

Incorporating Diversity and Inclusion into Clinical Research Protocol Templates: An Outline of Suggested Recommendations

Purpose:

Clinical research protocols summarize the background of scientific rationale for and objectives of a research study. They describe and justify the design, methodology, and statistical analysis plan when conducting research with human participants. Here, we highlight specific areas within the protocol that are important for and can advance diversity, equity, and inclusion (DEI) efforts within clinical research. Examples of detailed Protocol Templates (PT), including prompts of a similar nature to those listed below, are available [here](#). This overview document may be used concurrently with any detailed PT or as a stand-alone guidance for incorporating DEI elements into a clinical research protocol.

Before preparing any clinical research protocol, it is necessary to understand what is known about the burden, epidemiology, demographics, and non-demographics (e.g., social determinants of health) of the disease, including any unmet medical need. While it is not always possible or desirable to enroll a representative participant population, it is necessary to understand the population and make protocol design decisions based on the needs of that population and/or those for whom the intervention is intended. If this is not done, protocols may inadvertently exclude patients who may benefit from the treatment.

Please note that the detailed PT document was developed based on the [NIH's Protocol Template for Phase 2 and 3 IND/IDE Clinical Trials](#) and [TransCelerate's Common Protocol Template \(CPT\) v009](#). The prompts inserted into the detailed PT, which illuminate diversity, inclusion, and equity, were annotated by the MRCT Center.

Approach:

To assist in consideration of DEI in research protocol templates, we suggest considering the following criteria, outlined by protocol section, as applicable. Please note, not all sections of a protocol are included in the list below.

A. Protocol Title

- i. In the protocol title, consider if 'sex' needs to be distinguished as an important feature in the research study. If it is not a specific requirement or characteristic of the study, consider using inclusive language/terminology throughout the protocol and in study documents. The National Academies of Sciences, Engineering, and Medicine released a consensus study report on [Measuring Sex, Gender Identity and Sexual Orientation](#) as guidance.

B. Protocol Summary

- i. *Purpose of the study:* Explain if this a study focused on a specific disease, disease pathway, or intervention. As applicable, present the burden and epidemiology of the disease to the best extent possible. Any unmet medical need or needs of the population, and/or of a specific subgroup, should be described here.

- ii. *Study details:* During the design phase, the study should consider features that enable ease of access to the trial including the possibility of doing virtual visits, weekend hours, using local labs or home health care for visits (when possible) to allow those who may have challenges with transportation, time away from their normal working hours, or childcare. Visit frequency should be minimized to the extent possible consistent with the study goals. All of these considerations should be briefly noted in the 'study details.'
- iii. *Study population:* Provide a description of the study population(s) based on the burden, epidemiology, demographics and non-demographics (e.g., social determinants of health) of disease, as well as any unmet medical need. This should be further elucidated upon in later sections of the protocol that specifically address *study population*.
- iv. *Number of participants:* In addition to listing the estimated number of individuals that will be screened and the number of participants that will be enrolled/randomized, consider if/how the study includes defined subgroups based on demographics of disease or the intended population of the intervention. As relevant, reference to the subgroups should be described here.
- v. *Description of sites/facilities enrolling participants:* Explain the rationale for selecting the sites/facilities that will enroll participants into the study. Indicate how the sites will help the study reach its aggregate study population and if sites will contribute toward certain demographic and non-demographic variables of interest.
- vi. *Use of Data Monitoring Committee (DMC):* While not part of the written protocol, attention to diversity of the membership serving on the DMC and other committees should be considered.
- vii. *Schema:* For the schedule of activities, as necessary, include how each activity or procedure (i.e., informed consent, inclusion/exclusion criteria, scheduled lab tests) have been adapted to make the study as inclusive as possible. For example, if the study screens for HIV, Hepatitis B and C, as part of its exclusion criteria, the rationale should be scientifically, medically, and/or ethical justified. Unnecessary exclusion of populations is unethical. Recent [FDA guidance](#) provides direction for cancer trials for people with HIV, Hepatitis B and C, for example.

