BRAZILIAN NATIONAL BOARD OF HEALTH (CNS)

BRAZILIAN NATIONAL RESEARCH ETHICS COMMITTEE (CONEP/CNS/MS[1])

GUIDANCE MANUAL:

FREQUENT PENDING ISSUES

IN CLINICAL RESEARCH PROTOCOLS

Version 1.0

-2015-

[1] Ministry of Health (MS)

SUMMARY

INTRODUCTION 3
1. INFORMED CONSENT FORM (ICF) 6
1.1. Wording: 6
1.2. Reimbursement: 8
1.3. Assistance due to damage arising from the research: 10
1.4. Assistance during and after pregnancy due to damages arising from the research: 11
1.5. Indemnity 14
1.6. Birth Control: 15
1.7. Post-study access to the investigational product: 19
1.8. "Study drug" expression 23
1.9. Risks and Benefits: 24
1.10. Alternative therapeutic methods: 25
1.11. Access to exam results: 27
1.12. Confidentiality and data anonymization: 27
1.13. Freedom on refusing to participate in the study: 32
1.14. Freedom to withdraw the consent: 32
1.15. Treatment interruption: 34
1.16. Study interruption: 35
1.17. Contact with the responsible researcher: 35
1.18. Means of contact with the REC/CONEP System: 36
1.19. Field of signatures and initials: 37
1.20. Handling one original copy of the document, with signatures and initials: 39
1.21. Biological material (specific aspects of the ICF): 41
1.22. Human Genetics (specific ICF aspects): 43
2. BIOLOGICAL MATERIAL STORED IN BIOBANK OR BIOREPOSITORY 48
3. HUMAN AND MATERIAL RESOURCES 60
3.1. Budget: 60
3.2. Sponsor: 61
3.3. Institutional Infrastructure: 64
4. SCHEDULE 65
5. COVER PAGE 66
6. STUDIES PROPOSED FROM ABROAD 68
SUMMARY CHART: 70
FREQUENT PENDING ISSUES 70

INTRODUCTION

The history of REC/CONEP System started in 1988 with the publication of CNS Resolution No. 01 of 1988, which established that all institutions performing research with human beings should have an "Ethics Committee". The term "REC" (Research Ethics Committee) came years later, with CNS Resolution No. 196 of 1996. This same norm determined that an Executive Work Group (previously constituted by CNS Resolution No. 170 of 1995) would take responsibility for the process of organization of the Brazilian National Research Ethics – CONEP. The term "REC/CONEP System" appeared sixteen years later, when CNS Resolution No. 466 of 2012 thereby defined it: *"It is composed by the National Research Ethics Committee – Conep/CNS/MS of the Brazilian National Board of Health and by the Research Ethics Committees –RECs – composing a system using mechanisms, tools, and instruments adequate to inter-relation, in a cooperative work aiming especially at protection of research participants in Brazil, in a coordinated and decentralized manner through an accreditation process".*

The REC/CONEP System has as objective to protect research participants in their rights and ensure that studies are ethically performed. Research ethicality implies, necessarily, in: 1) Respecting participants in their dignity and autonomy; 2) Weighing risks and benefits; 3) Maximally avoid or decrease predictable damages; 4) Being socially relevant; 5) Being fair and equitable; 6) Not being futile; and 7) Respecting participant rights. The rights that must be minimally ensured to research participants are listed in Chart 1.

This manual highlights the so-called "repetition pending issues". They correspond to the main ethical pending issues that CONEP has been appointing in its technical opinion letters regarding clinical research protocols, especially clinical trials with new drugs. There is no intention to exhaust the subject, but only to help researches and sponsors in the preparation and submission of protocols on Plataforma Brasil. Thus, it is expected that the number of ethical notes performed by

CONEP is substantially reduced and with that, to accelerate the protocol course process in the System.

ABRACRO

CHART 1 – Research participants rights (*).

1) To receive study information in a clear manner;
2) To have the opportunity to clarify doubts;
3) To have the time that is necessary to take an autonomous decision;
4) To have freedom to refuse to participate in the study;
5) To have the freedom to withdraw their consent at any phase of the research;
6) To have the freedom to withdraw the consent for use and storage of biological material;
7) To receive (total and immediate) assistance for damages, at no cost;
8) To receive indemnity for damages;
9) To receive expenses reimbursement (including for companions);
10) To have access to results of tests performed during the study;
11) To request withdrawal of their genetic data from banks where they are stored;
12) To have post-study access to the investigational product at no cost (if appropriate);
13) To have access to the chosen contraceptive method at no cost (if appropriate);
14) To receive genetic counseling at no cost (if appropriate);
15) To have confidentiality of their data ensured;
16) To have their privacy ensured; and
17) To receive an original copy of the ICF (signed and initialed by the research participant and researcher).

(*) Based on CNS Resolutions No. 466 of 2012, 441 of 2011, 340 of 2004, and 251 of 1997

1. INFORMED CONSENT FORM (ICF)

The Informed Consent Form (ICF) is the document that, besides explaining research details (rationale, objectives, procedures, discomforts, risks, benefits, and assignment groups, among other aspects), also must inform and ensure participant's rights. The ICF is the most frequent reason of pending issues issued by CONEP, especially due to inadequate wording of the document, insufficient information, or failure to ensure research participant's rights.

1.1. Wording:

The ICF must be concise and of easy comprehension by a layman individual. It is not desirable that the document is extensive, with excessively detailed procedures and complex grammatical constructions.

Several pending issues are generated due to the use of technical terms inaccessible to a layman or inappropriate translations of terms and expressions from other language into Portuguese.

The most frequent pending issues related to the ICF wording are described below:

a) **To use inaccessible language:** CNS Resolution No. 466 of 2012, in item II.23, orientates that the ICF must "*contain all necessary information, in clear and objective language, of easy understanding, for the most complete clarification on the research to which it is proposed to participate".* One of the most frequent pending issues is the use of technical terms inaccessible to a layman, especially medical or biomedical technical terms used in clinical trials with new drugs or procedures. The person writing or revising an ICF must put him/herself in the place of a layman research participant. This person must resist using technical terms that are naturally used in his/her daily routine.

b) **To translate in an inappropriate manner:** Item IV.5.b of CNS Resolution No. 466 of 2012 orientates that the ICF must "*be adapted, by the responsible researcher, in researches with international cooperation designed in international scope, to ethical rules and to the local culture, always with a clear language, accessible to all, and in special, to research participants, taking special care so that it is of easy reading and comprehension".* It is very common that studies translated from English usually present the term *"estudo de pesquisa"* (from English "research study"), which does not apply in Portuguese, as it is a pleonasm. Although this is pending issue with minor implication in ethical terms, CONEP has insisted that the ICF must be adequately adapted to Portuguese. Therefore, the term "study" or "research" must be used, but not the expression "research study", which is redundant in Portuguese. Also, situations where poorly prepared translations make the sentence senseless are frequent. Therefore, it is essential to perform a thorough revision of the final version of the ICF in Portuguese.

c) **To write the ICF as a declaration:** The consent form is a document that should be written in an invitation format. It is not adequate that the body of the ICF is written as a declaration, as this may reduce the individual's autonomy. For example: "*I know there will be material collection"* or, still, *"I declare I will present to the visits", "by signing this document, I authorize consultation to medical charts",* etc. Sentences must be written with affirmations from the researcher addressed to the research participant. Examples: "some blood will be collect from the vein in your arm (…)", "we would like to ask you permission to check your medical chart". However, it is acceptable that the final part of the ICF, in which the signature fields are and in which the participant manifests his/her desire, is written as a declaration.

d) **To use the term "research subject":** CNS Resolution No. 466 of 2012 replaces the term "research subject" (provided for by CNS Resolution No. 196 of 1996) with "research participant". However, the old term is still frequently found in Consent Forms. It is understood that the terminology adopted by CNS Resolution No. 466 of 2012 must be used in all research protocol documents, including the ICF.

e) **To adopt inadequate title in the document (ICF):** The use of different terms and expressions to refer to the ICF is frequent, which are not acknowledged by CNS Resolution No. 466 of 2012. Such as *"research authorization form", "authorization form for study participation",* but not limited to. CONEP has been appointing pending issues in these cases, requesting the use of the expression "Informed Consent Form". It is acceptable that, additionally to this expression, some other specification is used, such as "for genetic study".

WHAT TO DO:

The ICF must be a concise document, with easy language, written in an invitation format. The ICF must be carefully revised searching for technical terms and terms inappropriately used or translated. Extensive and excessively detailed consent forms are not desirable. The document title must contain the expression "Informed Consent Form".

1.2. Reimbursement:

CNS Resolution No. 466 of 2012, item II.21, defines reimbursement as "*material compensation, exclusively for expenses of participants and their companions, where necessary, such as transportation and food".* Still, item IV.3.g orientates that the ICF must mandatorily contain *"make the guarantee of reimbursement explicit as well as how expenses incurred to the research participants and arising from it will be covered".*

Expense coverage can also be done through providing of previous material, as defined by item II.18 of CNS Resolution No. 466 of 2012: "*material compensation, exclusively for transportation and food expenses of the participant and his/her companions, where necessary, previous to his/her participation in the research".*

Reimbursement of expenses arising from participation in the research is a reason for pending issue due to the reasons below:

a) **To omit information about reimbursement:** this pending issue occurs when the researcher omits from the ICF the information that the research participant and his/her companion(s) have the right to reimbursement of expenses arising from the research.
b) **To limit items and value of the reimbursement:** it is frequent that the researcher limits reimbursement by stipulating items that will be reimbursed and/or maximum values. These limitations appear, for example, in sentences such as: *"you will receive R$ 100.00 for expenses you may have with the study"* (value limitation), or still, *"you will be reimbursed for food and transportation"* (item limitation). It is wise to note that the Resolution does not stipulate which items should be reimbursed, but only exemplifies (*"… such as transportation and food").*
c) **Do not ensure reimbursement to companion(s):** It is also a reason for pending issue when the researcher ensures the reimbursement only to the research participant, but not to his/her companion(s). It is wise to note that CNS Resolution No. 466 of 2012 (item II.21) predicts reimbursement of expenses arising from the research not only to the participant, but also for those who accompany him/her.

WHAT TO DO:

The ICF must ensure, in a clear and affirmative manner, the reimbursement of all expenses that the participant and his/her companion(s) will have while participating in the research.

1.3. Assistance due to damage arising from the research:

CNS Resolution No. 466 of 2012 defines damage associated with the research (or arising from it) the "*immediate or posterior worsening, direct or indirect, to the individual or collectivity, arising from the research*" (item II.6). Still in item V.6, the mentioned Resolution defines that *"The researcher, sponsor, and institutions and/or organizations involved in different research phases must provide immediate assistance, in terms of item II.3, as well as take responsibility for full assistance to research participants regarding complications and damages arising from the research".*

Pending issues more frequently related to this item are described below:

a) **To omit information about assistance:** This pending issue occurs when the researcher omits in the ICF the information that the research participant has the right to assistance in case of damages arising from the research;

b) **To condition the assistance to proving of causal relationship of the damage:** It is noteworthy that guarantee of assistance to the research participant may not be conditioned to proving of causal relationship, i.e., the establishment of a definitive causality between the study and the damage. Such proving process may demand time, which ultimately, would harm even more the research participant. It is not reasonable, from the ethical point of view, to declare in the ICF that the participant will receive assistance if it is proved that the research caused damages.

c) **To limit the type of assistance to the research participant:** It is common to find in the ICF sentences such as the following: "*you will receive medical assistance if you suffer damages in the study".* The problem, in this case, is

that there is a limitation for the type of assistance that will be offered to the research participant (medical assistance, in this case). Depending on the type of damage, it is possible that the participant needs assistance from other professionals, such as, from the areas of Nursing, Physical Therapy, Psychology, Nutrition, Occupational Therapy, but not limited to. The Resolution is clear in stating the researcher must provide full assistance, not only from a determinate area.

d) **To limit the time of assistance to the research participant:** It is not reasonable, from the ethical point of view, to limit the maximum time during which assistance will be given to the research participant in case of damages. For example: *"you will have assistance while participating in the study"*. CNS Resolution No. 466 of 2012 predicts that damages may be identified subsequently to the research and, therefore, responsibility for assistance does not end with the study end.

e) **Do not inform about the assistance at no cost:** Sometimes, the pending issue is not related to the limitations above described, but simply because the researcher does not make explicit in the ICF that the assistance will be given at no cost (by the sponsor).

ABRACRO

WHAT TO DO:

The ICF must ensure, in a clear and affirmative manner, that the research participant will receive full and immediate assistance, at no cost (by the sponsor), for as long as necessary in case of damages arising from the research.

1.4. Assistance during and after pregnancy due to damages arising from the research:

Although there is no specific item in CNS Resolution No. 466 of 2012 regarding this, this is a result of the guarantee of assistance to damages already

described previously, but with implications not only to the mother (research participant or participant's partner), but also to the child.

This is not about taking responsibility for pre-natal follow-up, but to give the necessary assistance in case of damage arising from the research to the mother and/or child, during and after pregnancy. Below are the pending issues frequently related to this item:

a) **To omit information about assistance during and after pregnancy:** This pending issue occurs when the researcher omits in the ICF the information that the mother and the child have the right to assistance in case of damages arising from the research;

b) **To condition the assistance to proving of causal relationship of damage to mother and/or child:** It is not reasonable, from the ethical point of view, to condition the assistance to proving causal relationship of damages caused by the study to mother and/or child. Statement such as: "*You will receive assistance during pregnancy if it is proved that the research caused damages to you and your baby" are not acceptable.*

c) **To limit the type of assistance to the mother and/or children:** The type of assistance to be given to the mother and/or child must be total. The expression *"medical follow-up of the pregnancy"* is frequently found in the ICF to refer to the assistance that will be given to the research participant. It is understood that the word "follow-up" has a passive connotation and therefore, would not be adequate to use it to describe the assistance that should be given in this period. It is also not adequate to limit assistance to only one medical area; this should extend to all areas when needed. For example, it is possible that a research participant needs assistance of a professional from the Psychology area due to emotional suffering due to a miscarriage secondary to the use of an experimental drug.

