EXPLANATORY INFORMATION

Key words: Patient and Healthcare Data, Big Data, Study Participant Rights, Informed Consent, Minimal Data Privacy Wording, Explanatory Information

I- INTRODUCTION

This Explanatory Information is intended for sponsors, study sites and other interested stakeholders in the healthcare system who deal with Informed Consent Forms (ICFs). Specifically, it is aimed at stakeholders who use the ICFs for clinical studies in a drug development programme as well as for study participants' optional participation in future scientific research. Developed as part of a public private collaboration, the IMI2 BD4BO DO→IT consortium, this Explanatory Information introduces and facilitates the implementation of personal data protection law subject to the European General Data Protection Regulation (2016/679, GDPR). It is intended to be read alongside the corresponding informed consent templates that were also developed by the DO→IT consortium.

DO→IT is the Coordination and Support Action (CSA) of the Innovative Medicines Initiative's (IMI) "Big Data for Better Outcomes" (BD4BO) programme. For more information see http://bd4bo.eu/. DO→IT is a multidisciplinary European consortium uniting the pharmaceutical industry, academic research institutions and patient organisations.

DO→IT has developed model data privacy provisions for ICFs. These enable the use of study participants' health data and biosamples while respecting the rights of study participants as data subjects. These standard provisions were discussed with leading stakeholders including representatives of several European data protection authorities and ethics committees as well as from the user community throughout Europe. The objective is to enhance health research based on (big) data, while maintaining high ethical and personal data protection standards.

These materials might not necessarily reflect the position that each one of the members of the consortium might take individually in the context of their business operations and activities in each jurisdiction. As a result, the standards elaborated in the ICF templates are not mandatory; they might be used in full or in part, as it is or adapted to the materials already in place in the different companies and to local requirements.

Due to the current scenario regarding the interpretation that the relevant stakeholders in the EU Member States have on the application of the GDPR and the legal framework for conducting further research activities in the EU, the consortium understands that the

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competent authorities might provide further guidance in the following months. In this sense, the members of the consortium shall continue their activity and explore the different options that the applicable legislation might provide in order to conduct research activities in a consistent manner in the territory of the European Economic Area.

Additionally, the development of complementary operational guidance is being evaluated by some WP4 member organisations.

Study participant data: scientific opportunity and study participant information & consent

Study participants' data are of major relevance to address scientific questions in health-related research and drug development. There is already a considerable amount of patient and healthcare data available with much more on the horizon. These data have the potential to transform health-related research and healthcare across the entire pathway for every stakeholder, with the ultimate outcome of improved patient care and value.

Study participants' data are regularly collected in clinical studies under Ethics Committee/Institutional Review Board approved clinical study protocols and Informed Consents. Although originally collected to answer questions defined in the clinical study protocol, they also have the potential to accelerate general scientific progress. They enable an innovative and powerful approach to answer current and future scientific questions in pharmaceutical-based research and development, in the academic environment and in the field of public health. They may also release new opportunities in biomedical research.

Introduction to the data privacy background

The GDPR is the latest legal instrument enforcing privacy. It has replaced the EU Data Protection Directive 95/46/EC which failed to regulate its heterogeneous implementation in the EU Member States.

The GDPR refers to the protection of natural persons whose personal data are processed. The principles set out in this regulation are considered to be fundamental rights originating from the protection of privacy. The concept of privacy implies the right for individuals "to determine when, how and to what extent information about them is communicated to others" (Alan Westin, Privacy and Freedom, 1967). The right to privacy is largely recognised in international, European and national laws. This issue is particularly noteworthy today because of technological development and the desire to use health databases for health research.

Specific sections of the GDPR are related to the use of personal data in health and research. Health and genetic data are considered to be sensitive data. By principle, it is forbidden to process them unless strict conditions are respected. Thus, there is a need to establish good practice standards for researchers in the processing of these sensitive data in order to operationalise the GDPR requirements. Another issue is raised by the multiplicity of the legal instruments when using health data in clinical research where compliance with the Clinical Trial Regulation (CTR)[1] should be also demonstrated.

