MRCT Ethics Essential Elements and Points to Consider Reference Document

MRCT Ethics Essential Elements Preamble

The purpose of this guidance is to encourage protocol authors to address ethical issues in the design of studies, documenting their rationale, in a section of the protocol easily understood by review boards and investigators. **Thus, we recommend that there be a dedicated "Ethics section" of the protocol in which these Essential Elements are addressed or cross-referenced to other sections of the protocol.** This tool will enable a quality and efficient review of a protocol's ethical considerations by ethics committees.

The following **List of Essential Elements** and associated **Detailed Points to Consider** provide guidance and suggestions - not requirements or mandates - on key ethical questions likely to arise in the course of writing a protocol and informed consent (or templates for such documents) for clinical trials and clinical research. This tool will assist protocol authors in writing ethically sound protocols. The guidance provided may also prove useful beyond the protocol, to the extent that it can prompt the protocol author to consider policies, procedures and local regulatory requirements.

In many cases, there will be several reasonable approaches and we strive simply to clarify the possibilities and various rationales. Some of these topics may already be addressed within a protocol. Where they are relevant and left unaddressed, completion should offer the ethics committee a better sense of the protocol's ethical issues within the proposed clinical trial.

How to Use this Document

The MRCT Ethics Tool Kit should be used in conjunction with the accompanying reference document, the MRCT Ethics Essential Elements and Points to Consider. They are meant to complement one another; the Tool Kit provides space for users to consider and answer questions while the reference document provides additional background information or guidance.

Tool Kit - The Tool Kit contains an introduction and questions to consider for each Essential Element. The questions are provided for protocol writers' more complete consideration of the ethical considerations of their study. Protocol writers should consider and answer the applicable questions, which will assist in drafting their protocols and increase potential for expeditious review by their Institutional Review Board or Ethics Committee. As noted in the Preamble, not all Essential Elements will apply to every protocol.

MRCT Ethics Essential Elements and Points to Consider Reference Document - Provides further guidance, protocol writers and tool kit users should see the examples, references, and additional resources, which are in the MRCT Ethics Essential Elements and Points to Consider document.

We want your feedback to improve this resource! Let us know your suggestions for refining the essential elements themselves, and also share with us how you have adapted the Essential Elements of Ethics Toolkit to meet the needs of your institution.

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Part I: MRCT Ethics Tool Kit

Essential Element 1: Addressing Relevant Question

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Introduction

An ethical research study must have (a) scientific integrity, (b) social value and (c) contribute to medical knowledge (1). Each element is necessary but not individually sufficient, as these interrelate, to have scientific integrity or social value, the information that is expected to result from the study must be worthwhile (contribute to medical knowledge) in that it must be an "Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge." (2) Without these elements, human research participants are subjected to research risks without potential benefit to them or others. With all are met, the risks of research participation can be appropriately weighed against the potential benefits.

Therefore, the research study must address a relevant question. Many different kinds of studies can provide useful, non-trivial information (e.g., Phase 1 pharmacokinetic and pharmacodynamics studies, hypothesis-generating exploratory studies, Phase 3 or 4 studies, or epidemiology studies). In all study types, the question being addressed and its relevance should be clearly laid out. Checklist item 6 from the SPIRIT 2013 Statement (3) indicates that the Introduction-Background and Rationale should include a "[d]escription of research question and justification for undertaking the trial, including summary of relevant studies examining benefits and harms for each intervention" and an "[e]xplanation for choice of comparators." Whatever the specific overall goal of the protocol, the ultimate unmet need, the particular characteristics of the proposed drug or therapy that makes it a good candidate for study, and the role of the specific study in the development or life cycle of the therapy should be clear in the protocol. The specific question or questions that will be approached in the study are formally stated in the Objectives and hypotheses which are also a required element in every protocol (4). For each study, the objectives of the study and, if appropriate, the hypotheses to be tested are central to defining the question to be answered. Taken together, it should be clear within the protocol that a relevant question is being addressed.

Although related elements may already be discussed in appropriate detail in designated sections in the protocol, it is useful to introduce the specific ethical section with a summary of the value of the study. The ethical section can highlight that the hypotheses being tested address basic questions or unmet medical needs. This is foundational to the argument that the study is ethical.

Points to Consider

You may want to refer to these examples when completing this section.

Why is the development of this therapy needed? What is the unmet need?

Is the question defined by the Objectives (and hypotheses) relevant and useful? Does it contribute to the development program or add to medical knowledge?

Explain the justification for this particular study.

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Continue to Essential Element 2: Choice of Control and Standard of Care

Essential Element 2: Choice of Control and Standard of Care

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Introduction

The choice of the control treatment arm affects multiple aspects of the trial, including its ethical acceptability. Three control categories should be evaluated: active comparator, placebo-alone, and placebo-in-combination (e.g. with background standard of care or in combination with an active comparator). As part of this assessment, it is necessary to consider the standard of care otherwise available to the subjects, because all of the arms of a study will be judged against the standard of care that subjects would or could receive if not enrolled in the research.

There is general agreement that active control trials pose less risk of harm to individual research participants than placebo-controlled trials because all participants receive active treatment and therefore have the potential to benefit from the study. However, active control trials are not without ethical concern. Some concerns include:

- Biased comparisons related to comparator selection and use, patient population, and selection endpoints;
- Increased overall participant exposure to risk due to a statistically requisite increase in sample size (versus placebo control);
- Threats to scientific validity due to assay sensitivity; and
- Concerns regarding availability/accessibility of active controls in host countries, including implications of regional standard of care.

In clinical trials that compare the efficacy of new therapeutic regimens against currently-available regimens, the control arm is often designed to be the "standard of care". The standard of care is usually assumed to be the standard regimen to treat the disease under study, based on the current best medical practices and best available therapeutics. But the concept of standard of care is often more complicated. For some diseases, there may be no single medical regimen accepted as best practice. The standard of care may be different in different countries, and even different within regions of the same country based on the local health care practices, availability of heath care resources, medical practice patterns, drug approvals or the ability to obtain approved medications.

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The most controversial issue in choice of control is the ethics of conducting placebo-controlled trials when an established intervention is available for treatment of the disease under study and is not provided in the control arm. On one side of the debate it is argued that placebo-controlled trials are methodologically superior to active-controlled trials and are often necessary to ensure the scientific validity of a trial (Temple and Ellenberg 2000; Miller and Brody 2002; Miller 2009). This argument is strengthened when the established intervention is one in general clinical use but has not been shown by randomized, blinded, controlled trials to be efficacious. On the other hand, it is argued that the use of placebo control is unethical because patients randomized to the placebo arm are denied available treatment thought to be effective (Freedman, Glass, and Weijer 1996; Glass and Waring 2002; Howick 2009). What has emerged from the debate is that there are circumstances in which the use of a placebo is ethically acceptable and circumstances in which the use of placebo is ethically not acceptable. When placebo is 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 (e.g. presenting placebo in combination with standard of care or the active comparator, or providing a "rescue" alternative).

Points to Consider

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

Active Control (You may want to refer to these examples when completing this section).

Is the active control an established effective intervention? If not, why is this ethically justified? (See Placebo Points to Consider)

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?

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?

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)

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?

Placebo (You may want to refer to these examples when completing this section).

Are there scientifically sound methodological reasons to use placebo?

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.

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.

Could withholding an established effective intervention result in an acute emergency, death, irreversible disease progression, prolonged non-trivial disability, or undue suffering?

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.

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?

Standard of Care

Standard of care can be ethically relevant to both active and placebo controlled designs. These issues may need to be considered in conjunction with either of the study designs. *You may want to refer to these examples when completing this section*.

Describe the care that all subjects in the study will receive, regardless of what arm they are randomized to.

If the care provided in the study does not conform to the local standard of care, explain why.

Does the local standard of care differ from the global standard of care?

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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Continue to Essential Element 3: Choice of Study Design

Essential Element 3: Choice of Study Design

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Introduction

In many studies, the chosen study design(s) may appear to be standard and well established for both the population and the question to be examined; no new or exceptional issues of scientific validity or risk are introduced by the study. Sections of the protocol other than the ethics section will detail the design, inclusion/exclusion criteria, specific interventions and assessments, timing, the plan to manage risk, and the outline of the plan for analysis. Nonetheless, potential areas of ethical compromise may exist and should be addressed. It is important to remember that, in general, the study design is developed to test a hypothesis by examining the behavior of a population of subjects of adequate size. At the overall population level, it is always important to determine if the study, as designed, can in fact achieve the stated desired outcome and has the potential to answer the questions being asked. Each study should have a robust statistical analysis included and reviewed. It is not ethical to expose subjects to risk if, for example, the study is underpowered or does not have necessary controls or a properly chosen endpoint. Further, the ethical question should address whether what is asked of the *individual* subject is reasonable and ethical. Although the design of the study may be scientifically valid, safeguards against any unnecessary or unacceptable risk or undue burden should be discussed. Any potential ethical concerns should be identified, discussed, and justified in the ethics section.

Points to Consider

You may want to refer to these examples when completing this section.

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?

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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Continue to Essential Element 4: Choice of Study Population

Essential Element 4: Choice of Subject Population

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Introduction

Individuals who agree to enroll as subjects in clinical studies are always exposed to risk and inconvenience that they would not otherwise experience. In general, if the proposed subjects represent a well-studied group for whom the risks including the safety profile have been well-defined, further discussion may not be necessary. 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. 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), and other populations who are not necessarily "vulnerable" but who present special challenges may need explanation in the ethical section.

The following points identify the key considerations for ensuring the equitable selection of subjects and the fair distribution of risks and benefits of research.

Points to Consider

You may want to refer to these examples when completing this section.

