

Research Protocol Review Committee: Request for review.

Below is a template and suggestions for writing and presenting a high-quality research protocol. The suggestions presented in *RED* should be deleted on the final submission. Standards for interventional trial protocols can also be found at <https://www.spirit-statement.org/about-spirit/> and standards for transparency in reporting guidelines put out by the EQUATOR network may be useful for **all study designs / questions**. <https://www.equator-network.org/>

Principal Investigator	
Name:	
Title:	
Mailing Address:	
Telephone:	Email:

Program Director	
Name:	Title:
Faculty Mentor	
Name:	Title:

Protocol Title
Consider putting the study design (see below) in the protocol title as well as the main aim. Even if the study type is not included in the final title on a publication, it is best to include it the title OR abstract. See below for study types.

Funding
Is this research sponsored? Yes <input type="checkbox"/> No <input type="checkbox"/> If Yes, list sponsor(s)
Has this research been submitted for funding? <input type="checkbox"/> Yes <input type="checkbox"/> No

Participation of Organizational Partners
Will another organization help in the recruitment and / or data collection? <input type="checkbox"/> Yes <input type="checkbox"/> No
If yes, list all institutions:

Is this project based on another individual's idea / initiative?
<input type="checkbox"/> No <input type="checkbox"/> Yes: Individual or department: _____
Has there been a discussion with the individual/department for inclusion/support of this project? <input type="checkbox"/> No <input type="checkbox"/> Yes

Research Team Member (anyone who interacts with subjects, research data, or PHI related to the study)

Name & Address Include the department	Degree	Contact Information Phone #s / email	Role on Project (PI., Co-PI, research team, coordinator, volunteer, etc)

1. Protocol Title: *descriptive title (see comment above)*

2. Version Date: *date the proposal was created*

3. Background:

Provide the scientific or scholarly background and rationale for the project based on the existing literature (include references). Describe the relevant prior literature and gaps in current knowledge. Describe any relevant preliminary data. Explain the significance of the project in terms of why it's important and how it will add to existing knowledge.

A broad or "high level" summary of the main aim and your hypothesis can help frame the rest of the protocol. For instance, after providing the relevant background information this section may conclude with;

"Given the paucity of data on XXX the main aim of this protocol is to evaluate if XXX is associated with improved outcomes in patients with XXX. Given prior observations and biologically plausibility we suggest XXX will improve XXX."

Or

"Given the need for rapid and valid diagnostic for "disease XXX", our aim is to evaluate of the validity of "diagnostic test" as compared to "gold standard". Given the prior literature we hypothesize that the "diagnostic test" will accurately distinguish "disease XXX" from other similar disorders."

4. Methods:

a. Objectives:

*Given the background described above please describe the specific objective(s) of the research. State the hypotheses to be tested after each primary and secondary objective. An objective is the reason for performing the study in terms of the scientific question to be answered. The Primary objective is the main question which generally drives statistical planning for the trial. Secondary objectives are goals that will provide further information. It is helpful to state your objectives using well-built clinical questions using the **PICO (TT) model**. This is a helpful tool to assist with focusing your question(s) to achieve the studies aim.*

P = Patient, Problem, Population

I = Intervention or Therapy, Prognostic Factor, Exposure

C = Comparison (Co-intervention, medication or placebo, intervention: another treatment, drug, placebo, a different diagnostic test (gold standard), not having or having a risk factor)

O = Outcome (What are you trying to accomplish, measure, improve or affect?)

T= Time is considered optional however it is frequently useful to evaluate the time frame for looking at the outcome

T = Type of question. Even though this is not included in the wording of the PICO question. It is important to think of the type of question you are asking as it can help with framing the question and study design. Study types include; therapeutic [an intervention / therapy / medication or medication exposure], diagnostic, prognostic accuracy, causation, and cost effectiveness.

Some examples by study type can be seen below

Intervention/Therapy

In adult patients with SLE (P), is consuming turmeric tea (I) more effective than Plaquenil (C) at reducing joint pain (O)?

In critically ill patients with SARS-CoV-2 related ARDS (P) does Tocilizumab (I) as compared to Baricitinib (C) increase the probability of survival (O) at 90 days (T)?

In patients with non-cardioembolic ischemic stroke (P) is Apixaban (I) more effective and placebo (C) at preventing vascular events (O) at one year (T)?

Diagnostic:

Questions addressing identifying a disease, state, or injury. Diagnostic tests compare to a gold standard (usually) and are evaluated with measures of validity.