[1] The Clinical Trial Regulation was adopted and entered into force in 2014 but is not yet applicable. The timing of its application depends on confirmation of full functionality of the Clinical Trials Information System through an independent audit. Work is in progress and the European Medicines Agency provide regular updates.

II- FORMAT

In order to limit the length of the ICF, information that was identified as essential for study participants has been put in the core part of the ICF while additional information is provided in Part 4 “Additional Information for Patients”, section “5. *Additional guidance to know more about the confidentiality of your data and biosamples*”.

1. The place of “data privacy“ provisions in an ICF

The ICF template only focuses on personal data protection. The model data privacy provisions parts are integrated as follows:

- Part 1 “Study Information” focusing on the use of data and biosamples to conduct the drug development programme, addressed in sections 11 to 14 of Part 1;
- Part 2 “Future Research Information” focusing on the use of data and biosamples to conduct future research;
- Part 3 “Consent Form” focusing on how to refer to the information of personal data protection in the consent to participate in the clinical study; and
- Part 4 “Additional Information for Patients”, especially section “*5. Additional guidance to know more about the confidentiality of your data and biosamples*”. This section explains how data and biosamples are used. The background of this section is article 13 of the GDPR.

2. Plain language

The ICF template uses clear and plain language that is easily understandable by the average person.

The ICF template refers to “data” as a general term when all data types are addressed or when no single type of data is specified. Instead of using “pseudonymous data”, which would be the legally correct term, the ICF template refers to “coded data” which is easier for study participants to understand. In addition, the terms “fully identifiable data” and “anonymised data” are used in order to be very clear. The use of these terms follows the recommendations of the patients’ focus groups.

3. Drawings

In order to make the ICF template more understandable, and as requested by patients’ focus group, drawings were added to explain some technical issues. The drawings explain coding and anonymisation of data and to whom these data could be shared.

III- CONTENT

1. Scope

The ICF language is based on the GDPR as it is now fully applicable. However, the GDPR enables the Member States to further regulate the processing of health-related data and to limit some of the data subject rights. This means the ICF template cannot reflect all the additional requirements implemented in Member States' or other countries laws.

The ICF covers the use of data and biosamples during the study and for future research. However, local regulations on biosamples and genetic data may exist in a given Member State and impose different or additional requirements.

Therefore, before its use, the ICF template must be reviewed according to any local GDPR implementation laws as well as local biosamples laws and further applicable local law.