Principles of Ensuring Fair Selection of Research Subjects

The Belmont Report's principle of justice demands the fair distribution of both the burdens and benefits of research. Historically, the burdens of research were borne disproportionately by disadvantaged populations largely for the sake of convenience. A famous example of this pattern is seen in the U.S. Public Health Service syphilis study of poor, black men in Tuskegee, Alabama.

To ensure the fair distribution of risks and burdens the selection of research subjects must be equitable. Federal regulations require that when making an assessment of the research subject selection process, "the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons."

Justice requires not only equitable distribution of burdens and benefits to individuals, but to population groups as well. Selection criteria should therefore ensure that the research subjects adequately represent the population that may benefit from the research. For example, it would be unethical to test a drug in a developing country that if proved safe and effective would then be marketed exclusively in the U.S.

The fair distribution of burdens and benefits is relevant to every step of the research process including the study design, subject selection and recruitment, and the conduct of the research.

Population Selection

The general considerations for selecting the target population include scientific basis, representation, and inclusion/exclusion criteria. The protocol should include the following:

Explain the scientific basis for targeting the specific study population. (Note: This does not refer to the eligibility criteria that define the disease).

Are healthy subjects to be studied? This always requires acknowledgement in the ethical section.

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).

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.

Are the subjects selected to participate in the research representative of the population most likely to benefit from the research?

If either vulnerable populations or special / unusual populations are included, their inclusion should be justified (see examples below).

Vulnerable Populations

Additional information should be included in the protocol if the research contemplates the inclusion of "vulnerable populations." ICH/GCP E6 1.61 defines special classes of individuals as vulnerable and requiring additional consideration for protection. Individuals who may be subject to undue influence or coercion are included in this list:

- pregnant women, human fetuses and neonates
- prisoners
- children
- cognitively impaired persons
- students and employees
- minorities
- economically and/or educationally disadvantaged
- AIDS/HIV+ subjects
- Terminally Ill Subjects

In addition, the regulations outline specific provisions for research involving:

- fetuses
- pregnant women, and in vitro fertilization
- prisoners, and
- children

A protocol for research involving a potentially vulnerable population should include information on the following:

What is the scientific justification for including the specific vulnerable group?

What are the inclusion and exclusion criteria specific to the vulnerable population and their rationale?

Explain how the vulnerable group is appropriate for answering the scientific question:

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.

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 section for more information.)

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.

If so, are there procedures in place to ease those burdens by providing housing or medical care for example?

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?

Recruitment

The protocol should include a subject recruitment plan that takes into consideration the following points:

Will it be effective in attracting the targeted group?

Will it be effective in attracting a representative group of volunteers?

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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Every protocol should provide sufficient information to allow assessment of whether there is a reasonable balance of benefit and risk. The evolving safety profile should have been provided and the monitoring and protections for subjects should have been described. The ethical discussion should focus on the potential risks and benefits that have ethical implications. CIOMS 2002 indicates that 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.

Points to Consider

You may want to refer to these examples when completing this section.

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?

What risks will immediate others or the community be exposed to from the conduct of the research, if any?

What benefits accrue to the research participants, if any? If there will be no benefits, what justifies asking the potential subjects to participate?

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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Introduction

Informed consent is the process for communicating information about the study to potential participants, beginning when the initial contact is made with potential research participants. The goal of the process is to ensure that they have the necessary information to make a decision about participating in the research.

The process for obtaining participants' informed consent must follow local legal requirements and incorporate local cultural standards. The investigators and their institutions will have primary responsibility for communicating the material information about the study, the benefits, and the risks, to potential participants; however, where the study involves a target population that is likely to have difficulty understanding the benefits and risks of the trial, or the consequence of participating, the sponsor and investigator should consider ways to help communicate such information.

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Points to Consider

You may want to refer to these examples when completing this section.

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.

If translation of consent document(s) is required, describe the process including whether family member can serve as an interpreter.

Does the Protocol allow for the requirement of obtaining informed consent to be waived? If so, please describe the justification/rationale.

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

Does the Protocol allow for the requirement for documentation of consent to be waived? If so, please describe the rationale.

Will short form consent be utilized?

Will local ethics review board approval(s) of the consent document be required, in addition to review by a central IRB/EC?

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?

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.

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.

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.

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.

Essential Element 7: Community Engagement

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Introduction

Community engagement is the process of working collaboratively with groups of people in the development and conduct of research who are affiliated by geographic proximity, special interests, or similar situations with respect to issues affecting their well-being. Research guidelines are increasingly emphasizing the importance of collaborating, engaging and partnering with host *communities* (as well as with local *investigators* and *policy makers*) when conducting research not only in community settings but also in developing countries [7]. The central aim of this practice is to minimize *exploitation* by ensuring that a community or developing country determines for itself whether the proposed research is acceptable and responsive to the community's local health problems [7].

One of the largest challenges to operationalizing this principle is that there is no consensus *definition* for the term *community*. Historically we understood communities to refer to geographical groups. However, today we have a more *social* and *temporal* concept of the term. We understand that "people who live in close proximity to one another do not necessarily" share the same value systems or other cultural characteristics that are relevant to the concept of community [7]. In fact a single individual community member can represent multiple and conflicting traditions and values. Furthermore, communities are not static and "outsiders may… define community differently from insiders," which makes defining them difficult. While there is no clear definition for the term, there are key features to help guide researchers in identifying relevant communities in relation to research (discussed in the points to consider). [4]

Options for Defining Key Terms

Community engagement: "the process of working collaboratively with groups of people who are affiliated by geographic proximity, special interests, or similar situations with respect to issues affecting their well-being." [5]

Community leader*:* It can be "unclear who speaks for a particular aboriginal community." An aboriginal community, for example, "may have both a tribal council and an elected mayor." None of the guidelines specify how to resolve this challenge or how to manage "conflicts between legitimate authoritative bodies." Some experts suggest that the community leader "decision will depend on the values and traditions of particular communities and whose authority encompasses the questions raised."

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Vulnerable populations versus communities: "Vulnerable groups are socially, economically, and otherwise disadvantaged and, therefore, are more susceptible to exploitation or harm." Communities are not necessarily vulnerable groups, but represent a population that has "interests that are entitled to respect and protection," relevant to the study program.

Points to Consider

There are six main points to consider when seeking collaboration with *communities* in research [1] [2]. In general communities should be engaged early, meaningfully, and throughout all phases of research, including the publication of research results.

1. Identify relevant community(ies) and local partners in research. See Details.

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2. Describe plans for community consultation in protocol development. See Details.

3. Describe plans for community involvement in consent process and drafting of informed consent document. See Details.

4. Describe plans for community involvement in research conduct. See Details.

5. Discuss plans for access to data and samples. See Details.

6. Describe plans for agreement with the community on dissemination and publication of trial results. See Details.

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Continue to Essential Element 8: Return of Individual and/or General Research Results and Management of Incidental Findings

Essential Element 8: Return of Research Results and Management of Incidental Findings

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Introduction

Many ethics guidelines and regulations applicable to the conduct of human research recognize that participants may have a right to be informed, where appropriate, of the results of their participation and other significant information. However, the degree of that right (for example, whether individual results, aggregated information, or a general progress report must be provided to participants) and the scope of any duty on investigators affirmatively to ensure ancillary health information and care is provided to participants beyond the scope of the protocol and research aims remain a matter of debate.

The increase of large-scale genomic research (i.e., whole-genome sequencing (WGS) and whole-exome sequencing (WES)), and the vast data-sets that follow, as well as national and international biobanking efforts has brought the return of research results (particularly genetic results) and incidental findings to the forefront of research ethics debate. Concerns around incidental findings also arise frequently in the context of other types of research, for examples imaging research (i.e., neuro-imaging research, colonography research, etc.), where the research procedures may explore more of the body (or genome) than what is directly necessary to the research aims.

Options for Defining Key Terms

Individual Research Result (IRR):

"[R]esults discovered during the course of a research project – and within its objectives – that concern an individual participant and have potential health or reproductive importance." Zawati , MH; Knoppers, BM. "International Normative Perspectives on the Return of Individual Research Results and Incidental Findings in Genomic Biobanks." *Genetics in Medicine* 14.4 (2012): 484-488. Web 9 September 2013.

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Incidental Finding (IF):

"[F]inding generated in the course of research but beyond the aims of the study" with clinical or reproductive significance." Wolf, SM; Lawrenz, FP; Nelson, CA, et al. "Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations." *Journal of Law, Medicine, and Ethics* 36.2 (2008): 219-248. Web 9 September 2013.

"[O]bservations of potential clinical significance unexpectedly discovered in healthy subjects or in patients recruited to…research studies and unrelated to the purpose or variables of the study." Illes, J, et al. "Incidental Findings in Brain Imaging Research." *Science* 311.5762 (2006): 783-784. Web 9 September 2013.

Points to Consider

You may want to refer to these examples when completing this section.

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).

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).

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).

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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Introduction

Post trial access can be broadly defined as any sponsor-provided access to medical benefits after the study has ended. For instance, it could involve continued access to interventions found to be safe and effective in the research, or it could involve other types of medical benefits such as general health care interventions or diagnostic services. Post trial access might be limited to those individuals who participated in the research, or it could be provided to a wider group such as all individuals affected with the disease being studied in a given region. Generally, post trial access is viewed as favorably affecting the overall risk benefit assessment of the research; though not an obligation, previous guidance has deemed post trial access "morally praiseworthy". Post trial access could also provide undue influence on subjects' decision-making if it provides too great of a benefit. There are several challenges in providing post trial access which must be considered, such as cost to the sponsor and determining the long term safety and effectiveness of trial interventions, which may continue to be offered to former participants.

Points to Consider

You may want to refer to these examples when completing this section.

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?

