Table 4: Supplementary Table: Summary of Essential Elements[a]

Essential Element	Explanations	Points to Consider
Essential Element 1- Addressing Relevant Question	An ethical research study must have (a) scientific integrity, (b) social value, and (c) contribute to medical knowledge. Thus, the research study must address a relevant question. Although related elements may already be discussed in appropriate detail in designated sections elsewhere in the protocol, it is useful to introduce an ethical discussion with a summary of the value of the study. The ethical discussion can highlight that the hypotheses being tested address questions of value or unmet medical needs. This is foundational to the argument that the study is ethical.[1, 5]	• Why is development of the therapy needed? Is the question relevant and useful? • Does it contribute to development program or add to medical knowledge? • What justifies this specific study?
Essential Element 2- Choice of Control and Standard of Care	The choice of the control arm affects multiple aspects of the trial, including its ethical acceptability. Three categories should be evaluated: active comparator, placebo-alone, and placebo-in-combination (e.g., in combination with background standard of care or with an active comparator). In addition, all arms of a study will be judged against the standard of care that subjects would or could receive if not enrolled in the research. Active control trials may pose less risk of harm than placebo-controlled trials because all participants have the potential to benefit from the study. Ethical concerns might include biased comparisons, increased overall participant exposure to risk, threats to scientific validity, or concerns regarding availability of active controls in host countries. If the control arm is the "standard of care", this regimen may be assumed to be the current best medical practice and therapeutics. However, there may be no single medical regimen accepted as best practice or the standard of care may be different in different countries or regions. The most controversial choice of control may be conducting a placebo-controlled trial when an established intervention is available, but not provided. Whatever comparator is chosen, even if preferred scientifically, and there is greater than temporary or minor discomfort, ethically acceptable methods for mitigating and managing risk should be incorporated into the study design. The ethical rationale for the choices should be clearly explained.[8, 12]	• Is the active control an established effective intervention? • Are there scientifically sound methodological reasons to use placebo? • Does the care provided in the study conform to the local standard of care? Global standard of care?

Essential Element 3- Choice of Study Design	The chosen study design(s) may appear to be standard and well established for both the population and the question to be examined as no new or exceptional issues of scientific validity or risk are introduced by the study. Nonetheless, potential areas of ethical compromise may exist and should be addressed. Does the study, as designed, achieve the stated desired outcome and does it have the potential to answer the questions being asked? Further, the ethical question should address whether what is asked of the *individual* subject is reasonable and ethical. Any potential ethical concerns should be identified, discussed, and justified in the ethics discussion.[1, 13]	• Does the study design adequately answer the question defined by the stated objectives and hypotheses? • Is the total number of assessments necessary and not overly burdensome? • Does the design compromise or expose the subjects to harm in any way? • Is the study adequately powered to answer the question?
Essential Element 4- Choice of Study Population	The specific choice of subject group may require no explanation beyond the scientific rationale to indicate why it is ethically acceptable to include the proposed subjects (e.g., a well-studied group for whom the risks including the safety profile are well established). However, the principle of fair distribution of benefit and risk for the research, the inclusion of vulnerable populations (who may either be at greater risk or may lack autonomy or capacity to directly consent to the research), or inclusion of other populations who are not necessarily "vulnerable" but who present special challenges may need explanation in the ethics discussion.[14, 15]	• Explain the scientific basis for targeting the specific study population. • Is the targeted group of subjects already burdened by poverty, illness, institutionalization, or age? • Will the subject recruitment plan be effective in attracting a representative group of volunteers?
Essential Element 5- Potential Benefits and Harms	Every protocol should provide sufficient information to allow assessment of whether there is a reasonable balance of benefit and risk, recognizing that, in early studies of a new therapy, little may be known about either benefit or risk (which is why a study is being proposed). The ethical discussion should focus on the potential risks and benefits that have ethical implications. Interventions that may provide benefit should be at least as advantageous as available alternatives. If there is no direct benefit to the individual, the risks must be reasonable and should be balanced by the benefit to society and the knowledge to be gained. [8]	• What are the risks to human research participants? • What steps have been taken to minimize risks? • What benefits accrue to the research participants? • What benefits will the community receive from the conduct of research?
Essential Element 6- Informed	Informed consent is the process for communicating information about the study to potential participants	• Describe the informed

