NATIONAL HEALTH COUNCIL

NATIONAL COMMITTEE ON RESEARCH ETHICS (CONEP/CNS/MS)

ORIENTATION MANUAL:

FREQUENT PENDING

IN CLINICAL RESEARCH PROTOCOLS

Version 1.0

- 2015 -

SUMMARY

PRESENTATION

The history of the CEP/Conep System began in 1988 with the publication of the CNS Resolution No. 01 of 1988, which established that all institutions that that carried out research with human beings should have an “Ethics Committee”. the term “CEP” (Research Ethics Committee) came years later, with CNS Resolution No. 196 of 1996. This same rule determined that an Executive Working Group (previously constituted by CNS Resolution No. 170 of 1995) would be responsible for by the creation process of the National Commission of Ethics in Research – Conep. O The term “CEP/Conep System” appeared sixteen years later, when the CNS Resolution No. 466 of 2012 defined it as follows: *“It is integrated by the National Commission on Ethics in Research – Conep/ CNS/ MS of the National Health Council and by the Ethics Committees in Research – CEP – composing a system that uses mechanisms, tools and own instruments of interrelation, in a cooperative work that aims, especially to the protection of research participants from Brazil, so coordinated and decentralized through an accreditation process”.*

The CEP/Conep System aims to protect research participants in their rights and ensure that studies are conducted ethically. A research ethics necessarily implies: 1) Respecting the participants in their dignity and autonomy; 2) Weigh risks and benefits; 3) Avoid or reduce to maximum damage that is foreseeable; 4) Have social relevance; 5) Be fair and equitable; 6) Don't be futile and; 7) Respect the rights of participants. The rights that must minimally be ensured to research participants are listed not Table 1.

This manual highlights the so-called “repeat issues”. correspond to main ethical issues that Conep has pointed out in its opinions consubstantiated data relating to clinical research protocols, particularly those clinical trials with new drugs. There is no intention of exhausting the subject, but, solely to assist researchers and sponsors in the elaboration and submission of the protocols on the Brazil Platform. Thus, it is expected to substantially reduce the number of ethical notes made by Conep and, with that, accelerate the processing of protocols in the System.

TABLE 1 – Rights of research participants (*).

1) Receive the study information clearly;
2) Have the opportunity to clarify doubts;
3) Take the time necessary to make an autonomous decision;
4) Freedom to refuse to participate in the study;
5) Be free to withdraw your consent at any stage of the research;
6) Be free to withdraw consent for the use and storage of biological material;
7) Receive assistance (full and immediate) for damages, free of charge;
8) claim compensation for damages;
9) Receive reimbursement of expenses (including those of companions);
10) Have access to the results of the tests carried out during the study;
11) Request removal of your genetic data from banks where they are stored;
12) Have free post-study access to the investigational product (when applicable);
13) Have free access to the chosen contraceptive method (when applicable);
14) Receive free genetic counseling (when applicable);
15) Having assured the confidentiality of your data;
16) Having your privacy assured; It is
17) Receive a copy of the TCLE (signed and initialed by the research participant and by the researcher).

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

1. TERMS OF FREE AND INFORMED CONSENT (TCLE)

The Informed Consent Form (TCLE) is the document that, in addition to to explain the details of the research (justification, objectives, procedures, discomforts, risks, benefits, allocation groups, among other aspects), also must inform and ensure the rights of participants. The TCLE is the reason most frequent review of pendencies issued by Conep, mainly by wording inadequate use of the document, insufficient information, or failure to ensure the rights of research participants.

1.1. Essay:

The TCLE must be concise and easy to understand by a lay individual. It is not desirable that the document be long, with excessively detailed and with complex grammatical constructions.

Several pendencies are generated due to the use of technical terms inaccessible to a layperson or inappropriate translations of terms and expressions from another language to Portuguese.

The pendencies most frequently related to the writing of the TCLE are described below:

a) **Use inaccessible language:** CNS Resolution No. 466 of 2012, in item II.23, directs that the TCLE must *"contain all the necessary information, in clear and objective language, easy to understand, for the most complete explanation of the research in which he/she intends to participate".*

One of the most frequent pendencies is the use of technical terms inaccessible to a layman, especially medical or biomedical technical terms used in clinical trials with drugs or new procedures.

Whoever writes or revises the TCLE must put himself in the place of a participant lay research. It must resist the use of technical terms that naturally use in your day to day.

b) Perform translation inappropriately: Item IV.5.b of CNS Resolution No. 466 of 2012 advises that the TCLE must *"be adapted by the researcher responsible, in researches with foreign cooperation conceived in international scope, ethical norms and local culture, always with language that is clear and accessible to all and, in particular, to the participants of the research, taking special care to make it easy to read and understanding".* It is very common that studies translated from the English language often feature the term "research study" (from English, *"research study"),* which does not apply in Portuguese because it is of pleonasm. Although it is pending with lesser implication in terms of ethical, Conep has insisted that the TCLE must be properly adapted to the Portuguese language. Therefore, the term should be used "study" or "research", but not the expression "research study", which, in Portuguese, it sounds redundant. are also frequent the situations in which poorly elaborated translations make the sentence meaningless sense. Therefore, it is absolutely essential to carry out a thorough review of the final version of the TCLE in Portuguese.

c) **Write the TCLE in the declaration format:** The consent form is a document that must be written in invitation format. not suitable that the body of the TCLE be written as a declaration, as this can reduce the autonomy of the individual. Example: *"I know there will be material collection"* or, even, *"I declare that I will attend the visits", "by signing this document, I authorize the consultation of the medical records",* etc. The sentences must be written with statements by the researcher addressed to the participant of search. Examples: "Some blood will be collected from your patient's vein. arm (...)", "we would like to ask for authorization to verify your medical record". However, it is acceptable that the final part of the TCLE, in which the signature fields and in which participant expresses his desire, be written as a declaration.

d) Use the term "research subject": CNS Resolution No. 466 of 2012 replaced the term "research subject" (provided for in CNS Resolution No. 196 1996) by "research participant". However, the old term is still often found in the Terms of Consent. It is understood that the terminology adopted by CNS Resolution No. 466 of 2012 must be employed in all research protocol documents, including the TCLE.

e) Adopt inappropriate title in the document (TCLE): It is frequent the use of different terms and expressions to refer to the TCLE, which are not recognized by CNS Resolution No. 466 of 2012. For example: *"research authorization form", "research authorization form", participation in study",* among others. Conep has indicated pending in these cases, requesting the use of the expression "Term of Free and Informed Consent". It is acceptable that, in addition to this expression, put some specification, such as, for example, "to genetic study".

WHAT TO DO:

The TCLE must be a concise document, with easy language, written in the format of invitation. Carefully review the TCLE in search of technical terms and inappropriately used or translated. Long consent terms and overly detailed are not desirable. The title of the document must contain the expression "Term of Free and Informed Consent".

1.2. Refund:

CNS Resolution No. 466 of 2012, item II.21, defines compensation as *"material compensation, exclusively for the expenses of the participant and his companions, when necessary, such as transportation and food".* yet, the item IV.3.g directs that the TCLE must contain *"explanation of the guarantee*

of reimbursement and how the expenses incurred by the participants of the research and resulting from it".

Expenses can also be covered through material provision prior, as defined by item II.18 of Resolution No. 466 of 2012: *"compensation material, exclusively for the participant's transportation and food expenses and their companions, when necessary, prior to their participation in the research".*

Reimbursement of expenses arising from participation in the research is a reason pending for the following reasons:

a) Omit information about the reimbursement: this pendency occurs when the researcher omits in the TCLE the information that the participant research and their accompanying person(s) are entitled to reimbursement of expenses resulting from the research.

b) Limit items and amounts of compensation: researchers often limit reimbursement, stipulating the items that will be reimbursed and/or the amounts maximums. These limitations appear, for example, in sentences like: *"you will receive R$ 100.00 for the expenses you have with the study"* (limitation of values), or, still, "you will be reimbursed for food and transportation" (item limitation). It is prudent to note that the Resolution does not stipulates which items must be reimbursed, but only exemplifies them *("... such as transportation and food").*

c) Failure to guarantee reimbursement to companion(s): It is also a reason of pendency when the researcher assures reimbursement only to the research participant, but not to their companion(s). AND prudent to note that CNS Resolution No. 466 of 2012 (item II.21) provides for the reimbursement of expenses resulting from the research not only to the participant, but also for those accompanying him.

WHAT TO DO:

The TCLE must clearly and affirmatively ensure the reimbursement of all expenses that the participant and his companion(s) will have when participating in the research.

1.3. Assistance due to damage resulting from the research:

CNS Resolution No. 466 of 2012 defines damage associated (or resulting) from research the *"immediate or subsequent harm, direct or indirect, to the individual or to the collectivity, resulting from the research" (item* II.6). Also in item V.6, the aforementioned Resolution defines that *"The researcher, the sponsor and the institutions and/or organizations involved in the different phases of the research must provide immediate assistance, under the terms of item II.3, as well as being responsible for full assistance to research participants with regard to complications and damage resulting from the search".*

The most frequently pending issues related to this item are described below:

a) Omitting information about assistance: This pendency occurs when the researcher omits in the TCLE the information that the research participant you have the right to assistance in case of damage resulting from the research;

b) Condition the assistance to prove the causal link of the damage: It is up to Please note that the research participant assistance guarantee cannot be conditioned to proof of a causal link, that is, of the establishment of definitive causality between the study and the damage. Such verification process could take time, which ultimately analysis, would further harm the research participant. it's unreasonable from an ethical point of view, declare in the TCLE that the participant will receive assistance if the research is proven to have caused harm.

c) **Limit the type of assistance to the research participant:** It is common to find in the TCLE sentences, for example, like this one: *"you will receive assistance*

doctor if you are harmed by the study". The problem in this case is that there are limitation for the type of assistance that will be provided to the participant of research (in this case, medical assistance). Depending on the type of damage, it is It is possible that the participant needs assistance from other professionals, such as, for example, in the area of Nursing, Physiotherapy, Psychology, Nutrition, Occupational Therapy, among others. The Resolution is clear in affirm that the researcher must provide comprehensive care, and not just in a certain area.

d) Limit the time of assistance to the research participant: It is not reasonable from an ethical point of view to limit the maximum time in which it will be Assistance provided to the research participant in case of damage.
Example: *"you will have assistance while participating in the study".*
CNS Resolution No. 466 of 2012 provides that damages may be identified after the research and, therefore, the responsibility of assistance does not end with the completion of the study.

e) Not informing about the gratuity of the assistance: Sometimes, the pendency is not related to the limitations described above, but, simply because the researcher does not explain in the TCLE that the assistance will be provided free of charge (by the sponsor).

WHAT TO DO:
The TCLE must clearly and affirmatively ensure that the research participant will receive full and immediate assistance, free of charge (by the sponsor), by the as long as necessary in case of damage arising from the research.

1.4. Assistance during and after pregnancy due to damage resulting from search:

Although there is no specific item in CNS Resolution No. 466 of 2012 to this In this regard, it is a breakdown of the damage assistance guarantee already described

previously, but with implications not only for the mother (research participant or partner of a participant), but also for the child.

It is not about taking responsibility for prenatal care, but provide the assistance that is necessary in case of damage resulting from the research to the mother and/or child, during or after pregnancy. Follow the pendencies often related to this item:

a) Omitting information about assistance during and after pregnancy: This pendency occurs when the researcher omits in the TCLE the information of that the mother and child are entitled to assistance in the event of damage resulting from the research;

b) Condition assistance to proof of a causal link to the harm to the mother and/or the child: It is unreasonable from an ethical point of view to condition the assistance in proving the causal link of the damage caused by the mother and/or child study. Statements such as: *"You will receive assistance during pregnancy if it is proven that the research caused harm to you and your baby."*

c) **Limit the type of assistance to the mother and/or the child:** The type of assistance to be provided to the mother and/or child must be integral. The expression *"medical monitoring of pregnancy"* is often found in the TCLE to refer to the assistance that will be provided to the participant of search. It is understood that the word "follow-up" has connotations passive and therefore would not be appropriate to use to describe the assistance that must be provided during this period. It is also not suitable limit assistance to the medical area only, which should extend to all areas that are needed. For example, it is possible that a research participant needs assistance from a professional in the field of Psychology because of emotional distress resulting from abortion secondary to the use of an experimental drug.

d) Limit the time of assistance to the mother and/or child: The responsibility assistance to the mother and/or child does not end with the end of pregnancy, and should also be provided in the period after, for as long as is necessary.

e) Not ensuring assistance to the child: Ensuring full assistance and at least time that is necessary for the mother is not enough from the point of view ethical, and this guarantee should also be extended to the child, before and after childbirth.

f) Not informing about the gratuity of the assistance: This pending issue is generated when the TCLE does not clearly and affirmatively ensure that the assistance provided to the mother and/or child is free (by the sponsor).

WHAT TO DO:

The TCLE must ensure, in a clear and affirmative way, that the mother and the child will receive, comprehensive and immediate assistance, during and after pregnancy, free of charge (at sponsor), for as long as it takes.

1.5. Indemnity:

CNS Resolution No. 466 of 2012 (item IV.3) defines that *"participants of the research that come to suffer any type of damage resulting from their participation in the research, foreseen or not in the Free and Informed Consent Form, have the right to compensation, by the researcher, the sponsor and the institutions involved in the different phases of the research" (item* V.7). It should be emphasized that the issue of compensation is not a prerogative of CNS Resolution No. 466 of 2012, being originally provided for in the Civil Code (Law 10,406 of 2002), especially in articles 927 to 954, of Chapters I (Obligation to Indemnify) and II (Da I (Obligation to Indemnify) Indemnify), Title IX (Civil Liability).

