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Introduction

The aim of the U-PGx project is to address major challenges and obstacles for implementation of PGx testing in patient routine health care in the European Union. One of these challenges is to take into account the diversity of healthcare systems and citizens in Europe. Thus, the purpose of U-PGx is to demonstrate, through a new model of personalized medicine, that pre-emptive PGx testing can be used in clinical practice, with cost-efficiency and better outcomes for patients.
Henceforth, many ethical and legal issues need to be address by the project for implementation of PGx testing in medical routine care. For this purpose, ELSI expertise is incorporated in the project through this Work Package. The aim is to ensure that ethical and legal aspects are taken into account in this work and the guidelines issued throughout the project.

In this manner, from an ethical angle, the project has to deal with questions as information, informed consent, return of results, disclosure and reporting of incidental findings, all with respect and protection of patients' rights. Moreover, a large volume of pharmacogens is discovered and collected; raising the question of data storage and re-contact. The aim would be to provide guidelines, including informed consent.

On the regulatory side, the current trend is to update European legislation through the revision of previous European Directives currently turned into European Regulations, limiting national interpretations and harmonizing Member States' legislations. In fact, three relevant legislations in particular were updated and finalized before and during the project and it is necessary to take stock of these legislations in the ELSI framework.

In this context, the purpose of this deliverable is also to analyze the ethical issues raised by the aim of the project for future guidelines and the proposals that have already been made on these ethical issues. From a legal point of view, the idea will be to discuss the novelties introduced by the new relevant Regulations applying to the project and the procedures foreseen in the PREPARE (Preemptive Phamacogenomic Testing for Preventive Adverse Drug Reactions) clinical study carried out in U-PGx.

Part 1 Pharmacogenomics ethical issues in Europe

A: General principles for genetic and genomic research on human samples

Inherited from research ethical principles[1] and medical ethics principles[2], genomic research should emphasise on the relationship between the research participant and researchers. Genomic practices are often seen as specific interventions due to the fact that the genome is carrying personal information allowing the identification of a given person. In addition the family dimension of genetics has also influenced the way genetic testing is currently framed. Even though the two practices, research and medical care, are usually regulated in different ways and instruments, the same basic ethical principles can be drafted:

- Principle of beneficence and non-maleficence: physicians/researchers have an obligation to maximize advantages and minimize harms in the conduction of their research. The best interest for patients should always be pursued by physicians/researchers, including advice given to the patient. For example, if an alternative to genetic testing exists and can be beneficial for the patient, it should be explained to the patient.
- Justice: an equitable access to care, genetic testing and counseling should be given to all patients.
- Principle of respect for patient autonomy: in particular in the process of informed consent, the physician has an advisory role but the final decision must be given to the patient. The consent of the patient must be voluntary, uninfluenced (including by his physician) or given under pressure. Patient-independent decision-making should be encouraged as much as possible.
- Guarantee of confidentiality: Patients' personal health data and information must be protected and kept confidential with relevant security measures.
- Principles of right to know and right to not know: the willingness of the patient must be respected. This may be a tricky question in pharmacogenomics because pharmacogenomic data have a family dimension and do not necessarily depend solely on the wish of one individual person.
- Protection of the individual interests: in pharmacogenomics, the individual interest of the patient should prevail over the common interest of society.

[1] Nuremberg code 1947, Helsinki Declaration 1964 updated, Oviedo Convention 1997.see full references below
[2] Beauchamp and Childress; Principles Biomedical Ethics, Oxford University Press, 7th edition, 2012

B: Informed consent

a- Definition elements

Before a genetic test is proposed, , the person must be fully informed of the aim of the test and its implications: potential risks and benefits, alternatives, medical consequences, etc. Patients should also be informed of their different rights, including the respect of right to privacy, the respect of their autonomy, etc. All this information must be contained in the informed consent form, prior to the test.

Informed consent is a binding step for any involvement of a person in a genetic test or more widely in a clinical trial. It is a right stated by the Helsinki Declaration[3] and several European and international conventions and regulations (the Oviedo Convention[4] for example, or the CIOMS[5] guidelines).
The patient's signature of the consent cannot be considered as sufficient to ensure the high level of autonomy requested by these recommendations. In fact, informed consent must be considered as a support to the decision-making of the patient and as a tool of communication between the physician and his patient. This tool is one of the elements that allow the patient to make an informed decision about his participation in any clinical trial.

For a long time, informed consent has become inseparable from genetic testing and more generally from clinical trials; As such, it is framed into legal rules and is considered for being harmonised amongnational legislations, at the European level. Informed consent is one of the topics of the new Clinical Trials Regulation EU No 536/2014 and Articles 28 and 29 of Chapter V (Title: Protection of subjects and informed consent) clarify the quality of information to be provided to patients and procedures for the collection of informed consent.
Article 28 sets out the general rules of informed consent that were already well known: no influence or pressure should be exerted on the patient in his or her decision-making, the patient has the right to withdraw from the study at any time etc.
Article 29 provides details on the content and the form of the informed consent. It must be documented and preferably be collected in writing. Adequate time shall be given for the patient to consider his or her decision and the article states that during the interview with

[3] The Declaration of Helsinki is a set of ethicals regarding human experimentation adopted by the World Medical Association (WMA) in 1964. Last version as amended in Fortaleza in 2013.
[4] The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, known as the Oviedo Convention, entered into force on 1999.
[5] The Council for International Organizations of Medical Sciences (CIOMS) published in 2016 the new CIOMS International Ethical Guidelines for Health-related Research involving Humans.

the patient to inform him / her, it should be verified that the patient has understood the information given.
This article also states that the information given must enable the patient or his or her legal representative to:
- understand "the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial",
- to know the rights of patients, "in particular his or her right to refuse to participate and the right to withdraw from the clinical trial at any time any detriment and without having to provide any justification",
- understand the conditions under which the clinical trial is to be conducted,
- know "the possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical trial is discontinued"[6],

b- Guidelines

Several guidelines adopted by professional organisations are completing the picture of the needed requirements to seek informed consent from patients or participants to research.

i. The Council for International Organizations of Medical Sciences (CIOMS) guidelines.

In 2016 the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Medical Association has revised its "International Ethical Guidelines for Health-related Research Involving Humans"[7]. This document is seen as one of the reference[8] for the conduction of Clinical Trials in complement to the Helsinki Declaration. The argument for pushing for a revision was that "several developments had taken place including: a heightened emphasis on the importance of translational research, a felt need to clarify what counts as fair research in low-resource settings, more emphasis on community engagement in research, the awareness that exclusion of potentially vulnerable groups in many cases has resulted in a poor evidence base, and the increase of big data research"[9]. Several articles are targeting the consent issues for competent adults but also for vulnerable persons. Although informed consent is required in Guideline 7 ("Researchers, sponsors, health authorities and relevant institutions should engage potential participants and communities in a meaningful participatory process that involves them in an early and

[6] REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
[7] http://cioms.ch/ethical-guidelines-2016/WEB-CIOMS-EthicalGuidelines.pdf
[8] van Delden JJM, van der Graaf R. Revised CIOMS International Ethical Guidelines for Health-Related Research Involving Humans. JAMA. 2017;317(2):135-136. doi:10.1001/jama.2016.18977
[9] Guidelines document p.9

sustained manner in the design, development, implementation, design of the informed consent process and monitoring of research, and in the dissemination of its results") it is not subject to a dedicated guideline *per se*. The originality of this document is to envisage informed consent as a process to be thought about during the whole development of a clinical trial considering the moment when the consent is seek and in which context it is asked for. This is the reason why it is referred to in several parts of the document and not only in one single guideline. However, the CIOMS Guidelines put an emphasis on persons unable to give consent such as children, adolescents[10] or vulnerable people[11]. As a common provision the CIOMS requires ensuring the autonomy of the incompetent person to be respected and gives a central role to the Ethics committees to ensure a stringent respect of the ethical principles in this case. Genetics is referred to, in these guidelines, in order to specify the requirements for communication and publication of the study results. They state that "research results in certain fields (for example, epidemiology, genetics, and sociology) may present risks to the interests of communities, societies, families, or racially or ethnically defined groups"[12]. In addition, a general guidance of the items to be included in the informed consent form is also provided by the CIOMS[13] where they recommend that the following information should be given to the participants prior the commencement of the protocol: "policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a participant's genetic tests to immediate family relatives or to others (e.g. insurance companies or employers) without the consent of the participant (Guideline 11)"[14].

ii. The 2016 ESHG Guidelines.

