to be out of the scope of the directive. The subsequent evaluation of thus collected data via neuGRIDs image processing capabilities can be understood to be a separate process.

The nature of analytical image processing functionality envisioned to be provided within the system is such that the results of such analysis should still be put in perspective of the analytic means used to acquire them. The algorithms that are envisioned to be embedded within neuGRID are not certified medical devices in their own right and thus the results acquired through them should be viewed as explanatory or illustratory. The system provides for important guidance information for the company to be used to boost the efficiency of its research, this information cannot however be used as the sole evidence of whatever results it suggests.

Therefore in this use case neuGRID cannot be considered a medical device within the scope of the directive.

As mentioned earlier, one of the goals of neuGRID is to enable new approaches within the medical science domain and to make the exploitation of image processing technologies widely accessible. It may well happen that the praxis in the field will change in the years to come because of projects like neuGRID and that new ways of perceiving and classifying such tools will have to be found to legally support their further exploitation.

Use case 4: Decision about patient treatment aided by neuGRID

A treating radiologist/neurologist would like to get some quantitative measurements from the MR scan of a patient – for example to assess the growth (or reduction) of a lesion over time or to measure the volume or shape of a brain structure in order to compare it against previous data from the same patient or against some normative data set. He uploads the images of the patient into the neuGRID infrastructure and performs analyses according to his needs. In the decisions about the treatment or diagnosis of the patient the doctor takes into account the information obtained from the system. The treatment of the patient is thus directly influenced by the results of analyses carried out via neuGRID.

Discussion of use case 4:

This use case is theoretically feasible from the technical point of view. However it is outside of current scope of neuGRIDs application. It is discussed here mostly to illustrate the possible directions the development might steer in the future and the issues this would bring.

In this use case the medical purpose and an impact of actual patient care is very straightforward. Therefore in this case the system would have to fulfil relevant requirements of the directive, because there is a clear view of diagnosis or treatment in the system usage.

The overall conclusion of use cases and their analysis is that within the scope of currently envisioned application the system doesn't fall within the medical devices category defined by the medical devices directive. The decision whether or not does neuGRID fall within the scope of the directive is directly connected with the relation of neuGRIDs usage to the treatment of individual patient. Should such link be identified at any point in the future, it would mean that neuGRID has to be considered a medical device.

Future Considerations

As stated above, within the current envisioned scope of usage the strict rules imposed on medical devices do not apply to neuGRID. On the other hand it was mentioned earlier that it is imaginable that this might eventually change in the future should it take part in some very specialized diagnostic processes or else.

To lay ground for future steps should this situation arise the impacts of change in status of neuGRID within the scope of the Medical Devices Directive were examined.

The current requirements on medical devices state that as of devices that take form of software, the only way how to prove that the risks associated with that device is acceptable within the scope of the Medical Devices Directive is by applying risk management policies according to relevant international standards [60601][14971] throughout the whole design and development process. In other words the directive and the guidelines state that the conformity of the software with the essential requirements of the directive cannot be proven by testing or by fail-pass criteria, but rather that the whole design and development process of the software has to be controlled.

The important question for the future of the project is how the decision not to employ the control process required by the directive at the present time will affect the system in the future.

This situation is not specific to neuGRID only but rather general for scientific technologies that at some point cross the borders set by the Medical Devices Directive. This problem was investigated in detail and discussed with competent authorities [EZU].

The outcome of the research is that for similar cases of well established products it is not uncommon that the certification assessment procedure can take form of thorough risk analysis at the time of certification. A typical condition making this possible is that there is enough scientific evidence and practical testing experience supporting the quality of the product.

The qualified opinion thus is that it is possible for neuGRID to be developed in the realm of science without being forever locked in there. It will be possible for it to be certified as a Medical Device through a special procedure even when the development is carried out without specific regards to the provisions of the Medical Device Directive.

Conclusions

We have carefully examined various sources concerned with regulations imposed on image processing and clinical data management tools and platforms with the view of compiling the legally binding requirements relevant to neuGRID functionality and scope of application identified within those sources into a code regulatory statement to be used with newly developed code bases and to be checked against the existing ones.

We have discovered that the most relevant source of regulation inherent to healthcare area is the Medical Devices Directive [MDD]. We produced a comprehensive set of envisioned use cases of the system and carefully analyzed them within the scope of the directive and accompanying explanatory and guidance documents with the aid of qualified professionals in this area. We have concluded that the system with its envisioned functionality does not fall within the scope of the directive and thus no regulation mentioned there applies to it.

We examined what are the implications of this conclusion for the future of the project. We have concluded that this decision does not influence or limit the system future potential in any way.

The system thus remains in the realm of science and there are no legal requirements to be fulfilled specific for the healthcare arena. This does not mean there is no desire to fulfil the highest standards within the work dedicated to the project, but rather that the project will enter the first phases of its life being considered a scientific research tool with a view of surpassing this border in the future.

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