Donor's Support Tool: Enabling Informed Secondary Use of Patient's Biomaterial and Personal Data

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Abstract.

Purpose. Biomedical research is being catalyzed by the vast amount of data rapidly collected through the application of information technologies (IT). Despite IT advances, the methods for involving patients and citizens in biomedical research remain static, paper-based and organized around national boundaries and anachronistic legal frameworks. The purpose of this paper is to study the current practices for obtaining consent for biobanking and the legal requirements for reusing the available biomaterial and data in EU and finally to present a novel tool to this direction enabling the secondary use of data and biomaterial.

Method. We review existing European legislation for secondary use of patient's biomaterial and data for research, identify types and scopes of consent, formal

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requirements for consent, and consider their implications for implementing electronic consent tools. To this direction, we proceed further to develop a modular tool, named Donor's Support Tool (DST), designed to connect researchers with participants, and to promote engagement, informed participation and individual decision making.

Results. To identify the advantages of our solution we compare our tool with six other relevant approaches. The results show that our tool scores higher than the other tools in functionality, security and intelligence whereas it is the only one free and open-source. In addition, the potential of our solution is shown by a proof of concept deployment in an existing clinical setting, where it was really appreciated, as streamlining the relevant workflow.

Keywords. Dynamic Consent, Electronic Consent, Secondary Use of Biomaterial and Personal Data, Biobank

1. Introduction

Recent reports by the eHealth Task Force [1] and by the European Alliance for personalized medicine [2] focus on redesigning health in Europe to achieve a vision of affordable, more personalized and less intrusive care, ultimately increasing the quality of life as well as lowering mortality. Such a vision to a large part, depends on the application of information technology, the effective use of data and biomaterial and requires a radical redesign of e-health to meet these challenges. Among others, three important levers for change have been identified: "*liberate the data*", "*connect up everything*" and "*my data, my decisions*". Fully capturing, integrating, linking participants and exploring health data will have a tremendous impact on improving the integrated diagnosis, treatment and prevention of diseases in individuals. In addition, it will allow the secondary use of

healthcare data for research, thereby transforming the ways of providing healthcare [3]. However despite the potential advantages of the above vision, specific technological, legal and policy barriers have significantly delayed the implementation and uptake of such a redesigned healthcare system within Europe.

Particularly, in realizing the vision of personalized medicine, the secondary use of patients' biomaterial and data is very important, as innovative research techniques could reveal interesting biomarkers that were hitherto overlooked. At the same time, rules pertaining to the processing of personal data as well as biomaterial have to be complied with irrespective of how divergent such rules may be. Although the rules for the processing of personal data are more or less legally harmonized in the EU by the Data Protection Directive [4] (now to be replaced by the General Data Protection Regulation [5] by May 2018), the secondary usage of bio-specimen and associated data lack a harmonized and sometimes coherent legal framework. This includes the fact that the requirements of valid informed consent for research with biospecimens differ from country to country. This is also coupled with the fact that there is a margin of variation in the national implementation of the Data Protection Directive regarding the validity, scope and format of informed consent. As such, complying with varying legal norms from different jurisdictions is a considerable hurdle for cross-border research, where data and biomaterial are going to be exchanged across national frontiers.

A discussion on consent is important here because it is the gateway to patients having control over their biomaterial and data, and a number of regulations require that informed consent is a prerequisite for any biomedical research involving humans. This is the case for example, in clinical trials [6], or other research use of human biomaterial and related data [7]. Thus obtaining informed consent is generally practiced by the scientific

community in medical research, and there are widespread checklists and tools for generating Consent Forms [8]. To safeguard the patient's autonomy, it is postulated that consent should be specific regarding, for example, the purpose of the planned research or the timeframe for usage of the biomaterial. This has led to the devevelopment of approaches such as "tiered" and "layered" consent that allow patients to agree to a specified use of their material for research, while placing restrictions on types of research they do not wish to be performed [9] [10]. However, as indicated by the term "biobank", which represents a scientific service infrastructure meant for sample storage and exchange, a donor's specific ("narrow") consent may hamper exchangeability of banked specimens. This will in turn hamper research and hence medical progress that could benefit future patients [7] [11]. For this reason, a number of commentators, such as Taupitz and Weigel have argued that a broad consent regime would be preferable for biobanks [12].

Other approaches, which aim at balancing the two positions of specific and broad consents have also emerged, including the notion of *dynamic consent* [13] [14] [15]. Dynamic consent frameworks offer an interactive personalized interface that allows participants to engage as much or as little as they choose, and to alter their consent choices in real-time. A number of projects have focused on developing IT systems for dynamic consent, such as EnCoRe [16], BIOSHARE [17], Reg4All [18]. However, the complexity of these solutions limits their immediate applicability in current clinical practice.

This paper focuses on the research activities within the recently concluded EU FP 7, the p-medicine project [19], for enabling the secondary usage of both patients' data and biomaterial. In this project, an infrastructure was created to facilitate the translation from current medical practice to personalized medicine. Part of the project's objectives

includes ensuring privacy, non-discrimination, while aligning access policies to maximize protection of and benefits to the patients.

In this paper, we elaborate on current practices for obtaining consent for biobanking and the legal requirements for reusing the available biomaterial and data. We review existing European legislation for secondary use of patients' biomaterial and data for research, we identify types, scope and formal requirements for consent and their implications when developing electronic consent tools. Against this background, we propose and describe a modular IT tool named "Donor's Support Tool", whose three modules are designed to be attached to existing biobanks and personal health record systems and to enable citizens to actively provide and update their consent according to applicable national laws. Among the advantages of our solution are the simplicity and the generality that allow for a quick deployment of the tool and its modular adaptation in various contexts, national laws, biobanks and patient communication systems. At the same time, we recognize that technology is not the only limiting factor against the secondary use of patients' biomaterial and data. Medical practice and culture, regulation as well as citizens' awareness also play some roles.