In its latest guidelines for diagnostic next-generation sequencing[15], the ESHG recommends that, in the context of informed consent, a written information leaflet should be provided to patients and / or provided through online information.

The ESHG also provides a lot of recommendations on how to manage incidental findings in informed consent[16].

Another issue concerns the future of data and the involvement of patients in this decision-making process[17]. The ESHG recommends integrating the possibility into the consent form that samples can be used for future research. Adequate information on the scope of these

[10] Guideline 19
[11] Guideline 9
[12] Guidelines 4 and Appendix 1
[13] Annex 2 of the International Guidelines, see Annex 1 of the deliverable
[14] See Annex 1 point 26-3
[15] ESHG, Guidelines for diagnostic next-generation sequencing, published in European Journal of Human Genetics (2016) 24, 2-5. www.nature.com/ejhg
[16] See relevant section
[17] See relevant section

potential future tests should also be given to the patient. For ESHG, patients should ideally be able to choose to participate only in present research or also in hypothetical future research.

c- Comments

The issues about informed consent for clinical trials and genetic testing are already well known and widely discussed. There are many guidelines in this area whose content coincides, which is why some have been selected in this deliverable. It is thus traditionally recommended to inform the patient as well as possible by giving him as much information as possible not only in writing but also orally and in particular on the use to be made of its data/samples in the future.

The remaining challenges for informed consent concerns its scope. These are issues inherent in pharmacogenomics, such as the detection of incidental findings and the future of genetic data. Should these questions be incorporated into informed consent? What is the best way to manage this return of information to the patient? Here, there is a potential risk of opposition between advancing science and respecting patients' rights. On the one side, the rapid evolution of Whole Genome Sequencing's scientific techniques presupposes that it is impossible for researchers and lawyers to foresee in advance all the discoveries that could result from the tests. Scientific progress could be promoted through simplified procedures of the consent form (such as opt-out procedures for further uses). On the other side, the principle of autonomy and respect for the patient's privacy should be reaffirm and ways for ensuring the correct information of the patients on the use of the samples and data, and the means for protecting the confidentiality, should be promoted.

d- Principles and proposals for U-PGx

- Respecting the decision-making autonomy of patients with respect to their genetic data implies an obligation of education: in order for patients to make an "informed" decision, by understanding implications and consequences of their decision, they need to understand how genes and preventive medicine work.
- The informed consent process should include clear and comprehensive information about the disease, expected benefits, potential risks and disadvantages, test limitations, family implications and probabilities of inheritance, and alternatives to the existing test.
- Researchers and clinicians should explain what happens to data, samples, or recordings.
- The patient should be told that his / her participation is voluntary and guarantee him /

her the possibility to withdraw at any time.

- The consent form must prevent the following issues:
  - Access to data and data conservation and possible future reanalysis (considering that all information on future research to be conducted on the data collected is not available at the time of the collection of the initial consent).
  - Research on genome must both guarantee the confidentiality of data and the privacy of patients. This means that there should be no risk of direct or indirect identification with computerized processing, in particular to prevent the risk of further stigmatization
  - Respect for patient autonomy extended to the family sphere since the field of genetics is the basis of heredity and filiation and gives information about the family members of the patient. Informed consent must measure the impact of this family dimension in relation to the return of results (and Incidental Findings).

C. Disclosure and reporting Incidental Findings

The trends of technological developments in genetics, such as Next Generation Sequencing or Whole genome/exome sequencing, increase the production of personal data (massive data) and, as a result, increase the risk to find unsolicited information about the donor. This information, usually called incidental finding, should be dealt with in respect with core ethical principles.

a- Definition Elements

The lack of legislation about incidental findings in genomics leads initially to a problem of legal and scientific definition. In the literature, several terms are used to designate them: unsolicited findings, off-target results, unsought for findings, unexpected results, secondary variants, etc.

The term "incidental findings" includes two dimensions: unexpected results and voluntary search for pathogenic variants unrelated to the initial indication of the genetic test. Should incidental findings be considered an accident or an expectation? It is now generally accepted that incidental findings are an inevitable part of the process when exploring the genome.

In the literature, the concept of a "clinically actionable" result is often mentioned which allows the following classification of incidental findings by category:

- "clinically actionable" would group the results for which prevention or treatment of the predicted disease are available. It could also be said that these results are

clinically useful, or relevant.

- "not clinically actionable" would characterize the results predicting an incurable disease from which there would be no preventive measures.

This classification usually serves as a basis for practitioners to identify the results that should be returned and those that should not.

b- Guidelines

Despite previous projects that have attempted to establish a consensus of "good practice" around the question of the future of incidental findings (IF) in pharmacogenomics, these remain only recommendations.

i. The American College of Medical Genetics and Genomics Guidelines

The American College of Medical Genetics and Genomics (ACMG)has initially produced recommendations from a report adopted in 2013. In this document the members encourage to systematically inform patients of IF of medically usable variants in a set of 56 genes, whether they had consented or not and regardless of their age. An additional modification provided an opportunity for patients undergoing full sequencing not to receive IF. The latest version of the ACMG recommendations, revised in April 2017, expanded the list to 59 genes.

The ACMG also preconizes a change in the rules of consent to research to allow for "open consent" that would allow for further laboratory research. In order to compensate the infringement of patients' rights, a solution envisaged in the United States would be to establish dissuasive penalties for breaches of privacy (the 2008 US law on non-discrimination of genetic information could serve as a model for penalties).

ii. The European Society of Human Genetics Guidelines

The European Society of Human Genetics (ESHG) has adopted a different policy[18]. It recommends that IF should be avoided as much as possible with a targeted approach to the clinical question and, in any case, to inform patients of possibility of discovering IF before the tests are carried out. Recommendation 2 encourages that "When in the clinical setting either targeted sequencing or analysis of genome data is possible, it is preferable to use a targeted approach first in order to avoid unsolicited findings or findings that cannot be interpreted. Filtering should limit the analysis to specific (sets of) genes. Known genetic

[18] Carla G van El, ,MartinaCCornel and al.Whole-genome sequencing in health care, Recommendations of the European Society of Human Genetics, European Journal of Human Genetics (2013) 21, 580–584

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variants with limited or no clinical utility should be filtered out (if possible neither analyzed nor reported)". As for research activities, they also preconizes to anticipate how these results will or will not be reported using the initial consent form.

iii. The CIOMS Guidelines

In the 2016 CIOMS guidelines, unsolicited findings are addressed in Guideline 11 concerning "Collection, storage and use of biological materials and related data" where it is recommended that "a procedure for determining whether unsolicited findings should be disclosed, and if so, how they should be managed". . The Guidelines clearly links the question of IF to the one of consent and recommend that "The informed consent process must clearly stipulate whether return of information derived from analysis of the materials is foreseen, if the donor wishes. The information given to the donor should clearly state that providing individual diagnosis is not the purpose of the biobank or future research project, in order to prevent that donors are falsely reassured by the absence of unsolicited finding". CIOMS recalls the three generally accepted principles to validate the return of results: analytical validity, clinical significance and actionable and in that case CIOMS recommends returning them to patients.

c- Comments

Deciding on the return of unsolicited results to patients according to whether they are clinically actionable or not may be problematic, considering that incidental findings predicting an incurable disease remain not actionable, even though the information that contains may be useful for the patient (from a medical and / or social point of view): some patients would like to know how to adapt their lifestyle and others would prefer to remain ignorant. It should also be considered that a patient who does not wish to know certain types of results at the time of consent collection may change his mind in the future. The guidance of ESHG has the advantage of putting the patient at the heart of the decision about the future of his genomic data and of compartmentalizing the responsibility of the physician in his relation to the patient.

The specificity of unsolicited results in genomics and pharmacogenomics is that their interpretation may change over time: for example, incidental findings may not be able to give rise to clinical action at the time of their discovery, but scientific advances will potentially make these results operational a few years later. It is therefore important to design this type of data in an evolutionary time dimension, considering that they are not "frozen". Many questions arise: how long can these data be kept? Can we have access and

who? Does access mean authorization for analysis? When, at the time of their discovery or in the future? Is there an ethical obligation to reinterpret results over a period? What financial implications?