The most frequently pending issues related to this item are:

a) Omitting information about the indemnity: This pendency occurs when the researcher omits in the TCLE the information that the research participant is entitled to compensation in case of damages resulting from the research;

b) Binding the indemnity to insurance contracted by the sponsor: Some Terms of Consent provide information that the sponsor contracted specific insurance to carry out the research. It is understood, however, that the indemnification responsibility rests with the sponsor, the researcher and institution, regardless of the existence of a safe. Insurance represents an instrument to minimize possible losses sponsor and does not add security to the participant of search. In addition, the amounts of compensation or other expenses do not may be limited by the amount contracted by the sponsor. O CEP/Conep system does not request proof of insurance existence to perform the search. What must be ensured in the TCLE is the information that the research participant is entitled to compensation.

WHAT TO DO:

Ensure, in a clear and affirmative way, that the research participant has the right to compensation in case of damage resulting from the study. It is not appropriate that the TCLE contains restrictions, upon contracting insurance, for the indemnification or assistance.

1.6. Contraception:

It is understood that certain experimental drugs or procedures may be embryotoxic or teratogenic and that, therefore, there is a need to use a method contraceptive during and/or after the research. Deciding the best method contraceptive to be used is a shared decision between the doctor and the research participant. So much so that article 42 of Resolution CFM 1931 of 2009 (Code of Medical Ethics) vetoes the doctor *"Disrespecting the patient's right to decide*

freely about the contraceptive method, always clarifying the indication, safety, reversibility and risk of each method".

It is worth noting CNS Resolution No. 466 of 2012, item III.2.t, which guides: *"The research, in any area of knowledge involving human beings, should observe the following requirements: (...) guarantee, for women who declare themselves expressly exempt from the risk of pregnancy, either because they do not engage in sexual practices or for exercising them in a non-reproductive manner, the right to participate in research without the mandatory use of contraceptives".* In this way, one should not condition the someone entering a research imposing a specific type of method contraceptive. Even because, there are situations in which pregnancy is not naturally possible and therefore it would be unreasonable from an ethical point of view to impose the use of any method of contraception.

When the contraceptive method chosen by the research participant imply expenses (example: oral contraceptive, condom, intrauterine device, etc.), it will be up to the researcher and the sponsor to provide the method in a free of charge for as long as necessary. CNS Resolution No. 466 of 2012 (item III.2.o) advises that research should *"assure research participants the conditions follow-up, treatment, comprehensive care and guidance, as appropriate, as necessary, including in tracking surveys".*

Below are the most frequent issues related to contraception:

a) Not respecting the participant's decision: It is not acceptable for the participant's doctor to study imposes the choice of the best contraceptive method for the research participant. Sentences such as *"the doctor will decide which method contraception is better for you",* in addition to violating the Code of Ethics Doctor, do not respect the research participant in his ability to make an autonomous decision. The TCLE must ensure that the choice of best contraceptive method is a shared decision between the study physician and the research participant.

b) Impose a contraceptive method: Some studies impose the contraceptive method contraceptive to the participant, which violates not only CNS Resolution No.

466 of 2012, as well as the Code of Medical Ethics. are unreasonable sentences like: “you should use a pill (oral contraceptive) during the study”. There are also studies that ask the participant to research sexual abstinence for a period before, during or after search. Such a request is only justified when there is a need methodological or clinical (example: to perform the Papanicolaou exam, healing from surgery performed on the vagina or cervix). In this case, it is the imposition of a contraceptive method. The TCLE must ensure that the choice of contraceptive method is a decision shared between the study physician and the research participant.

c) Not informing that there are situations in which it is not necessary to use a method contraception: The use of a contraceptive method may be waived in situations where pregnancy is not naturally possible, as in the case of women without a uterus or who are in the postmenopausal period, with history of surgical sterilization (tubal ligation or vasectomy), individuals who maintain a homoaffective relationship or who do not have any kind of sexual relationship. The TCLE must be clear in claim that the use of a contraceptive method can be waived in particular situations, such as, for example, those described.

d) Omitting information about the supply of the contraceptive method: This pendency occurs when the TCLE does not inform that the participant is entitled to the chosen contraceptive method free of charge, when this implies expenses;

e) Giving ambiguous information about the responsibility for providing the contraceptive method: The TCLE is not always clear regarding the free supply of the contraceptive method chosen by the research participant. There are consent forms that state that the research participant *“will have free access to the contraceptive method chosen".* This is an ambiguous statement, because “free access”

could also happen through the Unified Health System, which is not acceptable. The responsibility for providing the contraceptive method is of the sponsor/researcher and not of the Brazilian Government in a scenario of research.

WHAT TO DO:

The TCLE must clearly and affirmatively ensure that the choice of method contraception is a shared decision between the study doctor and the research participant and that there are situations in which contraception is not required. It should also be ensured that the chosen contraceptive method, when involve expenses, will be provided by the sponsor, free of charge and for as long as is necessary.

1.7. Post-study access to investigational product:

CNS Resolution No. 466 of 2012, item III.3.d, states that surveys must *"assure all participants at the end of the study, on the part of the sponsor, free and indefinite access to the best prophylactic methods, diagnostic and therapeutic methods that have been shown to be effective".* It still complements the sub-item (d1) that *"access will also be guaranteed in the interval between the end of the individual participation and the end of the study, in which case this guarantee may be given through an extension study, according to a duly justified analysis of the participant's attending physician".*

The benefit weighting of the investigational product is done in two ways distinct: collectively or individually. The individual benefit analysis is performed when the participant ends their participation in the study, and not when the research is completed. If the investigational product has proved to be beneficial to the individual, the supply of the product must be ensured for as long as necessary (guarantee of continuity). The definition of individual benefit is not a prerogative exclusive to the study physician, and may also be performed by the personal physician (assistant) of the participant. The collective benefit is the one defined in analyzes interim or final, when it is possible to conclude whether the investigational product proved to be

beneficial or not to the experimental group. In this case, the supply of the product investigation should also extend to the control group.

However, there are situations in which post-study access is not feasible, as in self-limiting clinical conditions (eg, studies in gastrointestinal infections acute 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 study closure.

Below are the pendencies frequently related to the issue of post-study access:

a) Omit information about post-study access: This pendency occurs when the researcher omits in the TCLE the information that the participant research has the right to access the investigational product after the termination of the study (or your participation in the study);

b) Not ensuring access to the investigational product in case of benefit individual: Access to the investigational product should not be guaranteed only after the end of the study, but at the end of the individual participation, in case of benefit. are not enough to guarantee access to the investigational product sentences such as: *"at the end of the study, you will receive the drug if it is beneficial".* In this case, the sentence contemplates only the collective benefit, not the individual benefit.

c) Not ensuring access to the investigational product to the control group: It is common for the researcher to ensure the continuity of treatment in the TCLE end of individual participation (individual benefit), but omits the guarantee of access to the product for the control group when there is benefit in the group experimental. It is necessary to ensure in the TCLE 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 (provided there is clinical indication for the use of the experimental product).

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

e) Link the supply of the investigational product to the study of extension: Frequently, the TCLE links the guarantee of post-study access mandatory participation in an extension study, which is not reasonable from an ethical point of view. The point is not to offer the study of extension as an alternative to access the investigational product (tell if in passing, permitted), but rather the imposed obligation. In case benefits, the sponsor must ensure the supply of the product investigation, even if the individual does not want to participate in the study of extension;

f) **Limit post-study access time:** Post-study provisioning does not may be limited to a specific period of time and must occur at least time as needed. It is not acceptable, for example, that the TCLE state: *"you will receive the investigational drug for a maximum of 6 months after you terminate your participation in the study".* However, it is understood that there are situations in which the investigational product does not may be administered beyond a maximum period of time, such as, for example, for reasons of toxicity. In this case, the justification for this limitation must be clearly explained in the TCLE;

g) Ensure access to the investigational product only to the group experimental: In case of benefit observed in interim or final analysis in the experimental group (collective benefit), one must ensure the

provision of the investigational product also to the control group (if there is a clinical indication for this).

h) Not informing about free post-study access: This pending is generated when the TCLE does not ensure, in a clear and affirmative way, that the post-study supply of the investigational product will take place in a free.

i) **Giving ambiguous information about the responsibility for post access study:** Sometimes, the TCLE is ambiguous when informing the conditions and post-study investigational product supply responsibilities, which must be provided free of charge by the sponsor. assert that the research participant *"will have free access to the medication experimental"* is not enough, because "free access" also could be given, in theory, by the Unified Health System if the product already was available, for example, in clinical trials for new applications of an already registered drug. The responsibility of post-study supply of investigational product is up to the sponsor and not from the Brazilian government.

WHAT TO DO:

The TCLE must clearly and affirmatively ensure that, at the end of participation in the study, subjects will continue to receive the investigational product free of charge by the sponsor in case of individual benefit, this being a weighting of the study physician or even the personal physician. Furthermore, the TCLE must ensure that the sponsor will provide the drug free of charge to all research participants (experimental and control group) if benefit is observed collective, identified in interim analysis or at the end of the study.

1.8. Expression “Study drug”:

It is very common to use the term “study drug” or “research drug” (or something similar) in the TCLE to refer, simultaneously, to the investigational product and to the placebo. although it is understood that, technically, the study drug is, in fact, the drug experimental or control, this concept is not easy to understand for a layman and leads to misinterpretation.

In general, the definition of “study drug” is found in the TCLE in a single sentence, short, embedded in a long document, which may not be noticed clearly by the reader and impair the semantic understanding of the term in the remainder of the document. Example: *“This term will refer to the experimental drug and the placebo as study drug”.* From this point of the text forward, only the The expression “study drug” is used throughout the rest of the TCLE, in order to indistinctly for the experimental and control groups.

In this context, certain sentences, such as *“you will receive the medicine from the study to treat your illness”* are inadequate. This apparent simplification of terms can make a layman mistakenly believe that he will receive the product investigation, when, in fact, they have a concrete possibility of being allocated in the group placebo. This may mislead the reader into misinterpretation, since not always what will be receiving is the investigational product. Ultimately, this error undermines the making an autonomous decision to participate or not in the research.

It should be remembered that, according to CNS *Resolution* No. 466 of 2012, in item IV.4.b and VI.5.b, alert to the fact that the TCLE is a document that must provide the information in clear, accessible and easy-to-understand language. still in item IV.4.b, the aforementioned Resolution advises that the TCLE must *“clarify, when relevant, about the possibility of including the participant in a control or placebo group, clearly explaining the meaning of this possibility”.*

WHAT TO DO:

The TCLE should not use the terms "study drug" or "medication of the research" (or something similar) to simultaneously refer to the product investigational and placebo. This leads to misinterpretation and damage to decision-making. an autonomous decision.

1.9. Risks and benefits:

CNS Resolution No. 466 of 2012, in item III.1.b, defines that *"The ethics of the research implies (...) weighing risks and benefits, both known and potential, individual or collective, committing to the maximum benefits and the least amount of damage and risk.* Furthermore, item IV.3.b states that *"The Term of Free and Informed Consent must contain, obligatorily: (...) explanation of the possible discomforts and risks arising from participation in the research, in addition to the benefits expected from this participation and presentation of the measures and cautions to be be employed to avoid and/or reduce adverse effects and conditions that may cause harm, considering characteristics and context of the research participant".* To the pending issues frequently related to this item are the following:

a) Omit description of the benefits and/or risks of the research: This pendency is pointed out when the researcher does not describe in the TCLE the potential benefits to the research participant and/or the risks involved in the study. Even if the research does not determine direct benefit to the research participant, this information must be clearly stated in the TCLE.

b) Overestimating the benefits of an experimental treatment: It is pointed out ethical pending when the researcher describes the benefits of a experimental treatment in an overvalued way. describe, by example, that the experimental treatment will be "capable of curing the disease" of the participant is unreasonable from an ethical point of view, since it can induce the individual to accept to participate in the research.

c) Underestimating the risks of an experimental treatment: By underestimating the risks involved in a study, the researcher does not convey the information necessary for the individual to make an autonomous decision about their participation in the research. Claiming, for example, that a new experimental drug "does not present significant health risks" is not likely in a clinical trial.

d) Not informing about measures and precautions: Sometimes, the pendency is not related to the description of the risks, but, simply, because the researcher does not explain in the TCLE the measures and the precautions that will be adopted to avoid or reduce the risks associated with the search.

WHAT TO DO:

1) The TCLE must present, in a clear and objective way, the potential benefits of the participant research, without overvaluing them;
2) If the study does not anticipate any direct benefit to the participant, this information must be explicitly stated in the TCLE;
3) The potential risks associated with the research must be described in the TCLE, without underestimate them;
4) The TCLE must explain the measures and cautions that will be adopted to avoid or decrease the risks associated with the research.

1.10. Alternative therapeutic methods:

According to CNS Resolution No. 466 of 2012, IV.4.a, *"The Term of Free and Informed Consent in research that uses methodologies experimental studies in the biomedical area, involving human beings, in addition to what is provided for in item IV.3 above, must obligatorily observe the following: (...) explain, when pertinent, existing alternative therapeutic methods".*

The main pendency related to this item is the omission of information in the TCLE about alternative therapeutic methods.

WHAT TO DO:

The TCLE must clearly describe the alternative methods of treatment to the research participant. If there are no alternative methods, this should be explained in the TCLE.

1.11. Access to exam results:

In some studies, the TCLE brings information that the research participant does not you will have access to the results of your exams carried out during the study. although in In some situations there is, in fact, a methodological reason for not revealing the result of exams performed on the research participant (when the information interferes with the outcome of the study), most of the time, there is no justification for this procedure in clinical trials. It should be remembered that CNS Resolution No. 251 of 1997, in item III.2.i, defines that *"The responsible researcher should: (...) Provide access to the results of examinations and treatment to the patient's physician or to the patient whenever requested and/or indicated".* To the best of our knowledge, the researcher should not limit access of research participants to the results of their exams that are performed during the study.

The pendency most commonly related to this item is the TCLE stating that the research participants will not have access to the results of the exams they perform during the study.