The remainder of this paper is structured as follows: Section 2 identifies the legal requirements for secondary use of patients' biomaterials and data, while Section 3 presents the implementation of the Donor's Support Tool as a novel, modular tool enabling the secondary use of patients' biomaterial and data. Section 4 discusses the proof of concept deployment of the tool in a clinical setting and compares it with other relevant approaches. Finally, Section 5 concludes this paper and presents plans for further initiatives in this direction.

2. Legal requirements for secondary use of patients' biomaterial and data for research

The legal landscape for the secondary use of biomaterial and data in the EU is complex. There is no harmonized European regulation that covers both the processing of biosamples and associated (personal) data at the same time. Different regimes apply to each. At present the use of personal data, as mentioned earlier, enjoys the more harmonized framework. Thus, though there are still differences in the Member States' implementations of the Data Protection Directive (including with regard to the scope and formal requirements for valid informed consent), the General Data Protection Regulation may be expected to reduce the amount of fragmentation in in many areas. Even so, as Article 89 (2) of the new Regulation suggests, there may still be national peculiarities in the area of derogations by the Member States in the field of research. It remains to be seen what these derogations will be and whether they will result to varying frameworks in the states [20]. But in any case, certain underlying principles are clear and will remain the starting point for any processing of personal data. These include the need for a legal basis for the processing, of which one may be the informed consent of the data subject, as well as the prohibition on further processing that is incompatible with the original purpose. Thus, secondary use of data is generally limited by the original purpose for which the data was collected. An exception is where Member States implement national regulations that allow processing of personal data in the public interest such as research, without consent, and subject to the provision of suitable safeguards (Art. 8 (4) Data Protection Directive [1]).

In this regard, some Member States have enacted specific laws on biobanks or health research that specify rules regarding the collection, storage and use of biomaterial

and data [21]. In the Member States where there is no such specific regulation, it must be considered whether data protection rules apply for biosamples - which enjoy a complicated dual status as biomaterial and (potential or in some views, actual) data. In this respect, one school of thought sees biomaterial as carriers of personal data, thereby necessitating the application of general data protection law in the absence of a more specific law on the processing of identifiable biomaterial [22]. This approach arguably is reflected e.g. in the publication of the Danish Data Protection Authority, which states that biobanks are covered by the Act on Processing of Personal Data [22].

In contrast, another school of thought believes that human samples are not personal data, because the information contained in the material must first be extracted before it can be regarded as personal data [23]. Be that as it may, it is arguable that the use of biomaterial should mirror limitations and protections seen in the area of data protection, since biomaterial is at the very least a carrier of personal data. The doctrine of analogical application of written legal regulations applicable in the German legal system could be cited as an example here of how this mirroring should be applied. The doctrine holds that where there is a non-regulated case, which is similar to a regulated case and requires (in particular for reasons of equivalence and justice) identical legal consequence, the rules in the regulated case should apply [24]. It may be appropriate then to apply data protection laws analogically to the processing of biomaterial where there is no existing regulation.

Although the Member States sometimes prefer to have their own national regulation in the field of research, harmonizing biomedical research rules would substantially benefit transnational research [25], especially, by reducing duplication of efforts in carrying out similar research in individual states, and also will reduce the burden of fragmented

compliance requirements for transnational researchers. This will also increase legal certainty in the area of research.

2.1. The concept of informed consent

Informed consent is one of the best-known elements of medical ethics and bioethics today, and is widely utilized in clinical practice and medical research. The concept entails that any intervention on the human body for diagnostic, therapeutic, preventive or research purposes should only proceed with the concerned person's informed consent or permission. Valid informed consent from an ethical perspective should include the following three elements: adequate information, voluntariness and competence. This concept reflects respect for the autonomy and dignity of the person and has been laid down in a number of significant international and national documents relating to research with humans. In clinical trials, for instance, Regulation 2014/536 [26] includes this concept. Informed consent is also applicable when obtaining and processing personal information (thereby serving to protect informational privacy) as seen in data protection laws. However, there could be cases where informed consent might be replaced by an authorization from a state authority or a national law for reasons of substantial public interest, or in the interests of the subject, such as when they are incapable of giving consent.

2.2. Different types and scope of consent

As indicated earlier, there are various types of consent: specific, partially restricted, multi-layered or broad consent. And one of the problems that developers of consent management tools usually encounter is how to integrate these different types of consent into a single tool. This is particularly the case where such tool is meant for different purposes, and/or is to be used in multiple jurisdictions with different compliance

requirements at the same time. For instance, a consent tool that is meant to be used for clinical trials, human tissue processing, personal data processing, etc, in the 28 States of the EU is likely to face some hurdles because, in clinical trials, only specific consent is allowed [27], while different approaches, ranging from specific to broad, or even simply 'presumed' consent, could be applied in the processing of human tissue among EU Member States [28] (see Table 1). Similarly, for personal data processing, multiple approaches could possibly apply in the Member States. In the UK for instance, broad consent is accepted in some instances as seen in the publication of the UK Medical Research Council (MRC) [29]. On the other hand, the Belgian data protection law requires that consent must relate to a well-defined, concrete situation in which the processing of medical data is envisaged, which suggests that only specific consent is permissible [30]. The situation is also unclear in Germany, where some German courts have viewed the use of a broad consent critically in non-medical fields [31], and it is not clear how this will be reflected in medical research. However, it is noteworthy that a model broad consent form for biobanks has been developed by the German Biobank Task-Force of the Working Party of Medical Ethics Committees based on recommendations of the National/German Ethics Council [32].

