Annex VIIIA

Guideline for correct preparation of a model patient information sheet and informed consent form (PIS/ICF)

Version 10th November 2016
Date of Publication: 15th March 2018

Clarification note: this document should not exceed 15 pages (including the ICF) and must be written in Arial or Times New Roman font with a font size of at least 11 points, minimum line spacing of 1.5, and no decrease in the document margins.

The minimum content required for each section is indicated in black, recommended content is shown in italics, and proposed text is shown in quotations, with unacceptable text in bold.

Patient information sheet

<table>
<thead>
<tr>
<th>STUDY TITLE</th>
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<tbody>
<tr>
<td>STUDY CODE</td>
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<tr>
<td>SPONSOR</td>
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<tr>
<td>PRINCIPAL INVESTIGATOR</td>
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<td>SITE</td>
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Introduction
(should contain the following information)

<<We are writing to inform you about a research study in which you are invited to participate. The study has been approved by an Ethics Committee for Investigation with medicinal products (CEIm) and the Spanish Agency for Medicinal Products and Medical Devices in accordance with current legislation, Royal Decree 1090/2015, of 4 December, and European Regulation 536/2014, of 16 April, regulating clinical trials with medicinal products.

Our intention is for you to receive correct and sufficient information so that you can decide whether or not to participate in this study. Please read this information sheet carefully and ask us to clarify any questions you may have.

In addition, you may consult with anybody you think appropriate>>
Voluntary participation
(should contain the following information)

Begin the section informing the patient of the reason he/she is invited to participate in the study. For example: We invite you to participate in the study because you have been diagnosed with...

<<You should know that your participation in this study is voluntary and that you can decide NOT to participate. If you decide to participate, you can change your decision and withdraw your consent at any time, without this affecting your relationship with your doctor or causing any penalty to your treatment>>

Study objective
(should contain the following information)

Briefly describe why the study is being done.

Define the objective without using technical terms or specifying the mechanism of action of the drug in excessive detail. The description of the main objective of the study should express in simple terms the main question of the trial.

Study description
(should contain the following information)

An exhaustive list of inclusion and exclusion criteria should not be included, but rather a simple description of the patient to whom the study is directed.

It should indicate the total number of subjects that are planned to be included.

It should state what drug or drugs are proposed to be administered and how many treatment groups there are, indicating what chances the patient has of receiving the study drug or the comparator if there is one.

It should explain that the procedure for assignment to one group or the other is done at random (when appropriate), avoiding any technical terms about randomisation.

It should state that “neither the doctor nor the patient will know what treatment you will receive”, if it is a double blind study.

It should explain, if appropriate, the existence of placebo and its definition: the dosage form (e.g., tablet or capsule) with the same appearance as drug x, but which does not contain a pharmacologically active substance and therefore is not expected to have an effect.

Technical terms such as double blind, randomisation, etc. that are described later should not be used. Directly use the non-technical description or explanation.
Study activities
(should contain the following information)

It should specify the duration of the study. When applicable, clearly separate the treatment phase from the follow-up phase.

It should state the number of visits and their frequency, specifying whether participation in the study involves more visits and more tests than would be performed if the patient did not participate.

It should explain the supplementary examinations and activities to be performed during the study without going into excessively technical details, clearly indicating which are part of the patient’s usual follow-up and which will be performed exceptionally as a result of participation in the study.

Do not repeat the same explanations for each visit, unnecessarily lengthening the document. Information should be discarded on common routine examinations such as: blood pressure, pulse, electrocardiogram, weight, height, etc.

It should include a calendar in table form. The activities to be performed should be written, for example, as “blood sample collection” (details of the type “determination of xxx biomarkers” or “quantification of drug levels” are not necessary if it has been explained that in some visits blood will be obtained for these purposes), physical examination, etc.

The same tables that appear in the protocol should not be included, preparing others that are simpler and easier to understand for the patient.