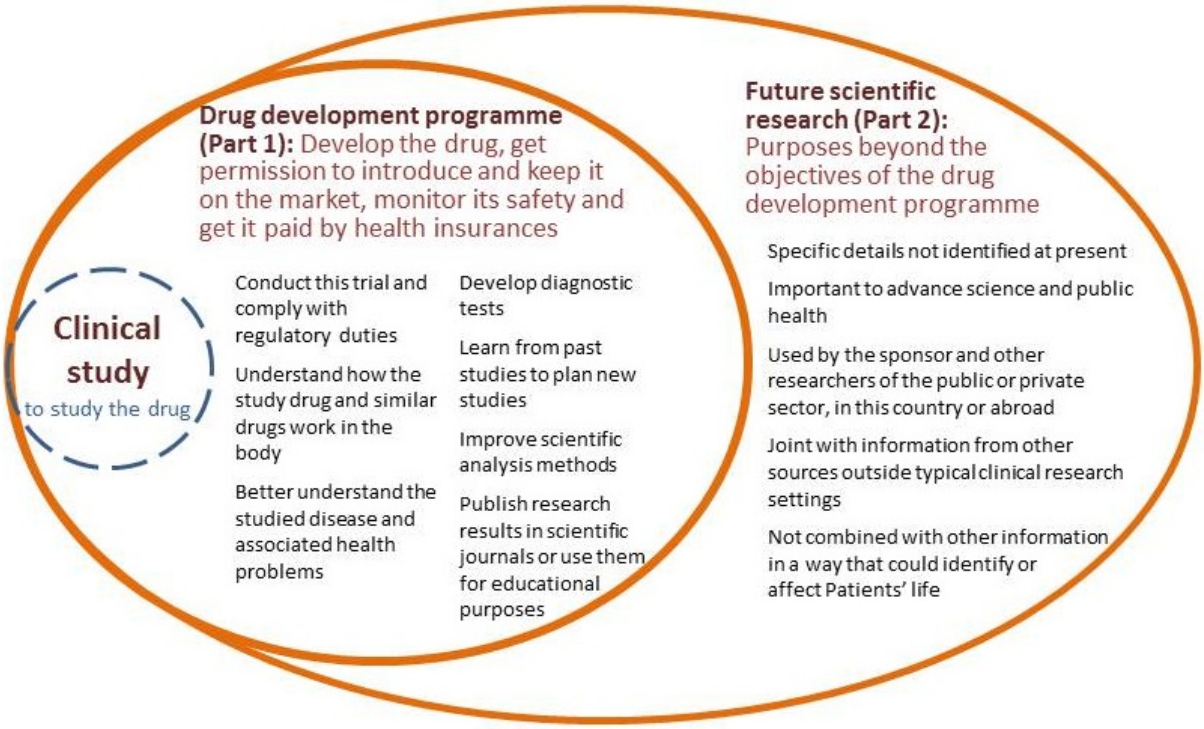
2. Primary use

Biotech's and Pharmaceutical companies' core business is to bring innovative medicinal products that improve the health or well-being of patients to the market. When these products qualify as a regulated drug, they must be tested to demonstrate that they are safe and efficacious for human use. This must be done through clinical studies in accordance with applicable regulations. For example within the EU these are the Clinical Trials Directive 2001/20/EC and soon the Clinical Trial Regulation 536/2014. Each clinical study is only one part of a drug development programme.

In addition to the use of study participants' data in such clinical studies, health authorities, social security and health insurance organisations ask for a drug's safety and/or efficacy evidence based on a series of studies in order to negotiate the cost of the medicinal product. Increasingly, the development of companion diagnostic tests is required in order to treat the correct patient population. Furthermore, continuous improvement of clinical study design and analysis methods is needed in the interest of safe and efficient clinical studies. Overall, in order to bring a specific therapy to the patient, the focus should be on a class of similar compounds instead of a single compound and on the mode of action instead of a single disease.

Therefore, clinical data is increasingly used not in a single study, but in the complete drug development programme. For transparency reasons, sponsors must inform the study participants that their coded data will likely be used and re-used for the complete drug development programme. For a global overview see the diagram below.

This is nothing new; it has been included in section 11.b. of the ICF template to enhance transparency for study participants.



3. Coding personal data

The coding process is one of the most important safeguards of study participant privacy which are enforced by the Good Clinical Practice standard. Coding is also one of the most important safeguards referred to in the GDPR. The description in the wording and in the drawing of Part 1, section 11.c of the ICF may vary by clinical study and must be tailored to the actual process followed.

Coding determines who can access which information and for which purposes, as summarised below:

Which data	**Who can access the data (categories of recipients)**	**For which purposes**	
		Primary uses (drug development programme)	**Secondary uses (future research)**
Directly identifiable data (non-coded data) such as data including the name of the study participant	Study doctor and team	To conduct the study, which includes contacting the study participant about the study; reimbursing him/her where applicable; and following-up on his/her health status if the study team is unable to contact him/her	N/A

Which data	Who can access the data (categories of recipients)	For which purposes	
		Primary uses (drug development programme)	**Secondary uses (future research)**
	Study doctor and team Monitors acting on behalf of sponsor (bound by confidentiality duties, in particular, vis-à-vis the sponsor) Health authorities and ethics committees	To check that the study is carried out as required by law	
Coded data	Sponsor (including its representatives, vendors and successors in law) and its research partners	To conduct the study and the drug development programme To publish summaries of study results where the study participants' identity will never be disclosed	To conduct future research
	Sponsor (including its representatives, vendors and successors in law) and its research partners, health authorities and ethics committees	To comply with relevant regulatory duties	

In addition to the above, third parties providing additional services for study participants in line with the study protocol and/or study participants' consent might receive a limited set of directly identifiable data. Services which are necessary for the protocol will be listed in the beginning of Section 11.d.1 of the ICF. Optional services will be listed in the second part of Section 11.d.1. The Sponsor must ensure that these third parties are obliged to confidentiality. Furthermore the third parties must follow the instructions of the study site.