2.3. Formal requirements for a valid consent

There are European or national legal requirements that stipulate the form of a consent. Mostly, they provide that consent must be in a written form, which means that evidence of the consent has to be signed by the consent-giver on a piece of paper. For the participation in a clinical trial, for instance, the EU Clinical Trial Regulation requires that consent shall be in a written form [26]. There is a similar formal requirement for tissue research in some Member States' national laws and/or ethical guidelines [33]

Although Art. 8 Data Protection Directive does not set up any formal requirements for consent, some national data protection laws contain the requirement that consent shall be in writing. In Germany for instance, consent principally must be in writing. Section 4a of the Federal Data Protection Act [34] requires an informed consent in writing, unless special circumstances warrant any other form. In the field of scientific research, a special circumstance shall be deemed to exist if the defined purpose of the research would be seriously affected if consent were obtained in writing [35]. Similarly, the Polish Data Protection Act requires a written consent for the processing of sensitive data [30] [36]. This is also the case in Belgium [37]. In contrast, there is no specific formal requirement in the UK or Austria.

The above state of affairs raises an issue of how to fulfill the formal requirements of an informed consent when such consent is given in an electronic format - digital consent [38]. This also has some implications regarding the evidentiary value of the consent. The EU Member States have for a long time recognized the need to give electronic documents the same value as paper documents in business and administrative proceedings, and developed their individual electronic signature framework. However, divergent rules with respect to legal recognition of electronic signatures and the accreditation service providers in the Member States led to the adoption of the e-Signature Directive, which has been replaced by Regulation 910/2014 since 1st July 2016 [39]. The purposes of this Regulation include to further harmonize electronic signature rules and to facilitate their use and legal recognition, as well as to establish a legal framework for electronic signatures and certification services for the internal market. According to Article 25 the Regulation, a qualified electronic signature, which means "an advanced electronic signature that is created by a qualified electronic signature creation device, and which is based on a

qualified certificate for electronic signatures" is equivalent to a handwritten signature. This will be required for instance, where by law, a declaration of will in writing is stipulated. However, in practical terms, the qualified electronic signature has not prevailed amongst the European public [39].

The new General Data Protection Regulation requires an explicit consent, and according to Recital 32, an electronic consent is valid as long the data subject clearly indicates through an affirmative act, such as ticking the box, that he or she agrees to the data processing. This means that pre-ticked boxes are not considered valid consent.

Table 1. Summarizing legal requirements through Europe

Member State	Scope of consent for use of personal data	Form of expression for data processing consent	Scope of consent for use of bio samples	Form of expression for tissue processing consent
Germany	Section 4a German Federal Data Protection Act (FDPA) [40] provides that data subjects shall be informed of the purpose of collection, processing or use of their personal data. There is debate over the specificity of consent in Germany with one school of thought arguing that consent has to be sufficiently precise and clear. Blanket and generalized consent, therefore, do not qualify as valid informed consent [41]. By contrast, the National Ethics Council (Deutscher Ethikrat) argues for the validity of broad consent forms [42].	Section 4a FDPA requires an informed consent in writing unless special circumstances warrant any other form. In the field of scientific research, a special circumstance shall by law be deemed to exist if the defined purpose of research would be seriously affected if consent were obtained in writing. The legal situation is unclear.	The permissible scope of consent is unclear due to a lack of national regulation. However, section 12 of the Hamburg Hospital Act (HmbKHG) which only applies to hospitals in the Land Hamburg allows the collection of personal data and specimen for general research purposes. In addition, the National Ethics Council [43], as well as the Arbeitskreis medizinischer Ethikkommissionen [44], prefer broad consent.	According to Section 7 (2) of the Hamburg Hospital Act (HmbKHG) consent shall be given preferably in writing [45].

Austria	§ 4a Nr. 14 Bundesgesetz über den Schutz personenbezogener Daten defines informed consent as the valid declaration of intention of the data subject, given without constraint, that he agrees to the use of data relating to him in a given case, after having been informed about the relevant circumstances.	Only explicit consent is required.	In order to prevent impediments to potential research developments and new questions, consent should also permit future investigations and research (which cannot be foreseen at the time the sample is taken); the duration of consent is not subject to any time limit [46].	Consent shall be given in writing [32].
Belgium	Personal data may only be processed: if the data subject has given his unambiguous consent which is only valid is it was freely given, specific (the consent has to relate to a well-specified processing operation) and informed [47].	Written consent is required for the processing of sensitive data. In other cases, consent needs not be in writing.	Use of biomaterial for research requires specific informed consent. An 'opt-out' system for residual tissue is implemented, whereby the patients are not asked for their consent, but can indicate that they do not want their tissue to be used for research purposes (prior notification required) [48].	Consent shall be given in writing [48].
United Kingdom	The Medical Research Council from the United Kingdom promotes broad consent [49].	DPA does not require written, but an explicit consent for the processing of sensitive personal data [30].	Donors are asked to consent to the specific experiment(s) already planned, and then to give consent for storage and future use for other research. Unless the sample is to be anonymized and unlinked prior to storage (in which case this should be explained to donors), it is not acceptable to seek unconditional blanket consent, for example using terms such as 'all biological or medical research' [29].	Consent shall be given in writing [29].

