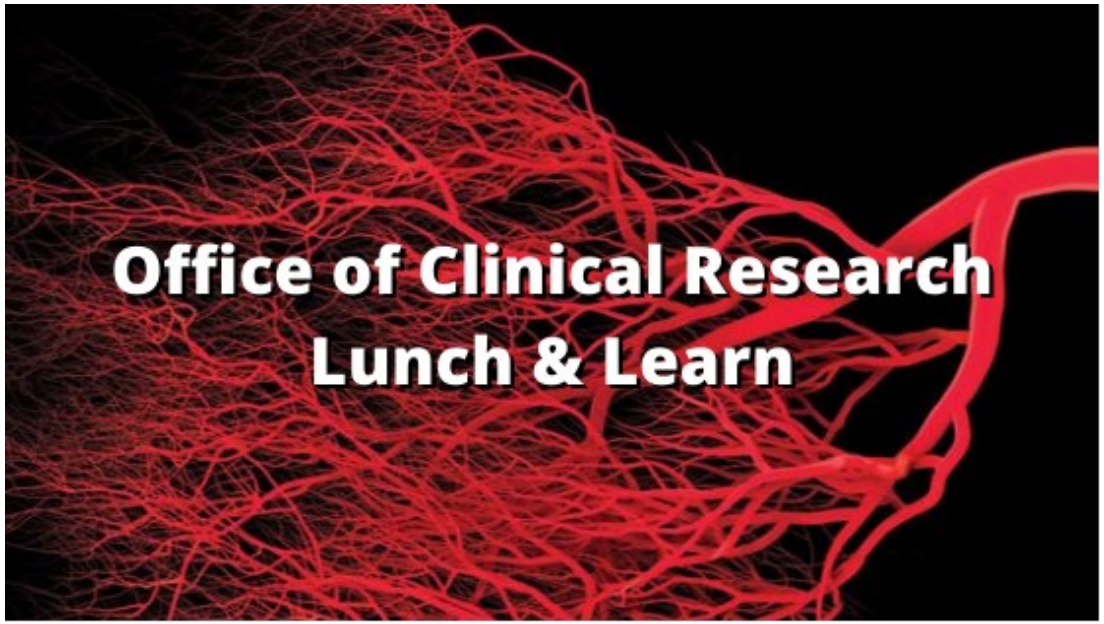


Clinical Trial Agreement (CTA/Contract) and Informed Consent Form (ICF) Reviews: When and When Not to Edit

Thursday, November 16th, 2023

University of CINCINNATI | next lives here

UC / UC Health
Clinical Research Orientation and Training (CRO&T)