ABRACRO

d) **To limit the time of assistance to the mother and/or child:** The responsibility of assistance to the mother and/or child does not end with the end of pregnancy, it should also be given in the period after it, for as long as needed.

e) **Do not ensure assistance to the child:** To guarantee full assistance and for as long as needed to the mother it is not sufficient from the ethical point of view; this guarantee should also be extended to the child, before and after delivery.

f) **Do not inform about assistance at no cost:** this pending issue is generated when the ICF does not ensure in a clear and affirmative manner that the assistance given to mother and/or child is at no cost (by the sponsor).

WHAT TO DO:

The ICF must ensure, in a clear and affirmative manner, that the mother and child will receive full and immediate assistance, during and after pregnancy, at no cost (by the sponsor), for as long as necessary.

1.5. Indemnity

CNS Resolution No. 466 of 2012 (item IV.3) defines that *"research participants that may suffer any type of damage resulting from their participation in the research, foreseen or not in the Informed Consent Form, have the right to indemnity, from the researcher, sponsor, and institutions involved in the different research phases"* (item V.7). It should be highlighted that the indemnity subject is not a prerogative of CNS Resolution No. 466 of 2012, being originally provided for by Civil Code (Law 10,460 of 2002), above all in Articles 927 and 954, Chapters I (Regarding the Obligation to Indemnity) and II (Regarding the Obligation to Indemnity), Title IX (Regarding Civil Responsibility).

Pending issues more frequently related to this item are:

a) **To omit information about indemnity:** This pending issue occurs when the researcher omits in the ICF the information that the research participant has the right to indemnity in case of damages arising from the research;

b) **To link the indemnity to insurance contracted by the sponsor:** Some Consent Forms present the information that the sponsor contracted a specific insurance to conduct the research. It is understood, however, that the responsibility for the indemnity belongs to the sponsor, researcher and institution, regardless of the existence of insurance. The insurance represents an instrument to minimize possible economical losses for the sponsor and does not aggregate safety to the research participant. Besides, values of indemnity and other expenses cannot be limited by the amount contracted by the sponsor. REC/Conep System does not request proving of the existence of insurance for the research performance. What may be ensured in the ICF is the information that the research participant has the right to indemnity.

WHAT TO DO:

To ensure, in a clear and affirmative manner, that the research participant has the right to indemnity in case of damages arising from the study. It is not appropriate that the ICF contains restrictions, upon contracting insurance, for indemnity or assistance.

1.6. Birth Control:

It is understood that certain experimental drugs or procedures may be embryotoxic or teratogenic and, thus, there is the need for using a contraceptive method during and/or after the research. The decision of the best contraceptive method to be used is a shared decision between the physician and the research participant. So much that Article 42 of the Federal Board of Medicine (CFM) Resolution 1,931 of 2009 (Medical Ethic Code) interposes the physician *"To*

disrespect the right of the patient to freely decide about contraceptive method, and always must clarify about indication, safety, reversibility, and risk of each method".

It should be observed that CNS Resolution No. 466 of 2012, item III.2.t orientates that: *"Researches, in any area of the knowledge, involving human beings, should observe the following requirements: (…) to guarantee, for women declaring to be expressly exempt from pregnancy risk, either for not exercise sexual practices or by exercising it in a non-reproductive manner, the right to participate in researches without mandatory use of contraceptives".* Thus, the inclusion of someone in a research should not be conditioned by imposing a specific type of contraceptive method. Even so, there are situations where pregnancy is not naturally possible; therefore, it would not be reasonable from the ethical point of view to impose the use of any contraceptive method.

When the contraceptive method chosen by the research participant imply in expenses (for example: oral contraceptive, condom, intrauterine device, etc.), providing the method at no cost will be a responsibility of the researcher and sponsor, for as long as necessary. CNS Resolution No. 466 of 2012 (item III.2.o) orientates that researches must "*ensure to research participants conditions of follow-up, treatment, full assistance and guidance, according to the case, for as long as necessary, including in tracking researches".*

Below, some of the most frequent pending issues related to birth control are listed:

a) **Do not respect the participant's decision:** It is not acceptable that the study doctor imposes the contraceptive method choice to the research participant. Sentences such as *"the doctor will decide which contraceptive method is better for you";* besides violating the Medical Ethics Code, do not respect the research participant is his/her capacity of making an autonomous decision. The ICF must ensure that the choice of best contraceptive method is a shared decision between study doctor and research participant.

b) **To impose a contraceptive method:** Some studies impose a contraceptive method to the participant, which violates not only CNS Resolution No. 466 of 2012, as well as the Medical Ethics Code. Sentences such as the following are not reasonable: *"you must use a pill (oral contraceptive) during the study".* There are also studies requesting sexual abstinence from research participants for a period before, during, or after the research. Such request is only justified when there is methodological or clinical need (for example: to perform Pap smear, healing of surgery performed in vagina or cervix). In this case, it is an imposition of contraceptive method. The ICF should ensure that contraceptive method choice is a share decision between the study doctor and the research participant.

c) **Do not inform that there are situations where contraceptive method use is not necessary:** The use of contraceptive method may be dispensed in situations where pregnancy is not naturally possible, as in cases of women without uterus or who are post-menopausal, with history of surgical sterilization (tubal ligation or vasectomy), individuals maintaining a homosexual intercourse or having no type of sexual intercourse. The ICF should be clear in stating that the contraceptive method may be dispensed in particular situations, such as those described.

d) **To omit information about contraceptive method supply:** This pending issue occurs when the ICF does not inform that the participant has the right to the chosen contraceptive method at no cost, when this implies in expenses;

e) **To give ambiguous information about the responsibility for the contraceptive method supply:** The ICF is not always clear in relation to supply of the chosen contraceptive method to the research participant at no cost. There are consent forms stating that the research participant "*will have access to the chosen contraceptive method at no cost".* This is an ambiguous

statement, because the “access at no cost” may also occur through the Public Health System, which is unacceptable. The responsibility for supplying a contraceptive method is of the sponsor/researcher and not of the Brazilian Government in a research setting.

ABRACRO

WHAT TO DO:

The ICF must ensure, in a clear and affirmative manner, that the choice of contraceptive method is a decision shared between the study doctor and the research participant and there are situations where birth control in not necessary. It also is ensured that the chosen contraceptive method, when it involves expenses, will be supplied by the sponsor, at no costs and for as long as needed.

1.7. Post-study access to the investigational product:

CNS Resolution No. 466 of 2012, item III.3.d, states that researches should "*ensure to all participants at the end of the study, through the sponsor, access to the best prophylactic, diagnostic, and therapeutic methods at no cost and for indeterminate time, that were shown to be effective*". Still, in sub-item (d1) it is complemented that "*access should also be ensured in the interval between the end of individual participation and the end of the study; in this case, the guarantee can be given through an extension study, according to analysis duly justified from the participant's assisting physician*".

The weighing of the benefit of an investigational product can be done in two different manners: collectively or individually. Individual benefit analysis is performed when the participant ends his/her study participation, and not when the research is completes. If the investigational product was shown to be benefic to the individual, product supply should be ensured for as long as necessary (guarantee of continuity). The definition of individual benefit is not exclusive prerogative of the study doctor; it may also be assessed by the participant's personal physician (assisting). Collective benefit is that defined in interim or final analyses, when it is possible to conclude if the investigational product was shown benefic or not to the experimental group. In this case, investigational product supply should also be extended to the control group.

However, in situations where post-study access is not feasible, such as in self-limited clinical conditions (for example, studies in acute gastrointestinal infections or upper respiratory tract infections), in which the investigational product is used for a short period of time. Thus, neither the experimental group nor the control group would benefit from receiving the experimental product after the end of the study.

Below are some of the pending issues frequently related to the post-study access issue:

a) **To omit information about post-study access:** This pending issue occurs when the researcher omits in the ICF the information that the research participant has the right to access to the investigational product after the end of the study (or after his/her participation in the study);

b) **Do not guarantee access to the investigational product in case of individual benefit:** Access to the investigational product must not be ensured only after the end of the study, but rather, in the end of the individual participation, in case of benefit. Sentences as the following are not sufficient to guarantee access to the investigational product: *"at the end of the study, you will receive the drug if it is beneficial".* In this case, the sentence includes only collective benefit, not individual.

c) **Do not ensure access to the investigational product to the control group:** It is common that the researcher ensures in the ICF the continuity of treatment after the end of individual participation (individual benefit), but omits the guarantee of access to the product to the control group when there is benefit in the experimental group. It is necessary to ensure in the ICF that, at the end of the study, the product will be offered to all research participants, including the control group, if there is evidence of benefit (as long as there is clinical indication for the use of the experimental product).

d) **To restrict the experimental drug prescription in case of individual benefit:** Although the researcher ensures in the ICF the access to the investigational product after individual participation in the study, frequently there is no information that the personal physician (and not only the study doctor), if any, there is also the prerogative to discuss individual benefit and prescribe the experimental drug.

e) **To link the investigational product supply to an extension study:** Frequently the ICF links the guarantee of post-study access mandatorily to the participation in an extension study, which is not reasonable from the ethical point of view. The question is not offering the extension study as an alternative to investigational product access (which is allowed, by the way), but the imposed obligation. In case of benefit, the sponsor should ensure the investigational product supply, even if the participant does not want to participate in the extension study;

f) **To limit the time of post-study access:** Post-study supply cannot be limited to a specific period of time, it should occur for the necessary time. It is not acceptable, for example, the ICF states that: *"you will receive the experimental product for no more than 6 months after you finish your participation in the study".* However, it is comprehensible that there are situations where the investigational product cannot be administered beyond a maximum time period, such as, for toxicity concerns. In this case, the rationale for this limitation should be clearly explained in the ICF;

g) **To ensure access to the investigational product only to the experimental group:** In case of benefit observed in interim or final analysis in the experimental group (collective benefit), the investigational product supply must also be ensured to the control group (if there is clinical indication for that).

h) **Do not inform about the post-study access at no cost:** This pending issue is generated when the ICF does not ensure, in a clear and affirmative manner, that the post-study supply of the investigational product will be at no cost.

i) **To give ambiguous information about the post-study access responsibility:** Sometimes the ICF is ambiguous when informing conditions and responsibilities of the post-study supply of the investigational product, which must be at no cost through the sponsor. To state that the research participant *"will have access to the experimental drug at no cost"* is not enough, because the "access at no cost" could also be through the Public Health System, if the product is already available, for example, in clinical trials for new applications of an already registered drug. The responsibility of post-study supply of the investigational product is of the sponsor and not of the Brazilian Government.

WHAT TO DO:

The ICF should ensure, in a clear and affirmative manner, that at the end of study participation, individuals will continue to receive the investigational product at no cost through the sponsor, in case of investigational product, this being a choice of the study doctor, or of the personal physician. Besides, the ICF must ensure that the sponsor will provide, at no cost, the drug to all research participants (experimental and control groups), in case collective benefit is observed, identified in interim analysis or at the end of the study.

1.8. "Study drug" expression

The use of the expression "study drug" or "research drug" (or something similar) in the ICF is very common, to refer simultaneously to the investigational product and to placebo. Although it is understood, technically, that the study drug is indeed the experimental or control drug, this concept is not easily understood by a layman and induces to an error in interpretation.

Overall, the "study drug" definition is found in the ICF in one single short sentence, immerse within a long document, which may not be clearly understood by the reader and may impair the semantic comprehension of the term in the remainder of the document. Example: *"This form will refer to the experimental drug and to placebo as study drug".* From this point on, only the expression "study drug" is used throughout the remainder of the ICF, in an indistinct manner for experimental and control groups.

In this context, certain sentences, such as *"you will receive the study drug to treat your disease"* are inadequate. This seemingly simplification of terms may make a layman erroneously believes that he/she will receive the investigational product, when in fact there is a concrete possibility that he/she is assigned to the placebo group. This may induce to an error in interpretation, since not always the product received will be the investigational product. Ultimately, this error impairs making an autonomous decision on participating or not in the research.

It should be remembered that according to CNS Resolution No. 466 of 2012, items IV.4.b and VI.5.b I call attention to the fact that the ICF is a document that should provide information in a clear, accessible, and easy-to-understand wording. Still in item IV.4.b, the mentioned Resolution orientates that the ICF must "*clarify, where relevant, <u>about the possibility of including a participant in a control or placebo group, making clearly explicit the meaning of this possibility".</u>*

WHAT TO DO:

The ICF should not use the terms "study drug" or "research drug" (or something similar) to simultaneously refer to the investigational product and placebo. This induces to an error in interpretation and jeopardizes the autonomous decision making.

1.9. Risks and Benefits:

CNS Resolution No. 466 of 2012, in item III.1.b, defines that "*Research ethics implies in (…) weighing between risks and benefits, known or potential, individual or collective, committing to the maximum of benefits and minimum of risks and damages.*" Besides, item IV.3.b states that "*The ICF must mandatorily contain (…) explanation of possible risks and discomforts arising from the participation in the research, besides the benefits expected from this participation and presentation of measures and cautions to be implemented to avoid and/or reduce adverse effects and conditions that may cause damage, considering characteristics and context of the research participant".* Pending issues frequently related to this item are the following:

a) **To omit description of research benefits and/or risks:** This pending issue is noted when the researcher does not describe in the ICF the potential benefits to the research participant and/or risks involved in the study. Even if the research does not determine direct benefit to the research participant, this information must be clearly contained in the ICF.

b) **To overvalue benefits from an experimental treatment:** This ethical pending issue is appointed when the researcher describes the benefits from an experimental treatment in an overvalued manner. To describe, for example, that the experimental treatment will be *"able to heal the disease"* of the participant is not reasonable from the ethical point of view, as it may induce the individual to accept to participate in the research.

c) **To underestimate the risks of an experimental treatment:** When risks involved in a study are underestimated, the researcher does not give the information needed so that the participant makes an autonomous decision about his/her participation in the research. To state, for example, that a new experimental drug "does not present significant risks to health" is not credible in a clinical trial.

d) **Do not inform about measures and cautions:** Sometimes, the pending issue is not related to risk description, but simply to not making explicit in the ICF which measures and cautions will be adopted to avoid or reduce risks associated with the research.