C. Introduction

- i. *Study Rationale:* Include summary information regarding what is known of the disease and its demographic and non-demographic factors,¹ the disease pathophysiology, the population(s) affected, and available diagnostics, therapeutics, and preventive measures with specific attention to any variability in safety/efficacy/other by subgroup, subpopulation, genetics, or other association.
- ii. *Background:* The protocol should include background information, prior research, and data regarding what is known of the epidemiology of the disease, its impact and pathway, the population(s), demographics and non-demographics of the populations affected, any variability in safety and/or efficacy by subgroup, subpopulation, genetics, and available drugs and/or intervention(s) for treatment by subgroup, if known. This information should be linked to the study rationale as relevant. Is the intended accrual population aligned with the demographics of the disease, including the incidence and severity of the population for whom the intervention is intended, or of the general population in the region?

¹ For this purpose, 'demographic factors' include variables, such as race, ethnicity, sex, and age. 'Non-demographic factors' are variables that are dynamic and able to change, such as gender identity, social determinants of health, co-morbidities, medications, etc.

- iii. *Benefit/Risk Assessment:* Assess and include any demographic or non-demographic differences in potential benefit, risk, or burden. Are certain subpopulations at greater risk, burden, or benefit than others? If so, how, and why? How does this study mitigate burden and risk, and does it provide additional safeguards for vulnerable, understudied, or underrepresented populations? Will the study impact health equity or disparity for individuals, communities or other groups?

D. Objectives, Endpoints, and Estimands

- i. If a table is included that lists objectives and endpoints, consider adding in 'patient reported outcomes' of relevance to the participant populations and subgroups.
- ii. As populations are listed for objectives, endpoints and estimands, include subgroup considerations. If subgroups are not included, state the rationale for why (i.e., no current data indicates necessity to investigate by subgroup).

E. Study Design

- i. *Overall Study Design:* Address the diversity of the population and potential subgroup differences for which the intervention is intended. Further, during the design phase, include features that enable ease of access to trial participation for all populations, such as extending clinic hours or offering the possibility of doing virtual visits, using local healthcare clinics, or arranging home visits. Flexibility in study conduct, and payment for expenses, burden, and time, will help those who may have challenges with transportation, work leave, or childcare to participate.
- ii. *Scientific Rationale for Study Design:* In addition to the scientific rationale, the study should address questions of interest and concern to the population it seeks to enroll. Ensuring a diverse, representative, and inclusive participant and community voice is essential to the success of the study. Include how participants and/or community input was sought, collected, evaluated, and included in the design of the study. Was the feedback and input solicited from representatives of the intended study population and or the condition under study? If not, was an explanation provided? Did input or feedback from the community and/or potential participants inform the study? If not, was an explanation provided? Was feedback provided to the individuals and/or communities who were engaged to explain how their input was considered and/or incorporated?
- iii. *Justification for Dose:* Include information about prior dosing amounts, approved or tested, by demographic in previously studied populations and any differences observed. Attention must be paid to subgroup representation in PK/PD studies in addition to other information available (e.g., preclinical data, drug class data, etc.).
- iv. *End of Study Definition:* As part of specifying when the end of study is for participants, which is normally when participants are no longer being examined or the last participant's last study visit, it is recommended to include information on timeline for return of aggregate results. Establishing procedures within the protocol for the return of aggregate results to the participant, the community, and the public, in plain language and translated in a culturally and linguistically appropriate manner is recommended. If this is not within the protocol, add an appendix or a statement on how this may be done.

F. Study population

- i. *Study population, general:* Does the protocol application provide a detailed explanation on the intended population that is based on the general populations' demographic distribution, the

epidemiology of disease, those expected to receive the intervention, and/or by any other demographic distribution? When feasible, the intended population to be enrolled should be described, and characteristics (whether demographic² or non-demographic³) elucidated in as much detail as possible here. Data collection and reporting guidelines standards can be found [here](#). Additional guidance is provided in the [NIH's policy on inclusion of women and minorities](#), and [FDA guidance on Enhancing Diversity in Clinical Trial Population](#).

