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SPECIAL ARTICLE

A need to simplify informed consent documents in cancer clinical trials. A position paper of the ARCAD Group

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Background: In respect of the principle of autonomy and the right of self-determination, obtaining an informed consent of potential participants before their inclusion in a study is a fundamental ethical obligation. The variations in national laws, regulations, and cultures contribute to complex informed consent documents for patients participating in clinical trials. Currently, only few ethics committees seem willing to address the complexity and the length of these documents and to request investigators and sponsors to revise them in a way to make them understandable for potential participants. The purpose of this work is to focus on the written information in the informed consent documentation for drug development clinical trials and suggests (i) to distinguish between necessary and not essential information, (ii) to define the optimal format allowing the best legibility of those documents.

Methods: The Aide et Recherche en Cancérologie Digestive (ARCAD) Group, an international scientific committee involving oncologists from all over the world, addressed these issues and developed and uniformly accepted a simplified informed consent documentation for future clinical research.

Results: A simplified form of informed consent with the leading part of 1200–1800 words containing all of the key information necessary to meet ethical and regulatory requirements and ‘relevant supportive information appendix’ of 2000–3000 words is provided.

Conclusions: This position paper, on the basis of the ARCAD Group experts discussions, proposes our informed consent model and the rationale for its content.

Key words: inform consent, oncology, clinical trial, good clinical practice, ethics, Institution Review Board

Background

In respect of the principle of autonomy and the right of self-determination, obtaining an informed consent of potential

participants before their inclusion in a study is a fundamental ethical obligation first stated in the Code of Nuremberg (1949) [1] and later rooted in the Declaration of Helsinki (1964, last

revised 2013) [2]. Obtaining the informed consent of the patients is thus mandatory before starting any investigational treatment. The informed consent refers to a process of patient–physician dialog followed by a written documentation that summarizes key points. Despite the acceptance and implementation of international Good Clinical Practice standards (ICH-GCP E6) [3], the variations in national laws, regulations and cultures contribute to complex informed consent documents for patients participating in clinical trials. Currently, only few ethics committees seem willing to address the complexity and the length of these documents and to request investigators and sponsors to revise them in a way to make them understandable for potential participants. It is urgent to provide an adequate, understandable and non-technical informed consent documentation that respects the participants' right to self-determination and thus better protects their treating physicians and others involved in clinical research.

The Aide et Recherche en Cancérologie Digestive (ARCAD) Group [4–6], an international scientific committee involving oncologists from Australia, Europe, Japan, Latin America and the United States, is concerned by the complexity and poor readability of the written information presented in many informed consent documents. Such issues can discourage patients from participating in a clinical trial or can prompt them to take a treatment that they would not have taken if they had more comprehensible information.

The purpose of this work is to focus on the written information in the informed consent documentation for drug development clinical trials and suggests (i) to distinguish between the information *necessary* for the patient to make an informed decision and the information that, although important, are not essential to the decision making process and (ii) to define the optimal format allowing the best legibility of those documents. In the interests of efficiency a simplified informed consent documentation also needs to comply with the requirements of the ICH-GCP E6, the Food and Drug Administration (FDA) 21 Code of Federal Regulations section 50.25 (21 CFR 50.25) [7], the recent National Cancer Institute (NCI) template [8] or any other local mandatory requirements.

Why are these documents so difficult to read and understand?

It is generally recognized that informed consent documents are too long, too complex and poorly developed, with numerous abbreviations, redundancies, contradictions, unjustified recommendations and unnecessary medical details that patients do not need to make an informed decision.

An important section of the informed consent document, which remains difficult to tackle, is the information on survival [9] and the treatment-inducing adverse reactions, their occurrence, duration and severity. The reasons for this propensity must have multiple causes. The most important being the desire to inform completely to the point that non-expert patients and/or those with reading disabilities or poor understandings of medico-technical issues are completely lost. Too much and too detailed information might be seen as *distracting from informed choice* [10]. One can hope that the new NCI template, made available in June 2013, will prove simpler. A randomized evaluation of

its effectiveness is underway. Many less useful information can make the informed consent document gratuitously lengthy, e.g. a lack of reference to the content of a package insert for drugs that have received a marketing authorization, the description risks of standard testing, biopsies and other procedures which are required in the protocol and that many patients already know and would have otherwise consented, and to substantial re-reviews and modification by local Institutional Review Boards (IRBs) or Research Ethics Committees (RECs) [11].