WHAT TO DO:

The TCLE must not contain restrictions for the research participant to have access to the results of tests performed during the study, unless there is justification methodology for such.

1.12. Confidentiality and anonymization of data:

The TCLE must bring the guarantee that the data that allow the identification of the research participant will be kept confidential in order to preserve the privacy and not causing harm, such as stigmatization and discrimination. Accordingly

with CNS Resolution No. 466 of 2012, item III.2.i, surveys must (...) *"predict procedures to ensure confidentiality and privacy, protection of image and the non-stigmatization of the research participants, guaranteeing the non-use of information to the detriment of individuals and/or communities, including in terms of self-esteem, prestige and/or economic-financial aspects".* A The same Resolution, in item IV.3.e, also defines that the TCLE must contain the *"guarantee of maintenance of confidentiality and privacy of research participants during all research phases.*

When research participant information is passed on to the sponsor or third parties, care must be taken to ensure that the data is anonymised. (encoded) in order to guarantee privacy. Particular attention should be paid to the case of monitors and auditors representing the sponsor. It is recognized the their role in ensuring compliance with Good Clinical Practices and, ultimately, analysis, ensure protection of research participants. monitors and auditors must have, obligatorily, a professional commitment to the secrecy of the information obtained during its activities.

However, it should be noted that, in order to have access to the source documents (including medical records) by monitors and auditors, the TCLE must: 1) Inform that, in addition to researchers, monitors and auditors will have access to documents source; 2) Clearly ensure that monitors and auditors will maintain the commitment to the secrecy of information in order to guarantee the privacy of research participants and; 3) Clarify which source documents will be consulted.

Special care must be given to the issue of consulting medical records, subject in which there are considerations of the Federal Council of Medicine (CFM). A CFM Resolution No. 1638 of 2002, in its preamble, considers the medical record as *"a valuable document for the patient, for the doctor who assists him and for the health institutions, as well as for teaching, research and public health services. health, as well as an instrument of legal defense".* Article 1 of the same Resolution defines *"medical record as the only document consisting of a set of information, signs and registered images, generated from facts, events and situations about the health of the patient and the assistance provided to him, of a legal nature, confidential and scientific, which enables communication between team members*

multidisciplinary approach and the continuity of assistance provided to the individual". The resolution CFM No. 1605 of 2000, in Article 1, notes that *"The physician cannot, without the patient's consent, disclose the content of the medical record or file".*

It clarifies in article 5 that *"If there is express authorization from the patient, both in the request or in a different document, the doctor may forward the form or medical record directly to the requesting authority".* Furthermore, CFM Resolution No. 1931 of 2009 (Code of Medical Ethics) defines in article 85 that *"It is forbidden for the physician to: Allow handling and knowledge of medical records by people not obliged to professional secrecy when under their responsibility".* Thus, if there is an intention to consulting the medical record in the research, this information must be clearly expressed in the TCLE, ensuring, above all, the issue of data confidentiality.

This aims to ensure that the individual receives the information necessary for making a decision. an autonomous decision about whether or not to participate in the research.

The pending items related to this item are usually the following:

a) Not guaranteeing that the data to be passed on to the sponsor or the third parties will be anonymized: In order to guarantee the privacy of the research participant, the data passed on to the sponsor or the third parties must be previously anonymized (coded). They are not reasonable sentences such as *"your personal data will be forwarded to the sponsor and University* X" without proper explanation about anonymization.

b) Provide broad access to source documents: Participants' data are confidential, limiting who will have access to them. Beyond the researchers, it is acceptable for sponsor monitors and auditors to have access to the research participant's source documents, provided who maintained the professional commitment with the secrecy of the information. However, sentences are often found in the TCLE that give broad access to research participant source documents sponsor or third parties, which is not appropriate from an ethical point of view, as it violates the right to privacy. Examples: *"the sponsor will have*

access to your personal data", "the representatives of the sponsor will be able to see your personal data", among others.

c) **Omitting that the medical record may be consulted:** There are several guidelines of the Federal Council of Medicine that prevent access to medical record when there is no express authorization from the patient. The TCLE is the instrument through which the participant will express his consent and authorization for the source documents to be consulted. Therefore, if there is an intention to consult the medical record during the research, it is unreasonable to omit this information from the TCLE, and clearly explain who will have direct access to the document (e.g. monitors and auditors).

d) Do not describe the mechanisms adopted for the anonymization of data: This pendency is pointed out when the researcher does not describe in the TCLE the mechanisms that will be adopted for the anonymization of data (for example: through data encoding, omission of data that may identify the participant, etc.).

WHAT TO DO:

The TCLE must be explicit in relation to the confidentiality and anonymization of the data, ensuring that:

1) Research participant data is confidential and will be forwarded to the sponsor or third parties only after due anonymization;
2) In addition to researchers, sponsor monitors and auditors may have access to the participants' personal data (if applicable), ensuring that the professional commitment to the absolute secrecy of the information in the TCLE.
3) The medical record may be consulted by the researchers, and also by sponsor's monitors and auditors. Therefore, this information must be expressly stated in the TCLE.

(continues...)

(Continuation...)

4) It should be explained how the mechanism will be used to guarantee the confidentiality and anonymization of data (example: data encoding, database access password, etc.).

1.13. Freedom to refuse to participate in the study:

CNS Resolution No. 466 of 2012, item IV.3.d, provides that the TCLE must ensure that the individual has full freedom to refuse to enter and participate in the study, without any penalty from the researchers. Although it is not pending Often, sometimes, the TCLE omits this right from the research participant, generating pending.

WHAT TO DO:

The TCLE must ensure, in a clear and affirmative way, that the individual has full freedom to refuse to participate in the study and that this decision will not entail penalty by researchers.

1.14. Freedom to withdraw consent:

Item IV.3.d of CNS Resolution No. 466 of 2012 guides that the TCLE must ensure full freedom to the participant to withdraw consent at any time time of performing the search. For this, it is not necessary any kind of written statement, except when related to the removal of material biological data from a biobank or biorepository (CNS Resolution No. 441 of 2011, item 10.I).

The withdrawal of consent covers a wide spectrum of situations that varies from withdrawing from participation in an isolated part of the research, but still with a clear willingness to carry out the others, to the extreme where the participant wishes withdraw completely from the study. If the participant decides to completely withdraw of research to which he had previously consented, it is implied that he does not wish to researchers' additional contact, respecting their privacy and the right

of your autonomous decision. Therefore, it is unreasonable from an ethical point of view to obtain participant information after complete withdrawal of their consent from the study, either by letter, telephone, e-mail, cell phone messages, or any other other way. The participant has the right to withdraw from the study at any time. and not wanting to provide more information or receive contacts from the researcher and your team.

One must also consider the situation in which the individual no longer wants to participate in study-related activities, but remain willing to be contacted by researchers to update data. This is the case, for example, of individuals who, because they are extremely debilitated by the disease, choose not to attend the research center more, but agree to answer a questionnaire by telephone, letter or *e-mail.* In this situation, provided that the participant has previously consented, the researcher may contact that (or with third parties) to update study-related data.

The most frequent issues related to this item are:

a) Omit information about the freedom to withdraw consent:

This pendency occurs when the researcher omits the information in the TCLE that the research participant is entitled to withdraw the TLCE from any time and that this decision will not result in any penalty.

b) Affirm that the researcher will contact the research participant research after withdrawal of consent: The participant has the right to withdraw from the study at any time and not wish to have further contact with the research team. CNS Resolution No. 466 of 2012, item IV.3.e, establishes that the TCLE must guarantee the privacy of the participants of the search. Thus, sentences such as *“if you give up participate in the study, staff may contact you or your family to find out how you are.”*

c) Affirm that the researcher will continue to collect data from the participant after withdrawal of consent: The participant has the right to

withdraw from the study at any time and no longer want your personal data is collected. CNS Resolution No. 466 of 2012, item IV.3.e, establishes that the TCLE must guarantee the privacy of the participants of the search. Thus, from an ethical point of view, sentences such as *"if you withdraw from participating in the study, the team may obtain information about you in your medical record".* It is understood, however, that the data of the research participants obtained until the withdrawal of the consent (or which are in the public domain) can be accessed by researchers. However, it should be noted that CNS Resolution No. 340 of 2004, in item III.7, determines: *"Every individual may have access to their genetic data, as well as the right to remove them from banks where are stored at any time".*

WHAT TO DO:

1) The TCLE must clearly and affirmatively ensure that the research participant you are free to withdraw your consent at any time research and that this decision will not generate penalties on the part of the researchers.
2) The TCLE must not state that the participant can be contacted, or that their data will continue to be collected after withdrawal of consent.

1.15. Interruption of treatment:

The pendency most commonly related to this item is the use, in a inappropriate, of terms or expressions in the TCLE to define the interruption or discontinuing treatment, such as "withdraw from study", "exclude from study" or "end participation" (or something similar). For example: *"You may be removed from study if you experience side effects or become pregnant."* It is unreasonable from the point of view of It is ethical to withdraw (exclude) someone from the study because of toxicity, pregnancy, or any other situation that requires follow-up and assistance to the participant of search. What actually happens is the interruption (or discontinuity) of the treatment, and not exactly the removal of the research participant.

WHAT TO DO:

The TCLE should not contain expressions such as “withdraw from the study”, “exclude from the study” or “terminate participation” to refer to the interruption (discontinuity) of the treatment during the research, as the participant may need follow-up and assistance, for example, for toxicity, pregnancy, etc.

1.16. Study interruption:

According to CNS Resolution No. 466 of 2012, item IV.3.c, the TCLE must contain explanations about how to monitor and assist participants in research if the study is stopped. This explanation is often omitted from the TCLE, with only the statement that the study may be interrupted. Example: *“This study may be stopped at any time by the researcher or sponsor for security reasons”.* However, there is often no explanation additional element that ensures the participant, in case of interruption of the research, the assistance as needed.

WHAT TO DO:

The TCLE must clearly and affirmatively ensure that, in the event of interruption of the study, the research participant will receive the assistance that is appropriate, in a way free of charge for as long as necessary.

1.17. Means of contact with the researcher in charge:

The TCLE must contain the means of contact with the responsible researcher, since that the research participant (or their legal guardian) may want guidance, clarify doubts, or even request assistance, for example, for a reaction adverse to the experimental drug. It is therefore necessary to provide of an easily accessible contact for the research participant, 24 hours a day, 7 days a week in case of emergency. According to CNS Resolution No. 466 of 2012, item IV.5.d, the TCLE must contain *“the address and telephone contact or other, of the responsible for the research and the local CEP and Conep, when applicable”.*

The most common issues related to this item are:

a) Not informing the means of contact with the researcher in charge: The telephone and address are minimally required by CNS Resolution No. 466 of 2012, but there is no restriction on also informing other means of contact, such as *e-mail,* SMS, FAX, among others;

b) Failure to provide an easily accessible means of contact for the participant in research in case of urgency (24 hours a day, 7 days a week).

WHAT TO DO:

The TCLE must explicitly bring the means of contact with the researcher person responsible (at least, address and telephone number), as well as providing means of contact easily accessible by the research participant in case of urgency (24 hours a day, 7 days a week).

1.18. Means of contact with the CEP/Conep System:

The TCLE often does not bring information from the CEP and Conep to the participant of search. Such information is relevant because the research participant (or his legal guardian) may wish to contact the CEP (or Conep, when if applicable) to clarify doubts, complain or report. The resolution CNS No. 466 of 2012, in item IV.5.d, directs that the TCLE must *"contain the address and telephone or other contact, those responsible for the research and the local CEP and Conep, when relevant".*

The most commonly pending issues related to this item are:

a) Not informing the means of contact with the CEP (or Conep, when applicable): Phone and address are minimally required by CNS Resolution No. 466 of 2012, but there is no restriction on informing also other means of contact, such as *e-mail,* SMS, FAX, among others;

b) Failure to inform the public of CEP service hours (and Conep, if applicable);

c) Not explaining in simple language the attribution of the CEP (and Conep, if applicable).

WHAT TO DO:

The TCLE must explicitly bring the means of contact with the CEP (at least, address and telephone number), as well as opening hours for the public. It is also It is necessary to explain in plain language what a CEP represents. When the study involve Conep's ethical review, these recommendations should be extended to this Commission.

1.19. Field for signatures and initials:

CNS Resolution No. 466 of 2012 defines in item IV.5.d that: *"The Term of Free and Informed Consent must also: (...) be drawn up in two copies, initialed on all its pages and signed, at the end, by the guest to participate in the research, or by their legal representative, as well as by the researcher person(s) responsible, or by the person(s) delegated by him/her, and the pages of signatures be on the same sheet (...)".*

The TCLE signature field is a frequent reason for pending issues, which is why he follows:

a) Field for the "responsible researcher": Frequently, the field for the researcher's signature is identified as "responsible researcher". Considering that the "researcher responsible" will not always obtain the term, and this function may be delegated to someone on your research team, it is unreasonable for there to be signature field exclusively intended for him. Remember that the CNS Resolution No. 466 of 2012 distinguishes the figures of "researcher" and "responsible researcher", defining the first as *"team member*

of research, co-responsible for the integrity and well-being of the participants research" (item II.15). Thus, Conep has systematically requested that the term "responsible researcher" be replaced by "researcher" in the signature field (and also in the initials field), which is more comprehensive and signals that some member of the research team (or the responsible researcher himself) will obtain the TCLE.

b) **Using inappropriate terms in the field of signatures and initials:** A Conep has insisted that the fields of signatures and initials contain the terminology recommended by CNS Resolution No. 466 of 2012 (items II.15 and II.16). Terms are often used in these fields. not provided for by the Resolution, such as "investigator" and "patient", which should be replaced, respectively, by "researcher" and "research participant/legal guardian".

c) Additional information in the signature field: Although it is understood that, from a legal point of view, the TCLE represents a contract between the research participant and the researcher/sponsor, the TCLE has the primary function of informing and respecting the autonomy of the participant of research and not exactly establishing a contractual link between the parts. Additional information, in addition to the name and date of signature, is not are considered essential from a bioethical point of view. Therefore, the Conep has requested that information such as RG, CPF, address, enter others are removed from the signature field.

d) Signature fields on a sheet separate from the rest of the TCLE: The signature fields must not be placed on a separate sheet of the remainder of the TCLE, except when, for reasons of configuration of the document, this is not possible. It should be remembered that CNS Resolution No. 466 of 2012, item IV.5.d, that the TCLE must *"be prepared in two copies, initialed on all its pages and signed, at the end, by the invited to participate in the research, or by their legal representative, as well as*

as by the researcher in charge, or by the person(s) delegated by him (s), and the signature pages must be on the same sheet (...)". When there is a clear break in the continuity of the TCLE and the signature fields are separated from the rest of the document, Conep has requested to fix this problem.