- i) A planned demographic table should be included in this section.
 - ii) Does the protocol (or an ancillary document) include a Recruitment Plan with details of where and how potential participants will be recruited? Is there a description of culturally and linguistically appropriate materials that will be used to recruit participants? See the [Recruitment Strategy Document \(RSD\) template from MRCT toolkit](#)
 - (1) Ensure congruency between self-reported race and ethnicity data, and other demographic and non-demographic factors, with data recorded in the CRFs.
- ii. *Inclusion Criteria:* Limits on inclusion should be explicitly justified and included in the written protocol. Any restrictive inclusion criteria should be scientifically, medically, ethically, and/or justified by safety. Ideally, inclusion criteria should be as broad as possible within safety parameters. When applicable, adjust the inclusion criteria for differences by subgroup of study population. Consider:
- i) 'Normal' values (e.g., hemoglobin, HgA1c, blood pressure, white blood cell count, creatinine, etc.) should account for known variations in different subgroups. Include and document subgroup-specific normal values in the eligibility criteria. This may require a conversation with the central lab on how this is monitored and applied correctly, but will mitigate inadvertent exclusion of individuals from participation.
 - ii) Is there a strong scientific and/or ethical rationale to exclude pediatric populations? Adolescent populations? How has the lower age limit been decided?
 - iii) Is there a strong scientific and/or ethical rationale to exclude participants above a certain age? Are there less restrictive alternatives to exclusion?
 - iv) Does the protocol make appropriate considerations and exceptions around body weight and BMI if they are part of the inclusion/exclusion criteria? Is BMI eligibility criteria justified based on scientific, medical, and/or ethical evidence?
 - v) Does the protocol include provisions for accommodation, or adjustments for different populations, such as:
 - (1) individuals with disabilities;
 - (2) individuals at the extremes of weight;
 - (3) individuals whose preferred language is other than English (or the preferred language of the region);
 - (4) individuals who are gender diverse;
 - (a) Consider the inclusion of transgender participants and capturing their gender appropriately. Consider if knowledge of hormonal therapy is necessary for the study.

² E.g., age, race, ethnicity, and sex.

³ E.g., gender identity, language preference, social determinants of health (SDoH) should be included. A list of variables for SDoH can be found [here](#).

- (5) if contraception is required, are there accommodations for religious beliefs? Are privacy and confidentiality protections in place for adolescents who may be sexually active?
- iii. *Exclusion Criteria:* Any exclusion criteria should be justified by scientific, medical, ethical, and/or safety explanations. Justifications should be explicit and included in the written protocol. Reference intervals and normal values for routine laboratory tests should consider race, ethnicity, geography, sex, age, weight, BMI appropriately so as not to exclude subgroups unnecessarily.
 - iv. *Lifestyle Considerations:* Participants should not be excluded because of language proficiency or preference, cultural or religious beliefs and practices, socioeconomic status, or other factors unless there are documented scientific, medical, ethical⁴, or safety reasons for exclusion. Lifestyle considerations should be presented in a culturally considerate and inclusive way for all potential participants.
 - v. *Screen Failures:* The intention to track and review screen failure data/rates should be included and described. Examining screen failure data/rates are important to determine if there is selection bias and whether the resulting data is representative. Whenever possible, offer the ability to rescreen to allow for more inclusive options for subjects. A template to track screen failures can be found [here](#).
 - vi. *Strategies for Recruitment and Retention:* A Recruitment and Retention Plan should be developed for the overall study and for each site that participates in the study. Details on where and how potential participants will be recruited should be outlined. How will potential participants be identified and approached? What methods will be used to recruit and retain participants? Is there a description of culturally and linguistically appropriate materials that will be used to recruit and retain participants? See the [Recruitment Strategy Document \(RSD\) from MRCT toolkit](#).

G. Study Interventions and Concomitant Therapy

- i. *Study interventions and dosing:* Attention should be paid to subgroup representation in PK / PD studies and other dosing decisions. Diverse representation should be affirmatively planned. Are any modifications of dose levels required for any subgroup included in the protocol? Are pediatric formulations included as an alternative (for either age-appropriate use or for individuals with disabilities)? Are the study intervention and dosing amount instructions provided in plain language, with appropriate design and imagery, and translated to be culturally and linguistically appropriate for the populations recruited? Instructions should be made available in alternative formats to accommodate individuals with disabilities.
- ii. *Study intervention compliance:* When asking participants about compliance and/or use of the study drug or device, consider how these questions are asked and whether the feedback is solicited in a neutral way.
 - i) If diaries or other reporting mechanisms are being utilized, ensure whatever reporting structure and application is implemented, that it is available in a language and through a technology the participant understands and can use easily and readily.