Thursday, December 14th, 2023

9:00 am - 3:00 pm

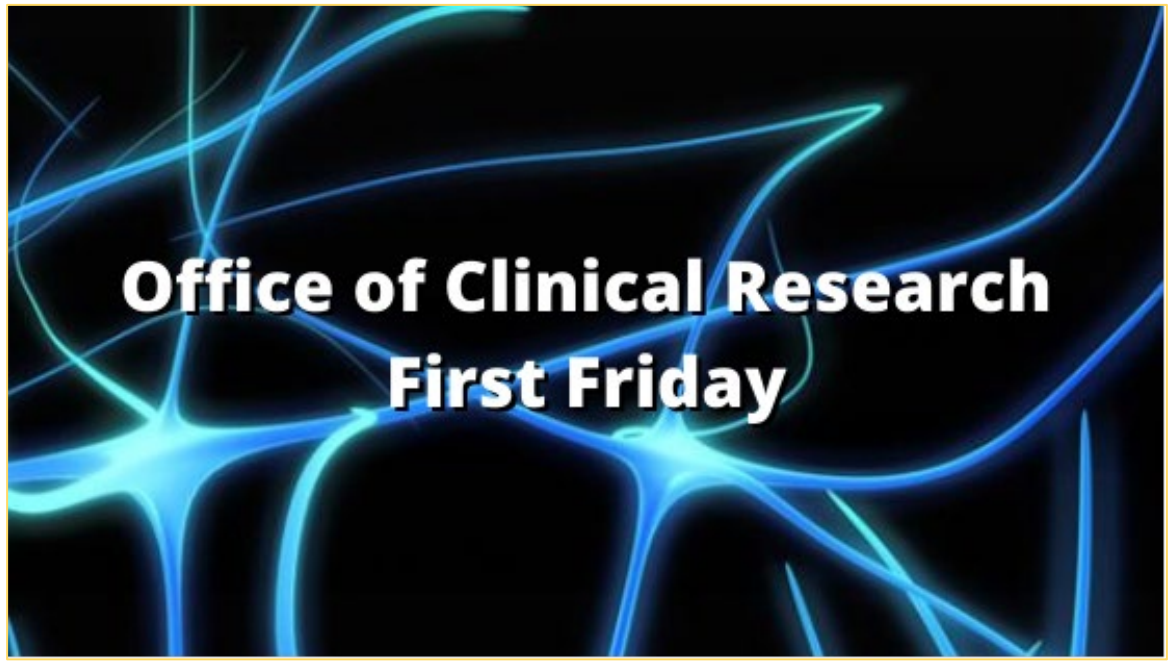
Virtual presentation

The last day of registration is Friday, December 8th, 2023

Register Here

Please reach out to Nate Harris, harrisnl@ucmail.uc.edu for any questions

University of CINCINNATI | next lives here



We will not hold the December 2023 First Friday

The next First Friday to kick off the new year is January 5th, 2024

University of CINCINNATI | next lives here

Compliance Corner

Recently updated OCR Standard Operating Procedures:

- **UCH-OCR-FIN-SOP-002-06:** UC Health Research Billing
- **UCH-OCR-OPS-SOP-014-06:** Prompt MIDAS Reporting of Serious Adverse Events that are both Unexpected and Related to the Research
- **UCH-OCR-REV-SOP-009-06:** Ancillary Research Services Review for UC Health Research approval

All OCR SOPs are accessible from the UC Health intranet home page utilizing the Compliance 360 policy search function or reach out to the Office of Clinical Research with any questions or concerns.

University of CINCINNATI | next lives here

Today's Presentation:

Clinical Trial Agreement (CTA/Contract) and Informed Consent Form (ICF) Reviews: When and When Not to Edit

Join us for a refresher of the review process for agreement between Informed Consent Form (ICF) Subject Injury (SI) language and other components of the document, with the parameters set forth in the Clinical Trial Agreement (CTA) for clinical trials that involve more than minimal risk. This presentation will also discuss updates to this process regarding the OCR online CTA submission system.

Nate Harris
Clinical Research Compliance Administration, Education and Training
Office of Clinical Research

Bridget Kellner
Sponsored Research Services (SRS)
Sponsored Research Administrator, II
Contracts Division/Industry Clinical Trials

Kareemah Mills
Director
Human Research Protection Program
University of Cincinnati Office of Research

University of CINCINNATI | next lives here

CTA and the Informed Consent (ICF) and HIPAA Authorization

Today's focus is the interaction and overlap of the CTA and ICF and HIPAA Authorization

University of CINCINNATI | next lives here

Parts of the ICF to be reviewed that may require editing regarding congruency with the CTA:

- **Reimbursement for injuries sustained by study subjects resulting from participation in the research**
- **Protections for maintaining the privacy and confidentiality of Study Subject participating in the research**
- **sponsor's future use of Study subject data**

The CTA, ICF and HIPAA authorization will each address these items.

To prevent the CTA from containing obligations contra those in the ICF and HIPAA Authorization (collectively the Authorization Documents), the CTA language should generally defer to the IRB approved and study subject signed Authorization Documents

Once the study subject data that may include PHI, is disclosed to Sponsor, it is no longer protected under HIPAA which protections last indefinitely or at least 50 years after the subject's death, although it may still be subject to the terms of the subject's written Authorization Documents.

UC will seek to obligate the Sponsor contractually to protect and use Subjects information only in accordance with the Authorization Documents signed by the subject. UC will also ensure that Sponsor's privacy and security obligations are documented in the CTA and survive the expiration or termination of the CTA.

IRB Oversight and HRPP Obligations

Apply Ethical Principles and Guidelines of Belmont Report for the protection of human subjects research

Satisfy federal regulations (HHS and FDA) and Good Clinical Practice guidelines regarding elements of consent disclosure

Maintain AAHRPP Accreditation for demonstrating the overall excellence of the UC HRPP

Ethical Principle: Respect for Persons

- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them
- This opportunity is provided with informed consent
- Consent process must contain 3 ethical elements:
  - Information
  - Comprehension
  - Voluntariness