WHAT TO DO:

1) The ICF must present, in a clear and objective manner, potential benefits from the research to the participant, without overvaluing them;
2) If the study does not anticipate any direct benefit to the participant, this information must be explicitly contained in the ICF;
3) Potential risks associated with the research must be described in the ICF, without underestimating them;
4) The ICF must explain measures and cautions that will be adopted to avoid or reduce risks associated with the research.

ABRACRO

1.10. Alternative therapeutic methods:

According to CNS Resolution No. 466 of 2012, IV.4.a, *"The Informed Consent Form in researches using experimental methodologies in the biomedical area, involving human beings, beyond what is provided for by item IV.3 above, must mandatorily observe the following: (...) make explicit, where relevant, the existing alternative therapeutic methods."*

The main pending issue related to this issue is the negligence in the ICF of the information about alternative therapeutic methods.

ABRACRO

WHAT TO DO:

The ICF should clearly describe alternative treatment methods to the research participant. If there are no alternative methods, this must be made explicit in the ICF.

1.11. Access to exam results:

In some studies, the ICF has the information that the research participant will not have access to results of his/her exams performed during the study. Although in some situations there is indeed a methodological reason for not revealing to the research participant the results of exams performed (when the information interferes in the study endpoint), most of the times there is no rationale for this procedure in clinical trials. It should be remembered that CNS Resolution No. 251 of 1997, item III.2.i, defines that "*The responsible researcher should: (...) Give access to exam and treatment results to the patient's physician or to the patient him/herself, whenever requested or indicated".* Except where necessary, the researcher must not limit the research participant's access to his/her results of exams performed during the study.

The pending issue more commonly related to this item is the ICF informs that the research participant will not have access to results of exams performed during the study.

WHAT TO DO:

The ICF must not contain restrictions for the research participant's access to results of exams performed during the study, unless there is a methodological rationale for it.

1.12. Confidentiality and data anonymization:

The ICF must guarantee that data allowing the research participant identification will be kept confidential in order to preserve privacy and to not cause damage, such as stigmatization and discrimination. According to CNS Resolution No.

466 of 2012, item III.2.i, researches should (…) "*predict procedures that ensure confidentiality and privacy, protection of image and the non-stigmatization of research participants, assuring non-use of information to damage persons and/or communities, including in terms of self-esteem, prestige and/or economical-financial aspects".* The same Resolution, item IV.3.e, also defines that the ICF must contain "*the guarantee of maintenance of secrecy and privacy of research participants during all phases of the research."*

When research participant information is transferred to the sponsor or third parties, caution must be taken so that the data is anonymized (codified) in order to ensure privacy. Special attention must be paid to monitors and auditors representing the sponsor. Their role in guaranteeing compliance with Good Clinical Practices and ultimately, ensuring protection of research participants is acknowledged. Monitors and auditors must mandatorily have the professional commitment to secrecy of information obtained during their activities.

Nevertheless, it must be emphasized that, for monitors and auditors to have access to source-documents (including medical charts), the ICF must: 1) Inform that, besides researchers, the monitors and auditors will have access to source-documents; 2) Ensure, in a clear manner, that monitors and auditors will keep the commitment with the secrecy of information, in order to guarantee research participant privacy and; 3) Clarify which source-documents will be consulted.

Special care must be taken regarding medical chart consultation, subject in which there are considerations from the Federal Board of Medicine (CFM). CFM Resolution No. 1,638 of 2002, in its preamble, considers the medical chart as *"valuable document for the patient, physician assisting him/her and for research institutions, as well as for teaching, the research and public health services, in addition to being and legal defense instrument".* Article 1 of the same Resolution defines *"medical chart as the single constituted document of a set of information, signs and registered images, generated from facts, events, and situations about the patient's health and assistance given to him, in legal, confidential and scientific character, making possible the communication among members of the multi-*

professional team and continuity of the assistance given to the individual". CFM Resolution No. 1,605 of 2000, in Article 1, observes that "*The physician cannot, without the patient's consent, reveal the contents of medical chart or sheet".* Article 5 clarifies that *"If there is express authorization of the patient, in the request or in a different document, the physician may refer the medical chart or sheet directly to the requesting authority".* Still, CFM Resolution No. 1,931 of 2009 (Medical Ethics Code) defines in Article 85 that "*It is forbidden to the physician: Allow handling and knowledge of medical charts by people not obligated by professional confidentiality, when under his/her responsibility".* Therefore, if there is intention of consultation to the medical chart in the research, this information must be clearly expressed in the ICF, ensuring, most of all, the data confidentiality issue. This aims to guarantee that the individual receives all necessary information to make an autonomous decision about participating or not in the research.

Pending issues related to this item generally are the following:

a) **Do not guarantee that data to be transferred to the sponsor or third parties are anonymized:** Aiming to ensure the research participant's privacy, data transferred to the sponsor or third parties must be previously made anonym (codified). Sentences such as the following are not reasonable: *"your personal data will be forwarded to the sponsor and to University X",* without the due explanation about anonymization.

b) **To give wide access to source-documents:** Participant's data are confidential; being necessary to limit who will have access to them. Besides researchers, it is acceptable that sponsor's monitors and auditors have access to research participant's source-documents, since the professional commitment is kept regarding secrecy of this information. However, sentences giving wide access to the research participant's source-documents to the sponsor or third parties are frequently found in the ICF, which is not adequate from the ethical point of view, as it disrespects the right to privacy.

Examples: *"the sponsor will have access to your personal data", "sponsor's representatives may see your personal data",* but not limited to.

ABRACRO

c) **To omit that the medical chart may be consulted:** There are several guidance from the Federal Board of Medicine precluding access to medical charts when there are no express authorization from the patient. The ICF is the instrument through which the participant will express his/her consent and authorization so that source-documents are consulted. Therefore, if there is intention to consult medical charts during the research, it is not reasonable to omit this information in the ICF, which should clearly explain who will have direct access to the document (for example, monitors and auditors).

d) **Do not describe the mechanisms adopted to anonymize data:** This pending issue is appointed when the researcher does not describe in the ICF mechanisms that will be adopted to make data anonym (such as: through data codification, negligence of data that may identify the patient, etc.)

WHAT TO DO:

The ICF must be explicit regarding confidentiality and anonymization of data, ensuring that:

1) Research participant's data are confidential and will be referred to the sponsor or third parties only after due anonymization;
2) Besides researchers, the monitors and auditors of the sponsor may have access to participants' personal data (if applicable), with the professional commitment with absolute secrecy of information must be ensured in the ICF.
3) The medical chart may be consulted by researchers, and also by sponsor's monitors and auditors. Thus, this information must be expressly declared in the ICF.
4) The mechanism used to guarantee data confidentiality and anonymization must be explained (for example: data codification, access password of databases, etc.).

1.13. Freedom on refusing to participate in the study:

CNS Resolution No. 466 of 2012, item IV.3.d, provides that the ICF should ensure that the individual has all freedom to refuse to enroll and participate in the study, without any penalization by the researchers. Although this is not a frequent pending issue, sometimes the ICF omits this research participant's right, generating a pending issue.

WHAT TO DO:

The ICF must ensure, in a clear and affirmative manner, that the individual has all the freedom to refuse to participate in the study and that this decision will not incur in penalization by the researchers.

1.14. Freedom to withdraw the consent:

Item IV.3.d from CNS Resolution No. 466 of 2012 orientates that the ICF must ensure all freedom to the participant to withdraw the consent at any time during research conduction. For this, no type of written manifestation is required, except when it is related to withdrawal of biological material from a biobank or biorepository (CNS Resolution No. 441 of 2011, item 10.I).

Consent withdrawal comprehends a wide spectrum of situations ranging from giving up to participate in an isolated part of the research, but still with clear willing to perform the remainder ones, to the extreme where the participant desires to completely withdraw from the study. If the participant decides to completely withdraw from a research that was previously consented, it is implicit that the participant does not desire additional contact from the researchers, his/her privacy and right to an autonomous decision being respected. Therefore, it is not reasonable from the ethical point of view to obtain information from the participants after their complete withdrawal of study consent, whether by letter, telephone, e-mail, cell phone messages or any other manner. The participant has the right to withdraw

from the study at any time and not wanting to make more information available or receive contact from the researcher and his/her team.

It should also be considered the situation in which the individual does not want to participate in the study related activities anymore, but keeps his/her willing to be contacted by researchers for data updating. This is the case, for example, of individuals that for being extremely debilitated by the disease choose not going to the research site anymore, however agree to answer a questionnaire by telephone, letter or e-mail. In this situation, as long as the participant has previously consented, the researcher may contact him/her (or third parties) to update study-related data.

Most frequent pending issues related to this item are:

a) **To omit information about freedom to withdraw the consent:** This pending issue occurs when the researcher omits in the ICF the information that the research participant has the right to withdraw the ICF at any time and that this decision will not result in any penalization.

b) **To state that the researcher will contact the research participant after the consent withdrawal:** The participant has the right to withdraw from the study at any time and no longer wants contact with the research team. CNS Resolution No. 466 of 2012, item IV.3.e, establishes that the ICF must ensure the research participant's privacy. Therefore, sentences such as the following are not reasonable *"if you give up participating in the study, the team may contact you or your family to know how you are".*

c) **To state the researcher will keep on collecting data from the participant after the consent withdrawal:** The participant has the right to withdraw from the study at any time and no longer wants his/her personal data to be collected. CNS Resolution No. 466 of 2012, item IV.3.e, establishes that the

d) ICF may guarantee the research participant's privacy. Thus, sentences such as the following are not reasonable from the ethical point of view: *"if you give up participating in the study, the team may obtain information from you in your medical charts".* It is understood, however, that research participant's data obtained until the consent withdrawal (or that are of public domain) may be accessed by the researchers. However, it should be noted that CNS Resolution No. 340 of 2004, in item III.7, determines: *"All individuals may have access to their genetic data, as well as the right to withdraw them from banks where they are stored, at any time".*

WHAT TO DO:

1) The ICF must ensure, in a clear and affirmative manner, that the research participant has all freedom to withdraw his/her consent at any time of the research and that this decision will not generate penalization from the researchers.
2) The ICF must not state that the participant may be contacted or that his/her data will continue to be collected after the consent withdrawal.

1.15. Treatment interruption:

The most common pending issue related to this item is the inadequate use of terms or expressions in the ICF to define the treatment interruption or discontinuation, such as "to withdraw the study", "to exclude from the study" or "to end participation" (or something similar). Example: *"You may be withdrawn from the study if you present with side effects or get pregnant".* It is not reasonable from the ethical point of view to withdraw (exclude) someone from the study due to toxicity concerns, pregnancy, or any other situation that requires follow-up and assistance of the research participant. What in fact happens is the interruption (or discontinuation) of the treatment, and not the withdrawal of the research participant him/herself.

WHAT TO DO:

The ICF must not contain expressions such as "to withdraw from the study", "to exclude from the study" or "to end participation" to refer to interruption (or discontinuation) of the treatment during research, as the participant may require follow-up and assistance, such as for toxicity, pregnancy, etc.

1.16. Study interruption:

According to CNS Resolution No. 466 of 2012, item IV.3.c, the ICF must contain information about follow-up and assistance to research participants if the study is interrupted. Frequently, this explanation is omitted from the ICF, presenting only the information that the study may be interrupted. Example: *"this study may be interrupted at any time by the researcher or sponsor due to safety concerns".* However, it is common not present additional explanations ensuring to the participant the required assistance if the research is interrupted.

WHAT TO DO:

The ICF must ensure in a clear and affirmative manner that, in case of study interruption, the research participant will also receive the adequate assistance, at no cost, for the time needed.

1.17. Contact with the responsible researcher:

The ICF must contain means of contact with the responsible researcher, as the research participant (or legal responsible) may want guidance, clarify doubts, or even require assistance, for example, for an adverse reaction to the experimental drug. It is necessary, therefore, that a easy access contact if given to the research participant, 24 hours per day, 7 days per week, in case of urgency. According to CNS Resolution No. 466 of 2012, item IV.5.d, the ICF must contain *"the address and telephonic or other contact of the research responsible and of the local REC and Conep, where relevant".*

The most common related pending issues to this item are:

a) **Do not inform the means of contact with the responsible researcher:** The address and telephone number are minimally required by CNS Resolution No. 466 of 2012, but there is no restriction to inform other contacts also, as e-mail, SMS, FAX, but not limited to;

b) **Do not inform an easy access mean of contact to the research participant, in case of urgency** (24 hours per day, 7 days per week).

WHAT TO DO:
The ICF must contain, in an explicit manner, the means of contact with the responsible researcher (at least address and telephone), as well as make available an easy access mean of contact to the research participant, in case of urgency (24 hours per day, 7 days per week).

1.18. Means of contact with the REC/CONEP System:

It is frequent that the ICF does not contain REC and CONEP information to the research participant. Such information is relevant because the research participant (or legal responsible) may want to contact the REC (or CONEP, when needed) to clarify doubts or make a complaint. CNS Resolution No. 466 of 2012, in item IV.5.d, orientates that the ICF "*must contain the address and telephonic contact or other, of the responsible for the research and of the local REC and CONEP, where relevant*".

The most common pending issues related to this item are:

a) **Do not inform the contact of the REC (and CONEP, where applicable):** The address and telephone number are minimally required by CNS Resolution No. 466 of 2012, but there is no restriction to inform other contacts also, as e-mail, SMS, FAX, among others;

b) **Do not inform public service hours of the REC (and CONEP, where applicable);**

c) **Do not explain in a simple wording the REC attribution (and CONEP, where applicable).**

WHAT TO DO:
The ICF must contain, in an explicit manner, the contacts with the REC (at least address and telephone), as well as public service hours. It is also needed to explain in a simple wording what is a REC. When the study involves ethical analysis from CONEP, these recommendations should be extended to this Committee.