Spain	Art. 3 h Organic Law 15/1999 of 13 December on the Protection of Personal Data defines consent of the data subject as any free, unequivocal, specific and informed indication of his wishes by which the data subject consents to the processing of personal data relating to him.	Explicit consent, but no written consent is required [50].	Consent can be given for: (a) specific project: use is time-restricted, samples must be destroyed at the end of that particular project; (b) collection: can only be used by the investigator who requested them and cannot be transferred to third parties or used in research projects outside the particular research line foreseen in the original consent; (c) the storage of the samples in a biobank which implies that the sample can be used for any research and shared with third parties [51].	Consent shall be given in writing [51].

2.4. Identification and authentication of the consent subject

Where there is a personal contact between the research institution/doctor and the patient, the issues of identification and authentication do not usually arise during the consent procedure. But in the case of electronic consent, where the parties are not in the same physical environment, the question arises how to ensure that the person giving the informed consent is the real subject. Here, authentication is much more difficult because most often, the conventional password-based system is considered insufficient for identifying and authenticating the user [52]. The stakes are even higher when the case concerns the use of biomaterial that contains all the genetic information of the donor and other sensitive health data. In such instances, verification of the consent-giver is very important.

Using a qualified electronic signature is one desirable option for verification and authentication. However, as indicated earlier, usage of qualified electronic signatures is not widespread among the European population. This, therefore, means that other options, at least in cases where it is necessary to give consent in a written form, should be explored.

In such cases, research participants could be asked for authentication purposes to send a copy of their ID along with their signed consent form, which could then be verified by the consent management authority.

3. Implementation of the legal and ethical requirements into a novel tool.

3.1. Implications of the above legal and ethical requirements for electronic consent tools

Against the background above, developing and integrating a consent management tool that captures all the granular details required by regulation in order to make such a tool usable in multiple jurisdictions appears to be an enormous task. In practical terms, this means that not only should the highest standards be observed, but multiple approaches should be aimed at (at least until a full harmonization is achieved on the legislative front) which will effectively achieve the purposes of the tool, and allow for the widest user uptake. This gave rise to the need to consider the following issues and implementations:

- In view of the fact that use of qualified electronic signature is not widespread in Europe, how could a more inclusive approach be implemented so as to give research subjects the possibility to complete the consent form online, print out the completed form and sign it manually, where such a formal requirement is mandatory or in cases where the evidentiary value of the consent is paramount?
- Considering the importance of authentication, could the identity of the user of the tool be verifiable through an existing personal information management system?
- In order to ensure that the user of the tool is sufficiently informed of the uses of the biomaterial and data, how could the researcher using the tool be able to include all relevant information that the user requires in order to give an informed consent, and

can a researcher also verify the type of consent upon which the biomaterial could be used?

- In order to be usable in the clinical environment, how should the tool be effectively and efficiently integrated with other information systems in the hospital, clinical trial centers or personal health record systems?

The aforementioned considerations resulted in the implementation of the p-medicine's Donor's Support Tool as a modular tool, allowing its modules to be attached rapidly to existing systems and enabling the quick deployment of the platform. The architecture of the tool and the three different modules are shown in Figure 1.

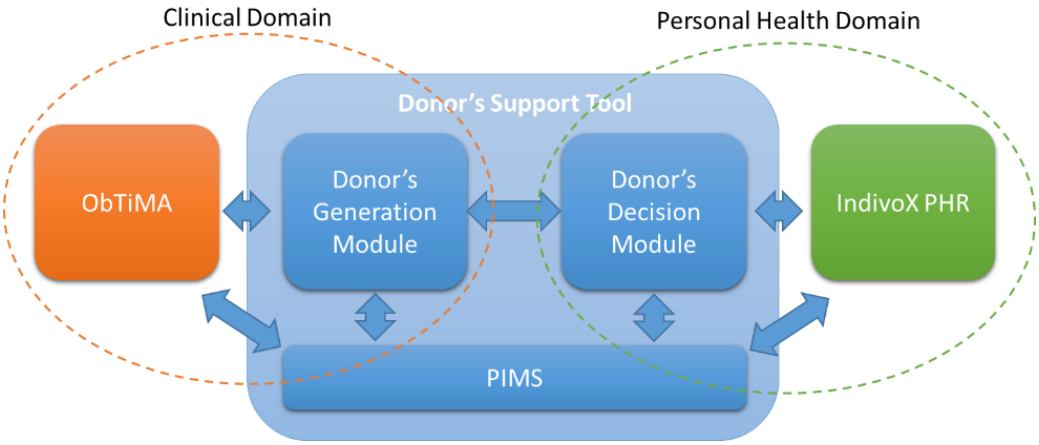

Figure 1. The three modules of the DST and its deployment in a real clinical setting

Bellow, we analyze in detail the three modules and then the corresponding deployment in a real clinical setting.

3.2. Personal Information Management System (PIMS)

This module provides the functionality to create and link pseudonyms among systems. A client (assume IndivoX PHR[2] from Figure 1) can call PIMS to register a patient using his encrypted ID as shown in Figure 2. This encrypted ID could be a patient's social security

[2] http://indivohealth.org/

number, a combination of demographic information or another pseudonym. The first time a patient is registered both a local (IndivoX pseudonym) and a central (Central pseudonym) are generated, linked together and the generated local pseudonym is returned to the system. As soon as another system (assume ObTiMA [53] from Figure 1), tries to register the patient with the same encrypted ID, PIMS will identify that this patient is already registered, will generate a local pseudonym (ObTiMA pseudonym), link it to a central pseudonym and return the local pseudonym to the system. Besides registration, PIMS provides a service for verifying whether two individual local pseudonyms belong to the same central pseudonym.