Regarding the data recipients, the GDPR enables to only refer to the categories of recipients rather than to provide their specific name or identity. Data processors, such as Contract Research Organisations (CROs) or monitors, may change from time to time without any detriment to the individual's rights or protection. If, despite the above, the CRO details are included, it is recommended to add it in Part 4, section 5 and not in the ICF body (part 1).

4. Data and biosamples retention

4.1. Data

The GDPR includes a storage limitation principle. This requires personal data to be stored for the minimum amount of time. Study participants should be informed about the length of the storage period or, if that is not possible, the criteria used to determine the period. The latter applies to future scientific research purposes and will be accompanied by appropriate safeguards as well as technical and organisational measures.

More precisely, the CTR requires the sponsor and the investigator to archive the content of the clinical study master file for 25 years after the end of the clinical study. However, regulations of countries outside the EU may impose a longer retention period. Therefore, as the coded data collected in all countries form one unique dataset, all the coded data must be kept for the length of the longest mandatory retention period. This is because deleting the data after 25 years would impair the marketing authorisation in countries that require a longer retention period.

In connection with this retention period, there is a restriction on the possibility of deleting study data. This restriction applies irrespective of the legal basis for the processing of personal data and even if the study participant stops participating in the study.

These are the reasons:

- Good Clinical Practice: The need to retain data that has already been collected is essential to guarantee the integrity of the study and assess the quality of the study results. This is the reason why all relevant clinical and research guidelines impose data retention for the following reasons:
  - To ensure and document the sponsor's requirements for completeness, accuracy, reliability, and consistent intended performance, in view of the potential to affect human subject protection and the reliability of study results.
  - To ensure that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).
  - To maintain adequate backup of the data.
- Legal retention periods: Delete an adverse event that arose during a clinical study or being unable to link an adverse event to a study participant from a specific study could put the study participant's health at risk and violate pharmacovigilance legal duties.
- Scientific research objectives: The GDPR specifies that data should not be deleted when the deletion would seriously impair the objectives of scientific research.

In other cases, the data will be deleted or anonymised. However, anonymisation depends on the state of the art of technology. In so far as the term anonymisation is used herein, it refers to the definition or specifications of the European Medicines Agency. If the sponsor keeps study participants data after their anonymisation, it may continue to use them for any purpose, as permitted by applicable law.

4.2. Biosamples

The retention period for biosamples will be governed by the biosamples (local) regulations that are applicable to biosamples if any exist.

5. Individuals' rights

Providing information to study participants before obtaining their consent is essential for them to make informed decisions, understand what they are agreeing to, and exercise their rights. The ICF template provides information about:

- the purposes of the personal data processing, the categories of data that will be used, and the recipients or categories of recipients of the personal data
- the period during which the personal data will be stored, or if that is not possible, the criteria used to determine the period
- the identity and contact details of the sponsor who is the data controller for at least part of the data. Where applicable the same information about the sponsor's representative will be provided
- the contact details of the data protection officer
- the fact that the sponsor intends to transfer personal data to a third country or international organisation, with reference to appropriate safeguards to protect the data
- where to find information about the summary results of the clinical study
- study participants' rights.

In addition, when the sponsor of the study is located within the EU, the local ICF must comply with the GDPR, i.e. all the elements mentioned above must be provided in a non-EU local ICF as well.

Incidental findings with an impact for study participants' health could arise during the clinical study of the drug development programme. There are no legal rules concerning the communication of these incidental findings, only several important recommendations. Despite this, information about whether and how incidental findings will be communicated should be provided in the research protocol and the original information given to study participants before obtaining consent. Study participants should be able to decide to know or not to know about these findings. Good practice would be to ask study participants if they still consent once results are available. In some countries, genetic counselling may be required by law when genetic research results are provided to study participants.