These questions could be answered in the consent form or possibly in an appendix to the consent form. However, the collection of informed consent is already a lengthy procedure and its heaviness could scare patients. There is no consensus in the guidelines.

d- Principles and proposals for U-PGx

- Reaffirmation of patients' right to know or not to know,
- Informed consent must be clear on the management of incidental findings. Several choices can be proposed to the patient: to be informed of all the results, to be informed of the results for which treatment or prevention is available, not to be informed of the results not related to the initial indication of the test, or to leave the physician the responsibility of choosing for his patient in its best interest.

D. Data storage and re-contact

The storage of data from whole genome sequencing has two issues: on the one hand, it is a matter of safeguarding the "proof" used to identify the results of the sequencing request. On the other hand, it is a matter of storing the results of the sequencing for a hypothetical future reanalysis.

On the question of the role of the laboratory in the re-analysis of stored data when the interpretation is likely to evolve with scientific progress, the consensus is that reanalysis should be limited to the initial clinical question and laboratories should not systematically re-analyze old data. However, the laboratory should be responsible for re-analyzing available data if a variant changes class.

It is traditionally recommended to store data during the diagnostic period or clinical trial but there is no consensus in Europe that determines how long this data should be kept, by whom or where it should be kept. This question poses the material and financial problem that has not yet been solved by health policy: by nature, WGS generates a huge amount of data that requires a solid infrastructure to ensure data conservation and protection, and then to make possible a potential future analysis. On the one hand, it can be considered, according to the ethical principle of transparency, that patients have the right to know all the medical information that concerns them. On the other hand, retention of data (and also

their return to patients) may prove to be irrelevant if that conservation can be complex and costly, and medically unhelpful data (for example, if their interpretation is Impossible or if they prove to have little impact on the patient's health or the object of the research).
The question of the future of data deserves to separate two types of data that do not have the same issues. On the one side, there are the data which are the pure product of the sequencing, which are called “raw data”. On the other side, there is interpreted data of the sequencing. The already interpreted data may seem the most critical as there is a legal duty to store it in the patient's medical record. However, the raw data are also sensitive since they can be reused in the future and be subjected to analysis and / or interpretation.

Principles and proposals for U-PGx

- Patients may have a choice over the future of data not yet interpreted, including choosing to destroy them.
- The protection of data and privacy must be discussed with the patient, given the risks of re-identification that exist due to the rapid evolution of storage and analysis techniques.

Part 2 European Union Legislations

A/ the Clinical Trials Regulation

On 16 April 2014, the European Parliament and the Council adopted the Regulation on clinical trials on medicinal products for human use[19], repealing the previous Directive. The purpose of this deliverable is to review the relevant elements of this Regulation which will apply to the project and to the clinical study PREPARE (Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions), even if the recruitment is already opened, but that the Regulation will only apply by 2018.[20]
One of the first interesting elements is that, from now, clinical trial is considered to belong to a broader category: the “clinical studies”[21]. The clinical study is defined as “*any investigation in relation to humans intended:*

[19] Regulation (EU) No 536/2014 of the Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/CE.
[20] http://upgx.eu/1124-2/
[21] Laude A, Droit de la Santé, Dalloz 2014, p.2021.

(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;

(b) to identify any adverse reactions to one or more medicinal products; or

(c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products;

with the objective of ascertaining the safety and/or efficacy of those medicinal products"[22].

Furthermore, a new subcategory of clinical trial could be interesting for pharmacogenomic studies as the one which takes place in the project: the 'low-intervention clinical trials' which is a "*clinical trial which fulfils all of the following conditions:*

(a) the investigational medicinal products, excluding placebos, are authorized;

(b) according to the protocol of the clinical trial,

(i) the investigational medicinal products are used in accordance with the terms of the marketing authorization; or

(ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and

(c) *the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned*"[23].

According to the Regulation, these trials should be subjected to less strict rules, as regards to the follow-up, the requirements concerning the contents of the permanent file and the traceability of experimental medicine; however it has to be the object of the same procedure of request as the other clinical trials with the aim of guaranteed the safety of the participants[24]. However, these trials must be led on the territory of a single Member State[25]. As regards the obtaining of the consent in this trial type, it can be obtained in a simplified means under certain specific conditions[26]:

(a) "the simplified means for obtaining informed consent do not contradict national law in the Member State concerned;

(b) the methodology of the clinical trial requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products in a clinical trial;

[22] Article 2, (2) 1) of the CTR
[23] Article 2 (2) 3) of the CTR.
[24] Recital (11) of the CTR.
[25] Recital (33) of the CTR.
[26] Giannuzzi V et al, "Clinical Trial Application in Europe: What will change with the new Regulation?", Sci Eng Ethics (2016) 22:451-466.

(c) the clinical trial is a low-intervention clinical trial and the investigational medicinal products are used in accordance with the terms of the marketing authorization

(d) there are no interventions other than the standard treatment of the subjects concerned;

(e) *the protocol justifies the reasons for obtaining informed consent with simplified means and describes the scope of information provided to the subjects, as well as the ways of providing information*"[27].

It does not apply to the PREPARE study because this one takes place on 7 Europeans countries and because of the Regulation enter into force date.

Nevertheless, future pharmacogenomic clinical trials could go into this qualification because it is a question of using medicine according to the marketing authorization and because the additional constraints are the one of taking of a sample of DNA for the PGx test and the monitoring system by feedback of information on the possible adverse effects.

For the authorization procedure, one of the first changes operated by the Regulation is the introduction by the European Medicines Agency of an EU portal, which is the single entry point to submit an application for the authorization of a clinical trial to the reporting Member State[28]; and an EU database[29] for the storage of the applications and data which are related[30]. Furthermore, the EudraCT number becomes the 'EU trial number'[31].

The clinical trial remains subject to a scientific and ethical assessment. The demand is made in a single document containing two parts of application and assessment:

- Part I concerns scientific design/relevance and the risk/benefit assessment,
- Part II corresponds to the assessment of the ethical aspects

The assessment of Part I is made by the reporting Member State. If the clinical trial is conducted in several Member States, as the PREPARE study, the assessment should include three phases:

(a) "an initial assessment phase performed by the reporting Member State within 26 day from the validation date;

(b) A coordinated review phase performed within 12 day from the end of the initial assessment phase involving all Member States concerned;

(c) A consolidation phase performed by the reporting Member State within 7 days from the end of coordinated review phase"[32].

[27] Article 30 (3) of the CTR.
[28] Article 80 of the CTR
[29] Article 81 of the CTR
[30] Flear ML, "The EU Clinical Trials Regulation: key priorities, purposes and aims and the implications for public health", J Med Ethics 2016; 42:192-198.
[31] Article 81 (1) al 3; Giannuzzi V et al, "Clinical Trial Application in Europe: What will change with the new Regulation?", Sci Eng Ethics (2016) 22:451-466.
[32] Article 6 (5) of the CTR

The assessment by the reporting Member State is made under strict deadlines: under 10 days as from the deposit of the file of application, the reporting Member State confirms the application[33], and under 45 days from the date of validation, he has to pass on, through the EU portal, the finale Part I of the assessment report, including his conclusion, to the promoter and to the other concerned Member States[34].
As for the Part II, the ethical assessment is made by the Ethics Committee of each concerned Member State[35]. This part focuses on the conformity of the trial with the requirements relative to the informed consent, the arrangements of remuneration or compensation of the participants, the recruitment procedures, data protection, suitability of individuals involved in conducting the clinical and clinical trial sites, the compensation of the damage and the applicable rules for the collection, storage and future use of biological sample of the subject[36].

Once the clinical trial ended, the submission of a summary of the results is made in a simplified way and in a structured format through the EU portal to be stored in the EU database, *EU Clinical Trials Register* newly established. It is accompanied with a written summary in an understandable language for laypersons[37]. Even though EU pushes for more transparency and accessibility of the information for the public[38], the confidentiality of the information is planned in the Regulation, in particular in the ground for protecting personal data or for protecting commercially confidential information[39].