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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Continue to Essential Element 10: Compensation for Study Related Injury

Essential Element 10: Payment for Participation

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Introduction

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 any expenses associated with participating in a study. This may be especially important for individuals with limited resources who might need additional support such as replacement for lost income. Participation should be revenue neutral and costs including lost income should not be a barrier to inclusion in studies and thus result in underrepresentation of people who might benefit now or in the future. The ethical discussion begins when there is concern about "undue inducement." Although this is touched on in various guidelines such as the "Common Rule", or CIOMS (Guideline 7), there is no accepted definition of "undue inducement" and there is little agreement about the approach to compensation. (Emanuel) For example, healthy individuals who will receive no benefit from a clinical trial often receive compensation beyond expenses. Although this may be acceptable, are people who are poor more likely to enroll because of the financial reward and thus bear a larger burden of the risks of early drug development? (Elliot) Does paying subjects really influence judgment about participating or understanding the risks involved? (Grady)

The other essential ethical elements should be addressed and found to be reasonable before compensation is considered. The circumstances for each study should be considered individually, but it should be clear in the protocol why the approach to compensation is considered warranted.

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Points to Consider

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?

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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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Continue to Essential Element 11: Study Related Injury

Essential Element 11: Study Related Injury

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Introduction

Interventional clinical trials often pose physical and other risks to research subjects. As such, it is important to develop a plan in advance for how to respond in the event a research subject experiences study-related injury or impairment. This plan may be reflected in Clinical Trial Agreements, sponsor policies, protocols, site-level documents, informed consent materials, and the like. The following points to consider may be used to guide decisions about how study-related injury will be handled. Plans should be clearly described to any committees responsible for ethical review and approval, as well as to research participants, clarifying key concepts such as limitations on coverage and the difference between care and compensation. However, note that it is unnecessary and potentially confusing to discuss study-related injury in the context of research studies that pose no more than minimal risk.

Points to Consider

You may want to refer to these examples when completing this section.

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?

What are the funder requirements/permissions?

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What are the ethical considerations?

More specifically, approaches to study-related injury or impairment, should address the following, as relevant:

What will count as a qualified harm (e.g., physical, psychological, economic, social, or other injury)?

Is it necessary to distinguish between injury (short-term, resolvable) and impairment (often longer-term, potentially manageable but not resolvable)?

What injuries will be considered "related" to study participation, on what standard, and who is responsible to decide?

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?

Will accommodation be made regardless of fault?

Will accommodation cover only the provision of/referral for medical treatment, or also free care (i.e., payment for treatment)?

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.?

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?

Is clinical trial insurance needed, and if so, what should it cover?

Is self-insurance possible or acceptable (e.g., a set-aside fund to pay claims related to the study)?

What process should a subject follow in the event of injury?

Part II: MRCT Ethics Essential Elements and Points to Consider Reference Document

Essential Element 1: Addressing Relevant Question

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Examples

General

- "Thorough scientific evaluation of any promising treatment before market authorization is an ethical requirement. In the continuing search for medications with improved efficacy and safety profiles, it is necessary to fully investigate and understand new products before public exposure."
- "Drug X has a different mechanism of action compared with marketed drugs and may potentially be a valuable addition in this field."

Pharmacokinetics

- "This study is being conducted to determine the pharmacokinetics of drug X in subjects who are patients with disease Y. The results of this study using healthy subjects will provide information on the pharmacokinetics and urinary recovery of drug X given at the current dosing regimen. These study results will provide valuable information with regards to dosing drug X in patients."

Pediatric pharmacokinetics

- "This study is being conducted to evaluate the single-dose pharmacokinetics of drug X at two different doses given to pediatric subjects in need of pain management therapy. These data are needed to assist in developing dosage adjustment guidance in children in need of pain management."
- "This purpose of this study is to collect concentration data across the pediatric age range in order to characterize the dose-exposure relationship in the pediatric population. This relationship is critical in determining the dosage regimen that will deliver [ ] concentrations at or above the minimum inhibitory concentration for a sufficient duration of the dosing interval. The information gathered from this study will guide dosing recommendations for drug X in children hospitalized for infections."

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Disease specific

- "This study is being conducted to determine the frequency of adverse event Z for drug X. The results of this study will influence the amount of safety information that will need to be collected in Phase 3 studies and will provide useful information for physicians treating patients with drug X."
- "Current long-term treatment of disease Y is unsatisfactory. Poor compliance with approved treatments frequently results in relapse and rehospitalization. Although gains have been made in treatment of some symptoms, other symptoms are not as responsive to presently available medications. Poorly tolerated side effects including ___ continue to be problematic in treatment of these subjects. Drug X is an investigational anti-disease Y therapy which is longer acting and does not require refrigeration. Drug X offers a number of potential advantages including more stable plasma concentrations, improved compliance and thus reduced rates of relapse, improved tolerability with improved personal and social functioning, and reduced healthcare resource utilization. Less frequent office visits may facilitate treatment access and medication adherence among patients with irregular or sporadic access to treatment."
- "On the basis of data accumulated to date, the sequential combination of drug X and drug Y has the potential to become an important addition for a group of subjects with limited therapeutic options for treatment of cancer Z and, thus potentially may become an effective first-line treatment strategy for subjects with this disease."
- "Major depressive disorder is a common, severe, chronic and often life-threatening illness. It is now the leading cause of disability worldwide. There is a clear need to develop novel and improved therapeutics for major depression. Drug X has shown rapid antidepressant effects in a small number of studies and has been well tolerated in these clinical studies."

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4. SPIRIT, Item 7. Web 9 September 2013.
5. Emanuel, et al.
6. SPIRIT, Items 1, 2. Web 9 September 2013.

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Continue to Essential Element 2: Choice of Control and Standard of Care

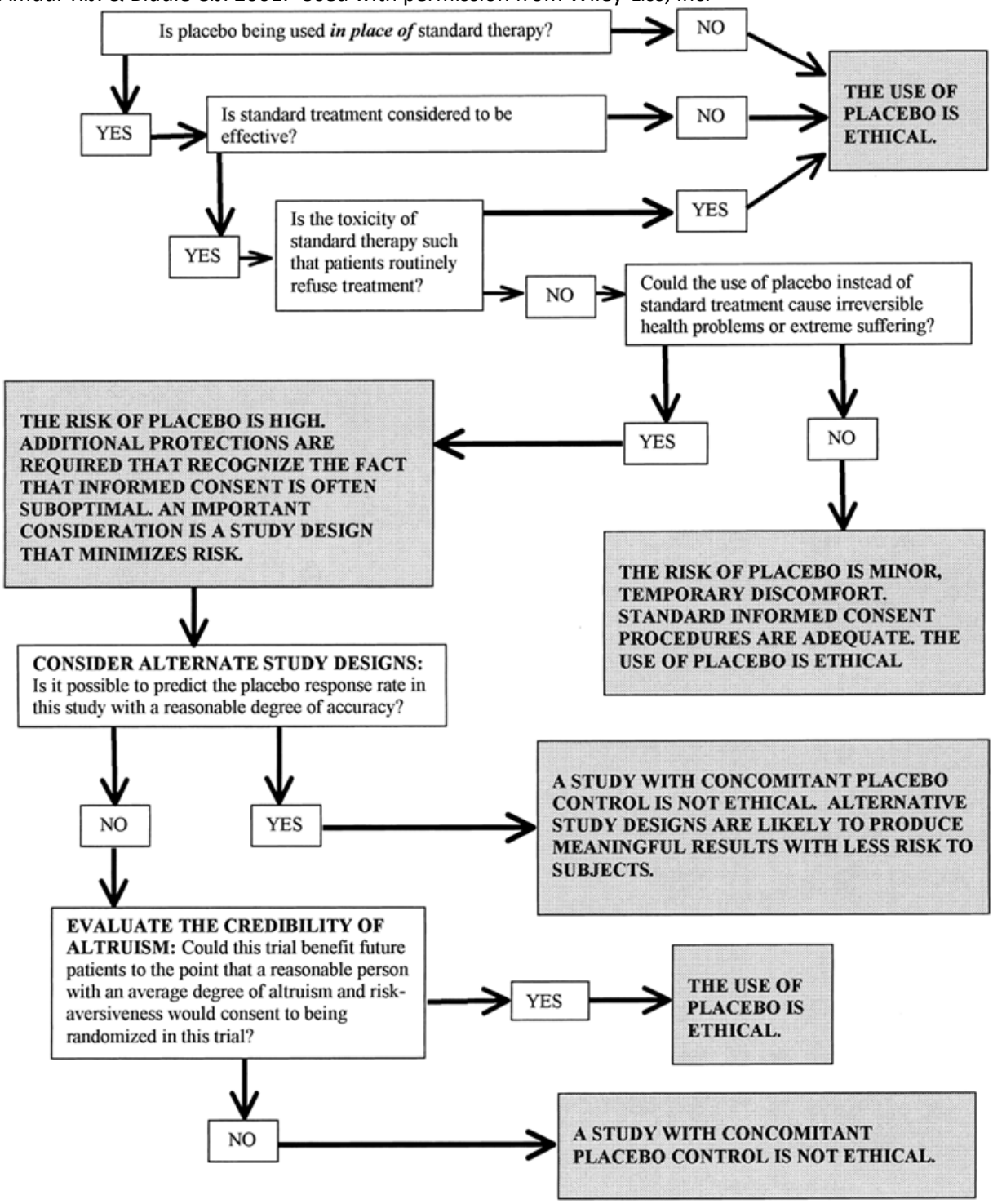
Examples

Standard of Care

- Obese/increased body mass index: "The main risks to subjects are exposure to a study drug whose safety profile is not yet well developed. Subjects randomly assigned to the active drug may have some benefit from participation in this study as it expected that they may lose weight to a greater extent than placebo subjects although this cannot be guaranteed. *All study subjects will be offered a lifestyle modification program including moderate physical activity and dietary counseling and will receive an adequate diet to treat obesity which may benefit all subjects.* Available non-clinical safety and toxicology data, as well as high unmet medical need for the new treatments of obesity, justify from an ethical and safety perspective, administration of total daily doses of ___ in well controlled in-patient settings."
- Diabetics: "Although subjects are not expected to receive any clinical benefit from a 2-week treatment period with XXX, this information will be useful in designing subsequent studies to evaluate the safety and efficacy of XXX in diabetic patients with nephropathy. *Subjects will continue to receive the medications prescribed by their physician during the course of this study. Thus, it is anticipated that there will be no loss of clinical benefit from the ongoing treatments to any subject*."