ARCAD fully agrees with the recommendations made by several guidelines on the informed consent documents currently in place [3, 12–16]. Using the NCI template [8], in compliance with the recommendations found in FDA 21-CFR 50.25 and ICH-GCP E6, ARCAD would like to improve the format and presentation of the content in those documents to ensure that the information is clear and can be understood and integrated.

The elements of the informed consent documents are dependent upon the stage of the disease under study, the complexity of the trial design, as well as the product to be tested and its stage of development. ICH-GCP E6 section 4.8.10 proposes 20 points of the informed consent that should be covered in some detail [3]. These 20 points are further taken up in FDA 21-CFR50.25 as well as in the NCI template [8]. This should ensure that patients receive the adequate information before their participation in a clinical research and can make an informed decision.

We propose that the informed consent documentation be divided into sections, but all sections are part of a single document. The first section should contain the leading information essentially based on the ICH-GCP E6 20 points; the second section can contain the supportive and detailed elements (including information required by local regulation, IRBs, RECs or investigators). An appendix section may contain more general information such as a glossary explaining simple terms, standard treatment or complex treatment concepts (e.g. placebo, cross-over, pharmacogenetic/genomic research, if necessary legal aspects). For those who wish and receive approval from their IRBs or RECs, the leading information section, alone, should allow the patient to make his own decision.

Every word should be weighed as it is in the protocol and as it will be in the final article. Its length must be predefined and imposed as required when submitting an article or abstract. This endeavor of simplicity and clarity is required throughout the entire document, text must be legible and easy-to-read that corresponds to an 'eighth grade' reading level according US standards or Flesch Reading Ease grade level of 60–70 provided by most word processing programs, a font of minimum 12 pc, be adequately paginated, bear a version number and the date of issue (<http://www.nlm.nih.gov/medlineplus/etr.html>). The same effort should be made assuring that the information is understandable for research participants in any language. Verbatim translation should be avoided as far as local and national particularities and requirements need to be taken into consideration.

Leading information

The leading information section should contain around 1200–1800 words (3–5 pages) and should enable a patient to make an informed decision. The content must describe the study name and background including the reason(s) for its conducting, a

brief description of the investigational treatment and the possible treatment alternatives. In addition, the duration of participation and the frequency of the visits with a summary of the examinations to be carried out that are not included in the routine practice must be included, the potential benefits and risks that the patients may encounter as well as a summary of the clinically significant known adverse reactions expected during treatment. Less significant adverse reactions can be placed in the additional information section. Everything that is related to the risk can obviously not be described, especially as the risks at the initiation of a trial, are not well known. The philosophy is to share the risks as we know them, explain that some events may lead to hospitalization and treatment of indefinite duration and that in rare occasions can cause death.

According to the NCI template, there is no standard definition of adverse events frequency in the United States. In Europe, the European guidelines for the summary of product characteristics (SmPC) (September 2009) require that the frequency of adverse events follows their requirements. In Table 1 you should use what is required in your country, but the frequency rate must be given.

NCI template. *Common* (>20% and up to 100% of patients receiving the drug/agent); *occasional* (between 4% and 20% of patients), *rare and serious* (in <3% of patients), *serious* (is defined as side-effects that may require hospitalization or may be irreversible, long-term, or life-threatening).

EU commission guideline on the SmPC September 2009. *Very common* ($\geq 1/10$), *common* ($\geq 1/100$ to $< 1/10$), *uncommon* ($\geq 1/1000$ to $< 1/100$), *rare* ($\geq 1/10\ 000$ to $< 1/1000$), *very rare* ($< 1/10\ 000$).