Finally, regarding the implementation of the Regulation, it relies on a well-functioning of the EU portal and database[40]. The confirmation of the full-functionality passes through an independent audit, scheduled for August 2017[41]. The Regulation will enter into force 6 months after the publication of this confirmation by the European Commission in the *Official Journal of the European Union*[42]. If the audit is affirmative, the Regulation will come into effect by October 2018, according to the information in the EMA website.
A three years transition period will start from the date of its application and "*it applies to clinical trials authorized under the previous legislation if they are still ongoing three years*

[33] Article 5 (3) of the CTR
[34] Article 6 (4) of the CTR
[35] Article 4 of the CTR.
[36] Article 7 (1) a) to h) of the CTR
[37] Article 37 (4) of the CTR ; Flear ML, "The EU Clinical Trials Regulation: key priorities, purposes and aims and the implications for public health", J Med Ethics 2016; 42:192-198
[38] Article 81 (4) of the CTR
[39] Article 81 (4) a) and b) of the CTR
[40] Article 82 of the CTR
[41] European Medicines Agency, *Clinical Trial Regulation* (Internet): http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp&mid=WC0b01ac05808768df
[42] Article 99 al 2 of the CTR

after the Regulation has come into operation"[43]. Thus, the procedures foreseen in the CTR for monitoring and data to be produced will be applicable to the clinical study PREPARE which still will be in progress when the Regulation becomes applicable by 2018.

The Clinical Trials Regulation is not the only relevant legislation for this project and/or for the clinical study PREPARE. Indeed, the study PREPARE plans the collection and the processing of several types of data from study's participants. The General Data Protection Regulation would then also apply.

B/ The General Data Protection Regulation

On 27 April 2016, the Regulation on the protection of persons with regard to the processing of personal data and the free movement of such data, and repealing Directive 95/46/EC, also called the General Data Protection Regulation (GDPR), was adopted on 27 April 2016[44].
As the study PREPARE plans the collection and the processing of genetic, pharmacogenomic data from participants for research purposes of the U-PGx project, it is important to consider what the GDPR provides for the use of this type of data in the case of clinical research and if what is provided for in the protocol would be in accordance with it.

Pharmacogenomics is the study of genetic variability affecting an individual's response to a drug; and pharmacogenomic data are genetic data. These are defined by the GDPR as "*personal data relating to the inherited or acquired genetic characteristics of a natural person which give unique information about the physiology or the health of that natural person and which result, in particular, from an analysis of a biological sample from the natural person in question*"[45]. They are regarded as a special category of health personal data.

Concerning the treatment of these special personal data, the Regulation provides for a prohibition in principle of the processing of genetic data, and hence pharmacogenomic data[46].
But, an exemption from this ban is planned. The processing of genetic data is possible for the purpose of scientific research, including clinical research[47]. This processing should

[43] European Medicines Agency, *Clinical Trial Regulation* (Internet): http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp&mid=WC0b01ac05808768df
[44] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)
[45] Article 4 (13) of the GDPR
[46] Article 9 (1) of the GDPR

comply with the safeguards provided in Article 89 (1) "*based on Union or Member State law which shall be proportionate to the aim pursued, respect the essence of the right to data protection and provide for suitable and specific measures to safeguard the fundamental rights and the interests of the data subject*"[48]. The necessary safeguards are "*the establishment of technical and organizational measures, in particular in order to ensure respect for the principle of data minimization*"[49]. One possibility then is to use the pseudonymisation of data, defined as "*the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person*"[50].

In addition, the general principles and other rules of the Regulation should apply in this case, in particular as regards to the conditions for the lawfulness of processing[51].
The general principles that should apply to all data processing, including the processing of genetic/pharmacogenomic data for research, are:

- Lawfulness, fairness and transparency;
- Purpose limitation;
- Data minimization;
- Accuracy;
- Storage limitation[52];

and two relatively new additional principles[53] which are integrity and confidentiality as well as the principle of accountability[54]. In addition to these general principles, the Regulation provides new tools for ensuring the data protection: data protection by design and by default[55].
As regards the lawfulness of the processing, it is lawful only if and to the extent that at least one of the conditions lay down in Article 6 is satisfied, notably that of the data subject consent concerned by the processing for one or more specific purposes[56]. Consent is defined by the Regulation as "*any freely given, specific, informed and unambiguous indication of the data subject's whishes by which he or she, by a statement or by a clear*

[47] Article 9 (2) (j) of the GDPR
[48] Maldoff G, "*How GDPR changes the rules for research*", The Privacy Advisor, April 19, 2016 (Internet): https://iapp.org/news/a/how-gdpr-changes-the-rules-for-research/
[49] Article 89 (1) of the GDPR
[50] Article 4 (5) of the GDPR
[51] Recital 51 of the GDPR
[52] Article 5 (1) (a) to (e) of the GDPR
[53] Chassang G, "The impact of the EU general data protection regulation on scientific research", ecancer 2017, 11:709.
[54] Article 5 (1) (f) and (2) of the GDPR
[55] Article 25 of the GDPR
[56] Article 6 (1) of the GDPR

affirmative action, signifies agreement to the processing of personal data relating to him or her"[57].

If the lawfulness of the treatment is based on the data subject consent by the treatment, conditions must be put in place[58]:

- The controller must be able to demonstrate the data subject consent;
- The request for consent must be in a form that clearly distinguishes it from any other consent seeking other matters;
- The person concerned has the right to withdraw his consent at any time, etc[59].

Concerning the PREPARE study, the aim is to study the impact of preventive genotyping of a panel of clinically relevant pharmacogenomic markers on patient outcomes. Pharmacogenomic tests will therefore be performed on these participants and these pharmacogenomic data will be processed and stored. It is expected that the data will be used only in a pseudonymous manner and will only be processed for research purposes in the scope of the U-PGx project. In addition, the only data stored will be those that are relevant to the research, there would be no excess data storage. The lawfulness would rest on the participants' consent and on the agreement of the ethics committees and/or the national data protection authority of each country research site.

Given all these technical and organizational aspects, the clinical study falls within the scope of the GDPR and should respect the principles and rules established for this purpose.

Moreover, several procedures will have to be followed in carrying out the PREPARE study from a data protection point of view[60].

The first would be the designation of the data protection officer (DPO)[61]. This is especially mandatory when the controller's[62] basic activities consist of large-scale processing of sensitive data, including genetic/PGx data[63]. A problem arises as to what is meant by large-scale processing[64]. Indeed, this notion is not defined by the Regulation. On the basis of what

[57] Article 4 (11) of the GDPR

[58] Wellcome trust, "*Analysis: Research and the General Data Protection Regulation – 2012/0011 (COD)*", July 2016 (v1.4) (Internet): https://wellcome.ac.uk/sites/default/files/new-data-protection-regulation-key-clauses-wellcome-jul16.pdf

[59] Article 7 of the GDPR

[60] Chassang G, "The impact of the EU general data protection regulation on scientific research", ecancer 2017, 11:709.

[61] Section 4 of the GDPR

[62] Definition of controller: '*the natural or legal person, public authority, agency or other body which, alone or jointly with others, determines the purposes and means of the processing of personal data; where the purposes and means of such processing are determined by Union or Member State law, the controller or the specific criteria for its nomination may be provided for by Union or Member State law*'. Article 4 (7) of the GDPR

[63] Article 37 (1) of the GDPR

[64] Chassang G, "The impact of the EU general data protection regulation on scientific research", ecancer 2017, 11:709.

is said in the relation to the data protection impact assessment[65], large-scale processing is intended to "*process a considerable amount of personal data at regional, national or supranational level and which could affect a large number of data subjects […]*". In addition, it is clearly stated that "*the processing of personal data should not be considered to be on a large scale if the processing concerns personal data from patients or clients by an individual physician, other health care professional or lawyer*"[66]. All this poses a problem in the application of this article. Nevertheless, it may be advisable to designate a DPO.

This DPO, if designated, may be a member of the controller or processor staff or perform duties on the basis of a service contract[67]. He is appointed on the basis of his professional qualifications, in particular his specialized knowledge of data protection law and practices and his ability to perform the tasks assigned to him[68]. Indeed, it has at least missions:

- "*to inform and advise the controller or the processor and the employees who carry out processing of their obligations pursuant to this Regulation and to other Union or Member State data protection provisions;*
- *to monitor compliance with this Regulation, with other Union or Member State data protection provision and with the policies of the controller or processor in relation to the protection of personal data, including the assignment of responsibilities, awareness-raising and training of staff involved in processing operations, and the related audits;*
- *to provide advice where requested as regards the data protection impact assessment and monitor its performance;*
- *to cooperate with the supervisory authority;*
- *to act as the contact point for the supervisory authority on issues relating to processing, including the prior consultation, and to consult, where appropriate, with regard to any other matter*"[69].

The second procedure which should be carried out for the processing of personal data in the context of research is the data protection impact assessment (DPIA). This is a risk-based procedure. This assessment must be carried out before processing where, in particular, by the use of new technologies and taking into account the nature, scope, context and purpose of the processing, it is likely to result in a high risk to the rights and freedoms of natural persons[70].