Choice of Control

Amdur R.J. & Biddle C.J. 2001. Used with permission from Wiley-Liss, Inc.



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Details Regarding the Points to Consider

Choice of control affects multiple aspects of the trial, including its ethical acceptability, the kind of endpoint that can be studied, how the results can be interpreted, the degree to which bias in conducting and analyzing the study can be minimized, the public and scientific credibility of the results, and the acceptability of results by regulatory authorities (ICH Guideline E10).

Based on the goals and characteristics of each clinical trial, the risk of harm to individual research participants from a placebo control needs to be weighed against the ethical concerns of using an active control. When evaluating the ethics, it's important to do so from the perspective of three control categories: Active comparator, placebo-alone, and placebo-in-combination (e.g. with background standard of care or in combination with an active comparator).

Active Control

Several clinical research guidelines recommend that research participants in the control group of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention, unless an exception is warranted by a defensible moral justification (e.g., CIOMS 2002, WMA Declaration of Helsinki 2008). An established effective intervention is a treatment that has widespread acceptance in the medical community and has been demonstrated to be considered effective in treating a particular disease or condition (either symptoms and/or disease mechanism). For instance, all newly diagnosed patients with a given condition likely would be offered this intervention at some point in the course of their disease or disorder. An established effective intervention may not necessarily be the best available treatment (e.g., first-line treatment in the developed world), since it may not be feasible in some locations and/or may not be sustainable after the research is complete.

Active control has the advantage (compared with placebo control or no treatment) of reducing ethical concerns that arise from failure to use treatments with validated important health benefits.

Furthermore, the results of an active control trial can indicate that the new intervention is equivalent or superior in some way to available treatments, thereby supporting evidence-based treatment decisions for patient care.

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With active controls, “fairness of comparison” and availability and access need to be considered. “Fairness of comparison” refers to the fair selection and use of active comparators. Study outcomes can be biased by selection of an ineffective active comparator, either by type, formulation, or dosage, or by selection of an active comparator with a poor safety profile. Critics of industry have highlighted instances of apparent bias associated with selection of active comparators in industry-sponsored trials (Lathyris et al. 2010). To mitigate the potential for bias to be introduced into study designs and the results of the research, active comparators should be selected and used fairly, considering all aspects of the investigational intervention, including type of comparator, dosage, dosage regimen, and formulation. Other considerations for fairness of comparison are selection of patient population and the selection and timing of endpoints, which can also bias study outcomes toward one treatment, if poorly selected.

In some host countries, an established effective intervention may not be available or accessible. Although beneficence might at times point toward using an active control design, a tension exists between beneficence and the need for a research design that is relevant to the health needs of the host country (which may constitute a competing demand of beneficence). In some cases (e.g., host countries with differing standards of care from developed countries), offering an established effective intervention may not be feasible, even in the context of a research study, and furthermore, the envisaged treatment may not be sustainable after the research is concluded. In resolving this problem, it is necessary to consider the potential harm that may occur to participants, the strength of the evidence that a new intervention will be useful and affordable to the host country, and the feasibility of implementing an existing established treatment during the course of the study (CIOMS 2002).

Placebo-Alone Control

A placebo-controlled trial is considered one of the most reliable ways to demonstrate the safety and efficacy of an investigational intervention because it provides a valid baseline against which the intervention can be compared. Placebo-controlled trials therefore are said to have good “assay sensitivity”. Assay sensitivity is the ability to distinguish between an effective treatment and an ineffective treatment (ICH 2000, p. 7).

While assay sensitivity can be an issue with placebo-controlled trials, it is much more challenging in active-controlled trials. With placebo-controlled trials, the goal is always to demonstrate that the investigational intervention is superior to placebo. With active control trials, the goal may be either to demonstrate superiority or non-inferiority (i.e. the investigational intervention is at least on par with an established effective intervention for specified safety and efficacy measures). A superiority trial allows for direct assessment of assay sensitivity while a non-inferiority trial is an indirect assessment of assay sensitivity. If a trial is designed to show superiority and it lacks assay sensitivity, it may fail to lead to a conclusion of superior efficacy. If a trial is designed to show non-inferiority and it lacks assay sensitivity, it may fail to recognize an ineffective treatment.

Situations where assay sensitivity may be an issue include study of diseases with waxing and waning symptoms or a historically high rate of placebo response, such as trials of depression. In such cases it may be necessary to use a placebo control to demonstrate efficacy. Use of an active comparator may also result in reduced ability to define the safety profile of an investigational intervention due to statistical requirements to reliably detect safety signals. This difficulty measuring safety outcomes is a key reason why some regulatory agencies require placebo-controlled trials for registration purposes. Good assay sensitivity for an active control superiority trial usually requires a larger sample size than for a placebo-controlled trial in order to achieve statistical significance. When the use of placebo control can reasonably be expected to result in only temporary or minor discomfort, it is generally considered ethical to use placebo because the trial can be completed more quickly, (thus exposing fewer participants to study risks [Leon 2000]), and the safety profile of the investigational intervention is more easily characterized.

Despite the scientific advantages of using placebo, there are lingering ethical concerns that some research participants by the very design of a placebo controlled trial will not receive active treatment (either investigational or established effective intervention). Thus, use of a placebo control may present the risk of serious or irreversible harm or undue pain and suffering. In such cases, use of placebo control would be unethical. Therefore, use of placebo must be specifically justified.
Ethical justification should include:

- Scientifically sound methodological reasons to use a placebo control;
- Withholding an established effective intervention will not result in irreversible disease progression, prolonged non-trivial disability, or undue suffering;
- Research participants are part of a robust informed consent process and provide voluntary informed consent;

The following factors may provide additional justification:

- There are no established effective interventions for the treatment of the disease or condition under study;
- Existing evidence raises legitimate doubt within the relevant expert community regarding the effectiveness of available treatments;
- Currently available treatments are highly toxic or cause intolerable side effects;
- A 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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When placebo is preferred scientifically, but there is greater than temporary or minor discomfort, risk management strategies should be instituted to minimize risks and ensure participant safety. Some methods for reducing the risk of placebo include:

- Providing appropriate background standard of care
- Utilizing a modified study design, for example
    - Placebo will be administered in combination with an active comparator; or
    - Monitoring study participants and making available rescue medications;
    - Utilizing a cross-over design such that participants will receive an active control at a pre-specified time point in the study.
- Using pre-specified criteria to ensure the early withdrawal of patients experiencing adverse events or significant disease progression.

Placebo-in-Combination

Standard of Care

Issues of standard of care receive particular attention when studies are conducted internationally; involving multiple countries or regions where the medical practices differ, or when studies are conducted in medically underserved countries where the local medical standards are inadequate in comparison to what the medical treatment would be in a developed country with better medical resources. There have been several notable cases which have received significant attention and made this a topic of much discussion in the field of research ethics, including a series of placebo-controlled studies on perinatal HIV transmission conducted in a region where the standard of care was no therapy, but the standard of care in other countries was an antiviral regimen with demonstrated benefit. For this reason, it is important to clearly address any potential ethical concerns in the protocol.

Care should also be taken to make sure the term “standard of care” is used correctly when used in protocols. The term does not have a true medical definition, but is of legal origin and refers to what a reasonable physician would do in prescribing care to a patient. Sometimes this care is determined by consensus of the medical specialty or by accepted treatment guidelines. Sometimes there is no single “standard of care” and what is really meant is that the regimen is chosen by the physician.

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Choice of Control

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Continue to Essential Element 3: Choice of Study Design

Essential Element 3: Choice of Study Design

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Examples

Statements indicating that the ethical impact of the chosen study design has been considered:

The ethics section should not repeat what is discussed in other sections of the protocol. The details of the design and the scientific rationale for the choice of each of the design elements should have been well explained elsewhere. However, because of the central importance of scientific validity as the basis for ethical soundness, it may be useful to introduce the ethical section with a statement summarizing and recognizing that the authors believe it is scientifically valid. The following examples in an ethical section acknowledge what should be completely supported in the rest of the protocol.

- "The study has been carefully designed to collect the data needed to reach its objective while enrolling the lowest possible number of subjects."
- "This study was designed with appropriate scientific rigor, with respect to hypothesis, methodological design and conduct, independent data monitoring committee, measures to ensure that findings can be confirmed upon independent review, and protective measures of randomization. The study will provide adequate data to validly test the primary and main secondary study hypotheses and objectives while protecting subjects from experiencing unacceptably high levels of risk or harm or suffering."
- "The general scientific aspects of this study are in accordance with established Food and Drug Administration and European Medicines Agency guidelines for the development of [diabetes][weight control drugs][other]."

Study design elements that might indicate ethical concerns:

Example 1: Ethical Issue: Concern about Scientific Validity

Example: An example of a design which may not support claims of efficacy is the open-label, single arm efficacy study. This design may be problematic, for example, in various psychiatric diseases. 1) Although validated endpoints are available (e.g., PANSS in schizophrenia), these are patient reported outcomes and subject to bias in an open-label, single arm study. 2) Although a measurable change from baseline (which is the only option as a control is not being used) might be demonstrable, placebo responses in many of these diseases can be substantial and can vary widely from region to region. A control arm for comparison is critical.