WHAT TO DO:

Signature and initials fields must be identified according to the terminology provided for in CNS Resolution No. 466 of 2012, that is, using the terms "researcher" and "research participant/legal guardian". The fields of signatures must not be separated from the rest of the document (except when, for configuration reasons, this is not possible) and must not contain fields additional information besides name and date.

1.20. Provision of an original copy of the document, with signatures and initials:

CNS Resolution No. 466 of 2012, item IV.5.d, guides that the TCLE must be prepared in two "COPIES" and initialed in all its pages (by the participant of research and by the researcher). These requirements are intended to ensure one of the participant's rights: to receive the TCLE duly signed and initialed by him and the researcher. This item is a frequent reason for pending issues, or because the researcher uses the term "copy" instead of "via" to refer to the TCLE, or why not ensures the provision of a copy of the TCLE. Still, it is pointed out pending whether the TCLE do not state that the document will be initialed on all pages.

a) Omit information about the right to have a copy of the TCLE: This pending happens when the TCLE does not inform that the research participant has right to a copy of the TCLE signed and initialed on all pages. The item IV.3.f of CNS Resolution No. 466 of 2012 clearly states that the TCLE must contain the *"guarantee that the research participant will receive a via the Free and Informed Consent Form".* So, stop ensuring this right to the participant is pending.

b) **Use the word “COPY”:** Not infrequently, the researcher declares that a “COPY” of the TCLE will remain with the research participant and another with the researcher. It is understood that the terms “COPY” and “COPY”, even if similar from a semantic point of view, do not have the same meaning practical, since the former comprises the original document, while the second may not be faithful to the primary document. In this way, do not must use the term “COPY” to designate the document, but “COPY”.

c) Not ensuring that all pages are initialed: Often, the researcher ensures that the participant will receive a copy of the TCLE, but does not inform that all pages will be initialed. CNS Resolution No. 466 of 2012 states in item IV.5.d that the Term of Free and Clarified should *“be prepared in two copies, initialed in all its pages and signed, at its end, by the person invited to participate in the research, or by their legal representative, as well as by the researcher responsible, or by the person(s) delegated by him(her) (...)”.*

WHAT TO DO:

The TCLE must clearly and affirmatively ensure that the research participant will receive a copy (not a copy) of the document, signed by the research participant (or his legal representative) and by the researcher, and initialed on all pages by both.

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

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

Stored biological samples can be used in future research, provided they are previously approved by the CEP/Conep System. However, one must obtain new consent in the case of biorepositories or biobanks in which participants chose to reconsent to each new survey. if there is intention future research with the biological material, this information must be clearly of the TCLE.

The most frequently pending issues related to this item in the TCLE are described below:

a) Failure to provide adequate information about the biological material: This pendency is generated when the TCLE does not bring, in an adequate way, information about the collection, storage, use and final destination of the biological material (example: nature of the biological material, quantity to be collected, purpose of collection, place and time of storage, etc.).

b) Failure to inform about the freedom to withdraw consent for custody and use of biological material: According to CNS Resolution No. 441 of 2012, item 10, *"The research subject, or his representative legally, at any time and without any burden or damages, may withdraw the consent for custody and use of stored biological material in a Biobank or Biorepository, giving up as of the date of formalization of this. I - The withdrawal of consent will be formalized by manifestation, in writing and signed, by the subject of the research or his legal representative, being responsible for returning the existing samples".*
A pendency is generated when the TCLE does not inform about the freedom of withdrawal of consent for the storage and use of biological material.

c) Not informing about the intention of future researches with the material biological (if any): If there is an intention to use the product in the future biological material in future research, the TCLE must inform this possibility and that the research participant will be contacted for further

consent. According to Ordinance No. 2.201 of 2011, article 18, *"The research subject must be contacted to consent, at each new research on the use of human biological material stored in biorepository, formalizing consent through TCLE specific".* A pendency is generated when the intention of future use of the biological material and the need for a new consent are not included in the TCLE.

d) Use the term "donated material": Some consent forms use the word "donated" to refer to the biological material that was provided by the participant for the research. It should be clarified that the legislation Brazil has well-defined rules for the donation of cells, tissue and bodies for health care, but not for the research scenario.

In this way, the research participant does not "donate" the biological material, but gives it away or provides it for research.

WHAT TO DO:

1) The TCLE must bring, in a clear and complete way, the information related to the collection, storage, use and final destination of biological material;
2) The TCLE must inform that the consent for the custody and use of the material biological can be withdrawn at any time by the research participant;
3) The TCLE must inform, when applicable, the intention of future use of the biological material and the need to obtain a new consent;
4) Do not use the term "donated material" to refer to biological material that was assigned (or provided) for the research.

1.22. Human Genetics (specific aspects of the TCLE):

Studies involving human genetics have certain ethical particularities that must be observed, especially when the study has the possibility of generating information capable of producing psychological harm, stigmatization and discrimination of individuals, families or groups (studies of clinical genetics, population genetics

and behavioral genetics). Item V of CNS Resolution No. 340 of 2004 guides the information that must be included in the TCLE in this type of study. The main pendencies are related to this item of the Resolution:

a) Not informing the genes or gene products that will be studied: a CNS Resolution No. 340 of 2004 determines that the TCLE must contain *"clear explanation of the exams and tests that will be carried out, indication of the DNA or RNA genes/ segments or gene products that will be studied and its relationship with the eventual condition of the subject of the research"* (item V.1.a). A pendency is generated when the TCLE does not discriminate the genes (or gene products) that will be evaluated in the study. However, the Circular Letter No. 041/2015/CONEP/CNS/MS of March 27, 2015 clarifies that, if impracticable, from a practical point of view, to list all the genes (for example, in studies that evaluate hundreds or thousands of them), the *"researcher will be able to describe the genes studied grouped according to functionality or effect (example: genes related to the onset of cancer, inflammation, cell death, response to treatment, etc.), not being need to list them individually.* It also clarifies that: *"In the case of studies involving large-scale genetic study (e.g., complete sequencing of the genome or exome), it is not feasible to aforementioned grouping, the TCLE must contain an explanation of the procedure to be carried out, respecting the capacity of understanding of the research participant".*

b) Failure to ensure confidentiality of genetic data and privacy to the research participant: The TCLE is often omitted in this regard, must ensure in a clear and affirmative way this right to participant. Additionally, the TCLE must ensure that the results of the genetic tests will not be provided to third parties (such as: insurers, employers, hierarchical supervisors, among others).

c) Failure to inform the mechanisms for protecting genetic data: A CNS Resolution No. 340 of 2004 (item V.1.f) determines that the TCLE inform the mechanisms that will be adopted for the protection of genetic data. AND omission of this information in the TCLE is frequent, which is a reason for pendency.

d) Failure to provide genetic counseling and clinical follow-up: It is understood that this item does not apply to all studies involving human genetics, but only those with clinical implications known or that actually require genetic counseling. However, where applicable, it is necessary to inform the research participant who genetic counseling and clinical follow-up (or, at least least the institution or location where they will take place). Besides, it's necessary to ensure that counseling and clinical follow-up will be offered free of charge by the sponsor. The flaw in these information is a frequent reason for pending.

e) Failure to ensure access to genetic test results: The result of any exam, not only those of a genetic nature, must be ensured to the research participant whenever requested by him, except when this information interferes with the outcome of the research. Therefore, sentences such as *"the results of genetic tests will not be reported to you"* or *"you will not have access to the results of the genetic testing".*

f) Not informing that the research participant has the option to take knowledge or not of the genetic results: The information generated in genetic study can cause harm when they have implications for the participant, especially in studies of clinical genetics and behavioral. According to CNS Resolution No. 340 of 2004 (item V.1.d), the TCLE must contain the *"type and degree of access to the results by the of the subject, with the option of acknowledging this information or not".*

Therefore, when there is risk to the research participant arising from the result of the exam, the TCLE must clearly inform this situation. This aims to guarantee the taking of an autonomous decision about the knowledge or not of the result of the genetic test. Omission is reason for pending of this information in the TCLE (when applicable).

WHAT TO DO:

1) The TCLE must explicitly bring the genes/DNA/RNA segments that will be studied. However, if it is impracticable from a practical point of view to list all genes, it is acceptable for the researcher to describe the genes to be studied in form grouped according to functionality or effect;
2) The TCLE must clearly and affirmatively ensure that the genetic data are confidential and that will not be passed on to third parties (such as, for example: insurers, employers, hierarchical supervisors, among others). besides the Furthermore, the mechanisms for protecting genetic data must be explained in the TCLE;
3) When applicable, the TCLE must clearly and affirmatively ensure that the sponsor will offer the research participant genetic counseling and necessary clinical follow-up. It should also be informed who perform these procedures (or where they will be performed);
4) The TCLE must ensure, in a clear and affirmative way, that the results of exams will be informed to the research participant if he so wishes;
5) When applicable, the TCLE must inform that the result of the genetic tests may bring risks to the research participant. In this case, the TCLE must inform that the participant has the option of knowing or not the results of these exams.

2. BIOLOGICAL MATERIAL STORED IN A BIOBANK OR BIOREPOSITORY

The use of human biological material in research is still a reason of doubts among researchers and Research Ethics Committees. In this matter, the following notes are required:

1) Both the biorepository and the biobank represent a collection organized collection of human biological material collected for the purpose of scientific research, as defined by CNS Resolution No. 441 of 2011 (Art. 1) and Ordinance MS No. 2,201 of 2011 (Art. 3). The main characteristics of biobanks and biorepositories are found highlighted in Table 2.

2) The storage time of the material does not define the constitution of a biorepository, ranging from a few minutes to many years. O that, in fact, defines the constitution of a bank of biological material is the collection intention for scientific research. Thus, it is considered that all the biological materials collected throughout a research constitute a biorepository. Clinical research protocols often constitute biorepositories, since biological samples are collected specifically for the study in question. even the samples intended for examinations considered routine in a clinical trial (such as, (e.g. blood count and kidney function) should be considered as constituents of a biorepository, of short duration, since they were collected specifically in a scenario involving research.

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

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

ÿ **Linked to a specific research project:** The biological material is used as provided for in the research protocol, with no additional future analyzes different from those provided for in the protocol. after the processing and acquisition of the results, the biological material remainder is usually discarded, but the researcher may choose to for keeping it stored a little longer for repetition and confirmation of tests previously carried out, or even transfer it to a biobank (after authorization by the Research Ethics Committee and adaptation to the regulations in force on the matter). So, in this type biorepository, its validity is, at most, the term of the project at which is linked. For this type of biorepository, the documentation required in the research protocol (see Box 3) is simpler than The type of biorepository described below has been requested.

ÿ **Linked to a research project, aiming at the possibility of use in future investigations:** in this type of biorepository, after the processing and acquisition of results, the researcher maintains the remaining stored biological material, aiming to use it in future studies. The researcher's intention to keep the samples stored after processing, carried out as provided in the research in which the samples were collected, it is not the possibility to repeat the tests and confirm the results obtained (although it may do so), but perform analyzes different from that of the current protocol in one or more studies in the future. The duration of this type of biorepository can be authorized for up to 10 years, with possible renewals authorized by the CEP/Conep System upon appraisal justification and report presented by the researcher. For each new research, there is a need to apply a new Term of Free and Informed Consent (or, when duly justified, obtaining approval of the waiver of the Term by the Committee) for the use of biological material stored and collected previously.

5) In the specific case of the biorepository, the TCLE model used in the research **should not contain** exclusionary alternatives for the participant choose to be consulted or not in each future survey. Such options are applicable only to biobanks (CNS Resolution No. 441 of 2001, item 5; Ordinance MS No. 2.201 of 2011, Art. 4th). At the end of the search, if there is an intention to transfer the material stored in a biorepository for a biobank, the research participant must sign the specific model of the biobank's TCLE, which was approved by Conep, on the occasion of the analysis of the respective Development Protocol. Therefore, you can present both documents to the research (TCLE intended for research that will constitute a biorepository and TCLE from the biobank that will receive the residual sample at completion of the research) and decide on their participation, consenting or not, at the same opportunity.

6) It is prudent to remember that the biological material belongs to the participant of research, which has the right to withdraw, at any time, the consent for custody and use of stored biological material in a biobank or biorepository. This manifest must be carried out by written by the participant or his legal guardian (CNS Resolution No. 441 of 2011, Articles 9 and 10; Ordinance MS No. 2.201 of 2011, Art. 6th).

7) Some studies use biological material from collections that do not corresponds neither to a biobank nor to a biorepository, having been collected for charitable purposes. This is the case, for example, of biopsies stored in paraffin blocks from a Pathological Anatomy service. The biological material obtained for assistance purposes can be used in research, as long as duly authorized by the participant, through of a Free and Informed Consent Form specific to the research (or, where duly justified, obtaining approval from the waiver of the Term by the Research Ethics Committee). Additionally, such banks may request their registration as a biobank at Conep for

through the presentation of a Development Protocol, which will be evaluated according to current regulations for biobanks.

