A Model Oriented Approach for Managing Traceability of Biological Samples and Tests of Patients in Assisted Reproduction Clinics

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Abstract: Assisted reproduction has become a service that more and more people access. Current problems such as the delay in the age of motherhood, single-parent couples, etc. they have proliferated the options and the different treatments that are put at the service of society. A fundamental part of these processes lies in the work of laboratories, in the samples that are handled in clinical processes and then be implanted in future mothers. The management of the samples is a critical aspect that requires all the opportune mechanisms that guarantee the traceability of said samples, avoiding fatal errors. The correct identification, monitoring and control of them is a fundamental aspect and of special relevance. However, the systems currently offered to clinics present important problems. On the one hand, they offer little security, are very expensive or very independent of a specific provider, so that the traceability system cannot be connected to the hospital central management system, or they are very intrusive control systems in the daily work of the laboratory technicians. In this paper a software solution based on the definition of automatic models and protocols is proposed. It includes the appropriate devices, to manage the traceability of the samples in parallel to the work of the laboratory technician.

1 INTRODUCTION

For some years now, assisted reproduction techniques have been part of the reproductive history of many couples. According to the most extensive epidemiological studies, infertility affects 15% of the population of reproductive age in Western countries, that is, one in six couples, and experiences an increasing evolution (País, 2017).

Spain is a leader in Europe in assisted reproduction techniques, with a total of 127,809 'in vitro' fertilization cycles and 38,903 artificial inseminations in 2015. In 2015, a total of 36,318 children were born in Spain thanks to assisted reproduction techniques, representing 8,6% of the more than 420,000 births that occurred that year, according to the latest data from the Ministry of Health (Mundo, 2017). Figure 1 and 2 show some results graphically.

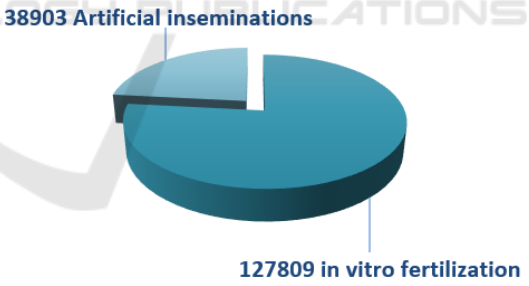

Figure 1: Assisted reproduction techniques, Spain 2015.

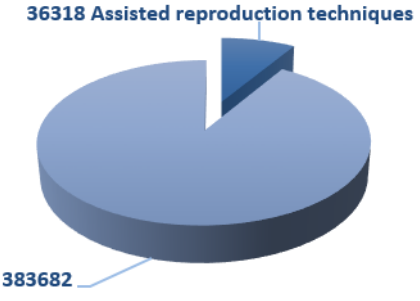

Figure 2: Children born in Spain in 2015.

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However, although this has allowed the centres to reach technological and service levels "leading", has also put Spain "in the crosshairs" of many European scientific societies and groups of other countries, since we still have a lot for improving in terms of control mechanisms (BMD, 2016).

Currently there is no control and transparent system for the professional to verify if the biological samples and patient tests are right, which prevents serious errors. This paper marks the challenge of increasing trust on the part of the patients involved by ensuring the control and monitoring of the samples and tests of the patient in such a way that the risk of error is reduced to minimum levels by proposing a software solution based on the definition of automatic models and protocols, which by incorporating the appropriate devices, control the traceability of the samples in parallel to the work of the laboratory technician. This solution must be affordable and compatible with the standards that govern hospital management processes and laboratory samples in assisted reproduction.

2 PROBLEM

Human reproduction laboratories are exposed to multiple incidents, but one of the most serious is that which causes the erroneous identification of biological samples (ovules, sperm and embryos), being the misidentification a common problem in all areas of health.

An identification error occurs when a patient is incorrectly paired with a test, treatment or procedure and is usually caused by stress, work overload, multiple interruptions, material errors, among many other factors.

University Hospital Utrecht has made public the possible fertilization of oocytes of 26 women with sperm outside their partner, that is, a score of women or couples have sired children with the sperm of the man who was not the indicated. Finally, the center detected that the pipette that had been used in some oocyte fertilization procedures was contaminated with the sperm of another patient (País, 2016).