Information: Elements of Consent Disclosure

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
- One of the following statements about any future research from the collection of identifiable private information or identifiable biospecimens:
  - *Information that could identify you will be removed from the study data. After removal, the study data could be used for future research studies. The study data could also be given to another researcher for future research studies. This may be done without getting additional permission from you.*
  - *Information that could identify you will be removed from the study data. The study data will not be used or shared for future research studies.*
- When appropriate, a statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit

Elements of Consent Disclosure Continued

Required for More than Minimal Risk Research

- An explanation of whom to contact in the event of a research-related injury to the subject
- An explanation as to whether any compensation is available if injury occurs, and, if so, what consists of, or where further information may be obtained
- An explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained

Elements of Consent Disclosure Continued

Required for Clinical Trials that Follow ICH-GCP

- Explanation that the monitors, auditors, IRB, and regulatory authorities, will be granted direct access to the subject's original medical records for verification of clinical trial procedures and data, without violating the confidentiality of the subject, to the extent permitted by applicable laws and regulations and that, by signing the consent document, the subject is authorizing such access
- A statement that if results of the trial are published, the subject's identity will remain confidential

Elements of Consent Disclosure Continued

Required for FDA-Regulated Research

- A statement describing the possibility that the FDA may inspect the records
- A statement that data collected on the subject to the point of withdrawal remains part of the study database and may not be removed
- **Confidentiality Consent Template Language**
  - *If you withdraw, the data collected to the point of withdrawal will remain part of the study data and may not be removed. You may be asked whether you wish to provide further data collection from your routine medical care.*
  - *Every effort will be made to maintain the confidentiality of your medical and research records related to this study. Agents of the United States Food and Drug Administration (FDA) if the study involves articles regulated by this agency, the University of Cincinnati, and the sponsoring company, [List relevant agencies like the National Cancer Institute, VA Medical Center, etc.] The monitor, the auditor, the Institutional Review Board (IRB), and other regulatory authority(ies) will be granted direct access to your original medical and research records for verification of clinical trial (research study) procedures or study data without violating your confidentiality, to the extent permitted by the applicable laws and regulations. By signing this consent form, you or your legally authorized representative are authorizing such access. The data from the study may be published; however, you will not be identified by name. Your identity will remain confidential unless disclosure is required by law.*

AAHRPP Accreditation Provision in Contracts

- Purpose: to contribute to the protection of research subjects in sponsored research
- Applicability: research when there is a potential for research-related injury (i.e., clinical research)
- UC requirements to address medical care for research subjects with a research-related injury:
  - Have contracts that indicate **who will provide care** and **who is responsible to pay for it**
  - Have process to confirm the terms specified in the contract and in the consent document are **consistent**

Provision in Contracts Continued

- Sponsors are NOT required to be responsible for paying for care for research-related injury
- UC is NOT required to be responsible for paying for care for research-related injury

Then What Is Required?

- UC must address payment for research related injury in the contract, regardless of whether it is available or not, BEFORE research starts
- Subjects MUST be able to consider this information during the consent process

Sample Language

- **AAHRPP Contract Sample Language**
  - *[The sponsor] will provide payment to the institution for reasonable, unreimbursed medical expenses, including hospitalization, which the institution may incur as a direct result of the treatment of a participant's injuries that directly result from the study drug or its administration during the clinical trial, as determined by [the sponsor] and the principal investigator.*
  - *Research-Related Injury. [The sponsor] shall be responsible for payment of the actual and reasonable medical expenses incurred in diagnosing and treating any injury, illness, or adverse reaction of a study participant that results from the administration of the study drug [or device] in accordance with the protocol or the proper performance of any Protocol procedure.*
- **Injury Consent Template Language**
  - *In the event that you become ill or injured from participating in this research study, emergency medical care will be provided to you. [Name of Sponsor OR the University of Cincinnati] will decide on a case-by-case basis whether to reimburse you for your out-of-pocket health care expenses.*
  - If the sponsor has a more generous policy, use the sponsor's statement (suggested language below). Ensure that the compensation in case of injury language in the consent is consistent with the clinical trials agreement with the funding organization when a funding sponsor is paying for study related injuries.
    If you think that you have been hurt by taking part in this research, call [name of PI] at [phone number], as soon as possible. If needed, emergency medical care will be provided. If the injury is a direct result of a study-related procedure or because you are taking [name of study drug], the cost of the emergency medical care will be paid by the sponsor, only if it is not paid BY your health insurance, a government program, or other third party. The Sponsor has no plans to pay for medical care for any other injury whether or not it might be related to taking part in this research.