Is d-dimer assay (I), as compared to ultrasound, (C) more accurate at ruling out deep vein thrombosis in critical ill patients (P)? Note in diagnostic accuracy the intervention is usually the diagnostic test of interest, and the “co-intervention” is the gold standard

Prognosis or prognostic accuracy:

Questions addressing the prediction of the course of a disease.

*Does dietary carbohydrate intake (I) influence healthy weight maintenance (BMI <25) (O) in patients who have family history of obesity (BMI >30) (P)? *Comparator (C) is implied as intensity of carbohydrate intake.*

*Does size of intracerebral hemorrhage on initial head CT (I) scan predict functional outcome (O) at 90 days (T) in patients presenting with intracerebral hemorrhage (P)? *The compared (C) is assumed to be some intensity of cut off for size of intracerebral*

hemorrhage. It could be explicitly stated if supported by the literature (i.e. does hematoma volume > 30cc as compare to < 30cc predict etc.)

Causality / Etiology

Questions that address the causes or origin of disease, the factors which produce or predispose toward a certain disease or disorder.

Are patients over 50 (P) who live within 5 miles of a McDonalds (I = exposure) as compared to > 5 miles (C) more likely to develop obesity (BMI >30) (O) over ten years (T)?

PICOT Research Question Generator (picotquestion.com) is one of many free resources to help you build questions (objectives) if the template above were not helpful. Even if you are not sure of your study type yet or which template it may fit, it is usually feasible to use the general PICO format as a starting point.

Example with hypothesis

Primary Objective:

- 1) Dose the use of CASS tubes, as compared to regular endotracheal tubes, reduce the risk (incidence) of early ventilator associated pneumonia in critically ill patients intubated for respiratory failure?
We hypothesize the use of CASS tubes will result in a statistically and clinically meaningful reduction the incidence of*

Secondary Objective (s):

- 1) Does the use of CASS tubes (as compared to non-CASS tubes) reduce the probability of death at 30 days in critically ill patients intubated for respiratory failure?
We hypothesize that CASS tubes will be associated with a significant reduction in 30-day mortality.*
- 2) Does the use of CASS tubes increase the probability of a good functional outcome at one year in survivors of respiratory failure requiring intubation in the ICU?
We hypothesize that CASS tubes will be associated with improved functional outcome.*

Stating the primary objectives as above allows the greatest clarity and is preferred in the protocol. However, this could be restated in a paragraph as below;

The primary objective of this research is to evaluate of the use of CASS tubes, as compared to regular endotracheal tubes, reduces the risk (incidence) of early ventilator associated pneumonia in critically ill patients intubated for respiratory failure? The secondary objectives are to evaluate if the use of CASS tubes, as compared to regular endotracheal tubes, reduces the probability of death by 30 days and increases the probably of good functional outcome at 90 days following intubation for respiratory

failure. We hypothesize the use of CASS tubes will result in a statistically and clinically meaningful reduction in the incidence of VAP and 30-day mortality while improving functional outcome in survivors following intubated for respiratory failure.

b. Study Design:

Please state the study design; examples are below

Non-experimental (observational)

- *Prospective or retrospective observational cohort study*
- *Retrospective (rarely prospective – nested) case-control study*
- *Prospective or retrospective cohort study of diagnostic accuracy or prognostic accuracy*
- *Descriptive cohort study (single arm or compared to historical controls)*
- *Case series or case report*

Controlled Studies

- *Randomized controlled study (could add double, triple, quadruple blinded, parallel group or other modifiers)*

c. Setting and Resources:

Please describe the following if applicable.

- *What is the timeline for recruitment in prospective studies and the date range for records reviewed in a retrospective study?*
- *How will participants be identified in retrospective studies?*
 - o *What data sources will be used?*
- *If participants will be recruited*
 - o *Where will recruitment take place*
 - o *Where will study interventions take place?*
Describe materials, such as advertisements, that will be used to recruit subjects (include these with submission materials).
 - o *Describe the amount and timing of any payments to subjects.*
- *How many participants are expected or may qualify for the study?*
- *Describe the time you will devote to conduct and complete the trial within the agreed trial period (i.e. 10% of PIs time, full time coordinator).*
- *Describe the qualifications of the study team*

d. Inclusion and Exclusion Criteria:

Describe the criteria that define who will be included or excluded in your final study sample. This is important to help inform generalizability (how will your sample compare to others or the general population with this disease?). This will define the “target” population. Commonly inclusion criteria specify age ranges, certain stages and/or severity of disease conditions willingness to engage in and complete the study as well as other criteria that defines the population. There may also be certain medications or other medical conditions that would exclude a patient from a research study