The consent form must state that out of respect for the patient's privacy, the confidentiality of their personal health information will not be disclosed by their healthcare providers without their authorization, that they will be informed in a timely manner of any relevant issue that may change their decision to participate, and that potential injury will be treated and covered by an insurance or other acceptable means to be specified. The patient should also obtain the name of a contact person. Further information on the rights of patient must be included in the 'detailed information' section.

Table 1 provides a sample of the leading information of the consent form.

Relevant supportive information

Additional information is available to complement the leading information, especially those concerning the conduct of the study, the patients' rights as well as the protections that the sponsor and the investigator will provide during and after their participation (monitoring and treatment of serious adverse reactions, insurance for study-related inducing damages, . . .).

Ideally, the detailed information section should be around 2000–3000 words. The text should not contain abbreviations, in particular those used for regulatory purposes (e.g. FDA, EMA, SAE, GCP, REC, IRB etc.) which is of little concern to the patient.

Redundancies should be banned and therefore the content of the information already provided in the leading information sheet should not be repeated in the detailed information section

unless it is supportive to any demands that are not involved in the decision-making. There is often not enough medical information on the effects of a new treatment on the unborn child; this means that sexually active patients (both woman and man) are required to use adequate methods of birth control during study treatment.

According to ICH-GCP E6, the investigational product(s) should be supplied by the sponsor and be provided to clinical trial patients free of charge. In many countries, it is legally acceptable that routine medical practice laboratory tests and medical imaging examinations are covered by the patients' health insurance. In Europe, many national laws require that a procedure be in place for the reimbursement for expenses such as travel and lodging for patients participating in clinical trials, or treatments for trial-related serious adverse reactions. Several national laws require that trial-related injuries be covered by a clinical trial insurance taken by the sponsor before the trial starts and be valid in the country where the trial is carried out. Regardless of the legislation, article 22 of the Declaration of Helsinki requires that a compensation scheme be in place in case of trial-related injuries. Potential participants should be informed about this. Such requirement can also be derived from general rules in liability laws.

Patients participating in clinical trials have the responsibility, as a clinical research partner, to provide correct and complete information about their health history, cooperate with their caregivers, and comply with the protocol by keeping all clinic appointments or canceling and rescheduling their visits. Withdrawal is permitted at all times, with no impact on further standard of care for their medical condition. Once a patient withdraws his consent, the withdrawal will prevent any further collection of information and data.

Table 2 provides relevant supportive information. Additional annexes can be added to the informed consent documents, as needed (Table A1).

Discussion

Legislation on informed consent has its origin in medical malpractices identified in the last century which were implemented without consideration for the people and without any ethical content [1, 17].

The content of informed consent documents stating what is required to properly inform the patient participation in drug trials has been agreed upon between various regulatory bodies within the ICH region [3, 11–13], as well as in those countries applying ICH standards. We did not expand here on the history that led to the recommendations currently in place or refer to the research carried out in this area. A recent review by Christine [18] addresses these issues in terms of emerging challenges of informed consent when changing models of health care and research, such as *what information should be disclosed, how it should be disclosed, how much the persons providing consent should understand and how explicit consent should be*. It seems that whatever the circumstances, the information provided to the patient must enable them to understand what is being done and what are the benefits and inconveniences of the proposed treatment. This involves information on life expectancy (usually