Study participants will be given adequate time to read the ICF and decide if they will participate in the study. The study participants should give their consent freely and in an unambiguous manner. The consent must be obtained before the study participant is included in the study and data is collected or processed.

In addition, for the consent to be truly "freely given", there should not be a clear imbalance of power between the potential study participant and the individual collecting the consent. This issue may arise when the researcher is also the treating physician of the study participant. If the study participant is considered to be dependent on the person requesting consent to the

extent that he/she may feel pressure to give consent, it is recommended that alternative staff organises the consent process. This also depends on the law of the Member State.

Personal data protection rights can be limited by (i) specific GDPR provisions on scientific research; (ii) local GDPR implementation acts; or (iii) as a result of the applicable legal basis that applies to the processing activity in questions, as shown in the following table:

Personal data protection rights according to the GDPR in general	**GDPR limitations linked to scientific research**	**Limitations to personal data protection rights according to GDPR in other laws**	
		Good Clinical Practice or other laws (e.g. safety laws)	**Local GDPR laws**
Access (Art. 15)	No restriction	Must be postponed to the end of the study if placebo is used. Scope limited to (i) medical records; and (ii) information that is relevant to life threatening and actionable information	Could be restricted/clarified by Member States (Art. 89 (2))
Correction (Art. 16)	No restriction	Errors must be corrected as soon as identified in accordance with GCP	
Portability (Art. 20)	Only applicable if processing based on consent or contract	Same limitations as access rights.	
Objection (Art. 21)	Only applicable if processing based on legitimate interests (Art. 21(1) GDPR) Not applicable where processing for scientific research purposes is considered necessary for reasons of public interest (Art.21(6) GDPR)	Not applicable: preservation of the integrity of the data set or legal retention duties (e.g. clinical study and safety)	
Restriction (Art. 18)	No restriction		
Withdrawal (Art. 7)	Only applicable if processing based on consent		Member States cannot further regulate on this matter
Deletion (Art. 17)	Not applicable (Art. 17.3.b) and d) GDPR)		Member States cannot further regulate on this matter

To simplify the ICF, the main body (Part 1) of the template refers broadly to the rights of study participants and signposts them to their study doctor for further information. Part 4, section 5 of the template goes into further detail about the rights that apply in each jurisdiction. The appropriate legal basis should be addressed in this section.

The study participant also has the right to complain to a Data Protection Authority (DPA). Part 4, section 5 of the ICF template includes an official link to the details of all DPAs in the EU. This is provided for two reasons: (i) to ensure that the same ICF template is used in a pan-European study; and (ii) to provide the most protective approach to the study participant. For instance, if the sponsor is located in the US, named a representative in Germany (as per art. 27(3) GDPR) and conducted a clinical study in a Spanish site, it would make the most sense for study participants to contact a Spanish DPA with any queries.

6. Control over the data

According to the CTR and several local laws related to clinical studies, the sponsor is the data controller if it determines the purposes and means of the personal data processing. Even if data processing is fully outsourced to a third-party such as a CRO, the sponsor remains the data controller while the CRO is a data processor.

The situation is more complex regarding study sites. Because the study site is the data controller of the data collected within healthcare framework and is also subject to specific obligations within clinical studies, it is difficult to consider it as a regular processor. One option is to consider the site a controller of the clinical data as long as the data are directly identifiable, and the sponsor (when different from the site) the controller of the coded data. However, other opinions on controllership in the frame of clinical studies exist.

In view of the above, it was decided that instead of labelling the parties as data controllers or data processors, their names and contact details would be provided in section "*5. Additional guidance to know more about the confidentiality of your data and biosamples*". Part. 4, section 5 also refers to the following related information:

- The legal representative when the controller is located outside the EU.
- The DPO details. Irrespective of the discussion regarding the site is or not a data controller, it must have appointed a DPO, who will be the person (jointly with the principal investigator) better placed to provide a useful answer to the study participant regarding his/her personal data protection rights (rather than the sponsor's DPO, who may only access to coded data).