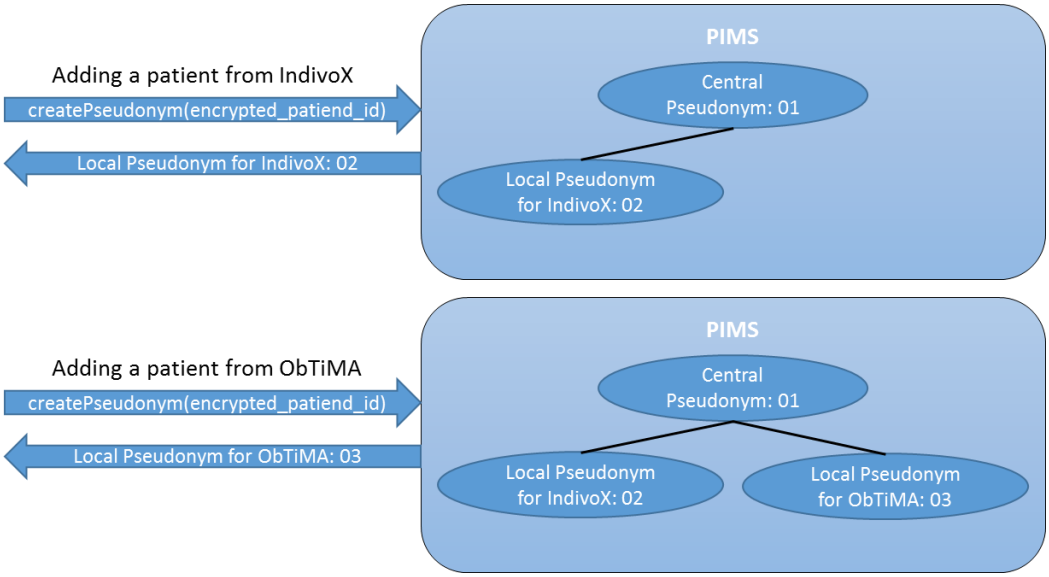

Figure 2. Registering a patient from two systems

3.3. *Donor's Generation Module*

Using this module a researcher or a trial manager can create a project request in order to get access to eligible patients' biomaterial. A screenshot of this module is shown in Figure 2. For each research project requesting access to a patient's biomaterial, the researcher/trial manager should provide the following: a) A short summary of the project in layman's language and in the mother tongue of the patient - this needs to explain the

reason why the biomaterial is needed and what will be the expected result. (Multiple languages per request are supported); b) the CV of the researcher and a contact person who will be available for answering relevant questions (plus the latter's contact details); c) the necessary consent files (as PDFs) and a short description of each consent file in layman's language.

There can be multiple consent files and the relevant descriptions or a single one. Admittedly, currently only textual information can be used, including links or embedded images/videos as well. As such, the consent can be specific or broad, multi-layered or partially restricted depending on the national and European legislation applicable in the target country.

In addition, in order to avoid overloading patients with unnecessary information, this module is able to target specific patients, allowing only the eligible patients to see the generated request. This is implemented by tight or loose integration with a Biobank system. In the first case, the Donor's Generation Module can communicate directly with the Biobank in order to retrieve the local pseudonyms of the eligible patients. To enable this communication, the Biobank should implement a specific API call (web service), receiving as input a set of search fields and returning the eligible patients. Currently, the fields that are used are the age, the gender, and the diagnosis of the patients (the corresponding ICD-10 terms) that should be contacted, but these can be extended at will. The service searches for those fields and returns as an output the corresponding local pseudonyms of the patients. If this automatic extraction is not possible, the biobank manager can manually generate the list with the eligible pseudonyms directly from the Biobank and paste them into the corresponding field of the Donor's Generation Module.

As soon as the project request is finalized, all information is forwarded to the Donor's Decision Module.

The Donor's Generation Module, in addition, retains and visualizes patients' responses and can call external web services as soon as a patient choice is retrieved (e.g. automatically notifying the associated biobank).

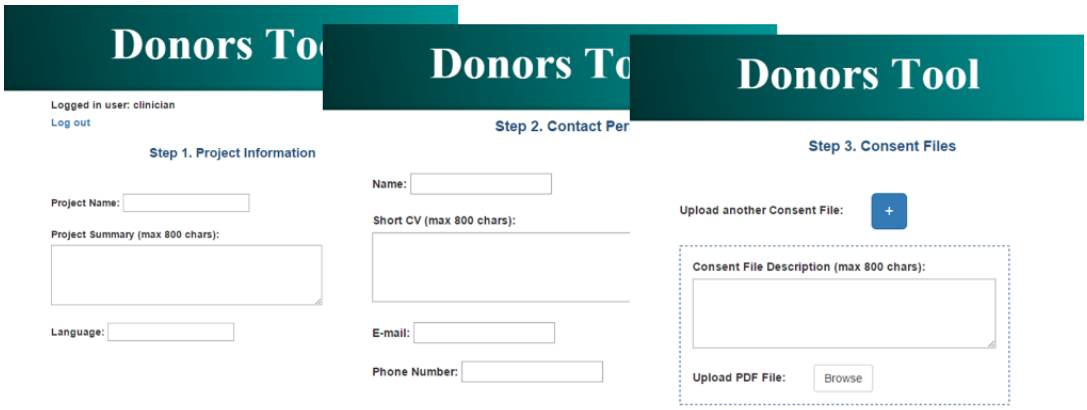

Figure 3 inserting a project request using donor's generation module

3.4. Donor's Decision Module

This module targets patients and can be attached to an existing personal health record system or another patient system. It is able to be used for opt-out and opt-in solutions, give consent or prohibit the use of personal data and samples and also to update this choice in future if required. As soon as a request is accepted by the Donor's Generation module, all relevant data such as project description, available person etc., are downloaded and stored in the internal database of the Donor's Decision Module. Then PIMS is called for all provided local pseudonyms and the eligible patients are identified. Next, a notification appears to the eligible patients' accounts, and these are then able to view a list of all available projects (see Figure 4 on the left), see the status of each request and the corresponding details. By selecting the appropriate button, more details can be provided on each project (see Figure 4 on the right). Each project may contain more than

one consent file and a patient can select to accept all or only some of them (in the case of multi-layered opt-in request). In addition, the patient is able to update his/her decision at will. As soon as a patient makes a choice, the result is transmitted back to the Donor's Generation Tool.