Ethical justification: The design is not scientifically valid and thus not ethically justified unless such concerns can be overcome in some way.

Example 2: Ethical Issue: Use of Experimental Drug in a First-In-Human (FIH) Study or Whenever the Dose or Regimen is Untested

Example: "The initial dose in this FIH study was calculated according to internationally accepted standards, and all assumptions and safety margins were conservatively estimated. Non-clinical toxicology findings do not indicate any severe toxicity within the range of doses and exposures anticipated in humans. Dose escalations to the next higher dose will only occur after all relevant safety, tolerability and pharmacokinetic data are available. To ensure optimal clinical judgment in cases where further advice on unblinded data is necessary, an internal Data Review Committee may be convened."

Ethical justification: It is critically important in a FIH study to justify the choice of dose given for the first time and the safety of any dose escalation scheme. International guidelines are available to help guide dose calculation and the details should be given in the body of the protocol. An important aspect of the FIH design is the approach to escalating the dose, the rules for stopping, and the use of monitoring committees. Although the very first administration to a human subject is the most uncertain use of a drug, other circumstances such use of a new formulation or a supratherapeutic dose also can present additional risk. The ethical section should acknowledge these considerations.

Example 3: Ethical Issue: Withdrawing a Demonstrated Effective Therapy from Some Subjects in a Randomized Withdrawal Study

Example: In randomized withdrawal designs, subjects are treated initially with the experimental therapy and those who respond by predefined criteria are randomized to continued experimental therapy or to no (placebo) therapy. The subjects on no (placebo) therapy are allowed to decline over some time frame or to a certain level.

Ethical justification: Part of the justification might be that the withdrawal period is for a short time that does not cause permanent harm or that a rescue therapy will be given if there is a defined level of decline. Quantification of the amount of that rescue therapy could be predefined as a secondary objective.

Example 4: Ethical Issue: Continuing Treatment with a Failed Therapy

Example: A study of a new treatment for hepatitis was proposed in which subjects who had failed to respond to the currently available therapy were to be enrolled. The new therapy was to be used in combination with the currently available therapy. If randomized to the control group, subjects would be given only the currently available therapy, a regimen that they had already received and no longer responded to.

Ethical justification: The protocol should explain that 1) although subjects had already failed to respond to the currently available therapy, using this regimen in the controlled setting of a clinical trial and with aggressive side effect management, there was an expected response rate of at least 10% which made it necessary and appropriate to have a control group, 2) there were early assessments of response, with opportunities for rapid discontinuation from the control group if no response was being seen to minimize side effects, and 3) control group subjects would have the opportunity to receive the new regimen if it was demonstrated to be effective.

Example 5: Ethical Issue: Washout Periods for Subjects who Need Therapy

Example: Washout periods are often needed to eliminate co-administered therapies that might interfere with the ability to detect the effect of the experimental therapy, might interact pharmacologically or pharmacokinetically with the experimental therapy, or might compromise the ability to define the safety profile of the experimental therapy. The therapies in question would in general be known to be effective in the disease.

Ethical justification: One way to support this approach is to select subjects who still have active disease even after a prior adequate course of standard therapy. Thus, these potential subjects might already be candidates for a different therapy and a washout period of some sort might be initiated in any case. A statement that a pre-existing therapy will not be withdrawn strictly to allow enrollment in a study is often appropriate.

Example 6: Ethical Issue: Duration of Exposure

Example: In some studies, the proposed time on the experimental therapy is shorter than what is has been necessary for other drugs of the same class with the same disease to determine if there is a clinical effect. Alternatively, as clinical development proceeds, the duration of exposure may be longer than previously examined. Why is this safe?

Ethical justification: Convincing arguments need to be made that the duration of exposure will at least give an indication of effect or that other equally important objectives will be addressed. If the duration of the study is longer than previously examined, there should be adequate preclinical data available to support longer exposures or, in the prior studies of somewhat shorter duration, it should be clear that the therapy was well tolerated.

Example 7: Ethical Issue: Use of Unequal Randomization

Example: Unequal randomization (e.g., 2:1 or 3:1 experimental therapy to placebo) is sometimes used to reduce the number of subjects who will not receive the experimental therapy. This may improve recruitment as subjects would have a higher likelihood of receiving the experimental therapy. This has also been used to help justify use of a placebo as fewer subjects would be denied the experimental therapy. However, withholding a potentially important therapy from even a small number of subjects has to be acceptable. Does the benefit to others outweigh significant harm to even one individual? This design element could also be challenged scientifically as this might make drawing inferences, for example, about the relative safety profile more difficult. For uncommon events, a few events in the active treatment arm but none in the control arm could be due to the unequal randomization. (Halpern, et al.)

Ethical justification- This will be dependent on the specific protocol. It should be statistically demonstrable that the sample sizes are adequate to demonstrate efficacy, that the control group size is adequate to detect an important safety signal, and that the placebo subjects are not placed at undue harm from the lack of experimental therapy for the duration of the study.

Example 8: Ethical Issue: Adaptive Trial Designs

Example: Adaptive trial designs involve pre-planned modifications that take place while the study is ongoing based on analyses that incorporate data accumulated over time. The design elements "adapt" to the accumulating knowledge albeit in a pre-specified manner. As a result, substantial changes may occur such as alterations in dose (e.g., eliminating an ineffective or unsafe dose or regimen), a change in the number of study arms (and thus more or fewer subjects on placebo), or an adjustment to the overall sample size. The study may be stopped early for futility. The technical challenges are significant. Adaptive designs may be more complex to carry out than fixed designs, the information that may be formally inferred from the data may differ or be more limited than what can be realized from a fixed design, and they may be hard to replicate (Van der Graaf et al.). The rate of enrollment or the difficulty of getting timely and adequate interim analyses could prolong the study. The potential efficiency, the possibility that fewer subjects may be exposed overall to study risks or to an ineffective dose, and that a larger population may receive a possibly effective therapy are major advantages of this design. In addition, as the sample size can be modified, adaptive designs help protect against a study being underpowered which in more traditional designs may not be known until the study is complete. Nonetheless, at the level of the individual subject, it may be difficult to adequately explain the concepts of ongoing modification of what will happen to participants and that this cannot be defined at the outset of the study.

Also, subjects who enroll later in the study may be more likely to receive a more effective (or a better tolerated) dosing regimen. Investigators might engage in differential selection of subjects by making assumptions about enrichment. Adequately informing subjects and feeling comfortable that informed consent has been obtained is a challenge.

Ethical justification: Adaptive designs can have real advantages in identifying better therapeutic regimens more rapidly and with fewer subjects. To support ethical justification, it is important that the specific adaptive design has addressed technical issues and can, in fact, be carried out and that the special challenges such as interim analyses and maintaining the blind are well thought out. A key issue is whether informed consent is adequate. The uncertainty of what a subject will undergo has to be conveyed and alternatives explained without overwhelming the subject. A potential subject should understand that there are a broader range of options early in the study and a lesser likelihood of receiving the ultimately chosen optimal dose or regimen and that the options will change as the study progresses without those changes being made transparent. Consideration should be given to modifying consent as the study progresses if unblinded data become available. The expectations of the subjects should be managed.

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Continue to Essential Element 4: Choice of Subject Population

Essential Element 4: Choice of Subject Population

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Examples

Special or Unusual Populations

Example 1: Overprotection of women: During the 1970s and 80s extensive research on heart disease was conducted on mostly male participants. As a result misleading information was generated that heart disease occurred primarily in men and symptoms of the disease in women were not well understood.

Example 2: Underrepresentation of elderly: Most breast cancer research conducted in the 20th century was done in women under the age of 65 despite the fact that almost half of all breast cancer is diagnosed in women over age 65.

Example 3: Research on overburdened populations: Researchers at the Kennedy Kreiger Institute designed a study to test the effectiveness of less expensive lead abatement processes by measuring the lead levels of children living in low income housing units.

Example 3: Research involving only black patients: The A-HEFT trial was designed to evaluate whether a particular drug provided additional benefits in black patients. A subgroup previously noted to have a favorable response to the therapy.

Enrollment of Healthy Subjects

Ethical issue: How to justify enrollment of healthy subjects who are exposed to risk and inconvenience without any possibility of benefit.

Example 1: "The primary ethical concerns of this study are that this study will be performed in healthy subjects who will receive no benefit from participation in the study, except for financial compensation for the time and inconveniences that may arise from participation in the study. Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled. No undue incentives will be provided."

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- Ethical justification- This reflects the principles outlined in the Belmont Report that competent subjects may make a choice to participate for their own reasons (respect for persons (Belmont Report).

Example 2: "Subjects with medical conditions that might benefit from drug X are likely to have underlying conditions and be receiving numerous concomitant medications. As a result, any potential effects that are a result of drug X rather than a result of some underlying condition or concomitant medication may be difficult to differentiate. Therefore, the subjects enrolled in this study will be healthy subjects. As the disposition and elimination profile of drug X is considered uncomplicated, the pharmacokinetics in healthy subjects should translate to the target patient population. Drug X in both healthy subjects and patients as subjects has been well tolerated."

- Ethical justification- The lack of co-morbidity, absence of concomitant medication use, and the more homogeneous nature of healthy subjects may be critical to answering the question and should be pointed out. This example makes the key point that the data will be relevant to the target patient population. A critical part of the justification that should be added is that the safety risks are not excessive and are limited. Also, no undue compensation will be provided.