8) In the registration of research protocols on the Brazil Platform, it is verified, with a certain frequency, error in filling out the item "There will be retention of samples for bank storage?". The term "bank" is mistakenly interpreted as "biobank", when, in reality, applies to both biobank and biorepository. So, whenever there is collection of biological material in a research, this field of Plataforma Brasil must be marked with the option “YES”.

9) In order to avoid pending issues in the evaluation of protocols, it is requested to verify the documentation provided for in CNS Resolution No. 441 of 2011 and in MS Ordinance No. 2201 of 2011. The necessary documents, according to the type of biological material bank, are highlighted in Table 3.

10) It should be noted that the regulation of a biorepository, mentioned in Resolution CNS No. 441/2011, item 2.IV, is nothing more than operational detail and the description of the existence of infrastructure, as well as the conditions storage of biological material and the form of disposal after its use, which may be contained in the research project itself (e.g. example, in the Material and Methods section), or in the form of a declaration separate.

11) The interinstitutional agreement must be signed when there is more than one institution contributing to the formation of a shared bank of Biological material. The document must contemplate the forms of operationalization, sharing and use of biological material stored in a biobank or biorepository, including the possibility of future dissolution of the partnership and the consequent sharing and destination of stored data and materials, as provided for in the TCLE (CNS Resolution No. 441 of 2011, item 13). When it comes to

shared biorepository, the agreement must be signed by the researchers responsible for each institution involved and for their institutional responsible. In industry-sponsored studies pharmaceutical, which use central laboratories (outsourced or own) for the storage of samples, it is acceptable to present a only document with the sponsor's declaration assuring the commitments provided for in item 13 of CNS Resolution No. 441 of 2011.

12) In research that constitutes a biorepository and that intends to use of biological material in future research, the TCLE must contain authorization consent for the collection, deposit, storage and the use of human biological material linked to the project of specific search. The same TCLE must also inform the participant the possibility of future use of the stored sample. The use of this will be conditioned:

- ÿ The presentation of a new research project to be analyzed and approved by the CEP/CONEP System and;
- ÿ Obligatorily, to the reconsent of the research participant through a specific TCLE referring to the new project of search.

13) For research protocols that intend to use samples previously collected and which are stored in a biorepository of a previous survey, you must submit to the CEP/Conep System two TCLE models for consideration:

- ÿ The model that was used at the time of collection and storage biological material (prior research); It is
- ÿ The model that will be used to request authorization for the use of the stored biological material (current research).

Below are the main pending issues most frequently related with banks of biological materials (biorepositories and biobanks) in protocols of search:

a) Declare that there will be no formation of a biological material bank: It is Often the researcher claims, mistakenly, that there will be no constitution of a bank of biological material in a given study. if there is a collection of biological material intended for specific research, it is unequivocal formation of a biorepository.

b) Failure to provide adequate information about the biological material in the TCLE: This pendency is generated when the TCLE does not bring, in an adequate way, information about the collection, deposit, storage, use and final destination of the biological material (example: nature of the biological material, quantity to be collected, purpose of collection, place and time of storage, etc.). A pendency is also issued when there is an intention to use the biological material in future research and this information is not contained in the TCLE.

c) Failure to present the necessary documentation for the constitution of a bank biological material: Failure to submit the documentation provided for in Table 3 of this Manual.

WHAT TO DO:

1) If human biological samples are collected in a survey, it should be declare on Plataforma Brasil that there will be formation of **a bank** of material biological;
2) The TCLE must bring, in a clear and complete way, the information related to the collection, storage, use and final destination of biological material (see item 1.21 of this Manual);
3) Submit the documentation provided for in Table 3 of this Manual.

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

FEATURE	BIOBANCO	BIOREPOSITORY LINKED TO ONE SPECIFIC PROJECT	BIOREPOSITORY LINKED TO A SPECIFIC PROJECT, AIMING FOR USE IN FUTURE RESEARCH For
Collection intention	No search defined *a priori.*	For specific search.	specific research and for others in the future.
Storage intention after processing the biological material (if there is storage)	Use in future research(es).	Repeat and confirm screen search results.	Repeat and confirm screen search results and use in future search(es) (new search protocols).
sample owner	Biobank participant (potential research participant)	research participant	research participant
Responsibility for the custody of biological material	Institutional	Institutional	Institutional
Responsibility for the management of biological material	Institutional	Researcher	Researcher
term of storage	While the biobank lasts.	While the search lasts.	Up to 10 years, extendable at the request of the researcher and approval of the CEP/Conep System.
Consent for the COLLECTION of material biological	Biobank TCLE approved by Conep (an integral part of the protocol development of biobanco).	Specific TCLE for the screen search.	Specific TCLE for the screen search.
Consent for the USE of biological material	Participant chooses whether or not to be consulted for each search in the TCLE. A new specific TCLE for each future research must be presented to those who wish to be consulted (reconsent).	Specific TCLE for the screen search.	Specific TCLE for the search on screen and new specific TCLE for each future search.
Regulation	protocol Development (approved by Conep).	Operational and infrastructure description of the biorepository, which may be included in the research project itself.	Operational and infrastructure description of the biorepository, which may be included in the research project itself.
Patenting and commercial use of the material biological	Not allowed	Not allowed	Not allowed

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

DOCUMENTS TO BE PRESENTED [1]	BIOBANCO	BIOREPOSITORY ATTACHED TO A PROJECT SPECIFIC	BIOREPOSITORY LINKED TO ONE SPECIFIC PROJECT, FOR USE IN FUTURE RESEARCH
Inter-institutional agreement (operationalization, sharing, use of material and sharing in case of dissolution of the partnership) [2]	It is presented only on the occasion of the consideration of the Protocol for the Development of biobanco.	Only if sample is stored after processing for results confirmation purposes and if any more than one institution contributing to the shared biorepository.	Only if there is more than one institution contributing to the shared biorepository.
Statement by the foreign official at the receiving Institution regarding access and future use of samples stored in the abroad, ensuring proportionality in participation.	Yes, if forwarded biological material to the outside.	No	Yes, if forwarded biological material to the outside.
Statement by the foreign official at the receiving Institution regarding the 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.
Justification for the use of biological material in future studies	It is presented only on the occasion of the consideration of the Protocol for the Development of biobanco.	Not applicable (no future studies are intended).	Yes, the justification must be presented in the protocol in which the collection of biological material is expected.
Commitment to submit the research protocol to CEP analysis and, when applicable, Conep, for each new research (future studies)	It is presented on the occasion of the appreciation of the Protocol of development of biobanco.	Not applicable (no future studies are intended).	Yes, the commitment must be presented in the protocol in which the collection of biological material is expected.
Regulation of the biological material bank	Yes, it corresponds to the Protocol itself development of biobanco.	Yes, the operational and infrastructure details, as well as the storage conditions of the material, may be contained in the research project or in the form of a statement.	Yes, the operational and infrastructure details, as well as the storage conditions of the material, may be contained in the research project or in the form of a statement.

(Continues...)

CHART 3 (Continuation) – Documents to be presented in the protocols intending to use biological material stored in a biorepository or biobank.

DOCUMENTS TO BE PRESENTED [1]	BIOBANCO	BIOREPOSITORY ATTACHED TO A PROJECT SPECIFIC	BIOREPOSITORY LINKED TO ONE SPECIFIC PROJECT, FOR USE IN FUTURE RESEARCH
Document proving the approval of the constitution and operation of the bank	Yes (Conep approval opinion, if the biobank is in Brazil). It is presented at the time of the research proposal.	Not applicable.	Not applicable.
Consent for the collection, storage, use and disposal of biological material	The TCLE model must be presented for the collection and storage in biobank on the occasion of appreciation of the Development Protocol respective. When proposing research with forecast use of material stored in the biobank, the model of TCLE for reconsent of participants who opted to be consulted at each search.	The TCLE model of the current research.	The TCLE model of the research, in which the intention of future use of the material is already explicit biological. consider the grades explanations [3] and [4] of this table.
Term of Transfer Biological material (TTMB)	A TTMB model must be presented for ethical analysis when proposing the research project.	Not applicable.	Not applicable.

EXPLANATORY NOTES TO TABLE 3:

[1] Relevant documents can be presented in a single document or separately.

[2] The interinstitutional agreement must be signed when there is more than one institution contributing to the formation of a shared bank of biological material. The document must cover the ways of operationalizing, sharing and using human biological material stored in a Biobank or Biorepository, including the possibility of future dissolution of the partnership and the consequent sharing and destination of stored data and materials, as provided for in the TCLE (CNS Resolution No. 441 of 2011, item 13). In the case of a shared biorepository, the agreement must be signed by the researchers in charge of each institution involved and by their institutional managers. In studies sponsored by the pharmaceutical industry that use central laboratories (outsourced or own) for the storage of samples, it is acceptable to present a single document with the sponsor's declaration assuring the commitments provided for in item 13 of CNS Resolution No. 441 of 2011.

[3] Biorepository for use in future research: The TCLE must contain authorization consent **for the 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; Ordinance MS No.

2,201 of 2011, Chapter II, Articles 5 and Chapter III, Article 8). The same TCLE should also inform the participant of the possibility of future use of the stored sample. The use of this will be conditioned to: (a) presentation of a new research project to be analyzed and approved by the CEP/CONEP System and (b) obligatorily, the research participant's consent through a specific TCLE referring 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 protocols that intend **to use samples previously collected and that are stored in a biorepository from a previous research,** two TCLE models must be presented to the CEP/Conep System for appreciation: a) The model that was used during the collection and storage of the biological material (prior research); and b) The model that will be used to request authorization for the use of stored biological material (current research).

3. HUMAN AND MATERIAL RESOURCES

CNS Resolution No. 466 of 2012, item III.2.h, establishes that surveys must *"Have the necessary human and material resources to ensure the well-being of of the research participant, and the researcher(s) must have the capacity suitable professional to develop their function in the proposed project".* the lack of these resources can make the study unfeasible, making it futile. Therefore, Conep has carried out a detailed analysis of funding sources and financial resources intended for research.

3.1. Budget:

The research project budget is pending when it is not compatible with the costs of the study, when there is not enough detail to understand the costs of the study or when the sponsor is not clear.
When the budget is complex, it is acceptable that it comes as a separate document, attached to the Brazil Platform.

CNS Operational Standard No. 001 of 2013, item 3.3.e, establishes that all research protocols must *"detail the resources, sources and destination; shape and amount of the researcher's 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 forecast of reimbursement of expenses of the participant and their companions, when necessary, such as transportation and food and material compensation in the cases excepted in item II.10 of the Resolution of CNS 466 of 2012".*

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

a) Not detailing the budget: All items necessary for the development of the study must be itemized in the budget. A Conep points out pending issues when the researcher does not explain adequately allocate research financial resources.
Describe the costs, for example, as "related to molecular analysis"

is too comprehensive and does not allow inferring the necessary investment with consumable and permanent materials.

b) Omitting items from the budget: it is a pending reason when the researcher omits from the budget the costs related to procedures that are foreseen in the study, even if they are already part of the care routine of the research participant. If, in a clinical trial, there is prediction, for example, performing a chest X-ray, the costs of the procedure must be budgeted in the research protocol.

c) **Declaring that the study will have no costs:** The researcher sometimes does not presents the study budget, justifying that the research "will not have costs". The CEP/Conep System understands that there are no studies without cost none. There will always be a need for some degree of investment, albeit minimal. It is unreasonable to imagine, for example, that a researcher carry out his study without recording the information in any form or other instrument, such as a tape recorder or camera, which requires Financial investiment. Even if the researcher understands that they will not be necessary resources for the acquisition of materials, purchase of equipment and other expenses, the researcher will use hours of work paid by the institution to which it is linked and make use of computer, services of archival science, among others that generate expenses, even if minimal.

WHAT TO DO:

The researcher must present a detailed budget, forecasting all costs necessary for the development of the research (human and material resources), not omitting those related to the procedures foreseen 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, through actions of*

financing, infrastructure, human resources or institutional support". The definition of the study sponsor is shown on the Cover Sheet, in the field "Sponsor Main". Failure to name the study sponsor is a reason for pending recurrent. The main pending items related to this item are described below:

a) Do not indicate the main sponsor: This pendency is very common in investigator-initiated studies. In case the researcher does not have own resources for research and the institution does not provide support specific financial support for this, even so, the institution is considered as the main sponsor of the study, as it supports the study through human and material resources. Therefore, studies initiated by the investigator, without financial resources specifically destined to them, must have the Main Sponsor Field of the Cover Sheet signed by the institutional representative.

b) Pointing to the Unified Health System as a sponsor: it is common for investigator-initiated studies state that research costs will be covered by the Unified Health System (SUS). It should be clarified that the SUS is not an individual or legal entity and, therefore, does not fall under the definition of sponsor described in item II.11 of CNS Resolution No. 466 of 2012. The researcher must indicate in the "Main Sponsor" field of the Plataforma Brasil the institution, body, agency or company that will provide the financial resources for the research.

WHAT TO DO:

1) Clearly indicate the main sponsor of the study on Plataforma Brasil and on Face Sheet. In the case of investigator-initiated studies, without resources themselves, the institution assumes the responsibility of sponsoring principal;
2) The SUS is not an individual or legal entity and, therefore, cannot be indicated as research sponsor.

3.3. Institutional infrastructure:

Research must have adequate institutional infrastructure for its realization. CNS Operational Standard No. 001 of 2013, item 3.3.h, establishes that the research protocols must contain: *"(...) Demonstration of the existence of infrastructure necessary and suitable for the development of research and to meet any resulting problems, with a document expressing the agreement of the institution and/or organization through its responsible person with competence".* Also, item 3.4.1.17 of the same Operational Standard defines that *"All protocols must contain, obligatorily (...) Declaration signed by responsible institutional, providing the necessary infrastructure for the development of the research and to deal with eventual problems resulting from it".* To the The most frequently pending issues related to this item are:

a) Failure to present a document proving the necessary infrastructure for the development of clinical research: You must present document demonstrating that the institution has adequate infrastructure for the development of research and conditions to provide assistance to participant, especially for clinical urgency/emergency situations. This document must be signed by the institutional manager who has the competence to do so (for example, the technical director in a hospital institution);

b) Submit a statement of institutional infrastructure signed by the researcher in charge: Who should ensure the infrastructure is the responsible institutional person who has the competence to do so, not being reasonable for the researcher himself to give this guarantee.