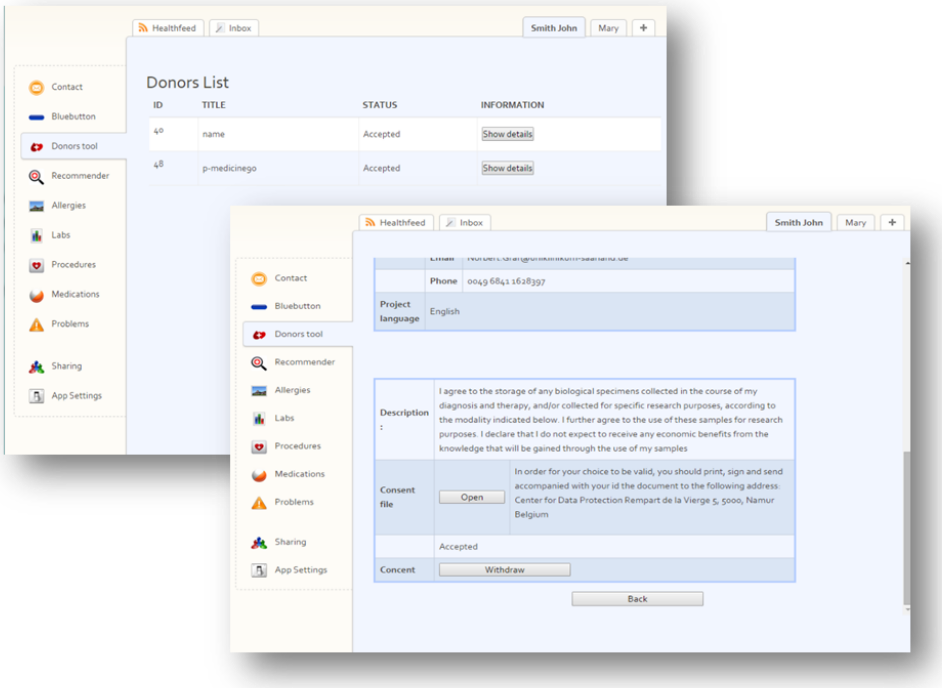

Figure 4. The list of projects requesting access to a patient's biomaterial (left) and the relevant information for a specific project (right)

3.5. Proof of Concept: Deployment of the Donor's Support Tool

As we hope the above shows, the Donor's Support Tool with its three modules is a simple tool to enable the informed secondary use of patient's biomaterial and data. However, technological simplicity alone does not usually make such a tool immediately usable in a clinical setting; restrictions stemming from the ethical, legal and socio-economic environment often hamper the secondary use of patients' biomaterial and data. Accordingly, the project also tested the proof of concept deployment of the Donor's

Support Tool in a current clinical setting (as shown in Figure 1). In this section we highlight preliminary experience gained in such environment.

3.6. Integration of the Donor's Generation Module to the ObTiMA biobank

Within p-medicine, ObTiMA [53] has been developed as an ontology-based trial management system and extended to serve as a Biobank repository as well. ObTiMA includes a module called Trial Biomaterial Manager to enable management of biomaterial data and biobanks in clinical trials. When a patient is registered by a clinician/trial manager to the ObTiMA, automatically PIMS is contacted and a new local pseudonym is generated for this patient. ObTiMA, in addition, is tightly integrated with the Donor's Generation module since it is implementing: a) the API web service described in the previous section, returning as an output the corresponding local pseudonyms of the patients; and b) an API allowing the automatic notification of the Biobank as soon as a patient decision is updated/received.

3.7. Integration of the Donor's Decision Module to the Indivo-X PHR

Personal Health Record (PHR) systems provide patients with the ability to become more active in their own care combining data, knowledge and software tools. PHRs, completely managed by individual patients, are emerging platforms for patient engagement and involvement [54]. Within p-medicine, the Indivo-X PHR has been adopted, a web-based platform for patient-centric integration of healthcare information and for the development of patient driven applications after a thorough review of similar platforms [55] [56]. Similar to the ObTiMA scenario, as soon as a patient is registered to the system, the PIMS is contacted and a local pseudonym is generated and linked to the patient's central pseudonym. Besides using PIMS services, Indivo-X integrates also Donor's Decision tool

as shown in Figure 4, as an individual app. As soon as a new project request occurs, the eligible patients are notified and they can use the corresponding Indivo-X app to see the list of the projects, the pending ones, and their past choices. In addition, they can update their choices at will and the results are automatically transmitted to the Donor's Generation Tool.

3.8. Beyond the IT platform

As already stated at the beginning of this section, national laws and/or ethical guidelines in some of the EU Member States require consent to be in written form. This requirement can in electronic settings either be met by using a qualified electronic signature, or by printing the consent form and signing it manually. In cases where the patient opts to print and sign manually, the corresponding documents will be sent to the Consent Management Authority (CMA). The p-medicine project has made use of an organization dedicated to providing support to the biomedical research community on issues of data protection. The CMA here is the Center for Data Protection (CDP), a non-profit organization registered under Belgian law [57]. In scenarios where CDP accepts signed patient consent forms and copies of their IDs, the copy of the ID could be used to verify this person. In these cases, the researchers have to contact the CDP to verify patients' choices, before actually using the biomaterial.