[65] Recital 91 of the GDPR
[66] Recital 91 of the GDPR
[67] Article 37 (6) of the GDPR
[68] Article 37 (5) of the GDPR
[69] Article 39 (1) (a) to (e) of the GDPR
[70] Article 35 (1) of the GDPR

It is particularly necessary in the case of large-scale processing of sensitive data[71]. As part of this assessment, the controller will seek advice from the DPO, if designated[72]. He must also consult the supervisor prior to processing when the assessment indicates that the processing would present a high risk if the person in charge didn't take measures to mitigate it[73].

This procedure should apply in the case of the PREPARE study as regards the processing of the data to be collected since an independent contract research organization (CRO) which guarantees the integrity of the data and its homogeneity on the seven research sites by risk-based monitoring of a random sample of data collected.

Finally, one of the last procedures that should be applied is the notification and communication in case of violation of personal data[74].

Personal data breach is defined as "*a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed*"[75]. Violation of personal data may, is there is no timeline and appropriate intervention, cause physical, material or moral damage, discrimination, theft or identity theft, financial loss, unauthorized reversal of pseudonymization, etc[76]. For this reason, new and more stringent reporting rules have been put in place in the GPDR for the data controller. Thus, in the event of a finding of a violation, in parallel with the relevant corrective measures to be undertaken, this information must be transmitted by the data controller without undue delay. Two types of actions are then implemented:

- First, the notification of the competent supervisory authority and the DPO

Whatever the nature, scope and context of the infringement, the controller must, as soon as possible, notify the competent supervisory authority of the infringement and, if possible, no later than 72 hours after becoming aware of it; unless the breach is not likely to entail a risk to the rights and freedoms of natural persons. If notification is not made within 72 hours, the notification to the competent authority must be accompanied by the reasons for the delay[77].

- Second, communication with the persons concerned in limited cases

This is the case where the violation is likely to entail a high risk to the rights and freedoms of nature persons. Thus, as a matter of principle, the controller must communicate the

[71] Article 35 (3) (b) of the GDPR
[72] Article 35 (2) of the GDPR
[73] Article 36 of the GDPR
[74] Chassang G, "The impact of the EU general data protection regulation on scientific research", ecancer 2017, 11:709.
[75] Article 4 (12) of the GDPR
[76] Recital 85 of the GDPR
[77] Article 33 (1) of the GDPR

violation to the data subjects as soon as possible[78]. Exceptions are provided if the data controller has implemented appropriate technical and organizational protection measures to stop or compensate for the violation, i.e. when acts making the personal data concerned unintelligible for those who do not have authorized access or when the communication involves disproportionate efforts. In the latter case, individual communications are replaced by general public information about the violation or by an effective similar means of communication, which readily enables the persons concerned to know the facts and the consequences of the violation[79]. Moreover, this communication must be made in clear and simple terms to describe the nature of the infringement of the data[80].

Finally, with regard to the date of application of this Regulation, it will apply from 25 May 2018[81]. However, it is recommended that the study PREPARE should start to comply with the regulation before that date.

One of the last point to be dealt with is that is has been proposed to carry out a sub study. Samples would be collected from patients included in the clinical study PREPARE to identify new clinically relevant drug-drug interactions and new generations sequencing (NGS) would be used to identify novel genetic variants in subjects with extreme phenotype. In this context, it was decided to anonymize the patient samples, data.
The question then arises as to whether this sub study would fall within the scope of the main PREPARE clinical study from the data processing point of view because of the anonymization of the data. Indeed, based on what is provided for in the GDPR, "*The principles of data protection should therefore not apply to anonymous information, namely information which does not relate to an identified or identifiable natural person or to personal data rendered anonymous in such in manner that the data subject is not or no longer identifiable. This Regulation does not therefore concern the processing of such anonymous information, including for statistical or research purposes*"[82]. Thus, the GDPR would not apply to this sub study. However, for the consistency of the study PREPARE as a whole and this sub-study, it may be more relevant to remain within the GPDR framework for processing these data.

Following the presentation of the GDPR and its relevant rules for the clinical study PREPARE, one of the last European Legislation relevant to the project is this one relating to in vitro diagnostic medical devices (IVDs) since PGx tests are genetic tests and hence IVDs.

[78] Article 34 (1) of the GDPR
[79] Article 34 (3) of the GDPR
[80] Article 34 (2) of the GDPR
[81] Article 99 of the GDPR
[82] Recital 26 of the GDPR

The draft Regulation revising the Directive was still under discussion in the Council when the project started in January 2016. Today, the Regulation was finally published in the Official Journal of the European Union (OJEU) last April. It is then possible to check in the novelties introduced in this Regulation that are relevant to pharmacogenomics and PGx tests.

C/ The *in vitro diagnostic* medical devices Regulation

In 2012, the European Commission presented two texts revising the Directives in place concerning medical devices and IVDs[83]; these were two Regulations. After five years of legislative procedure, the Regulation on IVDs (IVDR)[84] was published on 5 April 2017 in the OJEU. It is therefore interesting to focus on the relevant measures introduced by this new Regulation on genetic testing, including PGx tests.

Firstly, the scope of the Regulation remains rather unchanged. Extension and changes are being made to the introduction of important definitions and genetic testing and PGx tests in the definition of IVD[85]. Indeed, the new definition of IVD new includes tests "*[…]*

(c) concerning the predisposition to a medicinal condition or a disease; […]

(e) to predict treatment response or reactions"[86]

A definition of companion diagnostic is also given "*a device which is essential for the safe and effective use of a corresponding medicinal product to:*

(a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or

(b) *identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product*"[87]

This desire for precision is clearly stated in the recitals because "*it should be made clear that all tests that provide information on the predisposition to a medical condition or a disease, such as genetic tests, and test that provide information to predict treatment response or reactions, such as companion diagnostics, are in vitro diagnostic medical devices*"[88].

[83] For IVDS : Proposal for a Regulation of the European and of the Council on *in vitro diagnostic* medical devices, 2012/02678 (COD)

[84] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

[85] Bird & Bird, *The Changing Face of Medical Devices and In Vitro Diagnostic Medical Devices: White Paper on the New Regulations*, Lexology, February 8 2017 (Internet): http://www.lexology.com/library/detail.aspx?g=7fcb3733-edbd-44f8-a4c2-0fbd270c7f3

[86] Article 2 (2) (c) and (e) of the IVDR

[87] Article 2 (7) of the IVDR

[88] Recital 10 of the IVDR

Another novelty is the IVDs' classification. The new classification is now based on the rules of the Global Harmonization Task Force system.[89] The devices are divided into 4 classes according to the risk: from Class A (lowest risk) to Class D (highest risk) and according to their destination[90].

The classification rules can be found in Annex VIII of the Regulation. The classification rules apply according to the intended purpose of the devices[91]. According to Rule 3[92], PGx tests and companion diagnostics fall under Class C "*Devices are classified as class C if they are intended: […]*

(f) to be used as companion diagnostics;

(i) for human genetic testing"

The fact that PGx tests and companion diagnostics are part of Class C result in specific rules being applicable to them. This is the case for the conformity assessment procedure that requires a notified body (NB) involvement "*For class B, class C and class D devices, an appropriate level of involvement of a notified body should be compulsory*"[93].

Prior to placing a device on the market, the manufacturer must assess its conformity[94]. In particular, for manufacturers of class C devices, other than IVDs for performance study, a NB must occur in this procedure on the basis of the assessment of the quality management system (QMS) by the manufacturers and the technical documentation of the IVD[95]. Specific provisions are intended for companion diagnostics: the NB always occurs in the conformity assessment procedure by evaluating the manufacturer's QMS and the technical documentation; but also the consultation of a Competent Authority designated by the Member State or the EMA by the NB after the review of the technical documentation[96]. This is the standard conformity assessment procedure based on a quality management system and on assessment of technical documentation[97].