WHAT TO DO:

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

4. SCHEDULE

The study execution schedule is often inadequate in its filling, being reason for pending repetition issued by Conep.

According to CNS Operational Standard No. 001 of 2013, item 3.4.1.9., *"All Research protocols must contain, obligatorily: (...) Schedule: informing the total duration and the different stages of the research, in number of months, with researcher's explicit commitment that the research will only be started from approval by the CEP-Conep System".* The most frequent issues associated with this item are:

a) Present the start date of the study prior to the processing in the System CEP/Conep: Not rarely, the execution schedule indicates the beginning of the study on a date that precedes the processing of the ethical analysis. when this is observed, Conep issues a pendency, requesting an update of the timeline.

b) Not discriminating the stages of the research: this pendency is pointed out when the researcher does not discriminate all stages of the research in the schedule, or when the description of the steps is not sufficient or is incompatible with the research project.

WHAT TO DO:

The execution schedule must indicate the start of the study on a date compatible with the processing of the protocol in the CEP/Conep System. Commitment must be made explicit statement of initiating the study only after the final approval of the CEP/Conep System. Furthermore, all stages of the research must be detailed in the schedule.

5. COVER PAGE

Some fields on the Cover Sheet are a frequent reason for pending due to inappropriate completion of the Brazil Platform by the researcher, or even by leave blank the fields that are mandatory. The Norm Operational CNS No. 001 of 2013 defines in item 3.3.a: *"All protocols of survey must contain: (...) Front page: all fields must be completed, dated and signed, with identification of the signatories. The information provided must be compatible with those of the protocol. The identification of the signatures must clearly contain the full name and function of the person signing, preferably stamped. The title of the research will be presented in Portuguese and will be identical to the research project".* Below are the most outstanding often associated with the Cover Sheet of the research protocol:

a) Fill in the study area incorrectly: Field 3 of the Face ("Thematic area") is filled in, with some frequency, in a incorrectly, or by omitting the corresponding area of the study, or by improper completion of an area that does not apply to the survey. That field is directly related to the items that are checked in the Platform Brazil, no field "Thematic Area" (second page of filling out the Platform, tab "Study Area"), leaving the meticulous and accurate selection of the relevant items to the researcher. AND It is convenient to clarify that the researcher can mark more than one theme area option.

b) Failure to fill in mandatory fields: Certain fields on the Cover Sheet must be filled in manually after printing this, being some are mandatory. For the researcher, it is necessary to date and sign the Term of Commitment available on the Cover Sheet. At part referring to the proposing institution, you must complete obligatorily the name of the institutional manager, his position/function, the CPF, signature and date of commitment. Regarding the field of

sponsor, the same items are mandatory, when
there is a main financier. In the specific case of funding agencies
national (such as, for example, CNPq, FINEP, FAPs, etc.) and international
(e.g., US-NIH) and, understanding the difficulty of collecting the
signature, it is accepted that the fields name, position/function, CPF, signature and
date are blank in the part reserved for the sponsor, provided that the
funding body is expressly identified on the Cover Sheet and
that a document confirming the financing is presented. Fits
clarify that filling in the name of the sponsor (field 18 of the
Cover Sheet) is automatic, being linked to the field
“FUNDING” of Plataforma Brasil. Responsible name only
by “Primary Financing” will be listed on the Cover Sheet as
sponsor.

c) Presence of institutional conflict of interest: Sometimes, the
researcher is also the institutional responsible, which makes him sign
simultaneously the fields of the proposing institution and those
intended for the researcher. Such a situation is clearly conflicting and may,
under certain circumstances, compromise the safety of participants in
search. In order to reduce potential conflicts of interest,
in this situation, Conep requests that another institutional person,
devoid of conflicts of interest, sign the Cover Sheet.

WHAT TO DO:

For the proper completion of the Cover Sheet, it is necessary that the researcher
complete the information on Plataforma Brasil accurately, especially the fields
related to the thematic areas. After printing the Cover Sheet, the fields
that are blank must be filled in, especially those that sign
commitment of the researcher, the proposing institution and the sponsor. O
researcher, when he is also the institutional responsible, cannot sign the
fields intended for the Proposing Institution.

6. PROPOSED STUDIES FROM ABROAD

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

a) Do not present a document with the approval of the study by CEP in the country of origin: Conep issues a pendency when the researcher does not present the document with the approval of the study by the CEP (or equivalent) of the country source. CNS Resolution No. 292 of 1999 defines in item VII.1 that *"In elaboration of the protocol, special attention must be paid to the presentation of the following items: (...) Approval document issued by the Ethics in Research or equivalent institution of the country of origin, which promote or who will also carry out the project".* If there is not yet official approval of the study by the CEP of the country of origin, being still in ethical procedures, it is common for researchers to present a document ensuring that you provide the statement of approval as soon as you have it. In this situation, Conep has asked the researcher to ensure that, even though approved by the CEP/Conep System, the study will only begin after CEP approval (or equivalent) in the country of origin and that the approval document will be presented for the appreciation of the System CEP/Conep as soon as it becomes available.

b) Do not provide justification for the study not to be carried out in the country of origin: Although it is not frequent, sometimes the country proposing the study does not provide for the recruitment of research participants. That situation requires the presentation of a justification to the CEP/Conep System, as recommended by CNS Resolution No. 292 of 1999, which defines in item VII.2: *"In preparing the protocol, special care must be taken for the presentation of the following items: (...) When the development of the project in the country of origin, the justification must be placed in the protocol for appreciation by the CEP of the Brazilian institution".*

A pendency is issued if the researcher does not present a document justifying the non-recruitment of participants in the country of origin.

c) Not providing information about the product registration status research in the country of origin: Resolution CNS Nº 251 of 1997, in the item IV.1.j, establishes that the research protocol must contain: *"Information regarding the status of research and registration of the product in the country of origin".* CNS Operational Standard No. 001 of 2013 still defines in the item 3.4.2.a: *"If the purpose is to test a product or device for the health, new to Brazil, whether of foreign origin or not, must be indicates the current situation of registration with the regulatory agencies of the country of origin, if any".* A pendency is issued when the researcher does not informs about the registration situation of the investigational product in the country that proposes the study.

WHAT TO DO:

1) Present a document with the approval of the study by CEP in the country of origin. if the study is still in progress in the ethical system of that country, it must be present a letter assuring that, even if approved by the System CEP/Conep, the study will only start after CEP approval in the country of origin and that the approval document will be presented for the appreciation of the System CEP/Conep as soon as it becomes available. Provide justification for not carrying out the study in the country of origin (when applicable);

2) Present the status of registration of the investigational product in the country of origin.

SUMMARY TABLE:

FREQUENT PENDING

ITEM THEME		WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.1	**TCLE:** **Essay**	a) Use inaccessible language; b) Perform translation inappropriately; c) Write the TCLE in the declaration format; d) Use the term “research subject”; e) Adopt inappropriate title in the document (TCLE).	The TCLE must be a concise document, with easy language, written in the invitation format. The TCLE must be carefully reviewed looking for technical terms and inappropriately used or translated. Long and overly detailed consent forms are not desirable. The title of the document must contain the expression “Term of Free and Informed Consent”.	**CNS RESOLUTION No. 466 of 2012:** *II.10 - research participant - individual who, in an informed and voluntary manner, or under the clarification and authorization of their legal guardian(s), agrees to be researched. Participation must be free of charge, with the exception of Phase I or bioequivalence clinical trials.* *I.23 - Term of Free and Informed Consent - TCLE - document in which the free and informed consent of the participant and/or their legal guardian is explained, in writing, and must contain all the necessary information, in clear and objective language, easy to understand, for the most complete clarification about the research to be which one proposes to participate;* *IV.5.b - The Free and Informed Consent Form must (...) be adapted, by the researcher in charge, in research with foreign cooperation designed internationally, to ethical norms and to the local culture, always using clear and accessible language to everyone and, in particular, to the research participants, taking special care to make it easy to read and understand;*
1.2	**TCLE:** **Refund**	a) Omit information about the reimbursement; b) Limit reimbursement items and amounts; c) Failure to guarantee reimbursement to the accompanying person(s);	The TCLE must clearly and affirmatively ensure the reimbursement of all expenses that the participant and his/her companion(s) will incur when participating in the research.	**CNS RESOLUTION No. 466 of 2012:** *II.21 - reimbursement - material compensation, exclusively for expenses of the participant and their companions, when necessary, such as transportation and food;* *IV.3.g - The Free and Informed Consent Form must contain, obligatorily: (...) explanation of the reimbursement guarantee and how the expenses incurred by the research participants and arising from it will be covered;*

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.3	**TLCE: assistance in virtue of damage arising from search**	a) Omit information about assistance; b) Condition assistance to proof of causal link of the damage; c) Limit the type of assistance to research participant; d) Limit the assistance time to the research participant; e) Not informing about the gratuity of the assistance.	The TCLE must clearly and affirmatively ensure that the research participant will receive full and immediate assistance, free of charge (by the sponsor), for as long as necessary in case of damage resulting from the research.	**CNS RESOLUTION No. 466 of 2012:** *II.3.1 - Immediate assistance - is that which is emergency and without charge of any kind to the research participant, in situations where he/she needs it;* *II.3.2 - Comprehensive care - is that provided to deal with complications and damage arising, directly or indirectly, from the research;* *II.6 - damage associated with or resulting from the research - immediate or subsequent harm, direct or indirect, to the individual or the community, resulting from the research;* *III.2.o - Research, in any area of knowledge involving human beings, must observe the following requirements: (...) ensure that research participants are provided with follow-up, treatment, comprehensive care and guidance, as the case may be, as needed, including in tracking surveys;* *IV.3.c - The Informed Consent Form must contain, obligatorily: (...) clarification on the form of follow-up and assistance to which research participants will be entitled, including considering benefits and follow-up after the closure and/or stopping the research;* *V.6 - The researcher, the sponsor and the institutions and/or organizations involved in the different phases of the research must provide immediate assistance, under the terms of item II.3, as well as be responsible for the integral assistance to the research participants in what concerns refers to the complications and damage resulting from the research.*

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.4	**TLCE: assistance during and after pregnancy due to resulting damages of the research**	a) Omitting information about assistance during and after pregnancy; a) Condition assistance to proof of causal link of the damage to the pregnancy; b) Condition assistance to proof of a causal link between the harm to the mother and/or child; c) Limit the time of assistance to the mother and/or child; d) Limit the time of assistance to the mother and/or child; e) Failure to provide assistance to the child; f) Not informing about the gratuity of the assistance.	The TCLE must clearly and affirmatively ensure that the mother and child will receive full and immediate assistance, during and after pregnancy, free of charge (by the sponsor), for as long as necessary.	**CNS RESOLUTION No. 466 of 2012:** *II.3.1 - Immediate assistance - is that which is emergency and without charge of any kind to the research participant, in situations where he/she needs it;* *II.3.2 - Comprehensive care - is that provided to deal with complications and damage arising, directly or indirectly, from the research;* *II.6 - damage associated with or resulting from the research - immediate or subsequent harm, direct or indirect, to the individual or the community, resulting from the research;* *III.2.o - Research, in any area of knowledge involving human beings, must observe the following requirements: (...) ensure that research participants are provided with follow-up, treatment, comprehensive care and guidance, as the case may be, as needed, including in tracking surveys;* *IV.3.c - The Informed Consent Form must contain, mandatorily: (...) clarification on the form of follow-up and assistance to which research participants will be entitled, including considering benefits and follow-up after the closure and/or stopping the research;* *V.6 - The researcher, the sponsor and the institutions and/or organizations involved in the different phases of the research must provide immediate assistance, under the terms of item II.3, as well as be responsible for the integral assistance to the research participants in what concerns refers to the complications and damage resulting from the research.*

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.5	**TCLE:** **Indemnity**	a) Omit information about the indemnity; b) Bind the indemnity to insurance contracted by the researcher.	Ensure, in a clear and affirmative way, that the research participant is entitled to compensation in case of damage resulting from the study. It is not appropriate for the TCLE to contain restrictions, upon contracting insurance, for indemnity or assistance.	**CNS RESOLUTION No. 466 of 2012:** *II.7 - indemnification - material coverage to repair damage caused by the research to the research participant;* *IV.3.h - The Term of Free and Informed Consent must contain, obligatorily: (...) explanation of the indemnity guarantee in face of eventual damages resulting from the research.* *IV.4.c - The Free and Informed Consent Form in researches that use experimental methodologies in the biomedical area, involving human beings, in addition to what is foreseen in item IV.3 above, must obligatorily observe the following: (...) not demand from the research participant, under any argument, waiver of the right to compensation for damages. The Free and Informed Consent Form must not contain a disclaimer that removes this responsibility or that implies that the research participant waives his/her rights, including the right to seek compensation for eventual damages.* *V.7 - Research participants who suffer any type of damage resulting from their participation in the research, provided or not in the Free and Informed Consent Form, are entitled to compensation by the researcher, the sponsor and the institutions involved in the different phases of the research.* **CIVIL CODE (LAW 10,406/2002):** Articles 927 to 954, of Chapters I (Obligation to Indemnify) and II (Indemnity), Title IX (Civil Liability; Book I – The Law of Obligations).