Example 3: "Determination that a new drug mechanism may offer therapeutic benefit to patients with disease Y is very challenging. Clinical disorders of disease Y are syndromes that arise from multiple causes, wax and wane in severity, and have very high placebo rates. As a consequence, before going into large clinical trials, it is worthwhile to assess the effects on cerebral function in a limited number of healthy subjects using this technology."

- Ethical justification- This helps explain why use of healthy subjects at this stage of development is more appropriate than the target population by indicating that this will generate important and relevant information, but an explanation that the technology as well as the drug do not present significant risk in this population needs to be added.

First-in-Human (FIH) Studies

Ethical issue: How to justify exposing any subject whether healthy subjects, subjects with stable medical conditions, or subjects with life-threatening conditions to a drug or therapy that has never been given to humans. (Dresser)

Example 1: "This is the first-in-human study with drug X, an investigational drug being developed for the treatment of disease Y. The preclinical data have provided sufficient evidence of potential beneficial pharmacodynamic effects in the target disease population, and toxicology studies have established a sufficient safety margin to justify cautious and well-controlled human studies, initially in healthy subjects. Although the healthy male subjects that will be enrolled will receive no benefit from study participation, the data generated in this study will provide critical scientific information regarding the safety, tolerability, and pharmacokinetic profile of drug X."

- Ethical justification- In FIH trials, the preclinical data including relevant animal models and in vitro work, and the toxicology studies should indicate that there is good reason to move into human studies and that the anticipated exposure has been well thought out. This should be mentioned in the ethical section.

Example 2: "The initial dose was calculated according to internationally accepted standards, and all assumptions and safety margins were conservatively estimated. Non-clinical toxicology findings do not indicate any severe toxicity within the range of doses and exposures anticipated in humans. Dose escalations to the next higher dose will only occur after all relevant safety, tolerability and pharmacokinetic data are available. To ensure optimal clinical judgment in cases where further advice on unblinded data is necessary, an internal Data Review Committee may be convened."

- Ethical justification- It is critically important in a FIH study to justify the choice of dose given for the first time and the safety of any dose escalation scheme. International guidelines are available to help guide dose calculation and the details should be given in the body of the protocol. An important aspect of the FIH design is the approach to escalating the dose, the rules for stopping, and the use of monitoring committees. The ethical section should acknowledge and refer to those considerations.

Example 3: "Dose escalations in patients with disease Y will occur only after review of safety data from the previous dose level. The target concentrations for investigations in subjects with disease Y will not exceed those concentrations that have been achieved and found to be well tolerated in healthy subjects."

- Ethical justification- One approach to allowing subjects with the target disease to participate in FIH studies is to show adequate tolerability in healthy subjects first.

First Time in Women

Ethical issue: For most drugs women will be part of the target population and, from the perspective of fair distribution (NIH Guidelines), they should be adequately studied to identify any issues specific to women. For example, in some cases, the pharmacokinetics is sufficiently different that the recommended dosing regimen might need to be modified. If the target population includes women who might become pregnant, the concerns for these women especially when they are first exposed needs to be discussed.

Example 1: "No gender differences were observed in nonclinical studies of drug X. The reproductive toxicology studies revealed no relevant fetal malformations with the anticipated plasma exposure levels for this trial. As a safety precaution, during the trial all women of childbearing potential will need to utilize the double-barrier method of birth control from screening, and throughout the study until the follow-up visit."

Example 2: "The previous first-in-human study was conducted entirely in men. Since disease Y affects both men and women, evaluating the pharmacokinetics, pharmacodynamics, safety and tolerability of drug X in women is desirable for further development of this new agent. In the present study, it is planned to include post-menopausal or surgically sterile women. Based on the first-in-human study in healthy male subjects, it is justified to include women in this study at the planned doses."

- Ethical justification for both- Women must be studied in the development of new drugs. However, the possibility of pregnancy and the potential risk to the unborn child always has to be considered. Possible approaches include the initial use of women who are surgically sterile or postmenopausal. In fertile women, it is important to have reproductive toxicology studies completed and any risks of the particular class of drug reviewed.

Other Populations that May Need Specific Justification

Ethical issue: Other populations may be at special risk because of their underlying disease or other issues and this should be pointed out and the mitigations for their safe participation pointed out. Examples are subjects with renal or hepatic impairment.

Example 1: Renal impairment: "The main ethical consideration for this study concerns the risks associated with the use of study drug in healthy subjects and in subjects with end stage renal disease (ESRD) who are otherwise medically stable, and for whom there will be no direct therapeutic benefit. The results of this study will provide useful information on the effect of ESRD on study drug pharmacokinetics in order to develop safe and effective dosing recommendations in these subjects."

Example 2: Hepatic impairment: "The main ethical consideration for this study concerns the risk associated with the use of study drug in subjects, both healthy subjects without hepatic impairment and subjects with mild or moderate hepatic impairment who are otherwise healthy, for whom there will be no direct therapeutic benefit. The potential risks to subjects include exposure to study drug which may have increased exposure in subjects with hepatic impairment and the risk of side effects. An additional concern may be the capacity to consent if subjects develop severe hepatic impairment with an element of encephalopathy."

- Ethical justification for both- The details for protection of both healthy subjects and subjects with significant medical problems should have been provided in the protocol. However, in the ethical section it is important to recognize the potential risks and indicate why it is important and acceptable for these subjects to be studied.

Example 3: AHEFT study: A retrospective analysis of data from a clinical database indicated that response to ACE inhibitors tended to be less efficacious in blacks. This data was the basis for the A-HeFT (African-American Heart Failure Trial sponsored by NIH), which involved only African Americans and excluded all other racial groups with a low ejection fraction and a dilated left ventricle.

References

Department of Health and Human Services Subpart A: 45 CFR 46.111(a)(3) Criteria for IRB Approval of Research Web 9 September 2013.

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Continue to Essential Element 5: Benefits and Harms

Essential Element 5: Potential Benefits and Harms

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Examples

Risks

Risks inherent to the experimental drug or therapy:

- Safety profile: In every research study in which participants receive an experimental drug, there is a potential for harm that the subject would not face outside the study. If the safety profile is well described for the dose and regimen, there may not be particular ethical issues that need to be brought up in the ethical section. However, any special concern and the mitigations planned to deal with the concern should be acknowledged in the ethics section. Examples would be an unusual pre-clinical finding or a serious problem seen with other members of the drug class. Adverse events of special interest should be highlighted. Administration of an experimental therapy to individuals for the first time such as women, children, the elderly, or a sensitive population such as poor metabolizers or renal/hepatic impaired should be justified. Even if the drug is well-tolerated, a new formulation or supratherapeutic dose may need discussion. Radiation exposure from a radioactively labeled drug needs to be minimal such as no more than background exposure.
- Risks to others: In some studies, there may be risks to health workers, family members, or others in close contact with the subject. Examples would be the risks of radiation exposure, any risks associated with gene transfer studies, or the risks in vaccine studies.

Risks to vulnerable populations:

- See Essential Element 4: Choice of Subject Population

Risks from study procedures:

- The procedures in many studies will involve only minimal risks such as drawing blood. Taking large volumes of blood or blood sampling in children will need justification in the protocol and mention of why this is acceptable in the ethics section. Other procedures may be more invasive such as tissue biopsies, lumbar punctures, or excessive exposure to multiple x-rays or CAT scans. These should be appropriate and acceptable.

Non-physical harm:

- Risks can also involve non-physical harm, such as breach of confidentiality and privacy, damage to reputation, monetary harm, legal risk, loss of insurance coverage, emotional stress, genetics issues such as paternity, and discrimination. Information might be published that could stigmatize a group or expose its members to discrimination. For example, the information gained from a study could indicate, rightly or wrongly, that the group has a higher than average prevalence of alcoholism, mental illness or sexually transmitted disease, or is particularly susceptible to certain genetic disorders. There may be risks to family members from knowledge gained in genetics studies.

Benefits

Potential benefits to the individual subject:

- Ethically, considerations for the well-being of the subject should take precedence over the interests of science and society (CIOMS 2002, Declaration of Helsinki 2000, para 5). If there is lack of potential benefit, this should be stated. Benefits to subjects might include positive response to the study intervention (both products and procedures), additional medical care and oversight, possibility of life-style modifications (e.g., programs for diabetes or obesity), coverage of costs of additional medical care, payment for participation, or post-study continued access to study interventions.

Potential benefits to others including the community and society:

- Knowledge: The knowledge that results from a study and the application of that knowledge may benefit society. The kinds of knowledge may be the resolution of a safety issue or the proof that a new mechanism of action is relevant in a hard-to-treat disease. In spite of societal benefit, there may be some risks to the individual that are too great to support conducting the study, so how the balance is achieved is properly discussed in the ethical section.
- Community building: Community benefit might include capacity building for local sites, increased medical and scientific capabilities and training of local investigators and study staff, or brick and mortar facilities such as clinics or laboratory equipment.

References

Considerations for the well-being of the subject should take precedence over the interests of science and society

Council for International Organizations of Medical Sciences (CIOMS). "International Ethical Guidelines for Biomedical Research Involving Human Subjects." CIOMS. (2002) Web 9 September 2013.

World Medical Association (WMA). "Declaration of Helsinki." WMA. Web 9 September 2013. See paragraph 5

Research protocols should describe ethical considerations

Council for International Organizations of Medical Sciences (CIOMS). "International Ethical Guidelines for Biomedical Research Involving Human Subjects." CIOMS. (2002) Web 9 September 2013.

World Medical Association (WMA). "Declaration of Helsinki." WMA. Web 9 September 2013.

Special risk limitations for subjects unable to give informed consent

Council for International Organizations of Medical Sciences (CIOMS). "International Ethical Guidelines for Biomedical Research Involving Human Subjects." CIOMS. (2002) Web 9 September 2013. See Guideline 9.

Risks and benefits

World Medical Association (WMA). "Declaration of Helsinki." WMA. Web 9 September 2013.

