Instructions for Use

IMPORTANT: Please remove the instruction pages prior to finalization or distribution.

Purpose:

This Protocol Template should be used for **new, non-exempt, non-oncology, investigator-initiated research protocols that are seeking funds from the Clinical and Translational Science Collaborative (CTSC).** This template is designed to contain essential elements of a collaborative research protocol and can be used as the protocol for IRB submission at Case Western Reserve University, Cleveland Clinic, University Hospitals, and MetroHealth.

- Record Review or Discarded Specimen Research (ONLY) or Exempt Research: Please follow your local IRB process or, if unfamiliar, contact your local IRB for template guidance, as an abbreviated protocol template/form may be available for use.
- Oncology-based Research: Consult the following webpage for protocol templates: https://case.edu/cancer/research/clinical-research-office/protocol-templates.

Note: This protocol template an adaptation from the NIH Behavioral and Social Science Research (BSSR) Involving Humans. The full template contains additional sections and template language that can utilized during protocol development. This template can be found using the following link: https://grants.nih.gov/policy-and-compliance/policy-topics/clinical-trials/protocol-template

How To Use This Template:

- Remove any instructions within sections, these present to help guide investigators but should not be in finalized versions of protocols.
- Do not delete sections within the protocol template. If sections are not applicable to your research protocol, please denote them at such.
- There are sections denoted “DO NOT EDIT”. These sections should not be edited, as the language provided is consistent with federal standards and would have broad applicability for research trials.
- Avoid duplication of information. As appropriate, cross-reference information instead of duplicating it. In addition, each IRB will have a submission process that collects local information such as consent, recruitment and information related to confidentiality. It is not necessary to include this local information in this template.
- Users may add additional sub-headings. To preserve the format, please use appropriate header styles.

- Ensure your final version is clean (no comments or tracked changes) and free of grammatical errors.
- Once finalized, go to the “Table Of Context”, click on it, and select “Update Table”

What to consider during protocol development:

The following points are important for consideration when developing your non-exempt CTSC protocol. Not acknowledging or addressing can lead to delay in IRB review of your protocol. If you have any regulatory questions during protocol development, promptly talk with your local IRB.

- Ensure all study procedures and risk are well defined/delineated. For each study procedure, there should be a mirrored risk even if the risk is minimal.
- Protocols that randomize participants to different standard of care arms, assume the (standard of care procedures are now study procedures, and the research study assumes the risks of care. Both treatments (study procedures) and resulting risks must be fully detailed.
- FDA Regulated Research includes clinical investigations of drugs, devices, and biologics. If your test article <u>is not</u> FDA approved or cleared for marketing or is FDA approved but is being used outside the scope of the FDA approved indication (off-label), and you <u>do not</u> already have an IND/IDE, please reference “FDA Considerations” found in your CTSC folder packet or contact your local IRB to consult about use.
    - Note: Development or use of Artificial Intelligence (AI) can be considered Software as Medical Device (SaMD) if being used (or created) to treat, cure, or mitigate a disease.
- Consent must be obtained at each medical institution where study procedures will be conducted. The consent must be reflective of procedures that will be conducted at that site.
    - Please obtain or use the informed consent template from the IRB of Record.
    - If study procedures are limited to record review or surveys, waivers of consent or signed consent may be permitted by the IRB.
- Use of Protected Health Information (PHI) under a waiver of consent/HIPAA authorization will be limited and, in some cases, prohibited. Sharing PHI under waivers of consent/HIPAA authorization is not generally permissible, as well as use of PHI to train or develop AI.

- Cluster Randomized Trials, conducted under a waiver of consent, are not generally approvable across CTSC institutions
    - A cluster randomized trial is a study design where groups or “clusters” such as schools, hospitals or communities, are randomized to an intervention rather than the individual.
- Broad Consent is not permissible across CTSC Sites.

CASE WESTERN RESERVE UNIVERSITY
Clinical and Translational Science Collaborative

<Title>

Version Number	<Insert Version Number (v.<X.X>)>
Version Date	<Insert Version Date (YYYY-MM-DD)>
National Clinical Trial (NCT) Identified Number	<Number, once assigned by CT.gov or state "Not Applicable>
IND or IDE Number:	<Insert IND or IDE Number or state "Not Applicable">
Sponsor	Clinical and Translational Science Collaborative
Lead Principal Investigator	Name of Physician Name of Primary Institution Address of Primary Institution Telephone, including area code Email

Collaborating Site Principal Investigator(s):	<Copy and paste for each collaborating/relying site/PI> Name of Physician Name of Primary Institution Address of Primary Institution Telephone, including area code Email

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other Collaborating Principal Investigators.

Table of Contents

1. INTRODUCTION

1.1. STUDY RATIONALE

State the problem or question or the purpose for conducting the study.