Certain processes, such as the mixture of ovules and sperm, and the transfer of embryos to the uterus, are seen as critical, since they represent "the point of no return." If an erroneous identification is produced in assisted reproduction laboratories, it can be go unnoticed practically in each of the steps of the process involving gametes and embryos. The final result will be catastrophic for both the patient, as for the professional and the clinic, with legal implications that can lead to sanctions and even, in extreme cases, at the close of the clinic.

One of the most used solutions to avoid these possible errors, is the manual double-test protocol (MDT), defined as the obligation of "double control performed in all clinical and laboratory procedures" with the expectation that, if a " operator "makes a mistake, it will be captured by the other" witness "in time to be resolved. However, the evidence suggests that it may not be as safe and effective. The effects of mechanization of tasks can reduce the effectiveness of double testimony because the levels of attention decrease when the same action is carried out repeatedly by the same person. Therefore, the risk of error during the double-checking protocol may increase due to numerous problems, such as process redundancy, attentional blindness, ambiguous responsibility, errors in the verification, additional work overload and increased stress. In addition, the process of double control produces additional "paperwork" to an already overwhelming work environment and entails the duplication of resources in an already expensive process.

For these reasons, several alternatives have been developed based on less manual identification techniques in order to replace most of the steps required by human witnesses in assisted reproduction laboratories. The most widespread are:

- Systems based on barcode labels, which, moreover, are often used in collaboration with MDT protocols. It consists of identifying the pipettes with a bar code so that as a process is executed in the laboratory, the technician uses a reader of said bar code to collect the life cycle of the sample. In this regard, it is expected that the "Single European Code" (SEC) will be launched soon, which would increase confidence in the realization of these techniques in a quality framework (RHA Professional). However, this code consists of 40 characters, too large to be placed in cryopreservation devices: Semen, oocytes and embryos are conserved in devices called straws or vitrification supports. Even a simplification is not feasible through the use of 20 characters (RHA Professional).
- Systems based on silicon bar codes that are injected directly into the ovules or embryos, work in a similar way but the identification is found in the sample itself. This option is a bit aggressive in the eyes of the donor of the sample, since a marker is being introduced to his biological sample, to his possible son.

- Systems based on radio frequency identification (RFID) technology RFID systems involve placing an adhesive RFID tag on all fungibles that contain embryos and gametes related to a single patient. These labels are analysed in each station of the process to identify the patient with whom you are working at that moment. A digital record keeps track of the location of each label at each stage of the overall process and which staff member is manipulating the samples. Visual and auditory alarms indicate when an imbalance has occurred so that it can be corrected promptly. The RFID system also keeps a record of the imbalances, so it is possible to review and analyse the different stages, detecting the steps with the highest risk in order to reduce the imbalances accurately. There are already companies that have developed solutions, with a high cost, based on RFID, such as Cooper Surgical Company and its RI Witness. However, these solutions have little adaptability to different laboratory concepts, are not affordable and are closed to the specific fungibles of the companies, making it difficult to intercommunicate with the rest of the hospital management system.

In short, there is currently no control system, transparent for the professional, to verify if the biological samples that are being worked on are those indicated, which prevents serious errors from occurring.

For all this, our research aims to create a technological solution that allows to take control of the work of technicians in assisted reproduction laboratories when they execute processes that involve work with samples. This solution should be little or nothing invasive in the work of the technician, compatible with the management system and affordable and adaptable to the different realities of assisted reproduction clinics. It must also guarantee that any sample identification must be in accordance with current regulations and follow the guidelines set by the Ministry of Health.

3 GOALS

This project marks the challenge of designing a strategy that reduces the risk of error minimum levels making use of information technologies as the central axis of the solution. The objectives and requirements defined to achieve it are described below.

The main objective of the research is the definition and implementation of an ICT solution, which can be integrated in a simple way in the processes that follow the biological samples to provide a complete, univocal and safe traceability of each sample during its life cycle.

In order to carry out this objective, we propose the next research steps.

- Study the current situation in the identification and monitoring of samples in assisted reproduction.
- Define a protocol to incorporate the monitoring of the life cycle of biological samples and tests in a non-invasive and safe way in the work of health personnel.
- Develop a technological solution that allows executing the protocol in an affordable and adaptable way to the reality of the different clinics.
- Validate the solution in a real context.