The Clinical Trial Agreement

- The Clinical Trial Agreement (CTA) is a contract between the University of Cincinnati and an Industry Sponsor.
  - "Seals the deal"- what is the deal?
  - Contains the basic Study compliance obligations as between the Sponsor and UC/Principal Investigator

Failure to comply with a contractual obligation is breach of contract and cause for termination of the Contract. Breach may lead to litigation, and payment to the non breaching party for damages resulting from failing to meet an obligation.

Damages can exceed the financial terms of the CTA.

When the CTA contains Obligations related to the contents of the ICF

Some obligations in the CTA may require study subject informed consent and HIPAA authorization for UC to meet the obligation.

- Specifically, disclosure of study subject protected health information and permissions from the subject on its use by UC and the Sponsor

What to do:

Review the Protocol and ICF:

The Protocol should be reviewed to determine what the study contemplates regarding the level of risk to the study subject and the type of data needed to complete the objectives of the study

The ICF should address patient risks and what information about the study subject will be collected by UC, what information will be disclosed to the Sponsor, and how that information can be used by sponsor.

What we and the Sponsor agree to do under the CTA related to subject injury reimbursement and use of study subject data must be consistent with the Authorization Documents. (remember failure to meet a contractual obligation leads to breach)

- Preferred and standard verbiage in the CTA relating to patient consent

"Institution and Investigator shall obtain an informed consent document signed by or on behalf of each human subject, which informed consent shall be approved by Sponsor and IRB, prior to the subject's participation in the study."

"Sponsor shall not use or further share any study subject data for the study or future research uses , except as described in the informed consent and HIPAA authorization. "

"Principal Investigator shall ensure that all Subjects enrolled in the Study meet the legal age and other applicable requirements of the state in which Principal Investigator is located. The informed consent documentation shall include legally effective permission from the Subject, as necessary to enable the collection, processing, use, disclosure, storage, and transfer of Subject data in accordance with the Protocol and this CTA. Principal Investigator also shall ensure that any such consents will comply with the applicable requirements of 45 C.F.R. Part 160, § 160.101 et seq. (Health Insurance Portability and Accountability Act of 1996), applicable regulations thereto, and any corollary state law, as each such requirements have been and may be amended from time to time."

Example verbiage beyond the Standard.

Institution shall obtain an informed consent document signed by each subject in the study that addresses:

- the right for Sponsor and its designees and applicable government authorities to review raw Study data, including original subject records
- Permission for Sponsor to add Data collected under the Protocol to its research databases so that it, and/or its development partner(s) with regard to the Study Drug, may conduct additional reviews of the Data for further research uses.
- Data collected under the Protocol is disclosed to Sponsor in the form of a “Limited Data Set”, as these terms are defined by the Health Insurance Portability and Accountability Act of 1996, 45 C.F.R. Parts 160 and 164, (the “HIPAA privacy regulations”).

This is now an obligation on UC to assure rights of access to and use of study subject health records and personal information are in the ICF

Questions to be asked about the non-standard verbiage :

Does the ICF include:

the right for Sponsor and its designees and applicable government authorities to review the sources of Study data, including original subject medical and health records

The right for Sponsor to add study subject Data collected under the Protocol to its research databases for further/future research uses

Is a disclosure of a limited data set (contains Study subject individually identifiable information) by Institution to Sponsor contemplated in the IRB approved Protocol and addressed in the Authorization Documents?

- If the answer to any of these questions is “NO”, either
- The Investigator must be informed of the misalignment of the CTA and ICF to decide how to remedy
  - inclusion of the missing rights in the Authorization Documents

    Or
  - Removal of the obligations from the CTA that are not contemplated in the Protocol or contained in the Authorization Documents

When the protocol and Authorization Documents do not contemplate the disclosure of a limited data set (PHI)

- Ask: If the Authorization Documents do not contain study subject consent to disclose a LDS or PHI, is the LDS a separate, non-Protocol specific data set that Sponsor wants UC to disclose with the study data for unspecified, future research uses?
- Inform the PI who will:

  decide if the LDS will be disclosed to Sponsor in addition to the study data

  seek the appropriate internal reviews and authorizations required to disclose the LDS to Sponsor, and

  determine the method in which the LDS will be disclosed: i.e. with study subject Authorization Documents or a data use agreement.