Manufacturers of class C and D devices, other than IVDs for performance study, may opt for conformity assessment based on type-examination together with conformity assessment based on production quality assurance[98]. Even if this context, the NB shall assess the conformity of the manufacturer's QMS and the technical documentation. Indeed, "*EU type-examination is the procedure whereby a notified body ascertains and certifies that a device,*

[89] Bird & Bird, *The Changing Face of Medical Devices and In Vitro Diagnostic Medical Devices: White Paper on the New Regulations*, Lexology, February 8 2017 (Internet): http://www.lexology.com/library/detail.aspx?g=7fcb3733-edbd-44f8-a4c2-0fbd270c7f3

[90] Recital 55 ; article 47 (1) of the IVDR

[91] Annex VIII (1) (1.1) of the IVDR

[92] Annex VIII (2.3) of the IVDR

[93] Recital 56 of the IVDR

[94] Article 48 (1) of the IVDR

[95] Article 48 (7) al 1 of the IVDR

[96] Article 48 (7) al 3 of the IVDR

[97] Annex IX of the IVDR

[98] Article 48 (8) al 1 of the IVDR

including its technical documentation and relevant life cycle processes and a corresponding representative sample of the device production envisaged, fulfils the relevant provisions of this Regulation"[99] and in conformity assessment based on production quality assurance, "*the manufacturer shall ensure that the quality management system approved for the manufacture of the devices concerned is implemented, shall carry out final verifications, […], and shall be subject to the surveillance […]*"[100]. If this context, for companions diagnostics, the NB must also consult the Competent Authority designated by the Member State or the EMA[101].

As mentioned above, some IVDs must be subject of a performance study, in relation to clinical evidence, in order to be marketed[102]. These are innovative IVDs, concerning a new target population, or a new application or use planned, or if the tests are not established or standardized. In addition, this performance study concerns IVDs for which it is not possible to demonstrate compliance with the essential requirements by data from other sources[103]. The evolution is that the IVDR requires greater and more robust clinical and performance data. This is done through requirements on how clinical and performance data are to be obtained and by minimum requirements for the analysis of data for conformity[104].
Confirmation of compliance with relevant general safety and performance requirements under the normal conditions of the intended use of the device, and the evaluation of the interferences and cross-reactions and of the acceptability of the benefit-risk ratio should be based on scientific validity and clinical and analytical performance data providing sufficient clinical evidence[105]. The clinical evidence validates the intended use of the IVD alleged by the manufacturer and is based on a continuous process of performance evaluation, according to a performance evaluation plan[106]. This clinical evidence is important for the IVD, in particular for its life on the market and now this passes through this continuous evaluation process. Performance evaluation is defined as "*an assessment and analysis of data to establish or verify the scientific validity, the analytical and, where applicable, the clinical performance of a device*"[107].

[99] Annex X (1) of the IVDR
[100] Annex XI (1) of the IVDR
[101] Article 48 (8) al 2 of the IVDR
[102] Bird & Bird, *The Changing Face of Medical Devices and In Vitro Diagnostic Medical Devices: White Paper on the New Regulations*, Lexology, February 8 2017 (Internet): http://www.lexology.com/library/detail.aspx?g=7fcb3733-edbd-44f8-a4c2-0fbd270c7f3
[103] Baker N, '*Assessment of companion diagnostics under the new IVD regulation. Requirements of the IVDR*', Lloyd's Register LRQA, 2014 (Internet): http://medical-cluster.ch/media/archive1/pdf/anlaesse/2014/medtech_pharma/presis/S4P4NickBaker.pdf
[104] Squire Patton Boggs, *EU in vitro Diagnostic Medical Device Regulation Overview Part 3*, Lexology, February 7 2017 (Internet): http://www.lexology.com/library/detail.aspx?g=65dbdec6-c929-4eb3-b5d4-6939ff214a22
[105] Article 56 (1) al 1 of the IVDR
[106] Article 56 (2) of the IVDR
[107] Article 2 (44) of the IVDR

Furthermore, performance evaluation is carried out according to a defined and methodologically rational procedure aimed to demonstrating analytical and clinical performances as well as now scientific validity[108]. To repeat what is has already been written on this subject, "*in other words, the performance evaluation is where the manufacturer analyzes and assesses the clinical and performance data it collects regarding its IVD, and establishes how its device conforms to the regulations, confirms its performance and its risk-benefit ratio*"[109].

Finally, as regards in particular for IVD class C, the performance evaluation report and the summary of safety and performance shall be updated at least annually with the data obtained from the implementation of the manufacturer's post-market performance follow-up (PMPF) plan[110].

Regarding traceability and transparency, two novelties have been introduced in the Regulation:

- a Unique Device Identification system (UDI)[111] and
- a summary of safety and performance[112], similar to the summary of product characteristics for medicinal products.

The introduction of the UDI system should make it possible to identify and facilitate the traceability of devices, with the exception of those for performance studies[113]. This UDI is "*a series of numeric or alphanumeric characters that is created though internationally accepted device identification and coding standards and that allows unambiguous identification of specific devices on the market*"[114]. It consists of two parts:

- a UDI device identifier (UDI-DI), specific to a manufacturer and to a device;
- a UDI production identifier (UDI-PI), identifying unit of device production and, where appropriate, the packaged devices.

These UDIs shall be placed on the IVDs label and on all higher packaging levels[115]. In addition, prior to placing on the market, the manufacturer must assign them a basic UDI-DI and forward it to the UDI database together with other relevant data elements[116]. Lastly,

[108] Article 56 (3) ; Bird & Bird, *The Changing Face of Medical Devices and In Vitro Diagnostic Medical Devices: White Paper on the New Regulations*, Lexology, February 8 2017 (Internet): http://www.lexology.com/library/detail.aspx?g=7fcb3733-edbd-44f8-a4c2-0fbd270c7f3

[109] Squire Patton Boggs, *EU in vitro Diagnostic Medical Device Regulation Overview Part 3*, Lexology, February 7 2017 (Internet): http://www.lexology.com/library/detail.aspx?g=65dbdec6-c929-4eb3-b5d4-6939ff214a22

[110] Article 56 (6) of the IVDR

[111] See recitals 38, 38 of the IVDR

[112] See recital 45 of the IVDR

[113] Article 24 (1) of the IVDR

[114] Article 2 (15) of the IVDR

[115] Article 24 (4) of the IVDR

[116] Article 26 (1) of the IVDR

the UDI database will be incorporated into the European database on medical devices, Eudamed[117].

The other novelty is the summary of safety and performance. It is requested that, in particular for class C devices other than devices for performance studies, manufacturers produce this summary and the results of the performance evaluation in a document with the purpose of which is to make it available to the public via the Eudamed database[118]. The draft of this summary is also part of the technical documentation of the device submitted to the NB during the conformity assessment and validated by it[119]. A description of the elements contained in this summary is given by the Regulation, which includes at least:

- "*Identification information about the device and the manufacturer;*
- *The intended purpose of the device and its indications et contra-indications;*
- *A description of the device with a reference to any earlier versions and a description of the differences, and descriptions of any accessories or other devices intended to be used with the device;*
- *References to harmonized standards and common specifications;*
- *The summary of the performance evaluation and any relevant information on PMPF;*
- *The metrological traceability of assigned values*
- *Suggested users and user trainings;*
- *Information on any residual risks and undesirable effects, warnings and precautions*"[120].

Once the device is placed on the market, surveillance can start.

In that regard, it is expected that for each device, proportionate to the risk and appropriate for the type of device, a post-market surveillance (PMS) system must be planed, established, documented, implemented, maintained and updated by manufacturers[121]. It is a subsystem of the QMS[122]. As to its function, it must be adapted to actively and systematically gathering, recording, analyzing data about the quality, the performance and the safety of a device throughout its lifetime. It must be adapted to drawing conclusions and to determining, implementing and monitoring any preventive and corrective actions[123]. Finally, the data are used to:

- "*Update the risk-benefit determination for the risk management, the design and manufacturing information, the instructions for use and the labeling;*

[117] Article 30 (2) b) of the IVDR
[118] See recital 45, article 29 (1) of the IVDR
[119] Article 29 (1) al 3 of the IVDR
[120] Squire Patton Boggs, *EU Medical device and IVD Regulations Overview Series – Part 1*, Lexology, January 31 2017 (Internet): http://www.lexology.com/library/detail.aspx?g=2f833f97-f304-4123-a704-47fcb5db329
[121] Article 78 (1) of the IVDR
[122] Squire Patton Boggs, *EU Medical device and IVD Regulations Overview Series – Part 1*, Lexology, January 31 2017 (Internet): http://www.lexology.com/library/detail.aspx?g=2f833f97-f304-4123-a704-47fcb5db329
[123] Article 78 (2) of the IVDR

- *Update the performance evaluation;*
- *Update the summary of safety and performance;*
- *Identify needs for preventive, corrective or field safety corrective action;*
- *Identify options to improve usability, performance and safety of devices;*
- *Contribute to PMS of relevant other devices;*
- *Detect and report trends*"[124].