1.19. Field of signatures and initials:

CNS Resolution No. 466 of 2012 defines in item IV.5.d that: *"The Informed Consent Form must also, (…) be prepared in two original copies, initialed in all pages and signed at its end, by the person invited to participate in the research or legal representative, as well as by the responsible researcher, or by the people delegated by him/her, with the signature pages being on the same page (…)".*

The ICF signature field is a frequent reason for pending issue due to the following:

a) **Field addressed to the "responsible researcher":** Frequently, the field addressed to the researcher's signature comes identified as "responsible researcher". Considering that the "responsible researcher" not always will obtain the form, as this function may be delegated to someone from the research team, it is not reasonable the existence of a signature field exclusively addressed to him/her. It should be noted that CNS Resolution No. 466 of 2012 distinguishes the roles of "researcher" and "responsible researcher", defining the first as "*member of the research team, co-responsible for the integrity and well-being of research participants*" (item

II.15). Thus, CONEP has systematically requested that the term "responsible researcher" is replaced by "researcher" in the signature field (and also in the initials field), because it is more comprehensive and signals that some research team member (or the responsible researcher him/herself) will obtain the ICF.

b) **To use inappropriate terms in the signature and initials fields:** CONEP has been insisting that the signature and initials fields contain the terminology recommended by CNS Resolution No. 466 of 2012 (items II.15 and II.16). Frequently terms not predicted by the Resolution are used in these fields, such as "investigator" and "patient", which should be replaced, respectively, by "researcher" and "research participant/legal responsible".

c) **Additional information in the signature field:** Although it is understood that, from the juridical point of view, the ICF represents a contract between research participant and researcher/sponsor, the ICF has the anterior function of inform and respect the autonomy of the research participant and not properly establish a formal contractual link between both parties. Additional information, besides name and signature date, is not considered essential from the bioethical point of view. Thus, CONEP has been requesting that information such as, but not limited to, RG (ID number), CPF (Individual's Taxpayer Registry), address, is removed from the signature field.

d) **Signature fields in a separate sheet from the remainder of the ICF:** Signature fields must not be disposed in a separate sheet from the remainder of the ICF, except when this is not possible, due to the document formatting. It should be remembered that CNS Resolution No. 466 of 2012, item IV.5.d, states that the ICF must *"be prepared in two original copies, initialed in all pages and signed at the end, by the person invited to participate in the research or legal representative, as well as by the responsible researcher, or*

by the people delegated by him/her; signature pages must be in the same page (...)". When there is a clear break in the continuity of the ICF and signature fields are separated from the remainder of the document, CONEP has been requesting the correction of this issue.

WHAT TO DO:

Signature and initials fields must be identified according to the terminology provided for by CNS Resolution No. 466 of 2012, i.e., using the terms "researcher" and "research participant/legal responsible". Signature fields must not be separated from the remainder of the document (except when it is not possible due to formatting questions) and must not contain additional fields besides name and date.

1.20. Handling one original copy of the document, with signatures and initials:

CNS Resolution No. 466 of 2012, item IV.5.d, orientates that the ICF must be prepared in two "ORIGINAL COPIES" and initialed in all its pages (by the research participant and by the researcher). These requirements aim to ensure one of the participant's rights: receiving the ICF duly signed and initialed by him/her and the researcher. This item is a frequent reason of pending issue, or because the researcher uses the term "copy" instead of "original copy" to refer to the ICF, or because it does not ensure the supply of an original copy of the ICF. Still, pending issue is appointed if the ICF does not state that the document will be initialed in all pages.

a) **To omit information about the right of receiving an original copy of the ICF:** This pending issue occurs when the ICF does not inform that the research participant has the right to an original copy of the ICF signed and initialed in all pages. Item IV.3.f of CNS Resolution No. 466 of 2012 clearly states that the ICF must contain the *"guarantee that the research participant will receive one original copy of the Informed Consent Form".* Thus, not ensuring this right to the participant is a reason for pending issue.

ABRACRO

b) **To use the word "COPY":** Frequently, the researcher declares that a "COPY" of the ICF will be given to the research participant and the other will remain with the researcher. It is understood that "ORIGINAL COPY" and "COPY", even if similar from the semantic point of view, do not have the same practical meaning, because the first corresponds to the original document and the second must not be faithful to the primary document. Thus, the term "COPY" must not be used to designate the document, only "ORIGINAL COPY".

c) **Do not ensure that all pages will be initialed:** Frequently, the researcher ensures that the participant will receive an original copy of the ICF, but does not inform that all pages will be initialed. CNS Resolution No. 466 of 2012 states in item IV.5.d that the Informed Consent Form must *"be prepared in two original copies, initialed in all pages and signed at the end, by the person invited to participate in the research or legal representative, as well as by the responsible researcher, or by the people delegated by him/her (...)".*

WHAT TO DO:

The ICF must ensure, in a clear and affirmative manner that the research participant will receive one original copy (and not copy) of the document, signed by the research participant (or legal representative) and by the researcher, and initialed in all pages by both.

1.21. Biological material (specific aspects of the ICF):

The ICF must contain sufficient information so that the research participant minimally understands the nature of the biological material that will be collected, the amount, to which institution it will be forwarded, the purpose of the collection, the destination of the biological material after its processing (disposal or storage) and time of storage.

Stored biological samples may be used in future researches, as long as previously approved by the REC/CONEP System. However, a new consent must be obtained in case of biorepositories or biobanks that the participants chose by re-consenting at every new research. If there is intention of future research with the biological material, this information must be clearly contained in the ICF.

The most frequent pending issues related to this item in the ICF are described below:

a) **Do not give adequate information regarding biological material:** This pending issue is generated when the ICF does not adequately present information about collection, storage, use and final destination of biological material (for example: nature of the biological material, amount to be collected, reason for collection, place and time of storage, etc.).

b) **Do not inform about freedom to withdraw the consent for storage and use of biological material:** According to CNS Resolution No. 441 of 2012, item 10, *"The research subject, or his/her legal representative, at any time and without burden or prejudice, may withdraw the consent for storage and use of biological material stored at Biobank or Biorepository, the dropout being valid as of the date it is formalized. I – Consent withdrawal will be formalized by manifestation, written and signed, by the research subject or his/her legal representative, with return of existence samples being owned to him/her".* The pending issue is generated when the ICF does not inform about freedom of consent withdrawal for storage and use of biological material.

c) **Do not inform about intention of future researches with the biological material (if any):** If there is intention of future use of biological material in future researches, the ICF must inform this possibility and that the research participant will be contacted again for a new consent. According to Ordinance No. 2,201 of 2011, Article 18, *"The research subject must be*

contacted to consent, at every new research, to the use of human biological material stored on biorepository, formalizing the consent through a specific ICF". Pending issue is generated when the intention of future use of biological material and the need of a new consent are not described in the ICF.

d) **To use the term "donated material":** Some consent forms use the word "donated" to refer to the biological material that was given by the participant to the research. It should be clarified that the Brazilian legislation has well-defined rules for donation of cells, tissue, and organs to health assistance, but not in the research setting. Thus, the research participant does not "donate" biological material, but gives or supplies it to the research.

WHAT TO DO:

1) The ICF must contain, in a clear and complete manner, information related to collection, storage, use, and final destination of the biological material;
2) The ICF must inform that the consent for storage and use of biological material may be withdrawn at any time by the research participant;
3) The ICF must inform, if appropriate, about intention of future use of the biological material and the need for obtaining a new consent;
4) Do not use the term "donated material" to refer to biological material that was given (or supplied) to the research.

1.22. Human Genetics (specific ICF aspects):

Studies involving human genetics have certain ethical particularities that must be observed, especially when the study has the possibility to generate information that may produce psychological damage, stigmatization, and discrimination of the individuals, family members or groups (clinical genetics, population genetics and behavioral genetics studies). Item V of CNS Resolution No.

340 of 2004 orientates the information that must be contained in the ICF in this type of study. The main pending issues are related to this item of the Resolution:

ABRACRO

a) **Do not inform which genes or genic products that will be studied:** CNS Resolution No. 340 of 2004 determines that the ICF must contain *"clear explanation of exams and tests that will be performed, indication of genes/segments of DNA or RNA or genic products that will be studied and their relation with eventual condition of the research subject"* (item V.1.a). Pending issue is generated when the ICF does not discriminate genes (or genic products) that will be evaluated in the study. However, the Circular Letter No. 041/2015/CONEP/CNS/MS of March 27th, 2015 clarifies that if it is impracticable, from the practical point of view, to list all genes (for example, studies evaluating hundreds or thousands of them), the *"researcher may describe the studied genes in a pooled manner, according to functionality or effect (for example: genes related to emergence of cancer, inflammation, cell death, treatment response, etc.), not being necessary to list them individually".* It also clarifies that: *"In case of studies involving large scale genetic study (such as whole genome or exome sequencing), if the abovementioned pooling is unfeasible, the ICF must contain an explanation of the procedure, respecting the comprehension capacity of the research participant".*

b) **Do not ensure confidentiality of genetic data and research participant's privacy:** The ICF is frequently negligent in this aspect; this participant's right must be ensured in a clear and affirmative manner. Additionally, the ICF must guarantee that results from genetic exams will not be provided to third parties (such as, for example, insurance companies, employers, hierarchical supervisors, among others).

c) **Do not inform genetic data protection mechanisms:** CNS Resolution No. 340 of 2004 (item V.1.f) determines that the ICF informs mechanisms that will be adopted for genetic data protection. The negligence of this information in the ICF is frequent, which is a reason for pending issue.

d) **Do not ensure genetic counseling and clinical follow-up:** It is understood that this item is not applicable to all studies involving human genetics, but only to those with known clinical implications or that indeed require genetic counseling. However, where applicable, it is necessary to inform the research participant who will have the genetic counseling and clinical follow-up (or at least the institution or site where they will occur). Besides, it is necessary to ensure that counseling and clinical follow-up will be offered at no cost by the sponsor. Failure in this information is a frequent reason for pending issue.

e) **Do not ensure access to genetic exams results:** Results from any exam, not only those of genetic nature, must be ensured to the research participant whenever requested by him/her, unless when this information interferes in research outcomes. Therefore, sentences such as *"results from genetic exams will not be informed to you"* or *"you will not have access to genetic exams results"* are not acceptable.

f) **Do not inform that the research participant has the option to acknowledge or not genetic results:** Information generated in a genetic study may cause damage when they have implications to the participant, especially in cases of clinical and behavioral genetics. According to CNS Resolution No. 340 of 2004 (item V.1.d), the ICF must contain *"the type and grade of access to results of the subject, <u>with the option to acknowledge or not this information".</u>*

g) Therefore, when there is risk arising from the exam result to the research participant, the ICF must clearly inform this situation. This aims to ensure that an autonomous decision is made about acknowledging or not the results of genetic exams. The negligence of this information in the ICF (where applicable) is a reason for pending issue.

h)

WHAT TO DO:

1) The ICF must contain, in an explicit manner, the genes/segments of DNA/RNA that will be studied. However, if impracticable from the practical point of view to list all genes, it is acceptable that the researcher describes the genes to be studied in a pooled manner, according to functionality or effect;
2) The ICF must inform, in a clear and affirmative manner, that genetic data are confidential and will not be transferred to third parties (such as, for example, insurance providers, employers, hierarchical supervisors, but not limited to). Besides, genetic data protection mechanisms must be explained in the ICF;
3) Where applicable, the ICF must ensure, in a clear and affirmative manner, that the sponsor will provide the necessary genetic counseling and clinical follow-up to the research participant. It should also inform who will perform these procedures (or where they will be performed);
4) The ICF must ensure, in a clear and affirmative manner, that exam results will be informed to the research participant if he/she wants so;
5) Where applicable, the ICF must inform that genetic exams results may bring risks to the research participant. In this case, the ICF must inform that the participant has the right to acknowledge or not these exams results.

2. BIOLOGICAL MATERIAL STORED IN BIOBANK OR BIOREPOSITORY

The use of human biological material in researches is still reason of frequent doubts among researchers and Research Ethics Committees. In this subject, the following notes are necessary:

1) Either biorepository or biobank represent an organized collection of human biological material, collected with scientific research purposes, as defined by CNS Resolution No. 441 of 2011 (Art. 1) and MS Ordinance No. 2,201 of 2011 (Art. 3). The main characteristics of biobanks and biorepositories are highlighted in Chart 2.

2) The time of material storage does not define the constitution of a biorepository, with this ranging from some minutes to many years. What in fact defines constitution of a biological material bank is the intention of collection to scientific research. Thus, it is considered that all biological materials collected throughout a research constitute a biorepository. Frequently, clinical research protocols constitute biorepositories, as biological samples specific to the study in question are collected. Even samples addressed to exams considered routine in clinical trials (such as complete blood count and renal function) may be considered as parts of a short-term biorepository constituent, since they were collected specifically in a research setting.

3) Even if the biological material collected for a research is discarded after its processing, CONEP understands that the biological material will be stored before being processed and, because of that, considers there is formation of a biorepository (even if with a transitory and short-term character). This pre-processing storage period may be as short as a few minutes or as long as months or years.

ABRACRO

4) The biorepository may be of two types, namely:

- **Linked to a specific research project:** The biological material is used as provided for by the research protocol, without future additional analysis different from those predicted in the protocol. After processing and result acquisition, the remaining biological material is usually discarded, but the researcher may choose to keep it stored for some more time for repetition or confirmation of previously performed tests, or still, transfer it to a biobank (after authorization by the Research Ethics Committee and adequacy to current rules on the subject). Thus, in this type of biorepository, its validity is the period of the project to which it is linked, at most. For this type of biorepository, the required documentation (see Chart 3) is simpler than those required in the type of biorepository below.
- **Linked to a research project, aiming the possibility to use in future investigations:** in this type of biorepository, after processing and result acquisition, the researcher keeps the remaining biological material stored, aiming to use it in future studies. The intention of the researcher in keeping samples stored after their processing, performed as predicted in the research for which the samples were collected, is not the possibility of repeating tests and confirming obtained results (although it may be done), but to execute analysis different from those in the current protocol in one or more future studies. The validity period for this type of biorepository may be authorized for up to 10 years, with renovations authorized by REC/CONEP System being possible, upon presentation of rationale and report by the researcher. For each new research, a new Informed Consent Form must be applied (or, when duly justified, obtaining of Form waiver approval by the Committee) for use of previously collected stored biological material.