Subject Injury:

- An all encompassing term for any adverse event/reaction, illness, or injury experienced by a person due to their participation in a clinical trial.
  - Caused by the Study Drug/Study Device (or implementation thereof)
  - Caused by Protocol-mandated procedures/activities

- **Found in two places:**
  - The Informed Consent Form (ICF)
  - The Clinical Trial Agreement (CTA)

- **<u>CTA Subject injury language (SIL):</u>**
  - The CTA SIL is a specific paragraph or section addressing the following parameters of Subject Injury:
  - The associated costs:
    - How will the costs of subject injuries be handled?
    - Who will pay for them?
- The CTA SIL is regarded as the source of truth, to which the ICF language must agree.

- **Subject injury is not necessarily covered if not explicitly stated in the CTA:**
  - It is OK to acknowledge subject injury doesn't apply to studies that carry minimal or ZERO risk of subject injury, such as:
    - Chart review studies
    - Registry studies

- **CTAs for studies involving interventional care should always address sponsor responsibility for subject injury and the associated expenses, including:**
  - Diagnosis
  - Treatment
  - Hospitalization
  - Other associated costs

  This allocates the risk between Sponsor and/or CRO and the Site to avoid any confusion in the event of Subject Injury.

- **<u>ICF Subject injury language (SIL)</u>**:
  - The section or language in an ICF for a study that explains to the study participant what they should do if they think that they have been injured as a result of participation in a clinical research study.

    - **The ICF SIL specifically explains to the Research Subject/Participant who will pay for the healthcare costs and other expenses incurred as a result and in the event of a study-related injury.**

    - **Therefore, the ICF SIL must agree with the CTA SIL** *(The CTA is the Legal Source of truth)*
      - Agreement between the ICF and CTA doesn't need to be verbatim. The language simply needs to agree, making sure the ICF does not contradict the CTA.

    Government programs:
    - **The secondary payer rule** states that if there is more than one payer or insurer on any medical bill, none of the following Government programs will be the primary payer; they will be the secondary payer.
      - Medicare
      - Medicaid
      - TriCare

- **<u>Usual exceptions where a sponsor will not cover subject injury include:</u>**
  - **Failure to comply with the protocol by site or any site personnel involved with the study.**
  - **Site negligence, recklessness, or willful misconduct.**
  - **Normal or expected progression of the subject's condition or disease, unless exacerbated by the study participation.**
  - **Subject's failure to comply with the protocol.**
  - **If expenses are covered by the subject's medical or hospital insurance, or other third party coverage.** The subject's insurance will be billed first.
    - In some cases, the sponsor will pay for any expenses the subject's insurance doesn't cover.
    - In some cases, the sponsor will **not** pay any for expenses the subject's insurance doesn't cover.
      - *The subject would be responsible for out of pocket costs.*

When does a CTA/ICF review comparison process take place?

1. Subject injury language in the ICF is able to be reviewed upon submission in the UC REDCap contract submission system.
    1. The goal is to review this language and reach out to the study team with any suggested edits prior to or during IRB submission, prior to IRB approval

1. When a study team reaches out to ask for a review of the language.
    1. The study team is able to reach out to Nate Harris with any questions at any time once they have the CTA and ICF template.

- **Timing:**
    - **The goal always is to compare the ICF language to the CTA language prior to IRB approval**
        - If an edit to the ICF language is needed, it can be made in the IRB submission prior to IRB approval
        - If an edit to the ICF is needed **after** IRB approval, the edit will have to be submitted as a formal amendment

- **Timing Continued:**
  - **Regardless of the study review status:**
    - If an edit to any ICF language is needed in order to agree with the CTA:
      - The study team will receive notification from the REDCap system alerting them to the needed edit.

    - If the ICF language agrees with the CTA and no edits are needed:
      - This will be recorded in the submission, and the review marked complete.

CTA and ICF Subject Injury Compensation Language that Agrees

CTA:

Sponsor agrees to reimburse Institution for the actual cost of diagnostic procedures and medical treatment necessary to treat a Research Injury. Sponsor will also pay for any charges directly arising out of a Research Injury (defined below) that are not covered by an insurance policy, third party payer, or the government.

The term "Research Injury" means physical injury caused by treatment or procedures required by the Protocol that the Study subject would not have received if the subject had not participated in the Study.

ICF:

Imugene will pay for any charges directly arising out of a Research Injury (as defined below) that are not covered by your insurance policy, third party payer, or the government; except to the extent such charges result from:

- your or any third party's failure to comply with the Sponsor's written instructions;
- your or any third party's failure to comply with any applicable U.S. Food and Drug Administration or other Health Authority regulations or laws or other governmental regulations or laws;
- your or any third party's negligence or willful misconduct;
- any drug, treatment or product other than those administered in this study.