Table 1. Leading information

Protocol ID and title	Version no., date, page x/xx
	<p>You are being asked to take part in this trial because you have a cancer (describe the type and stage of the cancer such as 'colon cancer that has spread and has not responded to previous treatment' as well as the prognosis).</p> <p>In order to allow you to make a free and informed decision to participate in this trial, good clinical research practices and regulations require that you are fully informed about your disease, the available treatments and their possible benefits and risks. Your care provider will give you with all information and alternatives for your next treatment options. It is strongly recommended that you read the document and ask questions to your physician to clarify points that are not clear to you.</p>
Background	<p>Your physician will explain to you the purpose of this clinical trial that includes an investigational treatment for your disease. Clinical trials include only patients who freely choose to participate. You can only be chosen to join the trial if you understand what will be done to you. Please discuss this with your doctor and your family and ask about anything you are unclear of. Take as much time as you need to make your decision</p> <p><i>Explain the purpose of clinical research and how it is carried out</i></p>
Why is this trial being done?	<p>The purpose of this trial is to evaluate the tolerability and the efficacy of a new anticancer treatment called <i>Testdrug</i> against the standard treatment <i>Standardrug</i>. We are expecting that the new treatment may be more active (or <i>better tolerated</i>) than the current available ones, but we need to verify this hypothesis. If you agree to participate and your disease condition will allow it, you will arbitrarily – like tossing a dice – be selected to receive either an investigational treatment or a treatment already approved for your health condition.</p> <p>If appropriate: You may be selected to receive a placebo. A placebo is an inactive substance which has the same presentation, and is administered, as the active treatment tested. The choice of a placebo is necessary in order to properly evaluate the new treatment</p>
What are the characteristics of the proposed treatment?	<p>The following treatment is planned in this clinical trial:</p> <ul style="list-style-type: none"> • The investigational drug: Give the drug name and whether it is a new investigational product, chemical or new technology. • Give information on the frequency and the route of administration (3x/week for 4 consecutive weeks repeated every 6 weeks by oral/iv/im, etc) • The commercially available medication will be provided as in routine medical practice. • If you have completed the trial and did benefit from the new treatment, you may receive additional courses until the drug is available on the market in your country. In case further investigations with that particular product are abandoned for your disease, your treating physician will reevaluate your treatment options.
Duration of participation, frequency of visits and exams not done as routine practice	<p>Before taking part in the trial, your physician will ask you to perform some exams and tests to find out whether you can be in the trial. The majority of these exams and tests are part of routine medical care for your disease. Add whether invasive procedures are planned (e.g. biopsies, bone marrow procedure, etc.)</p> <p>The entire schedule of the planned visits and tests required during this trial are given in the appendix at the end of this document.</p> <p>You will receive either the investigational drug or the comparative treatment/placebo for up to XX weeks/months. When your treatment is completed you will be followed up for up to xx weeks/months/years. The entire duration of your participation can be up to XX months/years.</p> <p>The total number of patients planned in this trial is XXX, to be enrolled by XX centers in XX countries.</p>
What are my choices?	<p>Your choices may include:</p> <ul style="list-style-type: none"> • Participate in this clinical trial • Getting treatment or care for your cancer without being in this trial • Taking part in another trial • Getting no treatment • Getting comfort care, also called palliative care that helps reducing pain, tiredness, appetite problems and other problems caused by your disease. It does not treat the cancer directly, but instead tries to improve how you feel.
Are there benefits to taking part in this trial?	<p>Taking part in this trial may or may not make your health better. While doctors hope that this investigational treatment will be more useful against your disease compared with the known treatments, there is no proof of this yet. We do know that the information collected in this trial will help doctors learn more about this new treatment and this information may help future cancer patients.</p> <p>If appropriate: In case you receive the placebo you will also receive the most active treatment available today for your situation.</p>
What important adverse reactions can I expect being in the trial?	<p>As with any drug, you may experience mild or more serious adverse reactions during the trial. You will be monitored carefully for any of those reactions. However, doctors do not know all the adverse reactions that may occur. Many adverse reactions go away soon after you stop your medication. In some cases, adverse reactions can become serious, long lasting, or may never go away they may require hospitalization and even, but rarely, lead to death.</p>

