**Points to Consider Workbook**

“Points to Consider” are included in each module. This documentcontains all the points to consider for each Essential Element and should be used as a workbook for researchers who are completing the e-Learning course with a specific protocol in mind. Protocol writers should consider and answer the applicable questions as they work through the eLearning course, which will assist in drafting their protocols and increase potential for expeditious review by their Institutional Review Board or Ethics Committee. **Not all Essential Elements will apply to every protocol**.

**Essential Element 1: Addressing Relevant Question**

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| Why is the development of this therapy needed? What is the unmet need? |
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| Is the question defined by the Objectives (and hypotheses) relevant and useful? Does it contribute to the development program or add to medical knowledge? |
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| Explain the justification for this particular study. |
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**Essential Element 2: Choice of Control and Standard of Care**

When choosing a control (comparator) arm for a clinical study, the following are points to consider:

***Active Control***

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| Is the active control an established effective intervention? If not, why is this ethically justified? (See [Placebo Points to Consider](https://globalhealthtrainingcentre.tghn.org/elearning/education/essential-elements-ethics/essential-element-2-choice-control-and-standard-care/1877/)) |
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| Is there potential bias in the selection of the active control such that there will be an unfair advantage for the investigational treatment? For example, is the active control treatment known to be significantly less effective in this study population than another treatment? If so, why is this control being used over another option? |
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| Is the requisite sample size for an active control study ethically justified with regard to the number of participants who will be exposed to the risk(s) of the study? |
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| Will use of an active control threaten the scientific validity of the study? (e.g. diminished ability to determine assay sensitivity, inability to assess absolute effect size, greater difficulty measuring safety outcomes) |
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| For multiregional clinical trials, is the active control available to all study sites and will the active control be accessible to research participants at the close of the study? |
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***Placebo***

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| Are there scientifically sound methodological reasons to use placebo? |
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| Are there no established effective interventions for the treatment of the disease or condition under study? For example: Existing evidence raises legitimate doubt within the relevant medical community regarding the effectiveness of available treatments; or Currently available treatments are highly toxic or cause intolerable side effects; or There are contraindications that prevent some participants from being treated. |
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| Are there medically sound reasons to use placebo? For example: The patient population is known to be resistant to available therapies by virtue of genetic characteristics, past treatment history or known medical history. |
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| Could withholding an established effective intervention result in an acute emergency, death, irreversible disease progression, prolonged non-trivial disability, or undue suffering? |
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| Are methods for reducing risk incorporated into the study design? For example: Research participants will receive appropriate background care; or Placebo will be administered in combination with an active comparator; or The study design includes a rescue arm; or The study utilizes a cross-over design such that participants will receive an active control at a pre-specified time point in the study. |
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| Will research participants be part of a robust informed consent process, including being informed of the probability of receiving an inactive intervention and therefore little-to-no benefit? |
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***Standard of Care***

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| Describe the care that all subjects in the study will receive, regardless of what arm they are randomized to. |
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| If the care provided in the study does not conform to the local standard of care, explain why. |
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| Does the local standard of care differ from the global standard of care? |
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| If the study is being conducted in a low-resource environment, does the care provided to the control group match the local standard of care, or the global standard of care? |
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| If the care provided is the local standard of care rather than the global standard, explain the ethical acceptability of the study. Issues to consider include avoidance of exploitation, and the intended population that will receive benefit from the research results. |
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**Essential Element 3: Choice of Study Design**

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| Is the chosen study design adequate to answer the question defined by the stated objectives and hypotheses? |
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| Are the total number of assessments—and each assessment in a given visit—necessary and not overly burdensome? |
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| Although scientifically valid, does the design in any way compromise the individual or expose the subject to harm? If so, explain and justify. |
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**Essential Element 4: Choice of Subject Population**