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.6	**TCLE: contraception**	a) Failure to respect the decision of the participant; b) Impose a contraceptive method; c) Not informing that there are situations in which it is not necessary to use a contraceptive method; d) Omit information about the provision of the method contraceptive; e) Giving ambiguous information about the responsibility for providing the contraceptive method.	The TCLE must clearly and affirmatively ensure that the choice of contraceptive method is a shared decision between the study physician and the research participant and that there are situations in which contraception is not necessary. The research participant must also be assured that the chosen contraceptive method, when it involves expenses, will be provided by the sponsor, free of charge, and for as long as necessary.	**CNS RESOLUTION No. 466 of 2012:** *III.2.t - Research, in any area of knowledge involving human beings, must observe the following requirements: (...) guarantee, for women who declare themselves expressly exempt from the risk of pregnancy , either for not engaging in sexual practices or for exercising them in a non-reproductive manner, the right to participate in research without the mandatory use of contraceptives;* *III.2.o - Research, in any area of knowledge involving human beings, must observe the following requirements: (...) ensure that research participants are provided with follow-up, treatment, comprehensive care and guidance, as the case may be, as needed, including in tracking surveys*
1.7	**TCLE: Post-study access to investigational product** **(Continues...)**	a) Omit information about post-study access; b) Not ensuring access to the investigational product in case of individual benefit; c) Not ensuring access to the investigational product to the control group; d) Contain restriction on the prescription of the experimental drug in case of individual benefit; e) Link the supply of the investigational product to an extension study;	The TCLE must clearly and affirmatively ensure that, at the end of participation in the study, individuals will continue to receive the investigational product free of charge by the sponsor in case of individual benefit, this being a consideration of the study physician or even the personal physician. Furthermore, the TCLE must ensure that the sponsor will provide, free of charge, the drug to all research participants (experimental and control groups) if there is a collective benefit, identified in the interim analysis or at the end of the study.	**CNS RESOLUTION No. 466 of 2012:** *III.2.n - Research, in any area of knowledge involving human beings, must observe the following requirements: (...) to assure research participants of the benefits resulting from the project, whether in terms of social feedback, access to research procedures, products or agents;* *III.2.o - Research, in any area of knowledge involving human beings, must observe the following requirements: (...) ensure that research participants are provided with follow-up, treatment, comprehensive care and guidance, as the case may be, as needed, including in tracking surveys;*

ITEM THEME		WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.7	**(Continuation)** **TCLE:** **Post-study access to investigational product**	**(Continuation)** f) Limit post-study access time; g) Ensure access to the investigational product only to the experimental group; h) Failure to inform about free post-study access; i) Giving ambiguous information about responsibility for post-study access.	**(Continuation)**	**(Continuation)** *III.3.d - Research using experimental methodologies in the biomedical area, involving human beings, in addition to what is recommended in item III.2, should also: (...) assure all participants at the end of the study, on the part of the sponsor, free and indefinite access to the best prophylactic, diagnostic and therapeutic methods that have proven effective; (d1) access will also be guaranteed in the interval between the end of individual participation and the end of the study, and in this case, this guarantee may be given through an extension study, according to a duly justified analysis by the participant's attending physician.*
1.8	**TCLE:** **Expression "Medicine of study"** **(Continues...)**	Use expressions "study drug" or "research drug" (or something similar) refer to simultaneously with to the product investigational and placebo.	The TCLE should not use the expressions "study drug" or "medication research" (or something similar) to refer to both the investigational product and the placebo. This leads to misinterpretation and prejudice to making an autonomous decision.	**CNS RESOLUTION No. 466 of 2012:** *I.23 - Term of Free and Informed Consent - TCLE - document in which the free and informed consent of the participant and/or their legal guardian is explained, in writing, and must contain all the necessary information, in clear and objective language, easy to understand, for the most complete clarification about the research to be which one proposes to participate;* *IV.4.b - The Term of Free and Informed Consent in researches that use experimental methodologies in the biomedical area, involving human beings, in addition to what is foreseen in item IV.3 above, must obligatorily observe the following: (...) clarify, when relevant, the possibility of including the participant in a control or placebo group, clearly explaining the meaning of this possibility;*

ITEM THEME		WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.8	**(Continuation)** **TCLE:** **Expression "Study drug"**	**(Continuation)**	**(Continuation)**	**(Continuation)** *IV.5.b - The Free and Informed Consent Form must (...) be adapted, by the researcher in charge, in research with foreign cooperation designed internationally, to ethical norms and to the local culture, always using clear and accessible language to everyone and, in particular, to the research participants, taking special care to make it easy to read and understand;*
1.9	**Risks and benefits** a) Omit description of benefits and/or the risks of the research; b) Overestimating the benefits of an experimental treatment; c) Underestimating the risks of an experimental treatment; d) Not informing about measures and precautions.	1) The TCLE must present, in a clear and objective way, the potential benefits of the participant research, overestimate them; 2) If the study does not anticipate any direct benefit to the participant, this information must be explicitly included in the TCLE; 3) The potential risks associated with the research must be described in the TCLE, without underestimating them; 4) The TCLE must explain the measures and precautions that will be adopted to avoid or reduce the risks associated with the research.	**CNS RESOLUTION No. 466 of 2012:** *III.1.b - Research ethics implies (...) weighting between risks and benefits, both known and potential, individual or collective, committing to the maximum benefits and the minimal damage and risk.* *IV.3.b - The Informed Consent Form must must contain: (...) explanation of the possible discomforts and risks arising from participation in the research, in addition to the expected benefits of this participation and presentation of measures and precautions to be employed to avoid and/ or reduce adverse effects and conditions that may cause harm , considering characteristics and context of the research participant.*
1.10	**TCLE:** **Alternative therapeutic methods**	Omit information about alternative therapeutic methods.	The TCLE must clearly describe the alternative methods of treatment to the research participant. If there are no alternative methods, this must be made explicit in the TCLE.	**CNS RESOLUTION No. 466 of 2012:** *IV.4.a - The Term of Free and Informed Consent in research that uses experimental methodologies in the biomedical area, involving human beings, in addition to what is provided for in item IV.3 above, must observe, obligatorily, the following: (...) explain, when pertinent, the existing alternative therapeutic methods;*

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.11	**TCLE: Access to result of exams**	State, in the TCLE, that the research participant will not have access to the results of their exams.	The TCLE must not contain restrictions for the research participant to have access to the results of exams performed during the study, unless there is methodological justification for doing so.	**CNS RESOLUTION No. 251 of 1997:** *III.2.i – The researcher in charge must: (...) Provide access to test and treatment results to the patient's doctor or to the patient himself whenever requested and/or indicated.*
1.12	**TCLE: confidentiality** and **data anonymization** **(Continues...)**	a) Not guaranteeing that the data passed on to the sponsor or third parties will be anonymized; b) Give ample access to the source documents; c) Omit that the medical record may be consulted; d) Do not describe the mechanisms adopted to maintain confidentiality.	The TCLE must be explicit in relation to the confidentiality of the data, ensuring that: 1) The research participant's data will be forwarded to the sponsor or third parties in an anonymized form; 2) In addition to the sponsor's researchers, monitors and auditors, they may have access to the participants' personal data (if applicable), and a professional commitment to the confidentiality of information must be ensured; 3) The medical record may be consulted by the researchers, and also by monitors and auditors of the sponsor. In addition, it should be explained how the mechanism will be used to guarantee data confidentiality (example: data encoding, database access password, etc.) 3) The medical record may be consulted by the researchers, and also by monitors and auditors of the sponsor.	**CNS RESOLUTION No. 466 of 2012:** *III.2.i - Research, in any area of knowledge involving human beings, must observe the following requirements: (...) provide for procedures that ensure confidentiality and privacy, protection of image and non-stigmatization of research participants, ensuring that information is not used to the detriment of people and/or communities, including in terms of self-esteem, prestige and/or economic-financial aspects;* *IV.3.e - The Informed Consent Form must contain, obligatorily: (...) guarantee of maintenance of secrecy and privacy of the research participants during all phases of the research;* **CFM RESOLUTION No. 1.638/2002:** *Art. 1 - Define medical records as the single document consisting of a set of information, signs and registered images, generated from facts, events and situations about the patient's health and the care provided to him, of a legal, confidential and scientific nature, which enables communication between members of the multidisciplinary team and the continuity of care provided to the individual.* **CFM RESOLUTION No. 1.605/2000:** *Art. 1 - The doctor cannot, without the patient's consent, reveal the contents of the medical record or medical file.*

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.12	**(Continuation)** **TCLE: confidentiality and data anonymization**	**(Continuation)**	**(Continuation)**	**(Continuation)** **CFM RESOLUTION No. 1.931/2009 (CODE OF MEDICAL ETHICS):** *Art. 85. Physicians are prohibited from: (...) Allowing the handling and knowledge of medical records by people not bound by professional secrecy when under their responsibility.*
1.13	**TCLE: freedom from refusal to participate in the study**	Omit information about freedom of refusal.	The TCLE must clearly and affirmatively ensure that the individual is fully free to refuse to participate in the study and that this decision will not result in any penalty on the part of the researchers.	**CNS RESOLUTION No. 466 of 2012:** *IV.3.d - The Informed Consent Form must contain, obligatorily: (...) guarantee of full freedom to the research participant, to refuse to participate or withdraw their consent, at any stage of the research, without any penalty.*
1.14	**TCLE: Freedom to withdraw from consent**	a) Omit information about the freedom to withdraw the TCLE; b) Affirm that the researcher will contact the research participant after withdrawal of consent; c) Affirm that the researcher will continue to collect data from the participant after withdrawal of the consent.	1) The TCLE must ensure, in a clear and affirmative manner, that the research participant is fully free to withdraw their consent at any time during the research and that this decision will not generate penalties on the part of the researchers. 2) The TCLE should not state that the participant may be contacted, or that their data will continue to be collected, after withdrawal of consent.	**CNS RESOLUTION No. 466 of 2012:** *IV.3.d - The Informed Consent Form must contain, mandatorily: (...) guarantee of full freedom to the research participant, to refuse to participate or withdraw their consent , at any stage of the research, without any penalty.* *IV.3.e - The Informed Consent Form must contain, obligatorily: (...) guarantee of maintenance of secrecy and privacy of the research participants during all phases of the research;* **CNS RESOLUTION No. 340 of 2004:** *III.7 - Every individual may have access to their genetic data, as well as the right to withdraw them from the banks where they are stored, at any time.*

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.15	**TCLE: interruption of treatment**	Use inappropriate terms in the TCLE to define the interruption or discontinuity of treatment.	The TCLE should not contain expressions such as "withdraw from the study", "exclude from the study" or "terminate participation" to refer to the interruption (discontinuation) of treatment during the research, since the participant may need follow-up and assistance (eg : due to toxicity, pregnancy, etc.).	**CNS RESOLUTION No. 466 of 2012:** See other relevant textual references in the item: "TLCE: Assistance due to damage resulting from research".
1.16	**TCLE: Study interruption**	Omit assistance information in case of interruption of the study.	The TCLE must clearly and affirmatively ensure that, in case of interruption of the study, the research participant will receive the appropriate assistance, free of charge, for as long as necessary.	**CNS RESOLUTION No. 466 of 2012:** *IV.3 - The Informed Consent Form must contain, mandatorily: (...) clarification on the form of follow-up and assistance to which research participants will be entitled, including considering benefits and follow-ups after the closure and/or interruption of the research;* See other relevant textual references in the item: "TLCE: Assistance due to damage resulting from the research".
1.17	**TCLE: Means of contact with the researcher in charge**	a) Not informing the means of contact with the researcher in charge; b) Not informing a means of contact that is easily accessible to the research participant in case of urgency (24 hours a day, 7 days a week).	The TCLE must explicitly provide the means of contact with the researcher in charge (at least, address and telephone number), as well as provide an easily accessible means of contact for the research participant in case of urgency (24 hours a day, 7 days a day). week).	**CNS RESOLUTION No. 466 of 2012:** *IV.5.d - The Informed Consent Form must also: (...) be prepared in two copies, initialed on all its pages and signed, at the end, by the invited to participate in the research, or by their legal representative, as well as by the researcher in charge, or by the person(s) delegated by him/her, and the signature pages must be on the same sheet. Both copies must include the address and telephone or other contact details of those responsible for the research and the local CEP and Conep, when applicable.*
1.18	**TCLE: means of contact with the System CEP/Conep** **(Continues...)**	a) Failure to inform the means of contact with the CEP (or Conep, when applicable); b) Not informing the CEP's opening hours to the public (and Conep, when applicable);	The TCLE must explicitly provide the means of contact with the CEP (at least, address and telephone number), as well as the opening hours for the public. It is also necessary to explain in plain language what a CEP represents. When the study involves ethical analysis by Conep, the recommendations must be extended to this Commission.	**CNS RESOLUTION No. 466 of 2012:** *IV.5.d - The Informed Consent Form must also: (...) be prepared in two copies, initialed on all its pages and signed, at the end, by the invited to participate in the research, or by their legal representative, as well as by the responsible researcher (...). Both copies must include the address and telephone or other contact details of those responsible for the research and the local CEP and Conep, when applicable.*

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.18	**(Continuation)** **TCLE:** **means of contact with the System CEP/Conep**	**(Continuation)** c) Not explaining in simple language what a CEP (and Conep, when applicable) does.	**(Continuation)**	**(Continuation)**
1.19	**TCLE:** **Field of signatures and rubrics**	a) "responsible destined researcher" field; b) Using inappropriate terms in the field of signatures and headings; c) Additional information in the signature field; d) Signature field on a separate sheet from the rest of the TCLE.	The signature and initials fields must be identified according to the terminology provided for in CNS Resolution No. 466 of 2012, that is, using the terms "researcher" and "research participant/legal guardian". The signature field must not be separated from the rest of the document (except when, for configuration reasons, this is not possible) and must not contain additional fields besides name and date.	**CNS RESOLUTION No. 466 of 2012:** *II.10 - research participant - individual who, in an informed and voluntary manner, or under the clarification and authorization of their legal guardian(s), agrees to be researched. Participation must be free of charge, with the exception of Phase I or bioequivalence clinical trials;* *II.15 - researcher - member of the research team, co-responsible for the integrity and well-being of research participants;* *II.16 - researcher in charge - person responsible for coordinating the research and co-responsible for the integrity and well-being of the research participants;* *IV.5.d - The Informed Consent Form must also: (...) be drawn up in two copies, initialed on all its pages and signed, at its end, by the person invited to participate in the research, or by their legal representative, as well as the responsible researcher, or the person(s) delegated by him/her, and the signature pages must be on the same sheet. Both copies must include the address and telephone or other contact details of those responsible for the research and the local CEP and Conep, when applicable.*