Continued

Table 1. *Continued*

Protocol ID and title	Version no., date, page x/xx
Ethics and approvals	<p>The known clinical important adverse reactions of the investigational drug are listed by frequency grouping (<i>keep either EU or United States, as defined in the leading information above</i>):</p> <p>Information about standard treatment should also be given. For product(s) already on the market and used in this trial, give summary of adverse reactions and refer to the information available in the package insert of that drug (attached as an appendix). Patients should be informed that, outside of the present study trial, the same standard treatments are likely to be administered with a similar level of adverse reactions.</p> <p>This trial has been reviewed and approved by an independent Research Ethics Committee/Institutional Review Board being responsible for assuring that your safety, rights, and welfare are protected.</p> <p>The trial was also authorized by the health authorities in your country</p>
OPTIONAL Additional blood and tissue research	<p>Any additional research to this clinical trial:</p> <p>You may be asked to have a biopsy (or surgery) to evaluate your disease. Your doctor will remove some body tissue or perform analysis of blood samples to better define the nature of the tumor. The results of these analysis will be given to you and will be used to plan your care.</p> <p>We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future. The choice to let us keep the left over tissue for future research is up to you. No matter what you decide to do, it will not affect your care.</p> <p style="padding-left: 40px;"><input type="radio"/> Yes, you can use the left over samples <input type="radio"/> No, I do not want you to use the samples, they must be destroyed</p> <p>If yes, more information regarding this additional research is provided in the <i>Relevant Supportive Information document</i>.</p> <p>I have read the information about this clinical trial. I understand that clinical trials include only patients who freely choose to participate. I had the opportunity to ask questions and discuss them with my physician and my family. All of my questions have been answered and I understand enough about the trial information to judge that I want to participate in it.</p> <p>I am aware that I can withdraw at any time. In the event of trial-related injury, I will receive treatment and that the sponsor will cover the cost.</p> <p>I will be informed in a timely manner of any new relevant information that may change my decision to participate.</p> <p>The person of contact for further information is Dr. . . .</p> <p>I voluntarily give my consent to participate. My personal health information will not be disclosed and will be kept confidential, but I agree to and authorize the use of my anonymous personal health data by the sponsor and health authorities for regulatory purposes.</p> <p>I have been given a copy of xx pages of information.</p> <p>Delete what is not applicable to the trial</p> <p>I agree to take part in this clinical trial</p> <p><input type="radio"/>Yes <input type="radio"/>No</p> <p>Patient: (print name and signature) Investigator (print name and signature)</p> <p>Date Date</p> <p>I do agree to give blood/tissue samples for further research</p> <p><input type="radio"/>Yes <input type="radio"/>No</p> <p>Patient: (print name and signature) Investigator (print name and signature)</p> <p>Date Date</p> <p>If yes,</p> <p>1. My blood/tissue samples may be kept for use in research to learn about, prevent, or treat cancer.</p> <p><input type="radio"/>Yes <input type="radio"/>No <input type="radio"/>Not applicable</p> <p>2. My blood/tissue samples may be kept for use in research to learn about, prevent or treat other diseases.</p> <p><input type="radio"/>Yes <input type="radio"/>No <input type="radio"/>Not applicable</p> <p>3. Someone may contact me in the future to ask me to take part in more research.</p> <p><input type="radio"/>Yes <input type="radio"/>No <input type="radio"/>Not applicable</p>

For the purposes of this document, guidelines and instructions within the leading information template are provided as italic text. If this document is used to prepare your informed consent form, these should be deleted and specific information should be inserted.