⁴ For example, recruitment of a Muslim population for a study involving enoxaparin sodium, an anticoagulant directly derived from porcine intestinal mucosa, when synthetic and other alternatives are readily available.

H. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

- i. *Participant discontinuation/withdrawal from the study:* The protocol application should provide a plan to review participant discontinuation or withdrawal, by demographic and non-demographic factors. Examining discontinuation and withdrawal rates and associated data, including collection of detailed reasons from subjects willing to share, are important to determine if there is a pattern to withdrawal and/or selection bias that may influence the generalizability of the results. If a participant is withdrawn from the study, the reason for withdrawal should be documented, including the specific behaviors or compliance concerns that led to withdrawal by the investigator. If it is a sponsored trial, the sponsor should review and document the reason(s) for withdrawal.
- ii. *Loss-to-Follow-up:* The protocol application should provide a plan to review participant loss-to-follow-up, by demographic and non-demographic factors. Examining discontinuation / withdrawal rates and data are important to determine if there is a pattern to withdrawal. Further, it is important to assess whether there is selection bias influencing the generalizability of the results. Consider alternative methods to “visit” (e.g., videoconferencing, home visiting nurse, local laboratory) or decentralized or hybrid clinical trials that are generally less burdensome for participants.

I. Study Assessments and Procedures

- i. *Efficacy assessments and clinical safety laboratory assessments:* In addition to listing procedures or analyses that are necessary for evaluation of efficacy in the study, consider including a section on ‘Procedures for return of urgent (and other) results to the participant and/or their health care provider and referral for further medical care.’ This activity should be anticipated, planned, and consent obtained.
- ii. *Efficacy assessments, adverse events, and all exchanges with participants:* The list of procedures, evaluations, and return of any results (urgent or otherwise) should be asked, explained, and shared in the preferred language of the participant, their LAR, or through an interpreter if needed.
- iii. *Pregnancy:* If pregnancy is included as an assessment measure, consider referencing “individuals able to give birth” and “their partners,” rather than specifying any sex or gender.
- iv. *Genetics:* If genetic samples are being collected, the importance of a diverse and representative population should be appreciated. The informed consent form can include an affirmative statement to explain the necessity of adequate representation and how patient confidentiality and privacy will be protected. Further, the informed consent should explain if results of exploratory genetic studies will/will not be returned to participants. Consider directing participants to genetics counselling if their results will be returned.

J. Statistical Considerations

- i. *Statistical Analysis Plan:* The statistical analysis plan should include whether and how subgroup population differences will be evaluated and reported, and how multiplicity of the analyses will be considered. Determine and describe potential heterogeneity of treatment effect (HTE) and which analyses are needed to evaluate HTE. The 2021 publication [Assessing and Communicating Heterogeneity of Treatment Effects for Patient Populations](#) provides direction on HTE considerations.
- ii. *Populations for analysis:* The statistical analysis plan should include whether and how subgroup population differences will be evaluated and reported. Consider alternative statistical

approaches (e.g., Bayesian analyses). Consider descriptive reporting even if study is not powered for full analysis.

- iii. *Analysis of endpoints*: Patient-centered endpoints should be sought and included (e.g., cancer patients may be more concerned about energy, vitality, and quality of life, in addition to tumor shrinkage and remission).

K. Supporting Documentation and Operational Considerations

- i. *Informed Consent Process*: The informed consent document should be available in a language understandable to the participant or their LAR. Certified translations and interpreter services should be available for people who may not be able to read or understand the English consent form or an informed consent process conducted in English.
 - i) All points of communication and/or engagement after the informed consent process should consider the necessity of translation. The budget should anticipate the additional costs to the investigator for interpreters. Accommodations for people with disabilities should be anticipated.
- ii. *Source documents*: Self-reported data about race, ethnicity, and other demographic and non-demographic factors should be reconciled with data in the CRF forms to ensure congruency.
- iii. *Study site discontinuation or termination*: The reasons for termination should be explained to the participant in language understandable to them, provisions for follow up in the event of late potential adverse events should be made in addition to follow up care. The IEC/IRB should review the plans for currently enrolled participants as well as information planned to be provided to those who have completed all study-related procedures.
- iv. *Publication and data sharing policy*: Include when and how participants will be provided with plain language summaries and how the community and the public will be informed of aggregate results of the study.