Furthermore, a periodic safety update report (PSUR) should be prepared. Indeed, in particular for class C devices, manufacturers have to prepare PSURs annually for each device, summarizing the results and conclusion of analyses of the PMS data collected in accordance with the PMS plan. This PSUR must be updated annually and it is a part of the technical documentation for the conformity assessment procedure[125]. Moreover, PSURs must be available to the NB involved in the conformity assessment and to competent authorities on demand[126].

Additionally to this surveillance, a vigilance system is provided in the Regulation with a strengthening of the rules.

Throughout trends reporting, manufacturers report any statistically significant increases in the frequency or severity of non-serious incidents "*that could have a significant impact on the benefit-risk analysis […] and which have led or may lead to unacceptable risks to the health or safety of patients, users or other persons or of any significant increase in expected erroneous results established in comparison to the stated performance of the device*"[127]. More importantly, manufacturers have now formally the obligation to report serious incidents and field safety corrective actions to the relevant competent authorities, and no later than within a period of reporting taking account of the severity the serious incident[128].

With regards to definitions, "*the scope of the definition of 'incident' has broadened*"[129] in the IVDR, including:

- Any malfunction or deterioration in the characteristics or performance of a device made available on the market;
- Any inadequacy in the formation supplied by the manufacturer;

[124] Article 78 (3) of the IVDR ; Squire Patton Boggs, *EU Medical device and IVD Regulations Overview Series – Part 1*, Lexology, January 31 2017 (Internet): http://www.lexology.com/library/detail.aspx?g=2f833f97-f304-4123-a704-47fcb5db329

[125] Article 81 (1) of the IVDR

[126] Article 81 (3) of the IVDR

[127] Article 83 (1) of the IVDR

[128] Article 82 (1) and (2) of the IVDR ; Bird & Bird, *The Changing Face of Medical Devices and In Vitro Diagnostic Medical Devices: White Paper on the New Regulations*, Lexology, February 8 2017 (Internet): http://www.lexology.com/library/detail.aspx?g=7fcb3733-edbd-44f8-a4c2-0fbd270c7f3

[129] Bird & Bird, *The Changing Face of Medical Devices and In Vitro Diagnostic Medical Devices: White Paper on the New Regulations*, Lexology, February 8 2017 (Internet): http://www.lexology.com/library/detail.aspx?g=7fcb3733-edbd-44f8-a4c2-0fbd270c7f3

- Any harms as a consequence of a medical decision, action taken or not taken on the basis of information or result(s) provided by the device[130].

And a 'serious incident' is defined as "*any incident that directly or indirectly led, might led or might lead to:*

(a) The death of a patient, user or other person,

(b) The temporary or permanent serious deterioration of a patient's, user's or other person's state of health,

(c) A serious public health threat"[131].

Then, any information concerning a serious incident or a field safety corrective action has been or is to be undertaken within their territory will be evaluated centrally at national level by the competent authority, if possible together with the manufacturer, and, where relevant, the NB concerned[132].

Lastly, for IVDs presenting an unacceptable risk to health and safety, the competent authorities must require without delay the manufacturer to take all appropriate and duly justified corrective actions to bring the device into compliance, to restrict the making available of the device on the market, to withdraw or to recall it from the market, in manner proportionate to the nature of the risk[133]; knowing that the risk is defined as "*the combination of the probability of occurrence of harm and the severity of that harm*"[134]. But, in the case where the IVD is non-compliant but does not present an unacceptable risk to health or safety of persons, the competent authorities must require the relevant economic operator to bring the non-compliance concerned to an end within a reasonable period defined and communicated to the economic operator and proportionate to the non-compliance[135]. In case non-compliance is not ended within this period, the Member State concerned must take all appropriate measures to restrict or prohibit the IVD being made available on the market or to ensure that it is recalled or withdraw from the market[136].

In terms of compliance, another innovation introduced by the IVDR is the person responsible for regulatory compliance.

Indeed, manufacturers must have available in their organization a person responsible for regulatory compliance possessing requisite expertise in the field of IVD, such as:

- Any document related to university studies and one year of professional experience in regulatory affairs or in quality management systems relating in IVD;

[130] Article 2 (67) of the IVDR
[131] Article 2 (68) of the IVDR
[132] Article 84 (2) of the IVDR.
[133] Article 90 of the IVDR
[134] Article 2 (16) of the IVDR
[135] Article 92 (1) of the IVDR
[136] Article 92 (2) of the IVDR ; Bird & Bird, *The Changing Face of Medical Devices and In Vitro Diagnostic Medical Devices: White Paper on the New Regulations*, Lexology, February 8 2017 (Internet): http://www.lexology.com/library/detail.aspx?g=7fcb3733-edbd-44f8-a4c2-0fbd270c7f3

- Or four years of professional experience in regulatory affairs or in quality management systems relating in IVD[137].

For micro and small enterprises, they are not required to have this person in their organization but must have such person permanently and continuously at their disposal[138]. The duties of this person are to ensure that:

- The conformity of the devices is appropriately checked, in accordance with the QMS under which the devices are manufactured, before a device is released;
- The technical documentation and the EU declaration of conformity are drawn up and kept up-to-date;
- The PMS obligations are complied;
- The reporting obligations in terms of vigilance are fulfilled, […][139]

Furthermore, as for the EU database on clinical trials, similar changes are foreseen for the European database on medical devices in the Medical Devices Regulation (MDR): Eudamed. This database also includes IVDs.

This is set up by the Commission after consulting the Medical Devices Coordination Group (MDCG)[140]. Several electronic systems will be included in Eudamed, such as:

- The electronic system for registration of devices;
- The UDI-database;
- The electronic system on registration of economic operators;
- The electronic system on NB and on certificates;
- The electronic system on clinical investigations;
- The electronic system on vigilance and post-market surveillance;
- The electronic system on market surveillance[141].

Then, information may be submitted into Eudamed by the Member States, NB, economic operators and sponsors[142]. All those information must be accessible to the Member States and the Commission. For NB, economic operators, sponsors and the public, information is accessible to the extent specified in the provisions[143]. It contains "*personal data only insofar as necessary for the electronic system*"[144], in respect of the data subject rights in accordance with the Directive 95/46/EC, replaced by the GDPR.

Regarding its functionality[145], the Commission has to draw up a plan for the implementation of Eudamed's specifications by 26 May 2018. There is the necessity of an independent audit

[137] Article 15 (1) of the IVDR
[138] Article 15 (2) of the IVDR
[139] Article 15 (3) of the IVDR
[140] Article 33 (1) of the MDR
[141] Article 33 (2) of the MDR
[142] Article 33 (4) of the MDR
[143] Article 33 (5) of the MDR
[144] Article 33 (6) of the MDR
[145] See article 34 of the MDR

report about the full-functionality and functional specification of Eudamed before the verification about it by the Commission. Then, the Commission will inform the MDCG "*when it has verified that Eudamed has achieved full functionality and Eudamed meets the functional specifications drawn up*". It is only after the consultation with the MDCG and the independent audit report and verifications that the Commission will have to publish a notice about this confirmation in the *Official Journal of the European Union*. Here, we find the same thing as what is provided for the CTR.

To conclude this part, a few words on the transitional provisions and the dates of entry into force and of application.
Transitional provisions[146] are notably provided for NB notifications, certificates issues by NB, concerning conformity assessment bodies and IVDs of class D subject to the conformity assessment procedure; but also the authorizations granted the competent authorities of the Member States and the issuing entities when the rules of the previous Directive 98/79/EC are complied with.
Lastly, the IVDR shall apply from 26 may 2022[147]. But, several articles will be applied gradually. Indeed, derogations[148] are provided for in the Regulation, for example:

- As concerns to the electronic system of economic operators and certificates of conformity, the relevant provisions shall apply from 27 November 2023;
- The NB provisions will apply from 26 November 2017;
- Cooperation will apply from 26 May 2018;
- The provisions on the EU reference laboratories will apply from 25 November 2020;
- For class C and D IVDs, the affixing of the UDI will start from 26 May 2017.

For the Eudamed database, if not fully functional on 26 May 2022 (date of application of the Regulation), "*the obligations and requirements relating thereto shall apply from the date corresponding to six months after the date of publication of the notice*" by the Commission and the corresponding provisions of the previous Directive continue to apply pending[149].