NOTE: *Indicate specifically whether you will include or exclude each of the following special populations:*

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*

- *Pregnant women*
- *Prisoners*

(You may not include members of the above populations as subjects in your research unless you indicate this in your inclusion criteria.)

e. Variables of Interest:

This section expands on the primary and secondary objects of the research protocol by defining each variable and how it will be captured in your data. How you define your variables is important to ensure you are capturing what you intended to capture in a rigorous way. It may affect internal and external validity of the research. In most studies there are explanatory (independent) variables and outcome (dependent) variables. The explanatory variable is the “Intervention” in the PICO question (or Therapy, Prognostic Factor, Exposure) and the dependent variable is the “outcome” or “endpoint”. In diagnostic studies the Intervention could be the diagnostic test and the outcome the gold standard (to diagnose the disease of interest). There may be multiple explanatory variables or outcomes. In this section of the protocol these variables need to be defined explicitly.

Some variables are very objective such as “death” or “if an intervention was received or not (yes/no). However other variables are more subjective like “functional outcome”, “improved outcomes” or “adverse events”. These variables are challenging to measure reliability as it is not clear what is being measured. Even “myocardial infarction” or a “history of alcohol abuse” are not clear enough unless a definition is provided. These variables need to be defined further. Pay particular attention to how you are defining terms and the “tools” you are using to measure these variables.

For example, if you wanted to look at how a history of alcohol abuse was associated with the development of myocardial infarction and one-year functional outcome following hospitalization you would need a precise definition for these variables. Functional outcome can be measured by multiple “scales” such as the modified Rankin scale or Glasgow outcome scale and alcohol abuse has many definitions. Myocardial infarction can be diagnosed by many criteria (there are now 4 revisions by the AHA). It would be important to know if “MI” will be diagnosed by ICD-10 codes, retrospective chart review (documentation by the clinical team’s impression), or the rigorous AHA definition of “clinical Symptoms, elevated troponins and EKG changes. For a diagnostic study it is similarly important to define the test results and how the results are measured. Some tests use cut off values for positive or negative, whereas other tests may use continuous values or may have multiple categories (such as high risk, intermediate risk and low risk). For certain disease processes, there are usually outcome measurements considered valid based on prior literature that is supporting your research proposal.

Of note, there are other variables that describe the study group (baseline characteristics and demographics such as age, race/ethnicity, gender etc..) and variables that may be associated with the intervention and outcomes (confounders). It is important all variables are defined and recorded clearly.

*Not only is it important to have clear and specific definitions of variables, but it is also important to describe the **form of the variable** related to how it will be collected/captured in your data collection instrument. This will be important for clarity and analysis even if the variable is modified later during statistical analysis. It should be stated whether a variable will be documented as a **categorical vs continuous variable**. Categorical need to **further be classified as dichotomous (binomial 2 categories (yes/no, intervention/placebo, male/female or mortality (death)), ordinal or nominal**. Nominal variables are variables that have two or more categories, but which do not have an intrinsic order. Ordinal variables are variables that have two or more categories only the categories can also be ordered.*

Example:

Say you wanted to look at how a history or alcohol abuse was associate with risk of in hospital myocardial infarction and 90-day functional outcome follow admission for stroke. The independent variable would be history of alcohol abuse defined (binomial (yes or no) depending on if they patient consumed more than 2 standard drinks per day prior to admission. The dependent variables are mortality (binomial (yes or no) and functional outcome. Functional outcome will be measured by the modified Rankin scale documented as an ordinal variable 0-6 (reference). The confounders of age and NIHSS stroke scale will be documented as continuous variables. A history of Diabetes and Hypertension will be documented as continuous variables. BMI will be documented as an ordinal variable (< 30, 30-35, > 35) and ethnicity as a nominal variable (Caucasian, Hispanic white, black, Asian, other).

NOTE: If there is any medication (intervention) involved with the proposal please include a summary of potential risk / benefits. Justification for the route of administration, dosages, dosage regimen and treatment period. If this is an approved agent, but not an approved indication, state rationale and an IND maybe required.

It sometimes adds clarity to use a format that describes the primary and secondary (if applicable) explanatory variable(s), the primary and secondary outcomes, followed by other variables.

Example:

Explanatory variables:

The primary explanatory variable of interest is alcohol abuse defined as more than 2 drinks per day (binomial – yes/no).

Primary outcomes/endpoints:

The primary outcome(s) are mortality at discharge (binomial – yes/no). The second primary outcome is functional outcome 90days after discharge. This will be documented by the modified ranking scale as an ordinal variable (0-6).