A review where the language agrees

The Subject Injury Compensation Language agrees between the CTA and ICF:

- **Both the CTA and ICF Subject Injury Compensation language clearly state:**

  - **CTA:** Sponsor agrees to reimburse Institution for the actual cost of diagnostic procedures and medical treatment necessary to treat a Research Injury. Sponsor will also pay for any charges directly arising out of a Research Injury (defined below) that are not covered by an insurance policy, third party payer, or the government

  - **ICF:** Imugene will pay for any charges directly arising out of a Research Injury (as defined below) that are not covered by your insurance policy, third party payer, or the government;

University of CINCINNATI | next lives here

CTA and ICF Subject Injury Compensation Language that Agrees

CTA:
Sponsor will reimburse Institution, at usual and customary rates, for the reasonable and necessary out-of-pocket medical expenses in excess of a Study Subject's commercial medical or hospital insurance, that are incurred by Institution for the diagnosis and treatment of injuries that are determined jointly by Investigator and Sponsor to be the direct result of (i) use of the Study Drug in accordance with the Protocol; or (ii) a procedure that the Study Subject would not have undergone but for such Study Subject's participation in the Study; provided, that such injuries are not attributable to (A) an Institution Indemnitee's negligence, willful misconduct or failure to adhere to the Protocol; or (B) a pre-existing medical condition of the Study Subject or his/her underlying disease; and

ICF:
The reasonable costs of such treatment beyond that provided by your insurance will be covered by the Sponsor, IDEAYA. IDEAYA will provide payment for reasonable medical expenses for injuries:

- if you received reasonable medical care at the time that you were injured,
- if you followed instructions,
- if the injury is related to the study medication or to properly performed study procedures that are not part of your usual medical care, and
- that are not the result of the natural course of any underlying disease and/or pre-existing disease process present prior to the proper administration of the study medications.

A review where the language agrees

The Subject Injury Compensation Language agrees between the CTA and ICF:

Both the CTA and ICF Subject Injury Compensation language clearly state:

- **The CTA language states:** Sponsor will reimburse Institution, at usual and customary rates, for the reasonable and necessary out-of-pocket medical expenses in excess of a Study Subject's commercial medical or hospital insurance, that are incurred by Institution for the diagnosis and treatment of injuries

- **The ICF states:** The reasonable costs of such treatment beyond that provided by your insurance will be covered by the Sponsor, IDEAYA.

A review where the language does not agree between the CTA and ICF

CTA:
If a Subject suffers an adverse reaction, illness, or injury which, in the reasonable judgment of Institution, was directly caused by a Study Drug or any properly performed procedures required by the Protocol, Sponsor will reimburse for the reasonable and necessary costs of diagnosis and treatment of any Subject injury, including hospitalization, but only to the extent such expenses are not attributable to (a) Institution's negligence or willful misconduct or (b) the natural progression of a Subject's underlying or pre-existing condition.

ICF:
If your illness or injury is the result of the study drug, the sponsor will pay usual and customary medical fees for reasonable and necessary treatment, provided you have not already otherwise been properly reimbursed by your insurance, a government program, or other third-party coverage for such medical expenses. The sponsor is not responsible for expenses to the extent that they are due to pre-existing medical conditions, underlying disease, procedures which would have been performed even if you were not participating in the study, your negligence or willful misconduct, or the negligence or willful misconduct of institution, principal investigators or third parties.

A comparison that does NOT Agree

The Subject Injury Compensation Language does not agree between the CTA and ICF for the following reason:

- **The CTA language states:** If a Subject suffers an adverse reaction, illness, or injury which, in the reasonable judgment of Institution, was directly caused by a Study Drug or any properly performed procedures required by the Protocol, Sponsor will reimburse for the reasonable and necessary costs of diagnosis and treatment of any Subject injury, including hospitalization

- **The ICF states:** The sponsor will pay usual and customary medical fees for reasonable and necessary treatment, provided you have not already otherwise been properly reimbursed by your insurance, a government program, or other third-party coverage for such medical expenses.

The red font language poses a condition for sponsor payment that isn't included in the CTA language and must be edited out.

Please reference UC Health Office of Clinical Research Standard Operating Procedure:

UCH-OCR-OPS-SOP-015:

Process for Review of Informed Consent Form and Clinical Trials Agreement Subject Injury Language

University of CINCINNATI | next lives here