Risks and discomforts resulting from your participation in the study
(should contain the following information)

It should state whether the drug is or is not authorised/marketed. It should inform about the approved or endorsed indications for use in our setting in the case of “off-label use”.

It should briefly explain previous experience with the study drug(s). Data from animal studies should not be given when sufficient information is available in humans.

It should list the possible adverse events of the drug or combination of drugs that are under study (in terms the subject can understand and in a concise manner; if known, percentages should be included). It is recommended to include the most frequent and most serious events. The idea should be conveyed that there may be possible risks or events unknown at this time and that it cannot be ruled out that they may occur.

In the case of comparator drugs (marketed), a statement like the following may be included: “because it is a drug approved by the competent health authorities, there is information accessible to everyone on the side effects of the drug XXX. Please, talk to your study doctor to obtain a complete list of the side effects reported with this drug and in any case you will be given the drug leaflet”.


The risks and discomforts of the tests that are to performed as a result of the study should be described. Avoid technical terms and long, drawn-out writing with unnecessary details, but make it clear that visits may be lengthened by procedures derived from participation in the study such as, for example, questionnaires, kinetic samples, etc.

If discomforts were previously mentioned when describing the study activities, DO NOT repeat them here.

It should state the responsibilities of the participant with regard to:
- Compliance with visits and study activities
- Reporting any adverse event occurring to him/her or changes in medication, warning that, except in an emergency, they should not modify the medication they are taking or take other medications or "medicinal plants" without first consulting with the study doctor.

Possible benefits
(should contain the following information)

The expected benefits for the subject and society should be discussed, if there could be any, and it should be added that the patient may not obtain any benefit for his/her health from participating in this study.

Free medication, test results, close follow-up, etc., should not be included as a benefit of patient participation in the study.

Pregnancy warning

In the case of participation of women of childbearing age or male patients with partners of childbearing age, there should be a specific section on pregnancy or breastfeeding.

It should include the known risks of the drug to the foetus, and if not, state that they are unknown.

When necessary, it should mention the need to take contractive measures as specified in the protocol.

<<If you become pregnant during your participation in the study, you should inform your doctor immediately to receive appropriate medical care>>

It should indicate that in case of pregnancy, collection of data on the pregnancy and on the baby's health will be requested. It should inform of the period during which information is collected (until delivery, 3 months after delivery, etc.) and guarantee compliance with Law 15/1999 on Personal Data Protection (LOPD).

In case of pregnancy of the partner of a male participant, this information will be requested through a specific consent.
Alternative treatments
(should contain the following information)

Briefly explain, if they exist, the other effective alternative treatments currently available for treatment of the patient’s disease, which he/she could receive if he/she did not participate in the study (it should even be explained that the patient could receive the same drugs that are offered to him/her in the study, as would be the case, for example, in phase IV clinical trials).

Add that the study doctor will give more information if the patient wishes, but this does not avoid briefly listing the possible alternatives.

Insurance
(when required, it should contain the following information)

<<The sponsor of the study has an insurance policy that complies with current legislation (Royal Decree 1090/2015) and will provide compensation and indemnity in case of harm to your health or injuries that could occur in relation to your participation in the study, provided they are not a consequence of the disease being studied or of the progression of your disease as a consequence of the ineffectiveness of the treatment.

If you would like more information about this section, consult the principal investigator of the study at your site.

We inform you that it is possible that your participation in this clinical trial may modify the general and particular conditions (coverage) of your insurance policies (life, health, accident, etc.). Therefore, we recommend that you contact your insurer to determine whether your participation in this study will affect your existing insurance policy>>.

Personal data protection
(should contain the following information)

<<The sponsor undertakes to adhere to the Organic Law 15/1999, of 13 December on protection of personal data and the Royal Decree developing it (RD 1720/2007). Data collected for the study will be identified by a code, so that it does not include information that can identify you, and only your study doctor/staff will be able to link such data to you and your clinical records. Your identity will therefore not be disclosed to any person, except in the event of a medical emergency or as required by law. Processing, disclosure and transfer of personal data from all participants will comply with the provisions of this law>>.