Secondary Outcomes:

Etc....

Confounders:

Etc...

Demographics:

Etc...

f. Study Procedures and Schedule:

Consider:

- i. Including a flow chart or table to explain the design. Provide a timeline of all procedures being performed, including procedures being performed to monitor subjects for safety or minimize risks.*
- ii. Administration of questionnaires or other instruments for patient-reported outcomes, such as a daily diary—include time points*
- iii. Identify procedures being performed already for diagnostic or treatment purposes and differentiate between these and the procedures performed solely for the research.*
- iv. Provide the overall duration of the research.*
- v. Describe the procedures taken to lessen the probability or magnitude of risks. Describe the source records that will be used to collect data about subjects.*
- vi. Describe what data will be collected including long-term follow-up.*
- vii. Discussion of whether the results of any study specific procedure will be provided to the participant is applicable*

NOTE: *If there is a medication involved with the study, there should be specific sections that address: assessment of safety, halting rules, dose modifications, availability of the agent*

g. Data Management

- i. Describe the data and specimens to be sent out or received.*
- ii. Describe what information will be included in that data or associated with the specimens.*
- iii. Describe who is responsible for receipt or transmission of the data.*
- iv. Describe how specimens and data will be transported.*
- v. Describe the plan to manage the data. What data management tools will be used? Data should be stored in HIPAA approved secure environment when it includes PHI.*
- vi. Describe any procedures that will be used for quality control of collected data.*
- vii. Describe what data will be collected including long-term follow -up.*

h. Provisions to Monitor the Data for the Safety of Subjects (if applicable)

- i. Delete this section if your research involves no more than minimal risk to subjects OR there is no interaction with human subjects*
- ii. Describe the plans to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.*
- iii. Describe who will review the data.*

- iv. *Describe what data are reviewed, including safety data, untoward events, and efficacy data.*
- v. *Describe when data are reviewed.*

i. Withdrawal of Subjects (if applicable):

- i. *Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.*
- ii. *Describe any procedures for orderly termination.*
- iii. *Describe procedures that will be followed when subjects withdraw from the research (or request that their data be withdrawn), including partial withdrawal from procedures with continued data collection.*

NOTE: *If based on the design of the study, there is no possibility of withdrawal of subjects, state that in this section*

j. Statistical Plan:

i. Sample Size Determination

- 1. *Describe the statistical methods for determining the sample size for the study (reason for choice of sample size). Alternatively, you may have a sample size determined based on factors such as feasibility of collection and estimate the ability to detect a minimum effect size or other value (depending on the design).*

ii. Statistical Methods

- 1. *This should describe the statistical tests and analysis plans for the study and should indicate how the study will answer the most important questions with precision and a minimum of bias, while remaining feasible*
- 2. *Describe the statistical methods to be employed The selection of subjects to be included in the analysis (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluate-able subjects).*

5. Risks to Subjects (if applicable)

- a. *List the risks, discomforts, hazards or inconveniences to the subjects.*
 - i. *For each indicate the probability, magnitude, and duration.*
 - ii. *Consider physical, psychological, social, legal and economic risks.*
- b. *If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.*
- c. *If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.*

6. Potential Benefits to Subjects (if applicable)

- a. *Describe the benefits that individual subjects may experience.*

- *Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.*
- *When assent of children is obtained describe whether and how it will be documented.*
- *If the research involves **adults who may be unable to consent**, describe the process to determine whether an individual is capable of consent.*
 - *If permission of a LAR will be obtained list the individuals from whom permission will be obtained.*
 - *Describe the process for assent of the subjects. Indicate whether assent will be required of all, some, or none of the subjects.*
 - *If some, indicated which subjects will be required to assent and which will not.*
 - *If assent will not be obtained from some or all subjects, an explanation of why not.*
 - *Describe whether assent of the subjects will be documented and the process to document assent.*

12. Vulnerable Populations (if applicable)

- a. *If your project is Human Research involving individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.*
 - i. *Ensure that any vulnerable populations are listed in your inclusion criteria.*

13. Sharing of Results with Subjects (if applicable)

- a. *Describe if any results will be shared with subjects.*
- b. *If so, describe what results will be shared, how this information will be communicated to subjects, and circumstances when results will be shared.*

14. References (if applicable)

- a. *Use this section to provide all the references used throughout your proposal. Pick a format and use it consistently.*

15. Attachments (if applicable)

- *Attach any data collection tools, recruitment materials, etc.*