Consent	to ensure that they have the necessary information to make a decision about enrolling in the study. Special challenges or considerations such as the potential for coercion or undue influence of study subjects, illiteracy, research involving individuals incapable of giving informed consent, or "vulnerable populations" such as those cognitively impaired or children should be addressed as an ethical issue.[6, 16]	consent process, including any special challenges or considerations. • Will a local ethics review board or community advisory board review the consent documents? • If the research involves individuals incapable of giving their informed consent, what special procedures will be followed?
Essential Element 7- Community Engagement	Research guidelines are increasingly emphasizing the importance of engaging host communities (as well as local investigators and other stakeholders) when conducting research not only in community settings but also in developing countries to minimize exploitation. Engagement with communities in research should be part of the ethical discussion.[17]	• How will the community be consulted in protocol development, the consent process, and drafting of the informed consent document? • What are the plans for community involvement in research, and its access and use of data and biological samples? • Is there an agreement with the community on the dissemination and publication of the trial results?
Essential Element 8- Return of Research Results and Management of Incidental Findings [b]	Many ethics guidelines and regulations applicable to the conduct of human research recognize that participants may have a right to be informed of the results of their participation and other significant information. However, the degree of this right and the duty of investigators to provide ancillary health information (or findings such as genetic information or incidental findings) beyond the trial conduct is a matter of debate. The decisions as to how this will be handled should be clear to the participant and is	• What are the plans for disclosing the general (aggregated) research results to the public? • What are the plans for disclosing individual research results (IRRs) and incidental findings (IFs) to subjects? What are the

	appropriately discussed as one of the ethical issues.[18, 19]	criteria under which IRRs and IFs will be evaluated for the ability to return results? • What are the proposed referral policies for confirmation of the IRR, IF, or any necessary clinical care that might flow from the finding? • Will participants have the ability to opt-in or opt-out of receiving IRRs and/or IFs? Under what circumstances would a participant's stated preference about receiving their results be overruled?
Essential element 9-Post-Trial Access	Post-trial access can be any sponsor-provided access to medical benefits after the study has ended. Generally, post-trial access is viewed as favorably affecting the overall risk benefit assessment of the research. However, post-trial access could also provide undue influence on subjects' decision-making if it provided too great of a benefit and if there are challenges to continued provision of trial interventions after a trial has ended. How the proper balance is struck should be made clear.[20]	• What are the plans to provide study subjects and individuals other than the subjects, with continued access to study interventions or continued access to healthcare treatment and benefits after the study ends?
Essential Element 10- Payment for Participation	The ethical implications of providing any direct compensation to a subject in a clinical trial should be addressed in every protocol. Subjects should be reimbursed for expenses, and participation should be revenue neutral so that lost income should not be a barrier to inclusion in studies. The ethical discussion begins when there is concern about "undue inducement." Although there is no accepted definition of "undue inducement" and there is little agreement about the approach to compensation, it should be clear in the protocol why the approach to compensation is considered warranted.[8, 21]	• Is the compensation being offered beyond reimbursement for expenses? What is the justification? • Is there reason to be concerned that the decision to participate is overly influenced by the compensation offered? • Is the compensation approach adequate to allow participation of groups that might be underrepresented? Are minor children

		acknowledged for their participation?
Essential Element 11- Study Related Injury	Interventional clinical trials often pose physical and other risks to research subject. It is important to develop a plan in advance for how to respond if a research subject experiences study-related injury or impairment. The plans should be clear to committees responsible for ethical review and approval and to research participants and should distinguish between care and compensation. [22, 23]	• What counts as a qualified harm? • Is it necessary to distinguish injury from impairment? • Who decides what injuries are considered "related" to study participants, and on what standard? • Will accommodations be made regardless of fault? • Will accommodation cover only medical care or also additional compensation?

Footnotes

a) Refer to the MRCT Ethics Essential Elements Tool Kit (http://mrctcenter.org/file/299386) for further discussion and examples.

b) Refer to the MRCT Return of Results Guidance Document (http://mrctcenter.org/files/mrct/files/2015-03-19_mrct_ror_guidance_1.0.pdf) and MRCT Return of Results Toolkit (http://mrctcenter.org/files/mrct/files/2015-03-19_mrct_ror_toolkit_1.0.pdf)