If there is any special situation where the identity of the subject needs to be known to comply with a study requirement, it should be explained in this section

<<Access to your identified personal information will be restricted to the study doctor/staff, regulatory authorities (Spanish Agency of Medicinal Products and Medical Devices, foreign health authorities), Ethics Committee for Investigation with medicinal products (CEIm) and staff authorised by the sponsor (study monitors, auditors), when required to verify the study data and procedures, but maintaining confidentiality at all times according to current legislation>>.
Do not add lists with other possible access

<<The data will be collected in a research file of the institution and will be processed in the context of your participation in this study>>

If it is desired to use the data of this study for future research related to the study or analysis, **this should be specified and the following statement included:**

<<The sponsor will take appropriate measures to ensure the protection of your privacy and will not allow your data to be cross-referenced with other databases which would allow your identification>>.

If the sponsor cannot confirm this claim, the patient should be informed of the risk of re-identification derived from reuse of his/her data in future studies not defined at this time.

<<According to data protection legislation, you may exercise your right of access, modification, opposition and cancellation of data, for which you should contact your study doctor.>>

If you decide to withdraw your consent to participate in this study, no new data will be added to the database, but the data that have already been collected will be used.

The coded data **may be transmitted to third parties and other countries** but in no case will they contain information that can identify you directly, such as name and surname, initials, address, social security number, etc. Should this transfer occur, it will be for the same purposes as the described study or for use in scientific publications, but always maintaining the confidentiality of the data in accordance with current legislation.>>

**It is not acceptable:**

- For this section to exceed half a page.
- For the doctor to be released from his/her duty of confidentiality.
- Use of phrases like: “Although all reasonable and appropriate steps will be taken to maintain the confidentiality of your healthcare information, there is always the possibility that this information will be inadvertently revealed.”
- To state that the data are collected in a file owned by the sponsor, since the data are collected by the principal investigator of the site. The sponsor only receives coded information which, according to the standard ‘type code’, is no longer considered as personal data, since the sponsor CANNOT identify the patients.
- References made to laws other than Spanish law. They are not applicable here and are not useful for the patient.
- To make references to a “safe harbour”, etc. The proposed text contains what is essential for the patient to know that his/her data will be treated in a way that preserves his/her privacy, without needing to lengthen the text unnecessarily.
Expenses and economic compensation
(should contain the following information)

When appropriate, it should state that the investigator/site receives financial compensation for the conduct of the study. The following text is proposed for those documents that do not include it:

<<The study sponsor is responsible for managing study funding. For the conduct of the study, the sponsor of the study has signed a contract with the study doctor and the site where it will be performed.

You will not have to pay for the study drugs or the specific tests of the study. Your participation in the study will have no additional cost for you to the one you would have had in normal clinical practice and you will be reimbursed for extra expenses (e.g. meals, trips) generated by your participation in the study>>.

Exceptionally, if not applicable due to the characteristics of the study, it will be suppressed, but it will be explained in the cover letter to the CEIm.

In the cases where it is planned, due to the characteristics of the study (with no therapeutic benefit), to compensate the patients for the time spent in the study or for the inconvenience caused to them, the amount foreseen should be included in this section. It should also indicate that this compensation will be proportional to the participation in the study.

Sometimes reimbursements for travel expenses are made through contracted companies. Inform patients of this and that the data will be deleted at the end of the study.

Other relevant information
(should contain the following information)

<<A description of this clinical trial will be available at http://reec.aemps.es, as required by Spanish legislation>>

If the sponsor also uses other freely-accessible databases to publicise the study, they can be added in this section.

<<Any new information regarding the drugs used in the study found during your participation that may affect your willingness to participate in the study, will be notified to you by your doctor as soon as possible.