Table 2. Relevant supportive information

Protocol ID and title	Version no., date, page x/xx
Early termination or if you want to leave the trial	<p>Your participation in this trial may be ended without your consent for one of the following reasons:</p> <ul style="list-style-type: none"> • If your physician believes that it is in your best interest. • If during the trial, your physician discovers that your disease has gotten worse. • If you experience serious adverse reactions that your physician considers unacceptable. • If you require treatment with drugs that are not allowed on this trial. • If you refuse further treatment, or do not follow the schedule of assessments or do not return for follow-up as originally planned. • If the sponsor discontinues the drug development process. • If there are provisions in case of early termination or for post-trial access to the treatment of patients who still need an intervention identified as beneficial in the trial
What's happen to my data in case I withdraw my consent	If you withdraw your consent, this will prevent any further collection of data. However, your withdrawal does not affect the data and material that have already been collected. Those data will be used in the framework of this research.
The treatment plan	<p>The treatment schedule planned in this clinical trial is:</p> <ul style="list-style-type: none"> • The new drug will be administered at the following schedule: . . . • The standard treatment will be given at the following schedule: . . .
Appointments and exams to be carried out	Your physician will review with you the schedule of the planned visits and tests that are required before, during and at the end of the trial. The details are attached to this document as an appendix. It is your responsibility to attend the visits as planned.
Estimated blood volumes	<p>At each visit, XX ml of blood will be collected. At follow-up visit, XX ml of blood will be collected. Over the duration of your participation in the trial, an estimated total amount of blood drawn for blood tests will be XX ml. The blood tests will be drawn to evaluate your hematology, your blood chemistry, your kidney and liver function.</p> <p>Serum pregnancy test for women of childbearing potential will be taken before starting the trial and repeated once every 3 months.</p> <p>If you or a female partner of male patient become pregnant you should contact without delay the responsible person (name and details) for your own (or this of your partner) safety and this of the child.</p>
Risk of pregnancy	<p>There is often not enough medical information to know about the effect of an investigational treatment on the unborn child, this needs that patients sexually active (both woman and man and their partner) are required to use adequate methods of birth control during the trial period.</p> <p>If you are a woman of childbearing potential, you will have to make a pregnancy test to make certain you are not pregnant before starting the trial. The test must be negative to participate in this trial.</p>
Compensation reimbursement	You will not receive any financial compensation for participation in this trial. However, travel cost may be reimbursed by the sponsor. If you wish to claim travel costs, discuss this with your physician before you decide to participate.
Costs of treatment	<p>Neither you, nor your medical insurance provider will be expected to pay any costs directly related with this trial.</p> <p>All routine procedures that would normally be given by your health care provider would continue to be covered by you and/or your insurance provider.</p> <p>The investigational drug must be provided to you free-of-charge.</p>
Injury	<p>Complications may arise during the course of therapy either due to your disease or due to the treatment you are receiving for your disease. For any type of damages including injuries due to any substance or procedure properly given under the plan for this trial, contact your physician (the sponsor is responsible to cover the treatment of any trial-related injury).</p> <p>You agree to provide additional blood/tissue for researches that are not linked to this clinical trial.</p>
Optional (delete if not applicable) blood/tissue for additional research	<p>About using tissue for research</p> <p>Your tissue may be helpful for research whether you do or do not have cancer.</p> <p>Unless otherwise requested, reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.</p> <p>Things to think about</p> <p>If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research and will be destroyed.</p> <p>In the future, people who do research may need to know more about your health. While they may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.</p> <p>Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.</p> <p>Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new treatment in the future.</p>

Continued

Table 2. Continued

Protocol ID and title	Version no., date, page x/xx
	<p>Benefits The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.</p> <p>Risks The greatest risk to you is the release of information from your health records. We ensure that your personal information will be kept private and confidential, according to the National law.</p> <p>Contact information The physician in charge of this trial is Dr. _____. The telephone contact number is [telephone number]. If you need more information about this trial or if you have any questions at any other time, you may contact your physician.</p>

a few months for cancer patients), the potential survival benefit (often weeks) and risks related to treatment. Some members of ARCAD do not agree that the consent form is the best place to discuss prognosis because they think that the uncertainty around this information could be misleading to patients, but do feel that the aims of care (curative, palliative, etc.) and goals of treatment might help setting the scene of experimental intervention. They also agreed that if the patient cannot capture the essence of his situation, whatever the reasons, socio-cultural, intellectual, emotional or communication problems, he should not be part of a research program.

The informed consent documentation may be clearer if it is structured in several sections but remains a single document with the expected links between sections. The leading information should highlight the key information on the disease and its treatment which are essential to make an informed decision (in agreement with the ICH-GCP E6 20 points, the 21 CFR 50.25 requirements and the NCI template). The additional detailed information part of the informed consent document, should provide the details on the schedule of events during the trial as well as patient's rights and protection, the coverage in case of trial-related damages, data privacy, or the treatment option once the trial is completed, or other trial-related specific requirement. It could also contain additional information required by local authorities, REC or IRBs. A third section would concern, if indicated, research associated with the study and should contain only the details related to this research. Eventually annexes could contain more general information as a glossary. We think that the details on the disease status, the prognosis as well as the expected benefit of the treatment must be as explicit as possible. The reality, even if it is tough to hear, must be in the framework of an experimental treatment. Patients with cancer and especially with metastatic cancer must feel confident that the treatment option is in-line with their expectation. The hope for a cancer cure may push the patient to accept treatment he would refuse if he had realized that the potential benefits would be modest. According to some of the ARCAD Group members, this information does not need to appear in a document of general information but it is the duty of every physician to address these issues through a personalized relationship that is respectful of all persuasions. Therefore, it is of paramount importance that patients understand that patients' rights and regulations on patient protection

require that they are fully informed about their disease, available treatments and their possible benefit and risks. Patients must have the opportunity to ask as many questions as necessary for their understanding of the research and the formation of their opinion.