5) In the specific case of biorepository, the ICF template used in the research **must not contain** the excluding alternatives for the participant to choose to be consulted or not at every new research. Such options are applicable only to biobanks (CNS Resolution No. 441, of 2001 item 5, MS Ordinance No. 2,201 of 2011, Art. 4). At the end of the research, if there is interest to transfer the material stored in a biorepository to a biobank, the research participant must sign the specific ICF template for biobank, which was approved by CONEP, in the occasion of analysis of the respective Development Protocol. Therefore, both documents may be presented to the research participant (ICF addressed to research that will constitute a biorepository and ICF of biobank that will receive residual samples at the end of research) and decide about his/her participation, consenting or not, in the same opportunity.

6) It is wise to remember that the biological material belongs to the research participant, who has the right to withdraw, at any time, the consent to store and use the biological material stored in biobank or biorepository. This manifestation must be done in written by the participant or legal responsible (CNS Resolution No. 441 of 2011, Articles 9 and 10; MS Ordinance No. 2,201, of 2011, Art. 6).

7) Some researches use biological material from a collection that does not correspond neither to a biorepository nor to a biobank, being collected for assistance purposes. This is the case, for example, of biopsies stored in paraffin blocks of a Pathological Anatomy service. Biological materials obtained with assistance purposes may be used in research, as long as duly authorized by the participant, through an Informed Consent Form specific for the research (or, when duly justified, the obtaining of approval of Form waiver by the Research Ethics Committee). Additionally, such banks may require its registration as a biobank at CONEP, through presentation of a

Development Protocol, which will be evaluated according to the current rules for biobanks.

8) When registering research protocols on Plataforma Brasil, errors in the completion of the item "Will there be retention of samples for storage in bank?" are frequently verified. The term "bank" is mistakenly interpreted as "biobank", when, actually, it applies both for biobank and biorepository. Thus, whenever there is a collection of biological material in a research, this field on Plataforma Brasil must be marked with the option "YES".

9) In order to avoid pending issues in protocol evaluations, we request that the documents predicted in CNS Resolution No. 441 of 2011 and MS Ordinance No. 2,201 of 2011 are verified. The necessary documents, according to the type of biological material, are highlighted in Chart 3.

10) We emphasize that the regulation of a biorepository, mentioned in CNS Resolution No. 411/2011, item 2.IV, is nothing more than an operational detailing and the description of existence of infrastructure, as well as conditions of biological material storage and the manner they are disposed after use, which can be contained in the research project itself (in the Material and Methods section, for example) or as a separate declaration.

11) The inter-institutional agreement must be made when there is more than one institution contributing to the formation of a shared bank of biological material. The document must include how operationalization, sharing and use of human biological material stored in biobank or biorepository will be done, including the possibility of future dissolution of the partnership and the consequent sharing and destination of data and stored material, as predicted in the ICF (CNS Resolution No. 441 of 2011, item 13). In case of a shared biorepository, the agreement must be signed by the responsible researchers of each involved institution and by their institutional responsible persons. In

studies sponsored by the pharmaceutical industry, using (contracted or owned) central laboratories for sample storage, it is acceptable the submission of a single document with the sponsor declaration, ensuring the commitments provided for by item 13 of CNS Resolution No. 441 of 2011.

12) In researches constituting biorepository and which have intention to use the biological material in future researches, the ICF must contain consent to authorization for collection, deposit, storage, and use of human biological material linked to the specific research project. The same ICF should also inform the participant about the possibility of future use of the stored sample. Its use will be conditioned to:

- Submission of a new research project to be analyzed and approved by the REC/CONEP System and;
- Mandatorily, the re-consenting of the research participant, through a specific ICF referent to the new research project.

13) For research protocols intending to use previously collected samples that are stored in a biorepository of a previous research, two templates should be presented to the REC/CONEP System, for evaluation:

- The template that was used at the moment of biological material collection and storage (previous research); and
- The template that will be used to ask for authorization of use of stored biological material (current research).

ABRACRO

Below are the more frequently pending issues related to biological material banks (biorepositories and biobanks) in research protocols:

a) **To declare that there will be no formation of a biological material bank:** It is frequent the researcher states, erroneously, that there will be no formation of a biological material bank in a determinate study. If there is collection of biological material addressed to specific research, the formation of a biorepository is unequivocal.

b) **Do not give adequate information about biological material in the ICF:** This pending issue is generated when the ICF does no present, in a adequate manner, information about collection, storage, use, and final destination of biological material (for example: nature of the biological material, amount to be collected, reason for collection, site and time of storage, etc.). Pending issue is also issued when there is intention to use the biological material in future researches and this information is not contained in the ICF.

c) **Do not present the necessary documentation to constitute a biological material bank:** Failure in submitting the documentation predicted in the Chart 3 of this Manual is a reason for pending issue.

WHAT TO DO:

1) If there is collection of human biological samples in a research, it should be declared on Plataforma Brasil that there will be formation of biological material **bank.**
2) The ICF must present, in a clear and complete manner, information related to collection, storage, use ,and final destination of biological material (see item 1.21 of this Manual);
3) Submit the documentation predicted in the Chart 3 of this Manual.

ABRACRO

CHART 2 – Characteristics of human biological material banks used in research.

CHARACTERISTIC	BIOBANK	BIOREPOSITORY LINKED TO A SPECIFIC PROJECT	BIOREPOSITORY LINKED TO A SPECIFIC PROJECT, AIMING TO USE IN FUTURE RESEARCHES
Collection intention	Without research defined *a priori*.	For specific research.	For specific research and for others in the future.
Storage intention after biological material processing (if there is storage)	Use in future research(es).	Repeat and confirm results of the research at hand.	Repeat and confirm results of the research at hand and use in future research(es) (new research protocols).
Sample owner	Biobank participant (potential research participant.	Research participant.	Research participant.
Responsibility for keeping the biological material	Institutional.	Institutional.	Institutional.
Responsibility for managing the biological material	Institutional.	Researcher.	Researcher.
Deadline for storage	As long as the biobank exists.	As long as the research lasts.	Up to 10 years, extendable through researcher request and approval by the REC/CONEP System.
Consent for COLLECTION of biological material	Biobank ICF approved by CONEP (part of the biobank Development Protocol)	ICF specific of the research at hand.	ICF specific of the research at hand.
Consent for USE of biological material	Participant chooses if he/she wants to be consulted or not at every research in the ICF. A new specific ICF for each future research must be presented for those who desire to be consulted (re-consenting).	ICF specific of the research at hand.	ICF specific of the research at hand and new ICF at every future research.
Regulation	Development Protocol (approved by CONEP).	Operational and infrastructure description of the biorepository, which can be contained in the research project itself.	Operational and infrastructure description of the biorepository, which can be contained in the research project itself.
Patenting and commercial use of biological material	Not allowed.	Not allowed.	Not allowed.

ABRACRO

CHART 3 – Documents to be presented in protocols that intend to use biological material stored in biorepository or biobank.

DOCUMENTS TO BE SUBMITTED [1]	BIOBANK	BIOREPOSITORY LINKED TO A SPECIFIC PROJECT	BIOREPOSITORY LINKED TO A SPECIFIC PROJECT, AIMING TO USE IN FUTURE RESEARCHES
Inter-institutional agreement (operationalization, sharing, use of material and sharing in case of partnership dissolution) [2]	It is presented only in the occasion of analysis of the biobank Development Protocol.	Only if there is sample stored after processing for results confirmation and if there is more than one institution contributing to the shared biorepository.	Only if there is more than one institution contributing to the shared biorepository.
Declaration of the foreign responsible in the receiving institution regarding the access and future use of samples stored abroad, ensuring proportionality in participation.	Yes, if biological material is sent abroad.	No.	Yes, if biological material is sent abroad.
Declaration of the foreign responsible in the receiving institution regarding prohibition of patenting and commercial use of Brazilian biological material stored abroad.	Yes, if biological material is sent abroad.	Yes, if biological material is sent abroad.	Yes, if biological material is sent abroad.
Rationale for use of biological material in future studies.	Is presented only in the occasion of analysis of the biobank Development Protocol.	Not applicable (there is no intention of future studies).	Yes, the rationale should be presented in the protocol when there is prevision of biological material collection.
Commitment of submission of research protocol for the REC analysis and, where relevant, to CONEP, at every new research (future studies).	Is presented only in the occasion of analysis of the biobank Development Protocol.	Not applicable (there is no intention of future studies).	Yes, the commitment should be presented in the protocol when there is prevision of biological material collection.
Regulation of the biological material bank.	Yes, corresponds to the Development Protocol itself.	Yes, operational and infrastructure description, as well as material storage conditions, may be contained in the research project or as a declaration.	Yes, operational and infrastructure description, as well as material storage conditions, may be contained in the research project or as a declaration.
Document proving the approval of constitution and working of a bank	Yes (CONEP Approval Opinion, if the biobank is in Brazil). It is presented in the occasion of research proposition.	Not applicable.	Not applicable.
Consent to collect, store, use and send of biological material	An ICF template for collection and storage in biobank should be presented at the	The ICF template of the current research must be presented.	The ICF template of the research should be presented, in which the intention of future use of

CHART 3 – Documents to be presented in protocols that intend to use biological material stored in biorepository or biobank.

DOCUMENTS TO BE SUBMITTED [1]	BIOBANK	BIOREPOSITORY LINKED TO A SPECIFIC PROJECT	BIOREPOSITORY LINKED TO A SPECIFIC PROJECT, AIMING TO USE IN FUTURE RESEARCHES
	occasion of evaluation of the respect Development Protocol. When a research with prevision of use of material stored at the biobank is proposed, an ICF template for re-consenting of participants that opted to be consulted at every new research must be presented.		biological material is already explicit. Consider the explanatory notes [3] and [4] of this chart.
Form of Biological Material Transfer (FBMT)	A FBMT template should be presented for ethical analysis when the research project is proposed.	Not applicable.	Not applicable.

EXPLANATORY NOTES FOR CHART 3:

[1] Pertinent documents must be submitted in a single document or separately.

[2] The inter-institutional agreement must be done when there is more than one institution contributing to the formation of a shared biological material bank. The document must include how operationalization, sharing and use of human biological material stored in biobank or biorepository will be done, including the possibility of future dissolution of the partnership and the consequent sharing and destination of data and stored material, as predicted in the ICF (CNS Resolution No. 441 of 2011, item 13). In case of a shared biorepository, the agreement must be signed by the responsible researchers of each involved institution and by their institutional responsible persons. In studies sponsored by the pharmaceutical industry using (contracted or owned) central laboratories for sample storage, it is acceptable the submission of a single document with the sponsor declaration, ensuring the commitments provided for by item 13 of CNS Resolution No. 441 of 2011.

[3] Biorepository aiming the use in future researches: The ICF must contain consent to **authorization for collection, deposit, storage, and use of human biological material** linked to the specific research project (CNS Resolution No. 441 of 2011, items 2.II and 6; MS Ordinance No. 2,201 of 2011, Chapter II, Article 5

and Chapter III, Article 8). The same ICF should also inform the participant about the possibility of future use of the stored sample. Its use will be conditioned to: (a) Submission of a new research project to be analyzed and approved by the REC/CONEP System and; (b) Mandatorily, the re-consenting of research, through a specific ICF referent to the new research project (CNS Resolution No. 441 of 2011, item 6 and MS Ordinance No. 2,201/11, Chapter II, Article 5 and Chapter IV, Section II, Articles 17, 18 and 22).

[4] For research protocols intending to **use previously collected samples that are stored in a biorepository of a previous research**, two ICF templates should be presented to the REC/CONEP System for evaluation: (a) The template that was used at the moment of biological material collection and storage (previous research); and (b) The template that will be used to ask for authorization of use of stored biological material (current research).

ABRACRO

3. HUMAN AND MATERIAL RESOURCES

CNS Resolution No. 466 of 2012, item III.2.h, establishes that researches must "*rely on the necessary human and material resources that ensure the well-being of the research participant; researcher(s) must have adequate professional capacity to develop their function in the proposed project".* Lack of these resources may impair the study, making it futile. Thus, CONEP has been performing a detailed analysis of financial sources and financial resources directed to the research.

3.1. Budget:

The research project budget is a reason for pending issue when it is not consistent with the study expenses, when the detailing is not sufficient to understand the study costs or when the role of the sponsor is not clear. When the budget is complex, its submission as a separate document is acceptable, annex to Plataforma Brasil.

CNS Operational Rule No. 001 of 2013, item 3.3.e, establishes that all research protocols must *"details resources, sources, and destination: form and value of researcher remuneration; present in national currency, or when in foreign currency, with the official exchange rate in Real, obtained in the period of research proposal; present a prevision of participants and companions expense reimbursement, when needed, for items such as transportation and food and material compensation in cases listed in item II.10 of CNS Resolution No. 466 of 2012".*

The main pending issues related to this item are described below:

a) **Do not detail the budget:** All items necessary for study development must be discriminated in the budget. CONEP appoints pending issue when the researcher does not adequately explain destination of financial resources of the research. Describing costs, such as "related to molecular analysis" is too comprehensive and do not allow to infer the necessary investment with use and permanent materials.

b) **To omit items from the budget:** it is a reason for pending issue when the researcher omits from the budget costs related to procedures that are predicted in the study, even if they are already part of the research participant's assistance routine. If, in a clinical trial, performance of a chest x-ray is foreseen, the costs of the procedure must be budgeted in the research protocol.

c) **To declare that the study will not have costs:** Sometimes, the researcher does not present the study budget, justifying that the research "will have no costs". REC/CONEP System understands that there are no studies without cost. There will always be need for some degree of investment, even if minimal. It is not reasonable to imagine, for example, that a researcher does his/her study without registering information in some form or other instrument, such as recorder or camera, which requires a financial investment. Even if the researcher understands that resources for material acquisition, buying equipment and other expenses will not be needed, the researcher will use work hours paid by the institution to which he/she is linked, and use computers, filing services, but not limited, that generate expenses, even if minimal.