***Population Selection***

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| Explain the scientific basis for targeting the specific study population. (Note: This does not refer to the eligibility criteria that define the disease). |
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| Are healthy subjects to be studied? This always requires acknowledgement in the ethical section. |
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| Is the subject population being exposed for the first time? A first-in-human (FIH) study whether in healthy subjects or with patients as subjects always carries special risks that should be justified. Other groups eligible for a therapy will have to be studied for the first time and may need special consideration (e.g., women of child-bearing years, the elderly, individuals with significant co-morbidities). |
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| Is there substantial understanding of the use of the drug or therapy in the proposed population? Is the proposed subject population already well-studied? No discussion in the ethical section may be necessary. |
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| Are the subjects selected to participate in the research representative of the population most likely to benefit from the research? |
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| If either vulnerable populations or special / unusual populations are included, their inclusion should be justified. |
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***Vulnerable Populations***

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| What is the scientific justification for including the specific vulnerable group? |
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| What are the inclusion and exclusion criteria specific to the vulnerable population and their rationale? |
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| Explain how the vulnerable group is appropriate for answering the scientific question: |
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| What are the steps taken to protect individuals who may be subject to undue influence due to diminished capacity to consent to participation? For example, describe procedures that may enhance understanding for such subjects, such as including a legally authorized representative in the consent process. |
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| US regulations restrict most research on vulnerable populations that pose more than minimal risk to studies that hold out the prospect of direct benefit to the participants. Explain the risks and potential for *direct* benefits to participants. (See [Potential Benefits and Harms](https://globalhealthtrainingcentre.tghn.org/elearning/education/essential-elements-ethics/essential-element-4-potential-benefits-and-harms/1867/) section for more information.) |
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| Is the targeted group of subjects already burdened by poverty, illness, institutionalization or age? While the regulations establish a minimum, additional considerations must be addressed to ensure ethical conduct of research. |
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| If so, are there procedures in place to ease those burdens by providing housing or medical care for example? |
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| Will measures be taken to minimize risks for vulnerable subjects? For example, if an elderly population is targeted for a study of the benefits of moderate exercise, will measures be taken to ensure the safety of the exercise equipment? |
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***Recruitment***

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| Will it be effective in attracting the targeted group? |
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| Will it be effective in attracting a representative group of volunteers? |
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| Efficiency, often cited as a key factor in country selection, is not considered an ethical justification for selection of a population, country or region. |
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**Essential Element 5: Potential Benefits and Harms**

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| What are the risks to human research participants that are beyond minimal risk or that require specific attention? |
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| What steps have been taken to minimize or to mitigate risks? |
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| What risks will immediate others or the community be exposed to from the conduct of the research, if any? |
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| What benefits accrue to the research participants, if any? If there will be no benefits, what justifies asking the potential subjects to participate? |
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| What benefits will the community receive from the conduct of the research, if any? |
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**Essential Element 6: Informed Consent**

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| Describe the informed consent process including whether there are any special challenges or considerations, especially if there is a significant potential for coercion or undue influence of study subjects. |
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| If translation of consent document(s) is required, describe the process including whether family member can serve as an interpreter. |
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| Does the Protocol allow for the requirement of obtaining informed consent to be waived? If so, please describe the justification/rationale. |
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| Indicate if there are any challenges foreseen with regard to the documentation of informed consent:  If many or most of the study participants are expected to be illiterate, please describe how consent will be documented |
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| Does the Protocol allow for the requirement for documentation of consent to be waived? If so, please describe the rationale. |
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| Will short form consent be utilized? |
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| Will local ethics review board approval(s) of the consent document be required, in addition to review by a central IRB/EC? |
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| If the study is being conducted in a region where there is no local independent ethics review committee available or planned to be involved in the Study, has there been consideration about using a Community Advisory Board (CAB) to review the consent process? If so, what is the role and composition of the CAB? |
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| If the research involves individuals incapable of giving their informed consent, describe whether the protocol contemplates special procedures, such as surrogate consent for the participants. |
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| If the research will target or involve children, please indicate whether child assent is required and whether the permission of one parent is sufficient or both parents must give their permission. |
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| If the study involves recruiting “vulnerable” populations (such as a cognitively impaired population or an illiterate population, or an economically deprived population), describe additional requirements for ensuring their willingness to participate in a research study may not be unduly influenced. |
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| If the research will involve the use of biological specimens, a separate consent may be needed, especially when secondary use of these samples is a possibility. Please indicate if the need for a separate consent has been considered and if one is to be used. |
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**Essential Element 7: Community Engagement**