7. Legal basis

7.1. Legal basis to conduct the drug development programme

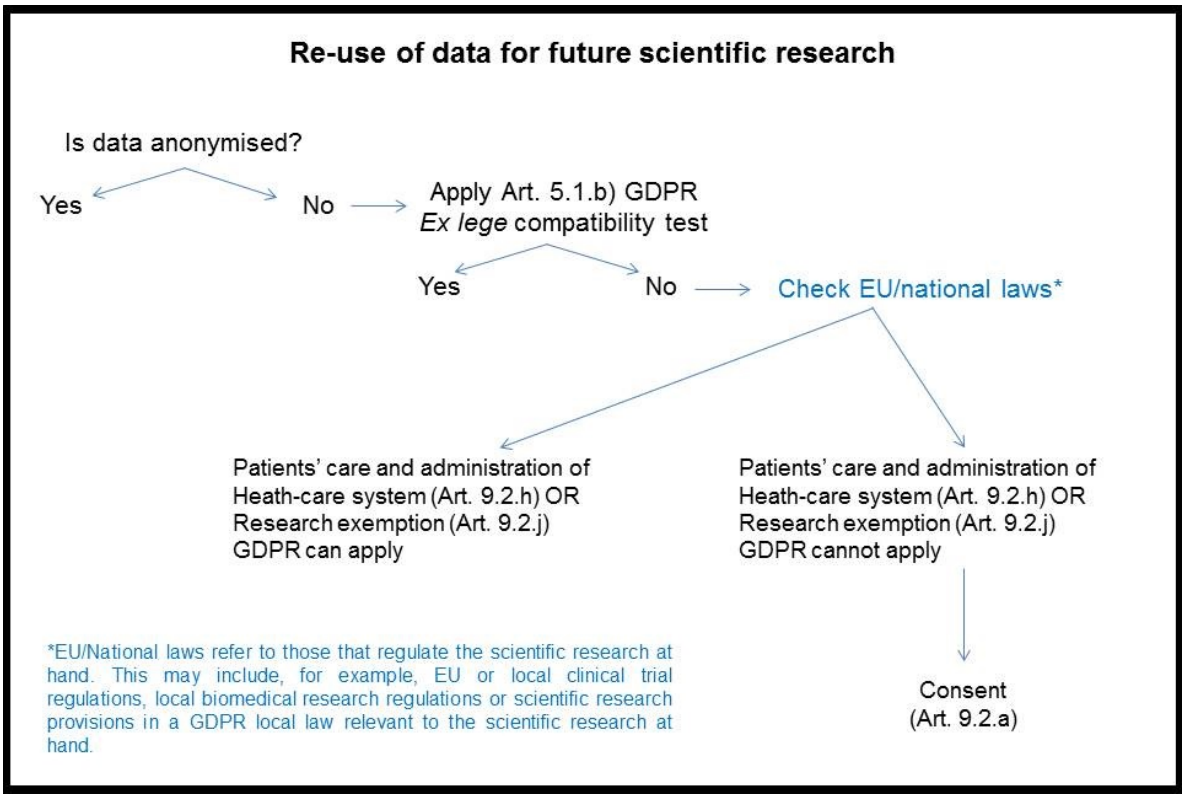
Consent to participate in a clinical study is required according to applicable regulations governing clinical studies.

However, different stakeholders (e.g. Health authorities, Ethics Committees and DPAs) have not yet agreed on a uniform legal basis for the processing of personal data to conduct a clinical study, informed by the GDPR.

As a result, the ICF template does not mention GDPR article. Instead, it describes the main concepts behind the different legal bases that may apply. It also uses a single "tick box"/ signature which study participants use to consent to participate in the whole drug development programme including the processing of personal data. This topic is covered in section "5. *Additional guidance to know more about the confidentiality of your data and biosamples*".

7.2. Legal basis to conduct future scientific research using data

Under the GDPR different alternatives are available regarding the use of the data already collected in the clinical trial for further scientific research uses (beyond the drug development program). In view of current discussions among different stakeholders on the legal basis, the following decision tree could provide guidance on how to proceed:



- *7.2.1. Future scientific research based on consent: ICF*

Part 2 of the ICF template is drafted under the assumption that the sponsor chooses to rely on the study participant's consent as the legal basis for both types of future research projects. These types are research using (i) only data and (ii) biosamples and associated data. This will be included in ICFs for all studies.