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.20	**TCLE:** **Supply** **an original copy of the document, with signatures and rubrics** **(Continues ...)**	a) Omit information about the right to have a copy of the TCLE; b) Use the word “Copy”; Not ensuring that all pages of the TCLE will be initialed.	The TCLE must clearly and affirmatively ensure that the research participant will receive a copy (and not a copy) of the document, signed by the research participant (or their 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 contain, mandatorily: (...) guarantee that the research participant will receive a copy of the Informed Consent Form;* *IV.5.d - The Informed Consent Form must also: (...) be drawn up in two copies, initialed on all its pages and signed, at its end, by the person invited to participate in the research, or by their legal representative, as well as the responsible researcher, or the person(s) delegated by him/her, and the signature pages must be on the same sheet. Both copies must include the address and telephone or other contact details of those responsible for the research and the local CEP and Conep, when applicable.*
1.21	**TCLE:** **Biological material (specific aspects of the TCLE)** **(Continues...)**	a) Failure to provide the biological material; b) Not informing about the freedom to withdraw consent for safekeeping and use of biological material; c) Not informing about the intention of future researches with the biological material (when any); d) Use the term “donated material”.	1) The TCLE must explicitly bring the nature of the material of the biological material that will be collected (example: blood, urine, etc.), the quantity, to which institution it will be sent, the purpose of the collection (analyses that will be carried out), the destination of the biological material after its use (disposal, processing, and time of storage; storage), the place or 2) The TCLE must inform that the consent for the custody and use of the biological material can be withdrawn at any time by the research participant;	**CNS RESOLUTION No. 441/2011:** *Art. 1.1.I - Biobank: organized collection of human biological material and associated information, collected and stored for research purposes, in accordance with regulations or pre-defined technical, ethical and operational standards, under institutional responsibility and management, without commercial purposes;* *Art. 1.1.II - Biorepository: collection of human biological material, collected and stored throughout the execution of a specific research project, according to regulations or pre-defined technical, ethical and operational standards, under institutional responsibility and under the management of the researcher, with no purpose commercials;* *Art. 6. Free and informed consent regarding the collection, deposit, storage, use and disposal of human biological material in a Biorepository is formalized through a specific TCLE for each research, as recommended in the resolutions of the National Health Council (CNS).*

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.21	**(Continuation)** **TCLE:** **Biological material (specific aspects of the TCLE)**	**(Continuation)**	**(Continuation)** **3)** The TCLE must inform, when applicable, the possibility of future use of the biological material and the need to obtain a new consent; **4)** Do not use the term "donated material" to refer to biological material that was donated (or provided) for research.	**(Continuation)** *Art. 15.II.c. Regarding the use of samples of stored human biological material: (...) research projects that intend to use stored samples must include: (...) Specific TCLE for new research or the request for its waiver, as provided in art. 5 of this Resolution.* **ORDINANCE No. 2.201/2011:** *Art. 5th. Free and informed consent regarding the collection, deposit, storage, use and disposal of human biological material in a biorepository is formalized through a specific TCLE for each research, as recommended by CNS resolutions.* *Art. 18. The research subject must be contacted to consent, for each new research, on the use of human biological material stored in a biorepository, formalizing consent through specific TCLE. Single paragraph.* *When based on the impossibility of contact with the research subject, it is up to CEP to authorize, or not, the use of stored human biological material.*
1.22	**TCLE:** **human genetics (specific aspects of the TCLE)** **(Continues...)**	a) Not informing the genes or gene products that will be studied; b) Failure to ensure confidentiality of genetic data and privacy of research participants; c) Not informing the mechanisms of protection of genetic data;	1) The TCLE must explicitly bring the genes/DNA/RNA segments that will be studied. However, if it is impracticable from a practical point of view to list all the genes, it is acceptable for the researcher to describe the genes to be studied grouped according to functionality or effect;	**CNS RESOLUTION No. 340 of 2004:** *V.1 - The TCLE must be prepared (...) with special focus on the following items:* *a) clear explanation of the exams and tests that will be carried out, indication of the genes/ segments of DNA or RNA or gene products that will be studied and their relationship with any condition of the subject of the research;* *b) guarantee of secrecy, privacy and, when applicable, anonymity;*

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
1.22	**(Continuation)** **TCLE:** **Human genetics** **(specific aspects of the TCLE)**	**(Continuation)** d) Failure to provide genetic counseling and clinical follow-up; e) Not ensuring access to the results of genetic tests; f) Not informing that the research participant has the option of being aware or not of the genetic results.	**(Continuation)** 2) The TCLE must ensure, clearly and affirmatively, that the genetic data are confidential and that they will not be passed on to third parties (such as, for example: insurers, employers, hierarchical supervisors, among others). Furthermore, the genetic data protection mechanisms must be explained in the TCLE; 3) When applicable, the TCLE must clearly and affirmatively ensure that the participant will have free access to genetic counseling and clinical follow-up. It should also be informed who (or where) these procedures will be carried out; 4) The TCLE must ensure, in a clear and affirmative way, that the results of exams will be informed to the research participant if they so wish; 5) When applicable, the TCLE must inform that the result of the genetic tests may bring risks to the research participant. In this case, the TCLE must inform that the participant has the option of knowing or not the result of that exam.	**(Continuation)** *c) genetic counseling and clinical follow-up plan, with the indication of those responsible, at no cost to the research subjects;* *d) type and degree of access to the results by the subject, with the option of knowing or not knowing this information;* *It is) (...)* *f) information regarding individual data protection measures, examination and test results, as well as the medical record, which will only be accessible to the researchers involved and that access to third parties (insurers, employers, hierarchical supervisors, etc.) will not be allowed;* *g) information regarding protection measures against any type of discrimination and/or stigmatization, individual or collective;* **CIRCULAR LETTER N° 041/2015/CONEP/CNS/MS:** *2.a) The researcher may describe the genes studied in groups according to functionality or effect (example: genes related to the onset of cancer, inflammation, cell death, response to treatment , etc.), it is not necessary to list them individually;* *2.b) In the case of studies involving large-scale genetic studies (for example, complete genome or exome sequencing), if the aforementioned grouping is not feasible, the TCLE must contain an explanation of the procedure to be performed, respecting the comprehension capacity of the research participant.*

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
2	**MATERIAL BIOLOGICAL STORED IN BIOBANK OR BIOREPOSITORY**	a) Declare that there will be no formation of a bank of biological material; b) Failure to provide adequate information about the biological material in the TCLE; c) Failure to present the necessary documentation for setting up a biological material bank.	1) If there is collection of human biological samples in a survey, it must be declared on the Plataforma Brasil that there will be formation of a bank of biological material; 2) The TCLE must bring, in a clear and complete way, the information related to the collection, storage, use and final destination of the biological material (see item 1.21 of this Manual); 3) Submit the documentation provided for in Table 3 of this Manual.	**CNS RESOLUTION No. 441/2011** (in its entirety). **ORDINANCE MS No. 2.201/2011** (in full).
3.1	**RESOURCES:** **Budget**	a) Not detailing the budget; b) Omit budget items; c) Declare that the study will have no costs.	The researcher must present a detailed budget, foreseeing all costs necessary for the development of the research (human and material resources), not omitting those related to the procedures foreseen in the study.	**CNS RESOLUTION No. 466 of 2012:** *III.2.h - Research in any area of knowledge involving human beings must observe the following requirements: (...) have the necessary human and material resources to ensure the well-being of being of the research participant, and the researcher(s) must have adequate professional capacity to develop their role in the proposed project;* **CNS OPERATIONAL STANDARD No. 001 of 2013:** *3.3.e) All research protocols must contain: (...)* *Financial budget: detail the resources, sources and destination; form and value of the researcher's remuneration; present in national currency or, when in foreign currency, with the official exchange rate in Real, obtained in the period of the research proposal; submit a forecast for reimbursement of expenses for the participant and their companions, when necessary, such as transportation and food and material compensation in the cases specified in item II.10 of CNS Resolution 466 of 2012;*

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
3.2	**RESOURCES: Sponsor**	a) Do not indicate the main sponsor; b) Appoint the Unified Health System as a sponsor.	1) Clearly indicate the main sponsor of the study on Plataforma Brasil and Folha de Rosto. In the case of studies of investigator's initiative, without own resources, the institution assumes responsibility as the main sponsor; of 2) SUS is not an individual or legal entity and, therefore, cannot be appointed as a research sponsor.	**CNS RESOLUTION No. 466 of 2012:** *II.11 - sponsor - natural or legal person, public or private, who supports the research, through funding actions, infrastructure, human resources or institutional support;* *III.2.h - Research, in any area of knowledge involving human beings, must observe the following requirements: (...) have the necessary human and material resources to guarantee the well-being of the research participant, and the (s) researcher(s) possess adequate professional capacity to develop their role in the proposed project;* **CNS OPERATIONAL STANDARD No. 001 of 2013:** *3.3.e) All research protocols must contain: (...)* *Financial budget: detail the resources, sources and destination; form and value of the researcher's remuneration; present in national currency or, when in foreign currency, with the official exchange rate in Real, obtained in the period of the research proposition; submit a forecast for reimbursement of expenses for the participant and their companions, when necessary, such as transportation and food and material compensation in the cases specified in item II.10 of CNS Resolution 466 of 2012;*
3.3	**RESOURCES: Infrastructure institutional** **(continues...)**	a) Failure to present a document proving the necessary infrastructure for the development of clinical research; o b) Submit a statement of institutional infrastructure signed by the researcher	The institutional responsible must present a document demonstrating that the proposing institution has adequate infrastructure for the development of clinical research and conditions to provide assistance to the participant in case of need, especially in urgent/ emergency situations.	**CNS RESOLUTION No. 466 of 2012:** *III.2.h - Research in any area of knowledge involving human beings must observe the following requirements: (...) have the necessary human and material resources to ensure the well-being of being of the research participant, and the researcher(s) must have adequate professional capacity to develop their role in the proposed project;*

ITEM	THEME	WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
3.3	**(Continuation)** **RESOURCES:** **Infrastructure institutional**	**(Continuation)**	**(Continuation)**	**(Continuation)** **OPERATIONAL STANDARD CNS No. 001 of 2013:** *3.3.d) All research protocols must contain: (...) Demonstration of the existence of the necessary and capable infrastructure for the development of the research and to deal with any problems resulting from it, with a document that expresses the agreement of the institution and/or organization through its responsible person with competence;*
4	**TIMELINE**	a) Present the start date of the study prior to the procedure in the CEP/Conep System; b) Do not discriminate the stages of the research.	The schedule must indicate the start of the study on a date compatible with the processing of the protocol in the CEP/Conep System. Submit an explicit commitment to start the study only after final approval by the CEP/Conep System. All stages of the research must be detailed in the schedule.	**OPERATIONAL STANDARD CNS No. 001 of 2013:** 3.4.1.9) All research protocols must contain, obligatorily: (...) Schedule: informing the total duration and the different stages of the research, in number of months, with an explicit commitment by the researcher that the research will only be started after after approval by the CEP-Conep System.
5	**COVER PAGE** a) Incorrectly fill in the study area; b) Failure to complete mandatory fields requirements; c) Presence of conflict of interest institutional.		In order to properly fill in the Cover Sheet, it is necessary for the researcher to accurately complete the information on Plataforma Brasil, especially the fields related to the thematic areas. After printing the Cover Sheet, the fields that are blank must be filled in, especially those that sign the commitment of the researcher, the proposing institution and the sponsor. The researcher, when assuming responsibility for the fields Proposing Institution.	**CNS OPERATIONAL STANDARD No. 001 of 2013:** *3.3.a - All research protocols must contain: (...) Front page: all fields must be completed, dated and signed, identifying the signatories. The information provided must be compatible with that of the protocol. The identification of the signatures must clearly contain the full name and function of the person signing, preferably indicated by a stamp. The research title will be presented in Portuguese and will be identical to the research project*

ITEM THEME		WHAT'S THE PROBLEM?	WHAT TO DO	TEXTUAL REFERENCE
6	**STUDIES PROPOSALS OF EXTERIOR**	a) Failure to present a document approving the study by CEP in the country of origin; b) Do not provide justification for the study not to be carried out in the country of origin; c) Not providing information about the registration status of the investigational product in the country of origin.	1) Present a document with the approval of the study by CEP in the country of origin. If the study is still in progress in the ethical system of that country, a letter must be presented assuring that, even being approved by the System CEP/Conep, the study will only start after approval by the CEP in the country of origin and the approval document will be presented for the appreciation of the System CEP/Conep as soon as it becomes available; 2) Provide justification for not carrying out the study in the country of origin (when applicable); 3) Present the status of registration of the investigational product in the country of origin.	**CNS RESOLUTION No. 292 of 1999:** *VII – When preparing the protocol, special care must be taken to present the following items: VII.1 – Approval document issued by the Research Ethics Committee or equivalent of an institution in the country of origin, which will promote or who will also carry out the project.* *VII.2 – When the development of the project in the country of origin is not foreseen, the justification must be placed in the protocol for appreciation of the CEP of the Brazilian institution.* **CNS RESOLUTION No. 251 of 1997:** *IV.1.j - The protocol must contain (...) Information regarding the status of research and registration of the product in the country of origin.* **OPERATIONAL STANDARD CNS No. 001 of 2013:** *3.4.2.a - If the purpose is to test a health product or device, new in Brazil, whether of foreign origin or not, the current status of registration with the regulatory agencies of the country of origin, if any.*