ABRACRO

WHAT TO DO:

The researcher must present a detailed budget, predicting all costs necessary to research development (human and material resources), without omitting those related to procedures predicted in the study.

3.2. Sponsor:

CNS Resolution No. 466 of 2012, item II.11, establishes sponsor as *"individual or legal entity, public or private, that supports the research, upon actions of*

financing, infrastructure, human resources or institutional support". The study sponsor definition is manifested in the Cover Page, in the field "Main Sponsor". Failure in pointing the study sponsor is a recurrent reason for pending issue. The main pending issues related to this item are described below:

a) **Do not indicate the main sponsor:** This pending issue is very common in investigator-initiated trials. In case the researcher does not have his/her own resources for the research and the institution does not provide financial contribution to that, even so the institution is considered the main study sponsor, as it supports the study through human and material resources. Therefore, investigator-initiated trials, without financial resources specifically addressed to it, must have the main sponsor field in the Cover Page signed by the institutional representative.

b) **To indicate the Public Health System as sponsor:** it is common that investigator-initiated trials state that research costs will be covered by the Public Health System (SUS). It should be clarified that SUS is not an individual or legal entity; therefore, it does not fall into in the definition for sponsor described in item II.11 of CNS Resolution No. 466 of 2012. The researcher may indicate in the "Main Sponsor" field on Plataforma Brasil, the institution, organ, agency, or company that will provide financial resources to the research.

WHAT TO DO:

1) Clearly indicate the main sponsor of the study on Plataforma Brasil and in the Cover Page. In case of investigator-initiated trials, without its own resources, the institution is the one taking responsibility of main sponsor;
2) SUS is not an individual or legal entity; therefore, it cannot be indicated as a research sponsor.

ABRACRO

3.3. Institutional Infrastructure:

Researches must rely on adequate institutional infrastructure to their performance. CNS Operational Rule No. 001 of 2013, item 3.3.h, establishes that research protocols must contain: *"(...) Demonstration of existence of infrastructure necessary and apt to the research development and to solve eventual problems arising from it, with a document that expresses institution and/or organization concordance through its major competent responsible person"*. Still, item 3.4.1.17 of the same Operational Rule defines that *"All research protocols must contain, mandatorily (...) Declaration signed by the institutional responsible, making available the existence of the infrastructure necessary for research development and to attend eventual problems resulting from it"*. The pending issues most frequently related to this item are:

a) **Do not present document proving the infrastructure necessary for clinical research development:** A document demonstrating that the institution has the adequate infrastructure for research development and conditions to give assistance to the participant must be presented, especially for situations of clinical urgency/emergency. This document must be signed by the institutional responsible that has competency for that (such as the technical director in a hospital institution);
b) **To present a demonstration of institutional infrastructure signed by the responsible researcher:** The person who has to ensure infrastructure is the institutional responsible with competence for such, not being reasonable that the researcher him/herself makes this guarantee.

WHAT TO DO:

The institutional responsible must present a document demonstrating that the proponent institution has the adequate infrastructure for development of the clinical research and conditions to give assistance to the participant in case of need, especially in urgency/emergency situations.

4. SCHEDULE

The study conduction schedule frequently presents inadequacy in its completion, being a reason for pending issue issued by CONEP. According to CNS Operational Rule No. 001 of 2013, item 3.4.1.9, *"All research protocols must mandatorily contain: (…) Schedule: informing total duration and different steps of the research, in number of months, with explicit commitment of the researcher that the research will only be initiated after approval by the REC/CONEP System".* The pending issues most frequently associated with this item are:

a) **To present study start date prior to the course on the REC/CONEP System:** Not uncommonly, the performance schedule indicates the study start on a date prior to the ethical analysis course. When this is observed, CONEP issues a pending issue, requiring schedule updating.

b) **Do not discriminate the research steps:** this pending issue is appointed when the researcher does not discriminate all research steps in the schedule, or when description of the steps is insufficient or inconsistent with the research project.

WHAT TO DO:

The execution schedule must indicate the study start on a date consistent with the course of the protocol on the REC/CONEP System. An explicit commitment of starting the study only after final approval of the REC/CONEP System must be presented. In addition, all research steps must be discriminated in the schedule.

5. COVER PAGE

Some fields of the Cover Page are frequent reason for pending issue due to inadequate completion of Plataforma Brasil by the researcher or, still, for leaving blank fields of mandatory completion. CNS Operational Rule No. 001 of 2013 defines in item 3.3.a: *"All research protocols must contain: (…) Cover page: all fields must be completed, dated, and signed with identification of the signatories. Information given must be consistent with those in the protocol. Signature identification must clearly contain full name and role of those who signed, preferably indicated by a stamp. Research title will be presented in Portuguese and will be identical to that in the Research Project."* Please find below the pending issues most frequently associated with the research protocol Cover Page:

a) **To complete in an incorrect manner the study area:** Field 3 of the Cover Page (Thematic Area) is incorrectly filled, with a certain frequency, or by negligence of the corresponding area of the study or by incorrect completion of an area not applicable to the research. This field is directly related to items marked on Plataforma Brasil, in the field "Thematic Area" (second page of completion on Plataforma Brasil, "Study Area" tab), being an obligation of the researcher the meticulous and accurate selection of pertinent items. It is convenient to clarify that the researcher may mark more than one thematic area option.

b) **Do not complete mandatory fields:** Certain fields of the Cover Page must be manually completed after printing, some being of mandatory character. In the case of researcher, it is necessary to date and sign the Commitment Term available in the Cover Page. In the part referent to proposing institution, name of institutional responsible, his/her role/function, CPF, signature, and date of commitment must mandatorily be completed. Regarding the sponsor field, the same items are of mandatory completion, when there is a main

sponsor. In the specific case of national (such as CNPq, FINEP, FAPs, etc.) and international (for example, US-NIH) funding agencies, and for understanding the difficulty to collect signature, it is accepted that the fields name, role/function, CPF, signature and date are left blank in the part reserved for sponsor, as long as the financial organ is expressly indicated in the Cover Page and a document proving the financing is presented. It should be clarified that the completion of the sponsor's name (field 18 of the Cover Page) is automatic, being linked to the field "FINANCING" of Plataforma Brasil. Only the name of the responsible for "Primary Financing" will be listed in the Cover Page as sponsor.

c) **Presence of institutional conflict of interest:** Sometimes, the researcher is also the institutional responsible, what makes him/her signs simultaneously the proponent institution fields and those addressed to researcher. This situation is clearly conflictive and may, under certain circumstances, compromise safety of research participants. Aiming to reduce potential conflicts of interest, in this situation, CONEP requires that other institutional responsible, without conflict of interest, signs the Cover Page.

WHAT TO DO:

For adequate completion of the Cover Page, it is necessary that the researcher completes information on Plataforma Brasil in an accurate manner, especially fields related to thematic areas. After printing the Cover Page, blank fields must be completed, especially those presenting commitment of the researcher, proponent institution, and sponsor. The researcher, when also institutional responsible, must not sign fields related to Proponent Institution.

6. STUDIES PROPOSED FROM ABROAD

Studies proposed from abroad must pay attention to CNS Resolution No. 292 of 1999, especially to requests of item VII. The pending issues most commonly related to this topic are:

a) **Do not present document with study approval by the REC in the country of origin:** CONEP issues a pending issue when the researcher does not present document with study approval by the REC (or equivalent) of the country of origin. CNS Resolution No. 292 of 1999 defines in item VII.1 that *"While preparing the protocol, special care must be taken for presentation of the following items: (…) Document of approval issued by Research Ethics Committee or institution equivalent in the country of origin, which will promote or that will also execute the project".* If still there is no official approval by the REC of the country of origin, being in ethical course, it is common that the researcher presents a document ensuring that he/she will provide the approval declaration as soon as it is issued. In this situation, CONEP has been requiring that the researcher ensure that, even if being approved by the REC/CONEP System, the study only starts after REC (or equivalent) approval in the country of origin and that the proving document is presented for acknowledgment of the REC/CONEP System as soon as it is available.

b) **Do not present rationale for the study not being performed in the country of origin**: Although not frequent, sometimes the proponent country of the study does not foresee research participant recruitment. This situation requires submission of a rationale to the REC/CONEP System, as provided for by CNS Resolution No. 292 of 1999, which defines, in item VII.2: *"While preparing the protocol, special care must be taken for presentation of the following items: (…) When project development is not foreseen in the country of origin, the rationale must be contained in the protocol for acknowledgment*

of the REC of the Brazilian institution". Pending issue is issued if the researcher does not submit a document justifying the recruitment or not of participants in the country of origin.

c) **Do not provide information about the registration status of the investigational product in the country of origin**: CNS Resolution No. 251 of 1997, in item IV.1.j, establishes that the research protocol must contain: *"Information about status of researches and product registration in the country of origin".* CNS Operational Rule No. 001 of 2013 defines on item 3.4.2.a: *"If the purpose is testing a health product or device, new in Brazil, of foreign origin or not, the current registration status at regulatory agencies of the country of origin must be indicated, if any".* Pending issue is issued when the researcher does not inform the registration status of the investigational product in the country proposing the study.

WHAT TO DO:

1) To submit document with the study approval by the REC in the country of origin. If the study is still in course in the ethical system of that country, a letter must be presented, ensuring that, even being approved by the REC/CONEP System, the study will only be started after approval by the REC in the country of origin and that the proving document will be presented by acknowledgment of the REC/CONEP System, as soon as it is available. To submit a rationale for not performance of the study in the country of origin (where applicable);
2) To submit registration status of the investigational product in the country of origin.