1.2. BACKGROUND

Describe the relevant prior experience and gaps in current knowledge describing how it will add to existing knowledge. Include any relevant preliminary data.

2. OBJECTIVES AND ENDPOINTS

An **objective** is the purpose for performing the study in terms of the scientific question to be answered. Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include the general purpose (e.g., feasibility, acceptability, engagement of the intervention target, identifying mechanisms of action, mediation, moderation, efficacy, effectiveness, dissemination, implementation).

A **study endpoint** is a specific measurement or observation to assess the effect of the study intervention. Study endpoints should be prioritized and should correspond to the study objectives and hypotheses being tested. Give succinct and precise definitions of the study endpoints used to address the study's primary objective and secondary objectives (e.g., specific diagnostic tests that define safety or efficacy, clinical assessments of disease status, assessments of psychosocial characteristics, patient reported outcomes, behaviors or health outcomes).

3. STUDY DESIGN

3.1. STUDY SCHEMA

Include a visual schema for the study. If preferred, a summary or synopsis may be provided.

3.2. STUDY DESIGN AND SCIENTIFIC RATIONALE

Describe and explain the overall study design. (e.g.: single visit, single-blind, double-blind, non-randomized, randomized, blood draw, investigational drug, device etc.). Include rationale for choosing this study design.

4. STUDY SELECTION

4.1. ENROLLMENT GOAL

State the maximum enrollment goal for all sites.

4.1.1. SAMPLE SIZE DETERMINATION

State the rationale for the maximum enrollment goal. As applicable, provide the size calculation used to determine this enrollment goal.

4.1.2. REPLACEMENT OF SUBJECT

This section should include a discussion of replacement of participants who withdraw or are discontinued early, if replacement is allowed. This section should not include a discussion of how these participants will be handled in the analysis of study data

4.2. INCLUSION/EXCLUSION CRITERIA

Describe how individuals will be screened for eligibility. Using the tables below, describe the inclusion and exclusion criteria that will define who will be included and excluded in your final study sample. Provide an inclusion and exclusion criteria table for each cohort/group.

	Inclusion Criteria
1.	Age range: from x to x
2.	
3.	
4.	

	Exclusion Criteria
1.	
2.	
3.	
4.	

5. STUDY PROCEDURES

5.1. EXPECTED DURATION OF SUBJECT PARTICIPATION

State how long total duration of subject participation will last.

5.2. STUDY INTERVENTION OF EXPERIMENT DESCRIPTION

Include a description of all –study-related research being performed.

5.2.1. ADMINISTRATION OF INVESTIGATIONAL DRUG(S) OR DEVICE(S)

Include all investigational drugs and/or investigational devices used in the research and the purpose of their use and their regulatory approval status.

5.3. TIMELINE OF EVENTS/SCHEDULE OF ACTIVITIES

State approximately how long each visit will take, how long total study enrollment will last for subjects and other information regarding the amount of time it will take participants to complete the research protocol. Use of a table of events is optional, but encouraged (if table is not used, please remove). Each Visit # should correspond to a day/week/month.

5.4. STUDY MEASURES

List all data to be collected for the research study, including a list of surveys or questionnaires that will be administered. Include a copy of the survey/questionnaire to this protocol (Appendix) or upload separately to your IRB submission.

6. RISK/BENEFIT ASSESSMENT

6.1. KNOWN POTENTIAL RISKS

List the reasonably foreseeable risks such as breach of confidentiality, discomforts, hazards, or inconveniences to the research participants related to their participation in the research. Include a description of the probability, magnitude, duration, and reversibility of the risks. Include the physical psychological, social, legal, and economic risks.

6.2. KNOWN POTENTIAL BENEFITS

Describe the potential benefits that individual research participants may experience from taking part in the research. Include the probability, magnitude, and duration of the potential benefits. If there is no direct benefit, state the potential benefit to society.

6.3. ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Include an assessment of known potential risks and benefits, addressing each of the following:

- Rationale for the necessity of exposing participants to risks
- A summary of the ways that risks to participants were minimized in the study design
- Justification as to why the value of the information to be gained outweighs the risks of participation in the study

7. ALTERNATIVES TO PARTICIPATION

List other available clinical treatments, what would be included if a subject continued standard of care therapy. If this is not a clinical trial, you may select the box indicating that the alternative is not to participate. If there is a viable alternative you must list it in the consent.

8. MONITORING PLAN

8.1. SAFETY OVERSIGHT PLAN

Every study must have appropriate safety oversight. This could include study team self-assessments, usually guided by sub-components of a Quality Management Plan (see Section 10.1.8) or assessments conducted by an independent monitor, committee or board. Examples of independent safety oversight include a Safety Monitoring Committee (SMC), Data Safety Monitoring Board (DSMB), Safety Assessment Committee (SAC), and/or an Independent Safety Monitor (ISM)1. In this section, the type of safety oversight should be clearly identified along with any known responsibilities for the oversight of safety and data integrity in the study. Describe the composition of the SMC or DSMB, frequency of interim data review, final data analysis and method of reviews. A separate DSMB Charter will provide further detail of DSMB membership, responsibilities and administration of the DSMB.