4 HYPOTHESIS AND SOLUTION PROPOSAL

The solution to be developed to achieve these objectives must be composed of the following aspects:

4.1 Theoretical Framework

For the management of traceability in clinics, which provides alignment with traceability management standards and allows the design, development and application of a theoretical framework, which, among other things, allows:

- A work methodology for the management of traceability biological samples and patient tests based on standards, good practices and international standards on biological samples and patient tests that contribute to structure and order the activities, documents or controls that are planned and implemented inside a clinic.
- The definition of the life cycle of the traceability management process focused on biological samples and patient tests that includes planning, compliance, evaluation and the correct adaptation of the standards that have been contemplated in the proposal. Stabilization of a standard does not only entail

compliance with it, it also implies the mobilization of the clinic in a process that ensures its future fulfilment.

- Following the paradigm MDE (Model-Driven Engineering) will be defined:
  - A meta-model of reference that describes the processes and artefacts necessary to carry out the entire life cycle of the management of the traceability of biological samples and tests of the patient in the clinic. This metamodel will serve as a basis to verify the control and monitoring of all biological samples and patient tests.
  - A series of checking mechanisms between the reference metamodel and the metamodel that is instantiated or executed in the information system.

4.2 Why the MDE Paradigm?

Model-Driven engineering (MDE) is one of the most deeply rooted paradigms in the area of software engineering. It focuses on creating and exploiting domain models, which are conceptual models of all the issues related to a specific problem. Therefore, highlight and point out abstract representations of knowledge and activities that require a particular application domain, instead of computer concepts.

An important aspect when using MDE is to guarantee traceability between the generated process models. This is essential in the context of the proposal that is made here and that allows maintaining the identity of a process among all the modules that guarantee traceability and the possibility of finding errors in the early stages, thus avoiding irrecoverable failures.

By ensuring that the traceability between the different processes that have to be carried out in a technique of assisted reproduction and avoiding possible irrecoverable failures during this process, the levels of error are reduced to minimum levels and they provide greater security to patients who want to undergo a process of assisted reproduction.

After explaining why we use MDE in our proposal, it is important to know what it is.

MDE came up in order to tackle the complexity of platforms and the inability of third generation languages to relief this complexity and effectively express the domain concepts of the problem. This new paradigm, apart from raising the level of abstraction, intends to increase automation during the life cycle of software development.

This paradigm works, as the primary form of expression, with definitions of models and transformation rules among these models which entail the production of other models. Every model corresponds to a phase of the life cycle and is generally specified by means of UML modelling language.

Standardization was necessary in order to implement this new paradigm in real projects. OMG presented MDA, which stands for Model-Driven Architecture (OMG, 2003), as a platform to support the paradigm of Model-Driven Engineering.

The main ideas of MDA consist in dividing the specification of the system functionality from its implementation on a specific technology platform, as well as control the evolution from abstract models to implementations. Thus, the degree of automation usually increases. MDA proposes to base the software development on models which make transformations be performed to generate code or another model with characteristics of a particular technology (or lowest level of abstraction). As transformations go on, it may be noticed that the models become more concrete and the abstract model changes into another one compatible with a particular technology or platform. MDA is based on four types of levels or models:

- The CIM level (Computation-Independent Model) is considered the highest level of business model and the most abstract level. It focuses on requirements specification and intends that anyone who knows the business and its processes can understand a CIM model, as this avoids any contact with the specific system.
- The PIM level (Platform-Independent Model) represents the business process model and system structure, without any reference to the platform on which the application will be implemented. It is usually the entry point for all the support tools for MDA.
- The PSM level (Platform-Specific Model) specifically relates to the platform where the system will be implemented, for example, with operating systems, programming languages or middleware platforms, among others.
- Finally, the Code level refers to the codification and suitable implementation of the system.

Figure 3 (Koch, 2006) represents a diagram with the adaptation of the MDA standard in Web development.

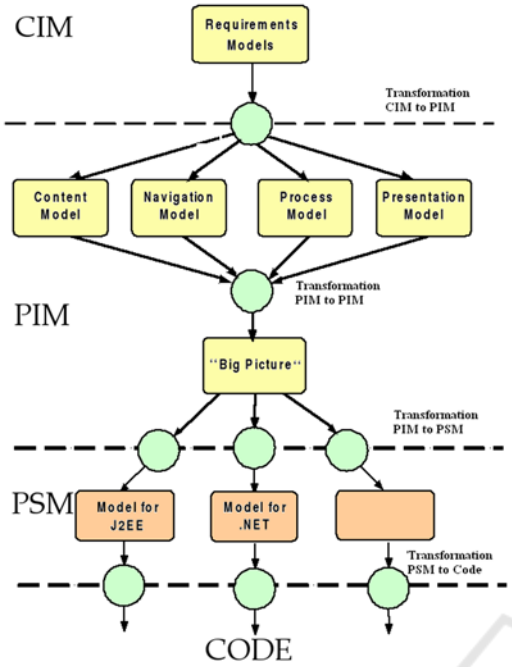

Figure 3: Model-Driven Web Engineering.