Although any clinical trial is currently based on the Declaration of Helsinki [2] and carried out according to the international quality standards defined in ICH-GCP E6 guidelines [3], some approaches and practices remain country-dependent. As pointed out by the Declaration of Helsinki and regardless the country in which you practice, patients enrolled in clinical trials must be able to fully understand the information provided on the experimental nature of the treatment, its benefits and risks. If this is not the case, they should not be recruited into any research activities.

An essential aspect of the communication is the ease of reading and the understanding of the text presented. Patients who receive the information could have more than one reason (psychological or physical) of not being able to read or understand the information: obsessed by cancer, emotional instability, attention disorders, low level of reading, eye disorders. Therefore, a special effort has to be made to make it clear, unambiguous and easy to read. This may require the help of a trained staff. In short recommendations are to keep the document within the boundaries previously defined, 1200–18 000 words for the leading part, 2000–3000 for the detailed one, to plan what needs to be written, to cut out any unnecessary detail, to present important ideas in a logical order and, eventually, to use simple, clear text with short sentences, simple punctuation and no jargon, acronyms or abbreviations [19].

Simplifying informed consent documentation alone does not always significantly improve participants' comprehension. There are still about 40% of the patients who do not understand a simplified information consent document [20]. They are many reasons causing such*** situation, including poor literacy skills, poor health knowledge and probably fear to ask for clarification of information even if they do not understand what the physician has said. Doing nothing cannot be a solution. Our only choice is to work on documents which can be understood by a larger number of patients. This being done, other approaches will be necessary to evaluate the process and, eventually, develop other communication strategies.

How patients participating in a clinical trial are informed and respected as a person is a key factor in clinical research. It reflects the interest that the sponsor, the investigators and the medical community owes to patients. It is a guarantee of the quality of the trial and the reinforced intrinsic value of the data.

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Appendix

Table A1. Appendix to Table 2: Sample of schedule of events (protocol number)

Protocol ID and title Visit day	Version no., date, page x/xx Exams, tests and other procedures
One week before starting	<ul style="list-style-type: none"> • A complete review of your medical history will be done prior treatments, as well as the medications you have taken the last 4–6 weeks • You will be asked about your ability to perform your daily activities • Your physical examination will include your weight, height, blood pressure and pulse rate. • You will have a blood test to check (approximately xx ml) your hematology, your blood chemistry, your kidney and liver function to ensure that you can safely receive the trial medication • You will have an electrocardiogram to measure your heart rhythm (if necessary) • You may have a radiography or other imaging systems to evaluate your disease status. • if you are a female of childbearing potential, a pregnancy test (B-HCG) will be carried out • You may have a lung function test to know how your lungs work •
Cycle 1Day 1	<ul style="list-style-type: none"> • You will be ask about your ability to perform your daily activities • A review of your signs and symptoms and your current medication will be done • The physical examination will include your weight, blood pressure and pulse rate. • Blood tests (approximately xx ml) will be drawn to evaluate your hematology, your blood chemistry, your kidney and liver function to ensure that you can safely receive the next treatment • You should provide information about the occurrence of any adverse event • The drug XXXX will be given through <i>your veins over xx hours</i>
Cycle 1Day 8	<ul style="list-style-type: none"> • A review of your signs and symptoms and your current medication will be done • Blood tests (approximately xx ml) will be drawn to evaluate your hematology, your blood chemistry, your kidney and liver function to ensure that you can safely receive your next treatment • You should provide information about the occurrence of any adverse event • The drug XXXX will be given through your veins over xx hours