Vulnerable groups

Department of Health and Human Services Subpart A: 45 CFR 46 Web 9 September 2013.

Procedure

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). "Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance." Department of Health and Human Services. (1996) Web 9 September 2013

Examples

For example, if the patient population is likely to speak languages other than English, the informed consent disclosures should be translated, in advance, and be available to the investigators for the study (i.e. in the local language(s) understood by the target population(s)). In addition, special care needs to be taken with regard to the processes for informed consent, whenever studies will target young children, adults with severe mental or behavioral disorders, or persons who would be unfamiliar with medical concepts and technology.

Investigators may want to use records or biological specimens that another investigator has used or collected for use, in another institution in the same or another country. If informed consent or permission was required to authorize the original collection or use of such records or specimens for research purposes, secondary uses are generally constrained by the conditions specified in the original consent. The process of seeking informed consent should describe whether there will or could be any secondary use, how broad such future uses might be, and any protections to be afforded to the subject's data or specimens.

Details Regarding the Points to Consider

- Address local literacy levels
- Address language capacity
- Role of study staff in obtaining consent
- Cultural considerations in giving and obtaining consent, such as family leader, tribal leader, signatures.
- Address whether an LAR can provide consent, and who the LAR can be, or whether the protocol is restricted to subjects who have capacity to consent. If relevant, who assesses capacity?
- Assent for pediatric subjects or adult subjects without capacity.
- Describe any future use of identifiable data or specimens, and any plans to re-contact subjects about test results.
- Logistics for consent, such as group consent process, consent in communities with cultural restrictions on access to individuals.

References

Council for International Organizations of Medical Sciences (CIOMS). "International Ethical Guidelines for Biomedical Research Involving Human Subjects." CIOMS. (2002) Web 9 September 2013. See Guidelines 4-6

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World Medical Association (WMA). "Declaration of Helsinki." WMA. Web 9 September 2013. See Sections 24-49; 33-35

Department of Health and Human Services Subpart A: 45 CFR 46 Web 9 September 2013.

Food and Drug Administration Policy for the Protection of Human Subjects: 21 CFR 50 Web 9 September 2013.

Additional Resources

Strauss, RP; Sengupta, S; Quinn, SC; Goeppinger, J; Spaulding, C; Kegeles, S M; Millett, G. "The Role of Community Advisory Boards: Involving Communities in the Informed Consent Process." *American Journal of Public Health* 91.12 (2001): 1938–1943. Web 9 September 2013.

Ntshanga, SP; Ngcobo, PS; Mabaso, MLH. "Establishment of a Community Advisory Board (CAB) for Tuberculosis Control and Research in the Inanda, Ntuzuma and KwaMashu (INK) Area of KwaZulu-Natal, South Africa." *Health Policy* 95.2-3 (2010): 211–215. Web 9 September 2013.

Shubis, K; Juma, O; Sharifu, R; Burgess, B; Abdulla, S. "Challenges of Establishing a Community Advisory Board (CAB) in a Low-Income, Low-Resource Setting: Experiences from Bagamoyo, Tanzania." *Health Research Policy and Systems* 7.16 (2009) Web 9 September 2013.

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Continue to Essential Element 7: Community Engagement

Examples

Examples of successful Community Engagement Efforts [5]

1. Community Action for Child Health Equity (CACHÉ)
2. Health-e-AME
3. Project SuGAR
4. The Community Health Improvement Collaborative (CHIC)
5. Healing of the Canoe
6. Formando Nuestro Futuro/Shaping Our Future
7. Improving American Indian Cancer Surveillance and Data Reporting in Wisconsin
8. Children And Neighbors Defeat Obesity/La Comunidad Ayudando A Los Niños A Derrotar La Obesidad (CAN DO Houston)
9. The Dental Practice-Based Research Network
10. Diabetes Education & Prevention with a Lifestyle Intervention Offered at the
11. YMCA (DEPLOY) Pilot Study
12. Project Dulce
13. Determinants of Brushing Young Children's Teeth

Details Regarding the Points to Consider

These details are numbered corresponding to the list of Points to Consider above.

1. There is a lack of evidence and discussion on which groups should or shouldn't be included in the collaboration and partnership process. The list of stakeholders may include local researchers, policy makers, academics, public health professionals, and policy makers and community representatives. Key features to help in identifying relevant communities in relation to research [4] include:

- Common culture and traditions, cannon of knowledge, and history
- Comprehensiveness of culture
- Health-related common culture
- Legitimate political authority
- Representative group/individuals
- Mechanism for priority setting in health care

- Geographic localization
- Common economy/shared resources
- Communication network
- Self-identification as community

2. There is broad consensus that partnering with communities should occur early in the research process. The engagement can be accomplished by incorporating community input into protocol design and development. The consultation process should discuss [1] [2]:

- whether the research is likely to prove useful or have value to the community.
- "how the research problem might be approached."
- whether it respects "oral tradition and other sources of communal knowledge(that) ought to be used in a respectful manner"

3. The IRB should determine the appropriate level of community engagement in the consent process: "(i) community consent and consultation, (ii) community consultation alone" or (iii) only customary individual consent.

It is important to remember that community consent supplements, but does not replace, individual consent. Like individual consent, community consent involves considerations of local languages as well as the simplicity, clarity and intelligibility of concepts and methods. Some guidelines note that it can be important to meet face to face with community representatives during their review and potential approval of research protocols.

4. The community should be meaningfully involved in the actual conduct of the research study. Methods for involving the community may include employing community members on the project, and/or training them " to help conduct the research, thereby transferring research skills and expertise." Although not common practice, a few standards call for reimbursing community members for any costs incurred through their participation, "such as accommodation for researchers, or water, power, or materials used during the conduct of the study."

5. To protect the community from unwanted uses of data or samples, and to maintain trust between the community and researcher – some guidelines suggest researchers should discuss how study data and samples will be stored, whether they will be destroyed, and who ultimately controls them once the study is complete.

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6. To help communities remain full partners in the full research process (from inception to end), it may be appropriate to consider including them as co-author on papers and discussing research results with them. They may be shown preliminary drafts of articles so that they may voice disagreements and comments about the interpretation of study results in publications (according to Emanuel et al).

References

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Continue to Essential Element 8: Return of Individual and/or General Research Results and Management of Incidental Findings

Examples

Challenging issues related to the return of IRRs include

- The research results indicate a significant health concern for a research participant; however, the results are de-linked from participants' identity and, although technically possible, re-linking them would violate the terms of the informed consent, which promised individuals that their confidentiality would be preserved through total anonymization and a promise not to re-identify research samples.
- The research aims intend to focus on a specific genetic variant; however, the proposed research methods call for WGS because it is a more efficient approach, notwithstanding the fact that researchers have no intention of analyzing the data gathered on other genetic markers (and such data may include information that would be relevant to participants' health care decision-making).
- The research results will be processed in a non-CLIA approved laboratory because there is no CLIA-laboratory that performs the research test at issue; however, the researchers anticipate that the results will uncover information that would be relevant to a participants' health care decision-making.

Examples of IFs include

- A spinal tumor detected through a research MRI where the protocol calls for the analysis of the image of an unrelated part of the body.
- A genetic variant indicating a high risk of a certain type of cancer found during a WGS protocol where the focus of the research is limited to a different portion of the genome.
- Genetic variants uncovered in the analysis of banked specimens and data under circumstances where the significance of the variant may have been unknown at the time the materials were banked, and the retrospective research is not targeting such variants.

Details Regarding the Points to Consider:

Therapeutic Misconception

Because research is not designed to convey individualized therapeutic benefit (even if therapeutic benefit may be a possibility under some clinical research protocols), it is a universal challenge to ensure that participants understand their individual care and treatment is not the primary goal of the investigators. There is some concern that providing IRRs or promising to return IFs may compound this misconception, particularly in genomic research, with participants expecting to learn information regarding their genetic health (or have latent health concerns diagnosed) through participation. Some international biobanks have a "no return" policy to avoid this issue. It is important in developing a plan for the return of any IRRs and IFs that the potential for therapeutic misconception is mediated; part of the way to accomplish that is to ensure that the criteria for which results will be returned are clearly established in the protocol and communicated to participants through the informed consent process.

Defining Returnable Results

The most challenging aspects of IRRs and IFs are defining the concepts themselves and the criteria under which each type should be returned. Examples of specific definitions are outlined in Options for Defining Key Terms. It is important in defining IRRs and IFs to also define what they are not (for example, do investigators have an obligation to annotate genomic data generated in the course of a WGS project to the extent the data are not relevant to the aims of the project, solely to determine if there are any returnable findings embedded?). Clearly delineating the scope of any investigator obligation to return results will help to manage both the expectations of participants and the liability of investigators.

Categorical criteria that are often cited in defining results that are returnable include:

a. *Analytically Valid*: The finding reliably communicates unambiguous information through established scientific methods
b. (*Clinically) Significant*: The finding indicates a serious threat to health and/or reproduction. (Some proposed standards go beyond the clinical realm, to findings that are of personal significance based on other factors, such as life planning.)
c. *Medically Actionable*: There is an established intervention that can be utilized in response to the finding such that the serious threat to health or reproduction might be averted or reduced.

d. *Permitted to be Returned*: Returning the finding does not violate the understanding of the participant as documented in the informed consent form (i.e., the participant has opted to receive the results or has not opted out of receiving results (see the discussion of Participant Preference below); furthermore the return is not inconsistent with applicable law (i.e., in the United States, the regulatory requirements of the Clinical Laboratories Improvement Amendments (CLIA) may limit the types of findings that can be returned for therapeutic or diagnostic purposes).