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| 1. Identify relevant community(ies) and local partners in research. |
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| 1. Describe plans for community consultation in protocol development. |
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| 1. Describe plans for community involvement in consent process and drafting of informed consent document. |
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| 1. Describe plans for community involvement in research conduct. |
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| 1. Discuss plans for access to data and samples. |
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| 1. Describe plans for agreement with the community on dissemination and publication of trial results. |
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**Essential Element 8: Return of Research Results and Management of Incidental Findings**

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| Address any planned disclosure of general (aggregated) research results (GRRs), e.g., such as posting of research results on ClinicalTrials.gov. |
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| Address any planned disclosure of individual research results (IRRs) to subjects and the criteria or framework under which IRRs will be evaluated for returnability (or justify a “no return” approach, if applicable). |
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| Address any planned disclosure of incidental findings (IFs) to subjects and the criteria or framework under which incidental findings (IFs) will be evaluated for returnability (or justify a “no return” approach, if applicable). |
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| If appropriate, include any proposed referral policies (i.e., for confirmation of the IRR or IF and/or any necessary clinical care that might flow from the finding). |
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| Describe whether participants will have the ability to opt-in or opt-out of receiving IRRs and/or IFs, and any circumstances in which a participant’s stated general preference to receive results will govern and/or a participant’s preference not to be informed of IRRs and/or IFs will be overruled. |
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**Essential Element 9: Post Trial Access**

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| What are the plans, if any, to provide study subjects with continued access to study interventions or continued access to other types of healthcare treatment or benefits after the study ends? |
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| What are the plans, if any, to provide individuals other than subjects with access to study interventions or continued access to other types of healthcare treatment or benefits after the study ends? |
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**Essential Element 10: Payment for Participation**

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| Is the compensation being offered beyond reimbursement for expenses? What is the justification? |
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| Is there reason to be concerned that the decision to participate is overly influenced by the compensation offered? |
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| Is the compensation approach adequate to allow participation of groups that might be underrepresented? Are minor children acknowledged for their participation? |
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**Essential Element 11: Study Related Injury**

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| In determining how to handle study-related injury or impairment, consider: What are the local legal requirements? |
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| What is the institutional policy? |
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| What are the funder requirements/permissions? |
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| What are the ethical considerations? |
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More specifically, approaches to study-related injury or impairment, should address the following, as relevant:

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| What will count as a qualified harm (e.g., physical, psychological, economic, social, or other injury)? |
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| Is it necessary to distinguish between injury (short-term, resolvable) and impairment (often longer-term, potentially manageable but not resolvable)? |
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| What injuries will be considered “related” to study participation, on what standard, and who is responsible to decide? |
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| How will compensable injuries be distinguished from harms that might be linked to the subject’s underlying medical condition? Will there be any appeals process? |
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| Will accommodation be made regardless of fault? |
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| Will accommodation cover only the provision of/referral for medical treatment, or also free care (i.e., payment for treatment)? |
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| If free care is provided, what limits are there (e.g., time limits, monetary limits, etc.)? |
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| Will accommodation cover only medical care or also additional compensation, e.g., for lost wages, dependent care, pain and suffering, etc.? |
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| If accommodation is provided, who is responsible for payment, e.g., research institution, sponsor, etc.? |
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| Must the injured subject utilize existing insurance coverage first? |
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| Is clinical trial insurance needed, and if so, what should it cover? |
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| Is self-insurance possible or acceptable (e.g., a set-aside fund to pay claims related to the study)? |
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| What process should a subject follow in the event of injury? |
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