You should also understand that you may be withdrawn from the study if the sponsor or study investigators deem it appropriate for safety reasons, for any adverse event due to the study drug, or because they think that you are not complying with the established procedures. In any case, you will receive an adequate explanation of the reason why you have been withdrawn from the study.

By signing the attached consent form, you agree to comply with the study procedures explained to you>>.

In those cases where the sponsor wishes to follow up patients who leave without withdrawing consent (they simply stop going to visits), it should be specified.
If it is desired to use a patient “locating” company, the name of the company and the uses it will be make of the data should be specified, since it is a transfer to third parties and the patient must consent explicitly and unequivocally, adding a box to authorise such transfer.

<<You should know that it is possible that your primary care doctor may be aware of your participation in this study>>.

What treatment will I receive when the clinical trial is ended?

It should be explained if the patient will be able to continue receiving the study medication and under what conditions.

For example:

<<When your participation ends, you will receive the best available treatment that your doctor considers most appropriate for your disease, but you may not be able to continue receiving the study medication. Therefore, neither the investigator nor the sponsor take on any commitment to maintain such treatment outside of this study>>.

Or in the case of serious diseases without available treatment:

<<If the study is suspended or terminated while you are under treatment with <<name of drug>>, your disease remains controlled, the study data indicate that <<name of drug>> shows a benefit in the management of your disease, and adequate stock of the drug is available, the sponsor will ensure an adequate and free supply of <<name of drug>>, until it is available, so that you may continue your treatment for as long as your disease remains controlled>>.
Contact in case of questions
(should contain the following information)

<<If during your participation you have any question or need to obtain more information, please contact <<study doctor, including name, department, how to locate, contact phone number>> (If exceptionally it is another professional, it should be indicated which professional)>>

It is not acceptable to refer to the mpREC as the contact point for patients.

Clinical studies in minors.
(when applicable)

For studies conducted in the paediatric population, the document prepared by KIDS Barcelona is provided as a recommendation. Young Persons’ Advisory Group of Hospital Sant Joan de Déu, as an aid or guide in its preparation”.

The document is published on the following Internet address:

When the study includes minors or is a study in paediatrics, the following information should be added to the PIS/ICF of the parents/guardians:

<<We inform you that your child will be given an information sheet and an informed consent adapted to his/her capacity of understanding which he/she must sign>>.

Taking into account the provisions in the new RD, consent should comply with the provisions of Article 156 of the Civil Code, where it is specified that “The informed consent document of the parents shall be valid provided that it is signed by one of them with the express or tacit consent of the other which should be adequately documented”. It is recommended to add the following:

☐ The parents (both)

In the event that only one of the parents is authorised, the authorising parent must declare one of the following:

☐ I hereby confirm that the other parent does not object to our child’s participation in the study.

☐ The signatory is the sole legal guardian.

Collection and use of biological samples

In the case of storage of clinical trial samples, once the trial is completed, the ethic and legal requirements provided in RD 1716/2011 must be complied with for their subsequent use in research. This document will mention this regulation and inform the patient of the points that are applicable.
When a substudy is performed in the main study:

There can be two cases:

1. ALL participants in the general study may be offered the possibility of participating in a substudy such as obtaining pharmacokinetic samples, imaging tests, etc.

In this case, it is not necessary to create a separate document for the substudy. It is sufficient to indicate it clearly in the general document in a separate section <<SUBSTUDY XXXX>>. This section will clearly explain what participating in this substudy involves, describing any special considerations for the patient’s participation, explaining the risk and benefit/absence of benefit and giving the patient the option to agree or NOT to this participation. For example,

☐ YES, I agree to participate in this XXX substudy (kinetics, imaging tests, etc.).
☐ NO, I do not wish to participate in this XXX substudy (kinetics, imaging tests, etc.).