To conclude, the question arises of how the IVDR and their requirements could have an effect on the U-PGx project. This would be the case if new PGx tests were developed and/or placed on the market by the test providers used in the project and in the clinical study PREPARE. This could also be the case if changes in the characteristics of the PGx tests used in the project are made. Therefore, manufacturers providing these PGx tests should begin to comply with all the procedures and requirements described above.

[146] See article 110 of the IVDR
[147] Article 113 (2) of the IVDR
[148] See article 113 (3) (a) to (e) of the IVDR
[149] Article 113 (3) (f) of the IVDR

Conclusion

Beyond scientific challenges, U-PGx has to respond to ethical issues raised by the aim of the U-PGx project and comply with European standards and requirements.

Although guidelines in the purely pharmacogenomic field are still rare today, the ethical rules of good pharmacogenomic practice can be compared with standards and practices in more general fields of genetics and genomics.
The study of ELSI issues ultimately show the importance of putting the patient at the centre of the genomic process and including it in the decision-making about the tests in which it participates and its consequences (especially on the processing of its personal data).
This decision-making must be guided in advance by informed consent. Informed consent should therefore try to anticipate all future problems for patients, physicians, people who will analyze and store data from a legal, social and financial and technical point of view.
However, the process of collecting informed consent is already lengthy and cumbersome, which is why it must be adapted according to these considerations. One solution could be the relationship between the physician-researcher and his patient and improved cooperation between all parties should be systematically sought.

In terms of compliance with European regulations, three regulations in particular were relevant to be developed within the framework of this deliverable: the Clinical Trials Regulation (CTR); the General Data Protection Regulation (GDPR) and the *in vitro diagnostic* medical devices Regulation (IVDR).
Thus, in the light of the analysis that has been carried out, the project and the planned clinical study PREPARE should follow the requirements imposed by the regulations, in particular with regard to the GDPR and should follow the procedures for monitoring and data to be produced in the CTR when it will be applicable since the clinical study will still be ongoing. Moreover, for the CTR, the purpose was to review the relevant elements of these regulations for possible future projects in pharmacogenomic and PGx testing. Lastly, in particular for the new IVDR published during the project, an overview had to be made and was made on the relevant elements and innovations introduced concerning PGx and companion diagnostics which are now clearly integrated into the scope of this European regulation. And if new PGx tests were to be developed and put on the market during the project, manufacturers would have to start following the procedures described earlier and which were strengthened in this Regulation.

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ANNEX 1

OBTAINING INFORMED CONSENT: ESSENTIAL INFORMATION FOR PROSPECTIVE RESEARCH PARTICIPANTS

Before requesting an individual's consent to participate in research, the researcher must provide the following information, in language or another form of communication that the individual can understand (see also Guideline 9):

1. the purpose of the research, its methods, the procedures to be carried out by the researcher and the participant, and an explanation of how the research differs from routine medical care (Guideline 9);

2. that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary (Guideline 9);

3. that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled (Guideline 9);

4. the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it;

5. whether money or other forms of material goods will be provided in return for the individual's participation, and, if so, the kind and amount, and that the time spent on the research and other inconveniences resulting from study participation will be appropriately compensated, monetary or non-monetary (Guideline 13);

6. that, after the completion of the study, participants will be informed of the outcomes of the research in general, if they so wish;

7. that individual participants during or after a study or collection of their biological material and health-related data will be informed of life-saving information and data of immediate clinical utility involving a significant health problem (see also Guideline 11);

8. that unsolicited findings will be disclosed if they occur (Guideline 11);

9. that participants have the right of access to their clinically relevant data obtained during a study on demand (unless the research ethics committee has approved temporary or permanent non-disclosure of data, in which case the participant should be informed of, and given, the reasons for such non-disclosure);

10. pain and discomfort of experimental interventions, known risks and possible hazards, to the individual (or others) associated with participation in the research, including risks to the health or well-being of a participant's direct relatives (Guideline 4);

11. the potential clinical benefits, if any, expected to result to participants from participating in the research (Guidelines 4 and 9);

12. the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge (Guideline 1);

13. how the transition to care after research is arranged and to what extent they will be able to receive beneficial study interventions post-trial and whether they will be expected to pay for them (Guidelines 6 and 9);

14. the risks of receiving unregistered interventions if they receive continued access to a study intervention before regulatory approval (Guideline 6);

15. any currently available alternative interventions or courses of treatment;

16. new information that may have come to light, either from the study itself or other sources (Guideline 9);

17. the provisions that will be made to ensure respect for the privacy of participants, and for the confidentiality of records in which participants are identified (Guidelines 11 and 22);

18. the limits, legal or other, to the researchers' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality (Guidelines 12 and 22);

19. the sponsors of the research, the institutional affiliation of the researchers, and the nature and sources of funding for the research, and, when they exist, any conflicts of interest of researchers, research institutions and research ethics committees and how these conflicts will be managed (Guidelines 9 and 25);

20. whether the researcher is serving only as a researcher or as both researcher and the participant`s physician (Guideline 9);

21. the extent of the researcher's responsibility to provide care for participants' health needs during and after the research (Guideline 6);

22. that treatment and rehabilitation will be provided free of charge for specified types of research-related injury or for complications associated with the research, the nature and duration of such care, the name of the medical service or organization that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment (Guideline 14);

23. in what way, and by what organization, the participant or the participant's family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation) (Guideline 14);

24. whether or not, in the country in which the prospective participant is invited to participate in research, the right to compensation is legally guaranteed;

25. that a research ethics committee has approved or cleared the research protocol (Guideline 23);

26. that they will be informed in case of protocol violations and how safety and welfare will be protected in such a case (Guideline 23). In specific cases, before requesting an individual's consent to participate in research, the researcher must provide the following information, in language or another form of communication that the individual can understand:

1. for controlled trials, an explanation of features of the research design (e.g., randomization, double-blinding), that the participant will not be told of the assigned treatment until the study has been completed and the blind has been broken;

2. whether all essential information is disclosed and, if not, that they are asked to agree to receiving incomplete information and that full information will be provided before study results are analysed and participants are given the possibility to withdraw their data collected under the study (Guideline 10);

3. policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a participant's genetic tests to immediate family relatives or to others (e.g. insurance companies or employers)

without the consent of the participant (Guideline 11);

4. the possible research uses, direct or secondary, of the participant`s medical records and of biological specimens taken in the course of clinical care;

5. for collection, storage and use of biological material and health-related data, that broad informed consent will be obtained, which should specify: the purpose of the biobank, the conditions and duration of storage; the rules of access to the biobank; the ways in which the donor can contact the biobank custodian and can remain informed about future use; the foreseeable uses of the materials, whether limited to an already fully defined study or extending to a number of wholly or partially undefined studies; the intended goal of such use, whether only for research, basic or applied, or also for commercial purposes, and whether the participant will receive monetary or other benefits from the development of commercial products developed from their biological specimens; the possibility of unsolicited findings and how they will be dealt with; the safeguards that will be taken to protect confidentiality as well as their limitations, whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, that participants have the right to decide about such future use, to refuse storage, and to have the material destroyed (Guidelines 11 and 12);

6. when women of childbearing potential are participating in health-related research, information about the possible risks, if they become pregnant during the research, to themselves (including future fertility), their pregnancies, their fetuses, and their future offspring; and the guaranteed access to a pregnancy test, to effective contraceptive methods and to safe, legal abortion before exposure to a potential teratogenic or mutagenic intervention. When effective contraception and/or safe abortion are not available and alternative study sites are not feasible, the women must be given information about: the risk of unintended pregnancy; the legal grounds for abortion; reducing harms from unsafe abortion and subsequent complications; and, when pregnancy is not terminated, the guarantee for a medical follow-up for their own health and that of the infant and child and the information that it is often difficult to determine causality in cases of foetal or infant

abnormalities (Guidelines 18 and 19);

7. when concerning pregnant and breastfeeding women, the risks of participation in health-related research to themselves, their pregnancies, their fetuses, and their future offspring, what has been done to maximize potential individual benefits and minimize risks, that evidence concerning risks may be unknown or controversial, and that it is often difficult to determine causality in cases of fetal or infant abnormalities (Guidelines 4 and 19);

8. when concerning disaster victims who mostly are under duress, the difference between research and humanitarian aid (Guideline 20); and

9. when research is done in the online environment and using online or digital tools that may involve potentially vulnerable persons, information about the privacy and security controls that will be used to protect their data; and the limitations of the measures used and the risks that may remain despite the safeguards put in place (Guideline 2).