4. Experiences & evaluation of the tool

4.1. Comparison with other systems

A key challenge for an e-consent mechanism relates to making it simple enough for patients to use, and at the same time ensuring that it retain its expressiveness, usability

and security without loss of information. In assessing how far our solution meets these criteria, we found it helpful to compare it with six other relevant approaches:

SecureConsent[3]: ConsentSolutions provide a robust and flexible approach for the collection and maintenance of the patient consents for biobanks. The tool helps patients to make educated decisions while facilitating compliance, transparency and efficiency. Detailed, real-time tracking and sophisticated analytics help support risk-based monitoring of the consent process from anywhere. Highly granular audit trails, to ensure that the right version of the document is presented in the right language, and signed with the correct date, help reduce compliance failures.

Mytrus[4]: Mytrus eConsent tool seeks to enable people to participate in clinical trials in a better-informed and convenient way. Multimedia presentations are used to augment user understanding of the papers that should be signed, and streamline the process of signing and updating the consent.

Educonsent[5]: EduConsent by Systemedicus is a patent-pending Apple iPad-based system, which informs the patient about every aspect of a relevant medical intervention, including the risks and benefits, and offers the patient the possibility to complete the consent electronically on the tablet. The participant's level of understanding is monitored in a stepwise manner, with questions and answer choices following blocks of information. In addition, the system also records the consent process and includes facial recognition and signature capture technology to authenticate documentation.

[3] https://www.secureconsent.com/
[4] http://www.mytrus.com/
[5] http://www.systemedicus.com/

iMedConsent[6]: The iMedConsent application enhances the education, discussion and documentation associated with the informed consent process for physicians, ambulatory surgery centres and hospitals. It can be integrated with other healthcare applications, and includes a library with procedure-specific consent forms for more than 3500 treatments and procedures.

FORCS e-Consent [7] : Forcs e-Consent is a solution provided by DataMationGroup in order to directly link an EMR record with the solution provided. Patients are provided with the corresponding forms on mobile devices and they can review the content and sign the form electronically. Everything is stored in a document repository and forwarded to the EMR as well.

Consentir: Consentir [58] is a policy (rule) based patient consent management system that utilizes patient consent information along with operational policies as input. The system aims to protect patient information in real time by applying policy based consent management. However, it is a research prototype and it does not appear to be in continued development.

To compare the aforementioned tools, we identified thirteen criteria based on a) the criteria formulated by the CONTRACT project [59]; b) by the set of principles established in Galpottage and Norris [60]; and c) cost. We separated those criteria into four categories, dealing, respectively, with functionality, security, other intelligent functionalities, and cost:

- **Functionality**

[6] http://www.dialogmedical.com/products/imedconsent_enterprise/

[7] http://www.datamationgroup.com/news-event/105-forcs-electronic-informed-consent-e-consent

- **Multiple types of consent**: According to national laws, different types of consent should be supported by the platform (opt-in vs. opt-out, broad vs. specific)
- **Granularity of consent**: In addition, consent could be granular, granting or prohibiting access to a specific part of the biomaterial/data.
- **Re-consent capability**: There should be an option for subjects to withdraw or re-consent at will after their initial decision.

- **Security**
  - **Access control:** Any secure information system needs to adopt access control mechanisms that clearly assign roles and regulate information sharing among multiple users.
  - **Flexible Patient Signature**: An e-consent system should allow the proper identification of the signatory, either with an electronic signature, a hand-written paper-copy, or a combination of both.
  - **Universally Unique Identifier:** A Universally Unique identifier should be available to refer to a specific person. However, the proper procedure should be provided to ensure a person's anonymity as well.
  - **Auditing mechanism**: This refers to the capability of the tool to provide audit trails, through which the path of a record/sample can be tracked.
- **Intelligence**
  - **Utilize existing resources**: The capability of a consent system to utilize legacy systems already available such as PHRs, EHRs, Biobanks, etc.
  - **Search engine for eligible persons**: Finding eligible subjects with the right health profile for a trial is often time-consuming and onerous, and failure to

line up enough patients in time often leads to lost days during clinical trials. As such, a search engine that allows to search for eligible persons would greatly benefit the whole process.

- **Mobile friendly:** Nowadays, mobile devices are widely used. According to recent research [60], mobile devices using new interfaces may facilitate better comprehension and awareness by persons as to what they are signing up to..
- **Multimedia Support**: Although recent evidence [61] is mixed as to whether audio-visual interventions enhance people's knowledge when giving their consent, this nevertheless has some positive effects on the quality of information disclosed, and may increase subject willingness to participate in the short-term.
- **Alerting System**: An alerting mechanism could notify eligible users to give their consent to relevant projects.

Cost

- **Free:** The free concept intends to free developers from any restrictions of proprietary software, such as cost and distribution limitations. Other organizations have extensive rights to study, copy and redistribute the software at their discretion.
- **Open Source:** In contrast, the open source concept aims to provide developers with the ability to modify the software according to their needs. They are able to access the source code of the software in order to understand the provided solution and possibly customize or extend it.