In this context, a set of metamodels in the CIM level is given which are requirements models. These models allow information requirements to be captured.

Analytical models are obtained systematically by means of the transformation CIM-to-PIM: content model, navigation model, presentation model, and some others. In addition, PIM level allows the application of some transformations (PIM-to-PIM) in order to get design models. Subsequently, models on the PSM level are obtained by applying Transformations PIM-to-PSM. Finally, the application of Transformations PSM-to-Code generates the system code.

4.3 Support Tool

The proposal of the solution will be supported by a support tool that allows accessibility from any position or workplace to the management process of biological samples and tests of the patient of the clinic with secure access through user profiles. In addition, it will act as a document manager of all the information generated in the process. On the other hand, a module that allows to represent the clinical process will be required. This system must be compatible with the central hospital management system, be in accordance with the standards and allow the administrator, or person who defines the process, to "mark" the points that have to be controlled.

5 VALIDATION

A module that allows to represent clinical processes and artefacts is required. This system must be compatible with the central hospital management system, be in accordance with the standards and allow the administrator, or person who defines the process, to even "mark" the most critical points that have to be controlled.

On the other hand, a second module will be developed that, by means of a specific device, automatically, and based on the process itself, make a control of those control points and refer them to the central hospital management system, launching an exception in the case the technician makes an error.

Finally, there will be a module to control and monitor biological samples and patient tests that will allow accessibility from any position or workplace to them and, in addition, act as a document manager of all the information generated in the process.

For its validation, a case study will be made taking the Inebir clinic as a reference (Schmidt 2016). Inebir is an assisted reproduction clinic located in Seville (Spain), more specifically in the Victoria Eugenia Hospital. This clinic has a laboratory designed and built following strict guidelines that result in a work space with the latest technological advances in the field of fertilization, where a team of highly qualified embryologists follows an exhaustive method of work (García-García, 2017).

Next, 4 activity diagrams are presented where 4 of the processes that are carried out in the laboratory of the Inebir clinic are illustrated (Figure 4 to 7). These

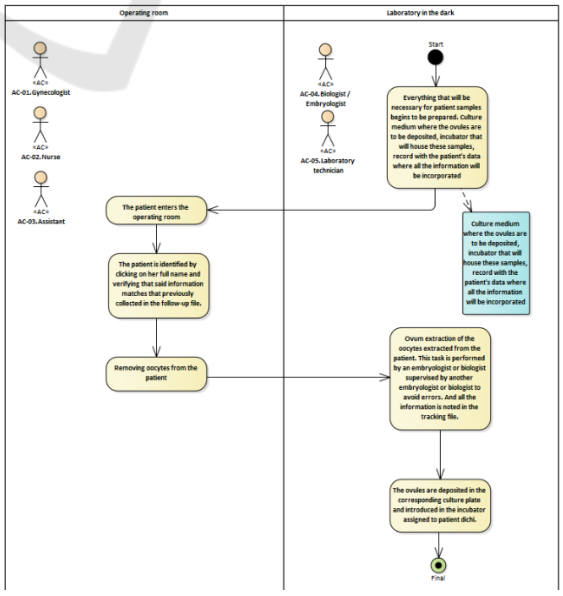

Figure 4: Preparation and extraction of ovules.

diagrams can be visualized, apart from the sequence of steps followed to carry out the corresponding process, the actors that are involved in this process and the places where they are carried out:

The first process that is illustrated is that which goes from the extraction of oocytes from a patient, to the conservation of the ovules extracted from said oocytes.

Afterwards, you can visualize the process that goes from the collection of semen samples to your treatment so that an ovule can be fertilized later.