SUMMARY CHART:
FREQUENT PENDING ISSUES

ABRACRO

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
1.1.	ICF: Wording	a) To use inaccessible language; b) To translate in an inappropriate manner; c) To write the ICF as a declaration; d) To use the term "research subject"; e) To adopt inadequate title in the document (ICF).	The ICF must be a concise document, with easy language, written in an invitation format. The ICF must be carefully revised searching for technical terms and terms inappropriately used or translated. Extensive and excessively detailed consent forms are not desirable. The document title must contain the expression "Informed Consent Form".	**CNS RESOLUTION No. 466 of 2012:** *II.10 - research participant – individual that, in an informed and volunteer manner, or with clarification and authorization of his/her legal responsible, accepts to be researched. Participation must be at no cost, unless when Phase I and bioequivalence clinical researches.* *I.23 – Informed Consent Form – ICF – document in which the informed consent form of the participant and/or legal responsible is explained, in written manner, containing all necessary information, in clear an objective, easy-to-understand wording for the most complete clarification of the research to which proposes to participate;* *IV.5.b – The Informed Consent Form must (…) be adapted, by the responsible researcher, in researches with international cooperation designed in international scope, to ethical rules and to the local culture, always with a clear language, accessible to all, and in special, to research participants, taking special care so that it is of easy reading and comprehension".*
1.2	**ICF: Reimbursement**	a) To omit information about reimbursement; b) To limit items and value of the reimbursement; c) Do not ensure reimbursement to companion(s).	The ICF must ensure, in a clear and affirmative manner, the reimbursement of all expenses that the participant and his/her companion(s) will have while participating in the research.	**CNS RESOLUTION No. 466 of 2012:** *II.21 - reimbursement - material compensation, exclusively for expenses of participants and their companions, where necessary, such as transportation and food;* *IV.3.g - The Informed Consent Form must mandatorily contain: (…) make the guarantee of reimbursement*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
				explicit, as well as how expenses incurred to the research participants and arising from it will be covered;
1.3	**ICF: Assistance due to damage arising from the research**	a) To omit information about assistance; b) To condition assistance to prove causal relationship of the damage; c) To limit the type of assistance to the research participant; d) To limit the time of assistance to the research participant; e) Do not inform about the assistance at no cost.	The ICF must ensure, in a clear and affirmative manner, that the research participant will receive full and immediate assistance, at no cost (by the sponsor), for as long as necessary in case of damages arising from the research.	**CNS RESOLUTION No. 466 of 2012:** *II.3.1 – immediate assistance – is that one in emergency and without burden of any type to the research participant, in situations when it is needed;* *II.3.2 - full assistance – is that regarding complications and damages arising, directly or indirectly, from the research;* *II.6 – damage associated with or arising from the research - immediate or posterior worsening, direct or indirect, to the individual or collectivity, arising from the research;* *III.2.o – Researches in any area of knowledge, involving human beings, should observe the following requirements: (…) ensure to research participants conditions for follow-up, treatment, full assistance and guidance, according to the case, for as long as necessary, including in tracking researches;* *IV.3.c – The Informed Consent Form must mandatorily contain: (…) clarification about which follow-up and assistance the research participants will have the right to, including benefits or follow-ups posterior to the closure and/or interruption of the research;* *V.6 - The researcher, sponsor, and institutions and/or organizations involved in different research phases*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
				must provide immediate assistance, in terms of item II.3, as well as take responsibility for full assistance to research participants regarding complications and damages arising from the research".
1.4	**ICF: Assistance during and after pregnancy due to damages arising from the research:**	a) To omit information about assistance during and after pregnancy; b) To condition assistance to proving of causal relationship of damage to mother and/or child; c) To limit the type of assistance to mother and/or children; d) To limit time of assistance to mother and/or child; e) Do not ensure assistance to the child; f) Do not inform about of assistance at no cost.	The ICF must ensure, in a clear and affirmative manner, that mother and child will receive full and immediate assistance, during and after pregnancy, at no cost (by the sponsor), for as long as necessary.	**CNS RESOLUTION No. 466 of 2012:** *II.3.1 – immediate assistance – is that in emergency and without burden of any type to the research participant, in situations when it is needed;* *II.3.2 - full assistance – is that regarding complications and damages arising, directly or indirectly, from the research;* *II.6 – associated damage or arising from the research - immediate or posterior worsening, direct or indirect, to the individual or collectivity, arising from the research;* *III.2.o – Researches in any area of knowledge, involving human beings, should observe the following requirements: (…) ensure to research participants conditions for follow-up, treatment, full assistance and guidance, according to the case, for as long as necessary, including in tracking researches;* *IV.3.c – The Informed Consent Form must mandatorily contain: (…) clarification about which follow-up and assistance the research participants will have the right to, including benefits or follow-ups posterior to the closure and/or interruption of the research;* *V.6 - The researcher, sponsor and institutions and/or*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
				organizations involved in different research phases must provide immediate assistance, in terms of item II.3, as well as take responsibility for full assistance to research participants regarding complications and damages arising from the research".
1.5	**ICF: Indemnity**	a) To omit information about indemnity: b) To link indemnity to insurance contracted by the sponsor:	To ensure, in a clear and affirmative manner, that the research participant has the right to indemnity in case of damages arising from the study. It is not appropriate that the ICF contains restrictions, upon contracting an insurance, for indemnity or assistance.	**CNS RESOLUTION No. 466 of 2012:** *II.7 – indemnity – material coverage for reparation to damage caused by the research to the research participant;* *IV.3.h - The Informed Consent Form must mandatorily contain: (…) explanation of the guarantee of indemnity upon eventual damage arising from the research.* *IV.4.c – The Informed Consent Form in researches using experimental methodologies in the biomedical area, involving human beings, besides the provision in item IV.3 above, must mandatorily observe the following: (…) do not require from the research participant, under any argument, renounce from right to indemnity for damage. The Informed Consent Form must not contain reservation that precludes this responsibility or that implies to the research participant to resign his/her rights, including the right to pursue indemnity for eventual damages.* *V.7 - Research participants that may suffer any type of damage resulting from their participation in the research, foreseen or not in the Informed Consent Form, have the right to indemnity, from the researcher, sponsor, and institutions involved in the*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
				different research phases. **CIVIL CODE (LAW 10,406/2002):** Article 927 to 954 of Chapters I (Regarding the Obligation to Indemnity) and II (Regarding Indemnity), of Title IX (Regarding the Civil Responsibility; Book I – From Rights and Obligations).
1.6	**ICF:** **Birth Control**	a) Do not respect the participant's decision; b) To impose a contraceptive method; c) Do not inform that there are situations where contraceptive method use is not necessary; d) To omit information about contraceptive method supply; e) To give ambiguous information about responsibility of contraceptive method supply.	The ICF must ensure, in a clear and affirmative manner, that the choice of contraceptive method is a decision shared between the study doctor and the research participant and there are situations where birth control in not necessary. It also is ensured that the chosen contraceptive method, when it involves expenses, will be supplied by the sponsor, at no costs and for as long as needed.	**CNS RESOLUTION No. 466, of 2012:** *III.2.t – Researches in any area of knowledge, involving human beings, should observe the following requirements: (…) guarantee, for women that expressly declare to be exempt from the risk of pregnancy, either for not exerting sexual practices or for doing it in a non-reproductive manner, the right to participate in researches without mandatory use of contraceptives;* *III.2.o – Researches in any area of knowledge, involving human beings, should observe the following requirements: (…) ensure to research participants conditions for follow-up, treatment, full assistance and guidance, according to the case, for as long as necessary, including in tracking researches;*
1.7	**ICF:** **Post-study access to the investigational product**	a) To omit information about post-study access; b) Do not guarantee access to the investigational product in case of individual benefit; c) Do not ensure access to the investigational product to the control	The ICF should ensure, in a clear and affirmative manner, that at the end of study participation, individuals will continue to receive the investigational product at no cost through the sponsor, in case of investigational product, this being a choice of the study doctor, or of the personal physician. Besides, the ICF must ensure that the sponsor will provide, at no cost, the drug to all research	**CNS RESOLUTION No. 466 of 2012:** *III.2.n – Researches in any area of knowledge, involving human beings, should observe the following requirements: (…) ensure to research participants benefits resulting from the project, being it in terms of social return, access to research procedures, products or agents;* *III.2.o – Researches in any area of knowledge,*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
		group; d) To restrict prescription of experimental drug in case of individual benefit; e) To link the investigational product supply to an extension study; f) To limit the time of post-study access; g) To ensure access to the investigational product only to the experimental group; h) Do not inform about post-study access gratuity; i) To give ambiguous information about post-study access responsibility.	participants (experimental and control group), in case collective benefit is observed, identified in interim analysis or at the end of the study.	*involving human beings, should observe the following requirements: (…) ensure to research participants conditions for follow-up, treatment, full assistance and guidance, according to the case, for as long as necessary, including in tracking researches;* *III.3.d – Researches using experimental methodologies in biomedical area involving human beings, besides the provision in item III.2, should still: (…) ensure to all participants at the end of the study, through the sponsor, access to the best prophylactic, diagnostic, and therapeutic methods at no cost and for indeterminate time, that were shown to be effective"; (d1) the access should also be ensured in the interval between the end of individual participation and the end of the study; in this case, the guarantee can be given through an extension study, according to analysis duly justified from the participant's assisting physician".*
1.8	**ICF: "Study drug" expression**	Using the expressions "study drug" or "research drug" (or something similar) to refer simultaneously to the investigational product and to placebo.	The ICF should not use the terms "study drug" or "research drug" (or similar) to refer, simultaneously to the investigational product and placebo. This induces interpretation errors and impairs making an autonomous decision.	**CNS RESOLUTION No. 466 of 2012:** *I.23 – Informed Consent Form – ICF – document in which the informed consent form of the participant and/or legal responsible is explained, in written form, containing all necessary information, in clear an objective, easy-to-understand wording, for the most complete clarification of the research to which proposes to participate;* *IV.4.b – The Informed Consent Form in researches using experimental methodologies in the biomedical area, involving human beings, besides the provision in*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
				item IV.3 above, must mandatorily observe the following: (…) clarify, where relevant, about the possibility of including a participant in a control or placebo group, making clearly explicit the meaning of this possibility; *IV.5.b – The Informed Consent Form must (…) be adapted, by the responsible researcher, in researches with international cooperation designed in international scope, to ethical rules and to the local culture, always with a clear language, accessible to all, and in special, to research participants, taking special care so that it is of easy reading and comprehension".*
1.9	**Risks and Benefits**	a) To omit description of research benefits and/or risks; b) To overvalue benefits from an experimental treatment; c) To underestimate risks of an experimental treatment; d) Do not inform about measures and cautions.	1) The ICF must present, in a clear and objective manner, potential benefits from the research to the participant, without overvaluing them; 2) If the study does not anticipate any direct benefit to the participant, this information must be explicitly contained in the ICF; 3) Potential risks associated with the research must be described in the ICF, without underestimating them; 4) The ICF must explain measures and cautions that will be adopted to avoid or reduce risks associated with the research.	**CNS RESOLUTION No. 466 of 2012:** III.1.b - *Research ethics implies in (…) weighing between risks and benefits, known or potential, individual or collective, committing to the maximum of benefits and minimum of risks and damages.* IV.3.b - *The Informed Consent Form must mandatorily contain (…) explanation of possible risks and discomforts arising from the participation in the research, besides the benefits expected from this participation and presentation of measures and cautions to be implemented to avoid and/or reduce adverse effects and conditions that may cause damage, considering characteristics and context of the research participant.*
1.10	**ICF: Alternative therapeutic**	To omit information about alternative therapeutic methods.	The ICF should clearly describe alternative treatment methods to the research participant. If there are no alternative	**CNS RESOLUTION No. 466 of 2012:** IV.4.a - *"The Informed Consent Form in researches using experimental methodologies in the biomedical*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
	methods		methods, this must be made explicit in the ICF.	*area, involving human beings, beyond what is provided for by item IV.3 above, must mandatorily observe the following: (…) make explicit, where relevant, the existing alternative therapeutic methods."*
1.11	**ICF: Access to exam results**	To state, in the ICF, that the research participant will not have access to results of their exams.	The ICF must not contain restrictions for the research participant's access to results of exams performed during the study, unless there is a methodological rationale for it.	**CNS RESOLUTION No. 251 of 1997:** *III.2.i - The responsible researcher should: (…) Give access to exam and treatment results to the patient's physician or to the patient him/herself, whenever requested or indicated*
1.12	**ICF: Confidentiality and data anonymization**	a) Do not guarantee that data to be transferred to the sponsor or third parties are anonymized; b) To give wide access to source-documents; c) To omit that the medical chart may be consulted; d) Do not describing the mechanisms adopted to anonymize data.	The ICF must be explicit regarding confidentiality and anonymization of data, ensuring that: 1) Research participant data are confidential and will be referred to the sponsor or third parties only after due anonymization; 2) Besides researchers, monitors and auditors of the sponsor may have access to participants' personal data (if it is the case), with the professional commitment with absolute secrecy of information must be ensured in the ICF. 3) Medical charts may be consulted by researcher, and also by sponsor's monitors and auditors. The mechanism used to guarantee data confidentiality and anonymization must be explained (for example: data codification, access password of databases, etc.).	**CNS RESOLUTION No. 466 of 2012:** *III.2.i – Researches in any area of knowledge, involving human beings, should observe the following requirements: (…) predict procedures that ensure confidentiality and privacy, protection of image and the non-stigmatization of research participants, assuring non-use of information to damage persons and/or communities, including in terms of self-esteem, prestige and/or economical-financial aspects;* *IV.3.e - The Informed Consent Form must mandatorily contain (…) guarantee of maintenance of secrecy and privacy of research participants during all phases of the research;* **CFM RESOLUTION No. 1,638/2002:** *Art. 1– Defines medical chart as the single constituted document of a set of information, signs and registered images, generated from facts, events, and situations about the patient's health and assistance given to him, in legal, confidential and scientific character, making possible the communication among members*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
			4) Medical charts may be consulted by researcher, and also by sponsor's monitors and auditors.	*of the multi-professional team and continuity of the assistance given to the individual.* **CFM RESOLUTION No.1,605/2000:** *Art. 1- The physician cannot, without the patient's consent, reveal the contents of medical chart or sheet* **CFM RESOLUTION No. 1,931/2009 (MEDICAL ETHICS):** *Art. 85 - It is forbidden to the physician (…) Allow handling and knowledge of medical charts by people not obligated by professional confidentiality, when under his/her responsibility*
1.13	**ICF: Freedom to refuse to participate in the study**	To omit information about freedom of refusal.	The ICF must ensure, in a clear and affirmative manner, that the individual has all the freedom to refuse participate in the study and that this decision will not incur in penalization by the researchers.	**CNS RESOLUTION No. 466 of 2012:** *IV.3.d - The Informed Consent Form must mandatorily contain (…) guarantee of full freedom to the research participant to refuse to participate or withdraw consent, in any phase of the research, without any penalization.*
1.14	**ICF: Freedom to withdraw the consent**	a) To omit information about freedom to withdraw consent; b) To state that the researcher will contact the research participant after the consent withdrawal; c) To state the researcher will keep on collecting data from the participant after the consent withdrawal.	1) The ICF must ensure, in a clear and affirmative manner, that the research participant has all freedom to withdraw his/her consent at any time of the research and that this decision will not generate penalization from the researchers. 2) The ICF must not state that the participant may be contacted, or their data collected, after the consent withdrawal	**CNS RESOLUTION No. 466 of 2012:** *IV.3.d - The Informed Consent Form must mandatorily contain (…) guarantee of full freedom to the research participant to refuse to participate or withdraw consent, in any phase of the research, without any penalization.* *IV.3.e - The Informed Consent Form must mandatorily contain (…) guarantee of maintenance of secrecy and privacy of research participants during all phases of the research;* **CNS RESOLUTION No. 340 of 2004:** *III.7 - All individuals may have access to their genetic*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
				data, as well as have the right to withdraw them from banks where they are stored, at any time.
1.15	**ICF: Treatment interruption**	Use inadequate terms in the ICF to define treatment interruption or discontinuation.	The ICF must not contain expressions such as "withdraw from the study", "exclude from the study" or "end participation" to refer to interruption (or discontinuation) of the treatment during research, as the participant may require follow-up and assistance, such as for toxicity, pregnancy, etc.	**CNS RESOLUTION No. 466 of 2012:** See other pertinent text references in item: "ICF: Assistance due to damage arising from the research"
1.16	**ICF: Study interruption**	To omit information about assistance in case of study interruption.	The ICF must ensure in a clear and affirmative manner that, in case of study interruption, the research participant will also receive the adequate assistance, at no cost, for the time needed.	**CNS RESOLUTION No. 466 of 2012:** *IV.3 – The Informed Consent Form must mandatorily contain: (…) clarification about which follow-up and assistance the research participants will have the right to, including benefits or follow-ups posterior to the closure and/or interruption of the research;* See other pertinent text references in item: "ICF: Assistance due to damage arising from the research"
1.17	**ICF: Contact with the responsible researcher**	a) Do not inform the contacts with the responsible researcher; b) Do not inform an easy access contact to the research participant, in case of urgency**.**	The ICF must contain, in an explicit manner, the contacts with the responsible researcher (at least address and telephone), as well as make available an easy access contact to the research participant, in case of urgency (24 hours per day, 7 days per week).	**CNS RESOLUTION No. 466 of 2012:** *V.5.d – The Informed Consent Form must (…) be prepared in two copies, initialed in all pages and signed at the end, by the person invited to participate in the research or legal representative, as well as by the responsible researcher, or by the people delegated by him/her, with the signature pages being in the same sheet. In both copies the address and telephonic or other contact, of the research responsible and of the local REC and Conep must be contained, where relevant".*
1.18	**ICF: Means of contact with**	a) Do not inform the contact of the REC (and CONEP, where applicable);	The ICF must contain, in an explicit manner, the contacts with the REC (at least address and telephone), as well as public service hours. It is	**CNS RESOLUTION No. 466 of 2012:** *IV.5.d – The Informed Consent Form must (…) be prepared in two copies, initialed in all pages and*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
	the REC/CONEP System	b) Do not inform public service hours of the REC (and CONEP, where applicable); c) Do not explain in a simple wording the REC attribution (and CONEP, where applicable).	also needed to explain in a simple wording what is a REC. When the study involves ethical analysis from CONEP, these recommendations should be extended to this Committee.	*signed at the end, by the person invited to participate in the research or legal representative, as well as by the responsible researcher, or by the people delegated by him/her, with the signature pages being in the same sheet. In both copies the address and telephonic or other, of the research responsible and of the local REC and Conep must be contained, where relevant".*
1.19	**ICF: Field of signatures and initials**	a) Field addressed to the "responsible researcher"; b) To use inappropriate terms in the signature and initials fields; c) Additional information in the signature field; d) Signature fields in a separate sheet from the remainder of the ICF.	Signature and initials fields must be identified according to the terminology provided for by CNS Resolution No. 466, of 2012, i.e., using the terms "researcher" and "research participant/legal responsible". Signature fields must not be separated from the remainder of the document (except when it is not possible due to formatting questions) and must not contain additional fields besides name and date.	**CNS RESOLUTION No. 466 of 2012:** *II.10 - research participant – individual that, in an informed and volunteer manner, or with clarification and authorization of his/her legal responsible, accepts to be researched. Participation must by at no cost, unless when Phase I clinical researches and bioequivalence.* *II.15 – researcher - member of the research team, co-responsible for the integrity and well-being of research participants;* *II.16 – responsible researcher – person responsible for research coordination and co-responsible for the integrity and well-being of research participants;* *IV.5.d – The Informed Consent Form must (…) be prepared in two original copies, initialed in all pages and signed at the end, by the person invited to participate in the research or legal representative, as well as by the responsible researcher, or by the people delegated by him/her, with the signature pages being in the same page. In both original copies, the address and telephonic or other contacts of the research*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
				responsible and of the local REC and Conep must be contained, where relevant".
1.20	**ICF: Handling one original copy of the document, with signatures and initials**	a) To omit information about the right of receiving an original copy of the ICF; b) To use the word "COPY"; Do not ensure that all pages will be initialed**.**	The ICF must ensure, in a clear and affirmative manner that the research participant will receive one original copy (and not copy) of the document, signed by the research participant (or legal representative) and by the researcher, and initialed on all pages by both.	**CNS RESOLUTION No. 466 of 2012:** *IV.3.f – The Informed Consent Form must mandatorily contain: (…) guarantee that the research participant will receive one original copy of the Informed Consent Form;* *V.5.d – The Informed Consent Form must (…) be prepared in two original copies, initialed in all pages and signed at the end, by the person invited to participate in the research or legal representative, as well as by the responsible researcher, or by the people delegated by him/her, with the signature pages being in the same sheet. In both original copies the address and telephonic or other contacts of the research responsible and of the local REC and Conep must be contained, where relevant".*
1.21	**ICF: Biological material (specific aspects of the ICF)**	a) **Do not give adequate information regarding biological material;** b) **Do not inform about freedom to withdraw the consent for storage and use of biological material;** c) **Do not inform about intention of future researches with the biological material (if any);** d) **To use the term**	1) The ICF must contain, in a clear and complete manner, information related to collection, storage, use and final destination of the biological material; 2) The ICF must inform that the consent for storage and use of biological material may be withdrawn at any time by the research participant; 3) The ICF must inform, if appropriate, about intention of future use of the biological material and the need to obtain a new consent; 4) Do not use the term "donated	**CNS RESOLUTION No. 441/2011:** *Art. 1.1.I – Biobank: organized collection of human biological material and associated information, collected and stored with research purposes, according to regulation or pre-defined technical, ethical and operational rules, under institutional responsibility and management, without commercial purposes;* *Art. 1.1.II - Biorepository: collection of human biological material, collected and stored throughout the performance of a specific research project, according to regulation or pre-defined technical, ethical and operational rules, under institutional*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
		"donated material".	material" to refer to biological material that was given (or supplied) to the research.	*responsibility and managed by the researcher, without commercial purposes;* *Art. 6. The informed consent referent to collection, deposit, storage, and disposal of human biological material in Biorepository is formalized through specific ICF for each research, according to the predicted in the resolutions of the Brazilian National Board of Health (CNS).* *Art. 15.II.c About use of stored human biological material samples: (…) research projects that intend to use stored samples must include: (….) specific ICF for each new research or request for its waiver, according to the disposed in Art. 5 of this resolution.* **ORDINANCE No. 2,201/2011:** *Art. 5. The informed consent referent to collection, deposit, storage, and disposal of human biological material in Biorepository is formalized through specific ICF for each research, according to the predicted in the resolutions of the CNS.* *Art. 18 The research subject must be contacted to consent, at each new research, to the use of human biological material stored in biorepository, formalizing the consent through a specific ICF. Sole paragraph. When the impossibility to contact the research subject occurs, it is the REC's responsibility to authorize or not the use of stored human biological material.*
1.22	**ICF: Human**	a) Do not inform which genes or genic products	1) The ICF must contain, in an explicit manner, the genes/segments of	**CNS RESOLUTION No. 340 of 2004:** *V.1 – The ICF must be prepared (…) with special focus*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
	Genetics (specific ICF aspects):	that will be studied; b) Do not ensure confidentiality of genetic data and research participant's privacy; c) Do not inform genetic data protection mechanisms; d) Do not ensure genetic counseling and clinical follow-up; e) Do not ensure access to genetic exams results; f) Do not inform that the research participant has the option to acknowledge or not genetic results.	DNA/RNA that will be studied. However, if impracticable from the practical point of view to list all genes, it is acceptable that the researcher describes the genes to be studied in a pooled manner, according to functionality or effect; 2) The ICF must inform, in a clear and affirmative manner, that genetic data are confidential and will not be transferred to third parties (such as, for example, insurance providers, employers, hierarchical supervisors, but not limited to). Besides, genetic data protection mechanisms must be explained in the ICF; 3) Where applicable, the ICF must ensure, in a clear and affirmative manner, that the sponsor will provide the necessary genetic counseling and clinical follow-up to the research participant. It should also inform who will perform these procedures (or where they will be performed); 4) The ICF must ensure,_in a clear and affirmative manner, that exam results will be informed to the research participant if he/she wants so; 5) Where applicable, the ICF must inform that genetic exams results may bring risks to the research participant.	*on the following items:* *a) clear explanation of exams and tests that will be performed, indication of genes/segments of DNA or RNA or genic products that will be studied and their relation with eventual condition of the research subject;* *b) guarantee of secrecy, privacy and if appropriate, anonymity;* *c) genetic counseling and clinical follow-up plan, with the indication of the responsible persons, without costs to the research participant;* *d) type and degree of access to results by the subject, with the option to acknowledge or not this information;* *e) (…)* *f) information about measures of protection of individual data, results of exams and tests, as well as medical charts, that will only be accessible to involved researchers and that will not be allowed to third parties (insurance providers, employers, hierarchical supervisors, etc.);* *g) information about measures of protection against any type of discrimination and/or stigmatization, individual or collective;* **CIRCULAR LETTER No. 041/2015/CONEP/CNS/MS:** *2.a) The researcher may describe the studied genes in a pooled manner, according to functionality or effect*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
			In this case, the ICF must inform that the participant has the right to acknowledge or not these exams' results	*(for example: genes related to emergence of cancer, inflammation, cell death, treatment response, etc.), not being necessary to list them individually";* *2.b) In case of studies involving large scale genetic study (such as whole genome or exome sequencing), if the abovementioned pooling is unfeasible, the ICF must contain an explanation of the procedure, respecting the comprehension capacity of the research participant.*
2	**BIOLOGICAL MATERIAL STORED IN BIOBANK OR BIOREPOSITORY**	a) To declare that there will be no formation of a biological material bank; b) Do not give adequate information about biological material in the ICF; c) Do not present the necessary documentation to constitute a biological material bank.	1) If there is collection of human biological samples in a research, it should be declared on Plataforma Brasil that there will be formation of biological material bank. 2) The ICF must present, in a clear and complete manner, information related to collection, storage, use and final destination of biological material (see item 1.21 of this Manual); 3) Submit the documentation predicted in the Chart 3 of this Manual.	**CNS RESOLUTION No. 441/2011** (in full) **ORDINANCE No. 2,201/2011** (in full)
3.1	**RESOURCES: Budget**	a) Do not detail the budget; b) To omit items from the budget; c) To declare that the study will not have costs.	The researcher must present a detailed budget, predicting all costs necessary to research development (human and material resources), without omitting those related to procedures predicted in the study.	**CNS RESOLUTION No. 466 of 2012:** *III.2.h – Researches in any area of knowledge, involving human beings, must observe the following requirements:* **(…)** *rely on the necessary human and material resources that ensure the well-being of the research participant; researcher(s) must have adequate professional capacity to develop their function in the proposed project;* **CNS OPERATIONAL RULE No. 001 OF 2013:** *3.3.e) All research protocols must contain: (…)*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
				Financial budget: details resources, sources and destination: form and value of researcher remuneration; present in national currency, or when in foreign currency, with the official exchange rate in Real, obtained in the period of research proposal; present a prevision of participants and companions expense reimbursement, when needed, for items such as transportation and food and material compensation in cases listed in item II.10 of CNS Resolution No. 466 of 2012".
3.2	**RESOURCES: Sponsor**	a) Do not indicate the main sponsor; b) To indicate the Public Health System as sponsor.	1) Clearly indicate the main sponsor of the study in Plataforma Brasil and in the Cover Page. In case of investigator-initiated trials, without its own resources, the institution is the one taking responsibility of main sponsor; 2) SUS is not an individual or legal entity; therefore, it cannot be indicated as a research sponsor.	**CNS RESOLUTION No. 466 of 2012:** *II.11 – sponsor - individual or legal entity, public or private, that supports research, upon actions of financing, infrastructure, human resources or institutional support;* *III.2.h - Researches in any area of knowledge, involving human beings, must observe the following requirements:* **(…)** *rely on the necessary human and material resources that ensure the well-being of the research participant; researcher(s) must have adequate professional capacity to develop their role in the proposed project;* **CNS OPERATIONAL RULE No. 001 of 2013:** *3.3.e) All research protocols must contain: (…) Financial budget: to detail resources, sources, and destination: form and value of researcher remuneration; present in national currency, or when in foreign currency, with the official exchange rate in Real, obtained in the period of research proposal;*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
				present a prevision of participants and companions expense reimbursement, when needed, for items such as transportation and food and material compensation in cases listed in item II.10 of CNS Resolution No. 466 of 2012".
3.3	**RESOURCES: Institutional Infrastructure**	a) Do not present document proving the infrastructure necessary for clinical research development; b) To present a demonstration of institutional infrastructure signed by the responsible researcher.	The institutional responsible must present a document demonstrating that the proponent institution has the adequate infrastructure for development of the clinical research and conditions to give assistance to the participant in case of need, especially in urgency/emergency situations.	**CNS RESOLUTION No. 466, of 2012:** *III.2.h - Researches in any area of knowledge, involving human beings, must observe the following requirements:* **(…)** *rely on the necessary human and material resources that ensure the well-being of the research participant; researcher(s) must have adequate professional capacity to develop their function in the proposed project;* **CNS OPERATIONAL RULE No. 001 of 2013:** *3.3.d) All research protocols must contain: (…) Demonstrative of existence of the infrastructure necessary for research development and to attend eventual problems resulting from it, with document that expresses agreement of the institution and/or organization, through its major competent responsible.*
4	**SCHEDULE**	a) To present study start date prior to the course on the REC/CONEP System; b) Do not discriminate the research steps.	The schedule must indicate the study start on a date consistent with the course of the protocol on the REC/CONEP System. An explicit commitment of starting the study only after final approval of the REC/CONEP System must be presented. Besides, all research steps must be discriminated in the schedule.	**CNS OPERATIONAL RULE No. 001 of 2013:** *3.4.1.9) All research protocols must mandatorily contain: (…) Schedule: informing total duration and different steps of the research, in number of months, with explicit commitment of the researcher that the research will only be initiated after approval by the REC/CONEP System.*
5	**COVER PAGE**	A) To complete in an incorrect manner the study area;	For adequate completion of the Cover Page, it is necessary that the researcher completes	**CNS OPERATIONAL RULE No. 001 of 2013:** *3.3.a - All research protocols must contain: (…) Cover*