2. When the SUBSTUDY is directed to a specific subpopulation (e.g., the first 20 patients, only sites having the test, only sites agreeing to participate, etc.), an information document should be written for the specific patient of the substudy, separate from the general study.

3. The same criterion will be taken into account for genetic studies. It is also recommended to review the considerations contained in Law 14/2007 on biomedical research regarding the information to be provided to the patient for these studies.
Participant Consent Form / Informed Consent
(should contain the following information)

It is not acceptable for the consent form to repeat the same information that was already provided in the Patient Information Sheet. If a clear and concise document is written, it is not necessary to repeat the information, encouraging patients to sign without reading it.

<table>
<thead>
<tr>
<th>Study title</th>
<th>&lt;&lt;Title&gt;&gt;</th>
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I, <<first and last name of the participant>>

☐ I have read the information sheet given to me about the study.
☐ I have been able to ask questions about the study.
☐ I have received enough information about the study.
☐ I have talked with <<name of investigator>>
☐ I understand that my participation is voluntary.
☐ I understand that I can withdraw from the study:
  - Whenever I wish.
  - Without having to give explanations.
  - Without this decision affecting my medical care.

I will receive a signed and dated copy of this informed consent document.

I freely consent to participate in the study.

Signature of participant
Date: ___/___/____
Name, signature and date in handwriting by patient)

When IC is obtained in persons with modified capacity to give their IC

Signature of legal representative, family member or related person
Date: ___/___/____
(Name, signature and date in handwriting by the person signing)
I would like to be informed of any information arising from this research that may be relevant to my health:

☐ YES
☐ NO

Signature of participant
Date: ____/____/____
Name, signature and date in handwriting by patient

Signature of investigator
Date: ____/____/____

I would like to be informed of any information arising from the genetic tests performed (only those studies including this type of tests, provided they are validated and may be relevant to the patient’s health). If they are part of the study objective, information about them should be given in the information sheet.

☐ YES
☐ NO

Signature of participant
Date: ____/____/____
Name, signature and date in handwriting by patient

Signature of investigator
Date: ____/____/____
Participant Consent Form before witnesses / Informed Consent
(should contain the following information)

It is not acceptable for the consent form to repeat the same information that is already provided in the Patient Information Sheet. If a clear and concise document is written, it is not necessary to repeat the information, encouraging patients to sign without reading it.

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I, <<name and last name of witness>>, as a witness, affirm that in my presence Mr/Ms <<name and last name of participant>> has been informed and it has been read the information sheet which was given to him/her about the study, and that:

- He/she has been able to ask questions about the study.
- He/she has received enough information about the study.
- He/she has talked with <<name of investigator>>
- He/she understands that his/her participation is voluntary.
- He/she understands that he/she can withdraw from the study:
  - Whenever he/she wishes.
  - Without having to give explanations.
  - Without this decision affecting his/her medical care.

I will receive a signed and dated copy of this informed consent document.

Signature of witness: __________________________ Signature of investigator: __________________________
Date: ____/____/____ Date: ____/____/____
Name, signature and date in handwriting by witness)

The participant would like to be informed of any information arising from this research that may be relevant to his/her health:

- YES
- NO

Signature of witness: __________________________ Signature of investigator: __________________________
Date: ____/____/____ Date: ____/____/____
Name, signature and date in handwriting by witness)
The participant would like to be informed of any information arising from the genetic tests performed (only those studies including this type of tests, provided they are validated and may be relevant to the patient’s health). If they are part of the study objective, information about them should be given in the information sheet.

☐ YES
☐ NO

Signature of witness
Date: ____/____/____
Name, signature and date in handwriting by witness)

Signature of investigator
Date: ____/____/____

The study participant has indicated that he/she cannot read/write.
A member of the study staff has read the consent document, reviewed and discussed it with the participant, and the participant was given the opportunity to ask questions or consult with other people.
The witness must be an impartial person, unrelated to the study.