Table 2. Comparison results of the e-Consent Tools

	Criteria	SecureConsent	Mytrus	EduConsent	iMedConsent	Forcs	Consentir	DST
Funct.	Granularity of consent	yes	yes	yes	yes	yes	yes	yes
	Multiple types of consent	yes	yes	yes	yes	yes	yes	yes
	Re-consent capability	yes	yes	no	yes	yes	yes	yes
Security	Access control	yes	yes	yes	yes	yes	yes	yes
	Flexible Patient Signature	yes	yes	yes	yes	yes	no	yes
	Universally Unique Identifier	no	yes	no	yes	yes	yes	yes
	Auditing mechanism	yes	yes	yes	yes	yes	yes	yes
Intelligence	Integrates with Existing Resources	no	no	no	yes	yes	no	yes
	Search engine for eligible persons	no	no	no	no	yes	no	yes
	Multimedia Support	yes	yes	yes	yes	yes	no	yes
	Mutli-device Capable	yes	yes	partial	yes	yes	no	yes
	Alerting System	no	yes	no	no	no	no	yes
Cost	Open Source	no	no	no	no	no	no	yes
	Free	no	no	no	no	no	no	yes

The results are shown in Table 2. As we can observe with respect to the functionality category, all tools except EduConsent permit multiple types of consent to be defined, thereby allowing the patient to select the specific information/bio-samples to be released.

With respect to the security category, all tools include some type of access control mechanisms and include auditing procedures. In addition, all except Consentir provide flexible means to capture the patient signature. Finally, most of the tools provide a Universally Unique Identifier for the patient. However, our approach is the only one that allows local identifiers (local pseudonyms) for all tools involved to be linked with a Universally Unique Identifier (central pseudonym), streamlining the whole process and ensuring patient's identity protection.

With respect to the intelligence category, only some of the tools allow direct integration with existing infrastructures (EMRs, PHRs, Biobanks etc.), whereas only two of those provide a search engine for the eligible patients. Our tool is the only one to combine a search engine and a system that alerts the eligible patients only to a given project request. Finally, most of the systems allow videos and images, as well as the usage of mobile devices. Educonsent, though, can only be used by Apple devices and as such its multi-device capability is partial.

Finally, with respect to the cost required to invest in the relevant tools, our approach is the only one that is free and open source, thereby minimizing the cost of the solution. A further unique advantage is the fact that our tool can be directly attached to the existing infrastructure.

4.2. Preliminary usability evaluation

The tool was developed in close collaboration between clinicians, software developers and lawyers to guarantee clinical relevance and data safety and security.

Initially, the system was tested by the University College of London using retrospective data from the SIOP 2001 study and showed excellent results. Specifically, the security and reliability of the tool received excellent scores, the functionality and efficiency score were also above average, while for the quality in use, the users proposed minor changes, which were taken into account by the development team.

Subsequently, a preliminary evaluation of the tool was performed analyzing its usability and performance within the p-medicine project. A scenario derived from the user requirements of the project illustrated the special tasks with the whole context of use for the tool. These tasks were taken into consideration with the usability standards of ISO 9241 [62], especially Part 10 of the standard (a general set of usability heuristics for the design of different types of dialogue) and Part 11 (general guidance on the specification and measurement of usability). The methodology for the usability evaluation followed by the p-medicine consortium can be found in the public deliverable D15.1 “Evaluation criteria and verification procedures of the p-medicine platform” [63]. During the p-medicine evaluation workshops, a clinician, a study nurse, and a data manager were invited to perform the scenario, and a patient was asked to use his PHR account for giving his consent to a specific project request. All participants were then asked to complete a

usability questionnaire (focused on the ISO norm 9241); at the same time a tool for recording the session and a microphone for the "thinking aloud" method were also used to provide a complete evaluation. The results of the evaluation showed a mature and promising tool. Scores over the average were achieved in all the categories of the quality characteristics based on the ISO product quality model. Functionality, reliability and security were marked as excellent from all the evaluators, efficiency and usability were marked as good, while the users proposed minor changes for the user interface. These suggestions were subsequently taken into account and the tool was updated accordingly. The clinicians appreciated the integration of the donor's tool within ObTiMA and the Indivo-X based PHR, as this offers unique possibilities within clinical trials and research dependent on biomaterial.

5. Conclusions

In an era when information is shared digitally at the global level, mechanisms of informed consent remain static, paper-based and limited by national boundaries and anachronistic legal frameworks [13]. In this paper we have studied the European Union legislation around effective and efficient secondary use of patient's biomaterial, and identified the requirements for building a set of simple and generic IT-based consent tools. The three modules of our platform place participants at the heart of decision-making and allow individuals to tailor and manage their own consent preferences. As described, we demonstrated the potential of our solution by a proof of concept deployment in an existing clinical setting, which participants judged positively as streamlining the relevant workflow.

Professor Norbert Graf introduced the system to the ENCCA ('European network for cancer research in children and adolescents') network of excellence project during the second general assembly meeting as an invited speaker. The ENCCA and SIOP community welcomed the effort and proposed to test and potentially use the system.

In a next step, this tool will be prospectively deployed in the upcoming international and multicenter SIOP (International Society of Paediatric Oncology) kidney tumor study, where clinical data and data about biomaterial from each patient are stored in ObTiMA. The biomaterial from these patients is collected in different biobanks. Patients will be asked to use the Indivo-X based PHR, and the applicable legal framework is installed. The tool will then be able to support researchers in receiving a high quality and sufficient biomaterial for answering their research questions more easily than occurs today. This SIOP study will be a proof of principle for other clinical trials and research projects that need biomaterial. Results will be reported in a separate paper. We are hopeful that the following deployment in the SIOP trial will further improve transparency and public trust, and contribute to more effective and efficient future participant recruitment.

Acknowledgements

We would like to thank Maria Hatzimina, Eirini Genitsaridi, Holger Stenzhorn and Elias Neri who were involved in the development of the tools presented in this paper. This work has been supported by the EU projects p-Medicine (FP7-270089) and iManageCancer (H2020-643529) and has been partially funded by the European Commission.

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