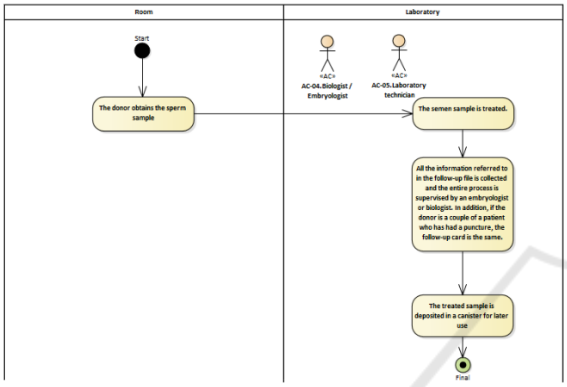

Figure 5: Preparation of semen samples.

The final step to which all the processes described here are directed is the one that can be visualized in this diagram, where the fertilization of the ovules and the subsequent transfer to the uterus of a patient is described.

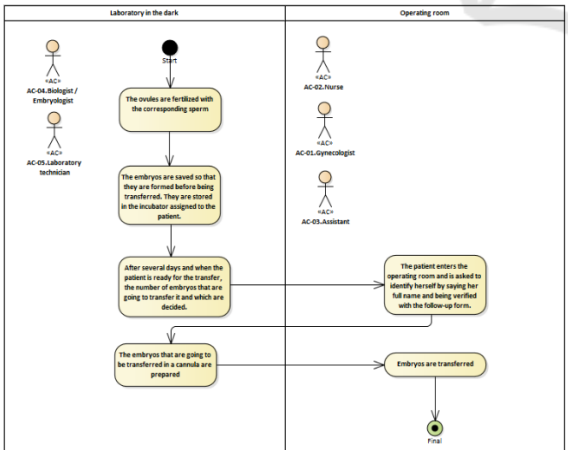

Figure 6: Fertilization and transfer.

Finally, the last process shown here is optional. It is the process that results in the freezing of samples.

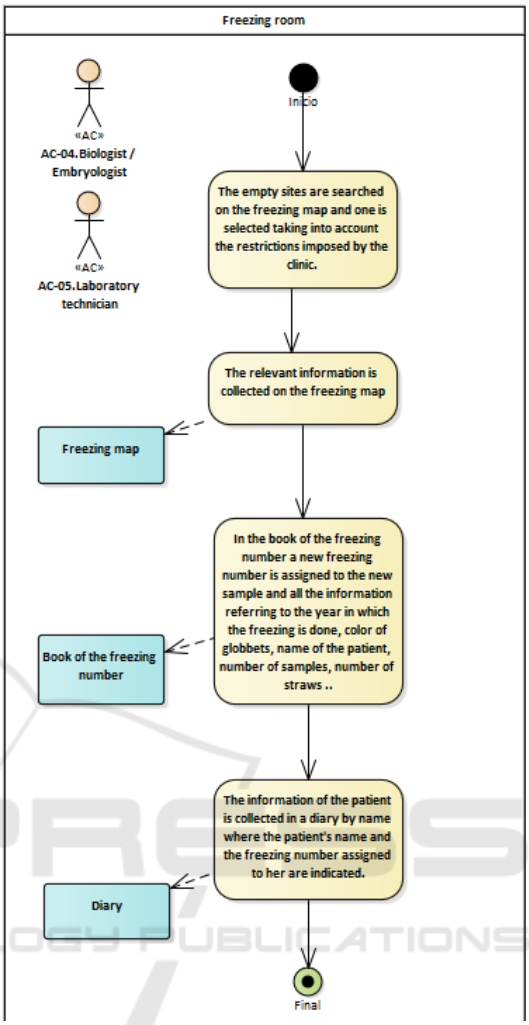

Figure 7: Freezing of samples.

For all this, it is a perfect scenario to validate the proposal presented here.

6 EXPECTED RESULT

The following are the results that await the solution presented here in a process of assisted reproduction:

- Greater control and monitoring of biological samples and tests of patients reducing the risk of error to minimum levels, an aspect that is fundamental and of special relevance to guarantee safety.
- Increase the confidence of the patient since reducing the risk of error brings greater peace of mind.

- Improve the common understanding and facilitate the continuous improvement of the clinic in terms of the implementation of standards, standards and good practices carried out by third parties.

7 CONCLUSIONS

The paper presents a global view of a model-driven approach to work with traceability in laboratories. This approach was obtained for a real necessity in the industry

The paper introduces the current situation and analysis the problem that it exists in the field of human reproduction.

We have, however a lot work to do. Fortunately, we count with a real clinic support and one of our main advantage is the real connection with users.

The use of the Model-driven paradigm also results a suitable and promised idea. In fact, we have used in other important areas with successful results (García-García, 2012; Escalona, 2013).

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