8.1.1. Stopping Rules

Provide any criteria that would warrant when individual participation should end early. These criteria should contemplate any safety signals that should prompt withdrawal.

8.2. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DO NOT EDIT SECTON

8.2.1. DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

8.2.2. DEFINITION OF SERIOUS ADVERSE EVENTS

This protocol uses OHRP definition of a serious adverse event (SAE), which is modified from FDA serious adverse drug experience in FDA regulations at 21 CFR 312.32(A)): Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;

1 An Independent Safety Monitor (ISM) is a physician, nurse, or other individual with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur or are reported, with follow-up through resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the study.

- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

8.2.3.CLASSIFICATION OF AN ADVERSE EVENT

The following sections describe the classification of Adverse Events

8.2.3.1.SEVERITY OF EVENT

All AEs should be assessed by the site principal investigator, and if necessary, another professional with clinical experience in the study population using a protocol defined grading system. Describe the method of grading an AE for severity.

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild –** Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate –** Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe –** Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.2.3.2.RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician

8.2.3.3.EXPECTEDNESS

A clinician with appropriate expertise will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.2.3.4.TIME PERIOD/FREQUENCY FOR AE ASSESSMENT/FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

8.2.3.5.ADVERSE EVENT REPORTING

In consultation with the site PI, a trained member of the study team will be responsible for conducting an evaluation of an adverse event.

8.2.3.6.SERIOUS ADVERSE EVENT REPORTING

In consultation with the site PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the Lead Medical PI for reporting to the IRB of Record as soon as possible, but event later than 5 working days after the investigator first learns of the event.

8.3. UNANTICIPATED PROBLEMS – DO NOT EDIT SECTION

8.3.1.DEFINITION OF UNANTICIPATED PROBLEM

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems

involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

8.3.2.UNANTICIPATED PROBLEMS REPORTING

In consultation with the site PI, a trained member of the study team will be responsible for conducting an evaluation of the unanticipated problem and shall report the results of such evaluation to the Lead Medical PI for reporting to the IRB of Record as soon as possible, but event later than 5 working days after the investigator first learns of the event.

9. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Describe the anticipated circumstances under which research participants will be withdrawn from the research without their consent. Also include the procedures that will be followed when a research participant withdraws or is withdrawn from the research, including partial withdrawal from procedures with continued data collection.

10.STATISTICAL CONSIDERATIONS

Describe the data analysis plan, including any statistical procedures. If applicable, provide a power analysis, describe primary and secondary study endpoints including safety endpoints.

11.FUTURE USE OF STORED SPECIMENS AND DATA

If specimens or data are retained after the study is complete, include the provisions for consent and the options that are available for the participant to agree to the future use of his/her questionnaires/assessment data, specimens, images, audio or video recordings, and other individual level participant data. Specify the location(s), if other

than the clinical site, where specimens or other data will be maintained, how long specimens or other data will be stored, if the site's IRB will review future studies, and protections of confidentiality for any future studies with the stored specimens or data (e.g., specimens will be coded, bar-coded, de-identified, identifying information will be redacted from audio recording transcripts). Describe how long this data will be used by the investigative team and if/when these data will be made publicly available on a data repository or data enclave. Include a statement that genetic testing will or will not be performed.

12. STUDY DISCONTINUATION AND CLOSURE

List possible reasons for termination or temporary suspension of the study (e.g., study closure based on PI decision, sponsor/funder decision, regulatory or other oversight bodies; review of serious, unexpected, and related AEs; noncompliance; futility). For any study that is prematurely terminated or temporarily suspended, the PI will promptly inform ongoing study participants, the IRB, and sponsor/funding agency and provide the reason(s) for the termination or temporary suspension.

13. CONFLICT OF INTEREST POLICY – DO NOT EDIT SECTION

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial must be disclosed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

Investigators and study personnel are responsible for disclosing conflict of interests to their main institution who will maintain responsibility for intaking the disclosure and issuing management. This disclose and management must be provided to the IRB of Record. The IRB of Record will retain the authority to determine the management sufficiently mitigates the actual or perceived conflict.

14. ADDITIONAL CONSIDERATIONS

If you have any additional information regarding your study not covered in the template, please include it here.

15. ABBREVIATIONS AND SPECIAL TERMS

Abbreviation	Definition

16. REFERENCES

Include a list of relevant literature and citations for all publications referenced in the text of the protocol.

17. APPENDIX