The development of broad-based consensus lists for returnable results (for example, in the area of genomics) is a possibility that is currently being pursued. For example, in the United States, the National Heart, Lung and Blood Institute (NHLBI) working group, in tackling the issues around returning IRRs, recommended that an independent, national advisory committee be established to serve as a resource to investigators on when a genetic finding and its clinical implications are sufficiently established to create an obligation to return (although such a committee has yet to be established). Certain literature on international standards for returning IRRs and IFs recommends creating an international "lexicon" that would harmonize global standards relating to definitions and the criteria under which return would be appropriate, similar to the International Conference on Harmonization, while retaining some degree of investigator discretion and appreciation of the distinct types of research in which such findings may arise (i.e., interventional vs. biobank research, substantive area of research, etc.). Others [Beskow LM, Burke W, cited below] argue that developing a universal threshold for return is unrealistic and the *context* of the research (the "scope of entrustment", "intensity and duration of interactions with participants", and "vulnerability and dependence of the study population") should be the primary factor in determining returnability.

Participant Preference

The degree to which participants should be invited to direct which results are returned (referenced above in the discussion of Defining Returnable Results (category d) is also a matter of debate. On the one hand, there is some evidence in the literature that participants are interested in receiving results. [Kaufman D, Murphy J, Scott J, Hudson K, cited below]. On the other hand, catering to individualized requests and parameters for the return of results begins to blur the line between research and individualized clinical care, contributing to the therapeutic misconception. [Beskow LM, Burke W, cited below.]

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In developing a proposal for how the return of IRRs and IFs will be handled, consideration should be given to whether (and to what degree) participants will be given the opportunity to state their preferences with respect to the information they would like to learn, and under what circumstances (if any) investigators might request that an ethics board overseeing the research override a participants' decision to opt-out of learning results (for example where an IRR or IF indicates an immediate threat to life that can be averted and a "duty to rescue" is established). A corresponding description of this process should be included in the informed consent form so that subjects understand the limits of information that will be provided, as well as circumstances under which they can expect that results will be returned.

Distinguishing Between GRRs, IRRs and IFs

When outlining a plan for the return of information to participants, consider tailoring the plan to the specific type of information at issue (whether GRR, IRR or IF). Each category is distinct and may raise different ethical issues that need to be addressed; as such they should not be conflated. For example, with IRRs, investigators should have the expertise to interpret the significance of the result; an IF, on the contrary, may be outside the realm of knowledge and experience of the investigator and may require the engagement of an expert to determine whether it would meet the criteria for return as outlined in the protocol. How that type of situation will be managed may be something that investigators want to detail when addressing the return of IFs in the protocol. Note that these distinctions may be less clear in the context of large-scale genomics and biobanking research, where the "aims" may not be as concretely defined at the time of the research interventions.

Financial Burden

Identifying, confirming (where applicable) and managing IRRs and IFs may have financial costs that investigators should consider at the outset and plan for in any research budget and funding.

References

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Essential Element 9: Post Trial Access

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Examples

Example 1: A drug approved for diabetes is found to be safe and effective for the treatment of a water-borne parasite in Sub-Saharan Africa. After the research ends, the sponsor agrees to continue to provide the study drug as needed for the former subjects.

Example 2: An HIV vaccine study is conducted in a small community. After the trial ends, the sponsor leaves an HIV testing equipment at the clinic and allows continued testing of prior study subjects.

Details Regarding the Points to Consider

The issue of post trial access of research subjects to continuing care has been greatly debated. CIOMS 2002 succinctly states, ""Although sponsors are, in general, not obliged to provide healthcare services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so." Post trial access can be thought of broadly as any sponsor-provided access to medical benefits after the study has ended. For instance, it could involve continued access to interventions found to be safe and effective in the research, or it could involve other types of medical benefits such as general health care interventions or diagnostic services. It might be limited to those individuals who participated in the research, or it could be provided to a wider group such as all individuals affected with the disease being studied in a given region. Generally, post trial access is viewed as favorably affecting the overall risk benefit assessment of the research. However, the post trial access could also provide undue influence on subjects' decision making if it provides too great of a benefit. There are several difficulties in providing post trial access. The first is the cost to the sponsor. The second is determining in a timely manner at the end of the trial whether the study interventions have been proven to be safe and effective and thus acceptable for provision to the former participants.

References

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Declaration of Helsinki, 2008, section 33: At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

Council for International Organizations of Medical Sciences (CIOMS). "International Ethical Guidelines for Biomedical Research Involving Human Subjects." (2002) See Guideline 21 Web 9 September 2013.

Ethical obligation of external sponsors to provide health-care services

External sponsors are ethically obliged to ensure the availability of:

- health-care services that are essential to the safe conduct of the research;
- treatment for subjects who suffer injury as a consequence of research interventions; and,
- services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available
- to the population or community concerned.

Commentary on Guideline 21

Obligations of external sponsors to provide health-care services will vary with the circumstances of particular studies and the needs of host countries. The sponsors' obligations in particular studies should be clarified before the research is begun. The research protocol should specify what health-care services will be made available, during and after the research, to the subjects themselves, to the community from which the subjects are drawn, or to the host country, and for how long. The details of these arrangements should be agreed by the sponsor, officials of the host country, other interested parties, and, when appropriate, the community from which subjects are to be drawn. The agreed arrangements should be specified in the consent process and document.

Although sponsors are, in general, not obliged to provide healthcare services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so. Such services typically include treatment for diseases contracted in the course of the study. It might, for example, be agreed to treat cases of an infectious disease contracted during a trial of a vaccine designed to provide immunity to that disease, or to provide treatment of incidental conditions unrelated to the study.

The obligation to ensure that subjects who suffer injury as a consequence of research interventions obtain medical treatment free of charge, and that compensation be provided for death or disability occurring as a consequence of such injury, is the subject of Guideline 19, on the scope and limits of such obligations.

When prospective or actual subjects are found to have diseases unrelated to the research, or cannot be enrolled in a study because they do not meet the health criteria, investigators should, as appropriate, advise them to obtain, or refer them for, medical care. In general, also, in the course of a study, sponsors should disclose to the proper health authorities information of public health concern arising from the research.

The obligation of the sponsor to make reasonably available for the benefit of the population or community concerned any intervention or product developed, or knowledge generated, as a result of the research is considered in Guideline 10: Research in populations and communities with limited resources.

Additional Resources

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Essential Element 10: Payment for Participation

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Examples

- In the context of phase 2-3 trials, pursuant to the UK's ABPI guidelines, compensation should be paid when, on balance of probabilities, the injury can be attributed to the intervention or procedures under the protocol. Generally, the assessment of attribution is made by the investigator. (APBI)
- In the context of phase 1 trials, under the UK's ABPI guidelines, compensation should be paid, irrespective of fault, in the case of injuries to participants; a minimum of £2.5 million in insurance coverage is recommended for each phase I protocol. (APBI)

Details Regarding the Points to Consider

Clinical trial claims are rare, with an EU government assessment showing claim rates of about 5 in 10,000 participants. In this regard, the cost of trial insurance is roughly EUR $50/year/patient. (EU)

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Continue to Essential Element 11: Study Related Injury

Essential Element 11: Study Related Injury

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Examples

There are a number of possible approaches to study-related injury or impairment, ranging from full compensation of loss and coverage of necessary care and treatment, to the provision of care charged at the usual rate without additional compensation, to providing compensation only in the event that the injured subject is successful in litigation. As indicated below, a policy that leaves injured participants to bear the costs of necessary medical care on their own will call for substantial ethical justification, even if it is legally sufficient. Please see Points to Consider and related Details sections for more information.

Details Regarding the Points to Consider

Local legal requirements regarding study-related injury differ. For example, with a few exceptions for research conducted or supported by the Department of Defense, Department of Veterans Affairs, NIH Clinical Center, the Environmental Protection Agency, and NASA, U.S. research regulations do not require that injured subjects be provided care or compensation; instead, they require for research involving more than minimal risk nothing more than "an explanation as to *whether* any compensation and an explanation as to *whether* any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained." Other countries (e.g., South Africa, India, Uganda, Brazil, and the EU) have much more stringent requirements regarding care and compensation for research-related injury, as well as clinical trials insurance. Note that many research regulations preclude any type of exculpatory language in the informed consent document, such that regardless of what is or is not promised to injured research subjects, they cannot be asked to waive their right to sue.

Research institutions themselves may have certain requirements or policies regarding study-related injury that are more stringent than what is required as a matter of law. It is also important to recognize that certain funding restrictions may limit the response that may be taken in the event of study-related injury. For example, when federal funding is provided for a defined period of time (e.g., in a grant or contract), there may be challenges associated with promising compensation or coverage of medical care for injury, since costs may be incurred after the funding period has ended. There are also CMS requirements for reporting payments to Medicare and Medicaid patients.

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Finally, it is important to be aware of various ethical considerations. Some commentators maintain that it is ethically obligatory to make injured participants whole both physically and financially without forcing them into litigation, given the benefits accruing to others from their research participation and the imperative to do no harm. Others suggest that so long as risks are adequately conveyed to and understood by research participants, the possibility of injury is an acceptable sacrifice for participants to endure on their own. A variety of advisory bodies and international groups have taken up this question, and most agree that there is an obligation to ensure that subjects do not individually bear the costs of medical care required to treat harms directly resulting from their participation in interventional clinical research, without regard to fault (e.g., CIOMS, the Institute of Medicine, the National Bioethics Advisory Commission, and the Presidential Commission for the Study of Bioethical Issues). There is less agreement, however, as to whether there is any obligation to compensate subjects for economic and noneconomic harms beyond the costs of care.

The bottom line is that whatever the approach taken to study-related injury, it should be at the very least compliant with the letter of the law, but should also be responsive to the ethical factors at play. A decision not to provide free care for study-related injury should be well justified.

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