ITEM	THEME	WHAT IS THE PROBLEM?	WHAT TO DO	TEXT REFERENCE
		B) Do not complete mandatory fields; C) Presence of institutional conflict of interest.	information in Plataforma Brasil in an accurate manner, especially fields related to thematic areas. After printing the Cover Page, blank fields must be completes, especially those presenting commitment of the researcher, proponent institution and sponsor. The researcher, when also institutional responsible, must not sign fields related to Proponent Institution.	*page: all fields must be completed, dated and signed, with identification of the signatories. Information given must be compatible to those in the protocol. Signature identification must clearly contain full name and role of those who signed, preferably indicated by a stamp. Research title will be presented in Portuguese and will be identical to that in the Research Protocol.*
6	**STUDIES PROPOSED FROM ABROAD**	a) Do not present document with study approval by the REC in the country of origin; b) Do not present rationale for the study not being performed in the country of origin; c) Do not provide information about the registration status of the investigational product in the country of origin.	1) To submit document with the study approval by the REC in the country of origin. If the study is still in course in the ethical system of that country, a letter must be presented, ensuring that, even being approved by the REC/CONEP System, the study will only be started after approval by REC on the country of origin and that the proving document will be presented by acknowledgment of the REC/CONEP System, as soon as it is available. 2) To submit a rationale for not performance of the study in the country of origin (where applicable); 3) To submit registration status of the investigational product in the country of origin	**CNS RESOLUTION No. 292 of 1999:** *VII - While preparing the protocol, special care must be taken for presentation of the following items:* *VII.1 - Document of approval issued by Research Ethics Committee or institution equivalent in the country of origin, which will promote or that will also conduct the project.* *VII.2 - When the project development is not foreseen in the country of origin, the rationale must be contained in the protocol for acknowledgment of the REC of the Brazilian institution.* **CNS RESOLUTION No. 251 of 1997:** *IV.1.j – The Protocol must contain (…) Information about researches and product registration status in the country of origin.* **CNS OPERATIONAL RULE No. 001 of 2013:** *3.4.2.a - If the purpose is testing a health product or device, new in Brazil, of foreign origin or not, the current registration status at regulatory agencies of the country of origin must be indicated, if any.*

ABRACRO