The ICF template contains a broad definition of future scientific research. This is compatible with Recital 33 of the GDPR and has not been challenged by the involved stakeholders who provided feedback about the ICF template. In particular, it was discussed that it is appropriate not to limit consent for future research to a specific disease. Instead, it should rather refer to diagnosis, prevention and treatment on health. In addition, it is important to be transparent. For this reason, general information about future research must be accessible to study participants in a manner that they understand the use of their data and biosamples.

- ***7.2.2 Future scientific research based on an alternative GDPR legal basis***

Regarding future scientific research, the proposed ICF includes the most conservative approach. This approach is based on consent, which was accepted by the stakeholders who provided feedback about the template because there were some uncertainties among the different countries regarding how to apply the *ex lege* compatibility test and which national/EU laws would be applicable in each potential scientific research scenario.

However, the GDPR includes the *ex lege* compatibility test and the research exemption outlined in the (Art. 9.2 j) GDPR, which could be coupled with legitimate interests (Art. 6.1f)). The question of the appropriate legal basis is currently under review by the European Data Protection Board (EDPB) following a questionnaire submitted by the Commission (DG-Santé), which also refers to the interplay between the GDPR and the CTR since Art. 28(2) could contradict the GDPR. This is why this Explanatory Information also contains an alternative approach to the use of coded data for future scientific research based on EU or local law and applying appropriate safeguards, which may include (see Appendix 1):

- Limiting access to the coded data to specific individuals subject to confidentiality obligations including the obligation to not attempt to re-identify individuals/ decode the clinical data.
- Protecting the coded data with security measures to avoid data alteration, loss and unauthorised access. In case something wrong would happen, study participants must be promptly informed about any problems that may occur, what it means for them and what is being done to address it.
- Applying a data protection impact assessment (DPIA) to identify and mitigate privacy risks, if any, associated with the scientific research.
- Ensuring that, when required by applicable law, scientific research is subject to the approval of Ethics Committees.
- Making sure that the coded data is not shared for direct marketing purposes or other purposes that are not legal duties or are not considered scientific research according to the applicable personal data protection legislation. In particular, it will not be used to make decisions about future services such as insurance.

7.3. Future scientific research regarding biosamples

National biosamples laws may apply which should be consistent with the spirit of the GDPR and adequately protect personal data. As a general rule, certain local laws require consent to use biosamples but they do not necessarily require that the consent is particularly specific. If local laws have a different approach as to the legal basis for future processing of samples and related or derived data, stating further conditions or limitations, the ICF template would need to be revised accordingly.

IV- APPENDIX 1

It has also developed an alternative version of the ICF providing possibility to use coded data for future research based on EU or local law and applying appropriate safeguards; i.e. using the specific *ex lege* compatibility test for the re-use of data for scientific research and the research exemption as the legal basis (instead of consent). This alternative ICF version is attached as Appendix 1 to this Explanatory Information and has the following structure:

- Part 1 “Study Information”, regarding the use of data and biosamples to conduct the drug development programme, addressed in sections 11 to 14 of Part 1, which includes the use of data for future scientific research;
- Part 2 “Future research information regarding the use of your biosamples”, in order to conduct future research;
- Part 3 “Consent Form”, regarding how to refer to the information of personal data protection in the consent to participate in the clinical study;
- Part 4 “Additional Information for Patients”, using section “*5. Additional guidance to know more about the confidentiality of your data and biosamples*”. This section explains how data and biosamples are used. The background of this section is article 13 of the GDPR. This section specifically addresses the safeguards of art. 89(1) GDPR in a broad manner to facilitate the study participants’ understanding and to enable flexibility to the sponsors regarding the details.

If this alternative ICF template is implemented, the related training materials for study participants, in a form of FAQs, would not need to be modified.

Alternative_ICF.docx