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## Commentary

# Eli Lilly and Company's bioethics framework for human biomedical research

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## Abstract

Current ethics and good clinical practice guidelines address various aspects of pharmaceutical research and development, but do not comprehensively address the bioethical responsibilities of sponsors. To fill this void, in 2010 Eli Lilly and Company developed and implemented a *Bioethics Framework for Human Biomedical Research* to guide ethical decisions. (See our companion article that describes how the framework was developed and implemented and provides a critique of its usefulness and limitations.) This paper presents the actual framework that serves as a company resource for employee education and bioethics deliberations. The framework consists of four basic ethical principles and 13 essential elements for ethical human biomedical research and resides within the context of our company's mission, vision and values. For each component of the framework, we provide a high-level overview followed by a detailed description with cross-references to relevant well regarded guidance documents. The principles and guidance described should be familiar to those acquainted with research ethics. Therefore the novelty of the framework lies not in the foundational concepts presented as much as the attempt to specify and compile a sponsor's bioethical responsibilities to multiple stakeholders into one resource. When such a framework is employed, it can serve as a bioethical foundation to inform decisions and actions throughout clinical planning, trial design, study implementation and closeout, as well as to inform company positions on bioethical issues. The framework is, therefore, a useful tool for translating ethical aspirations into action – to help ensure pharmaceutical human biomedical research is conducted in a manner that aligns with consensus ethics principles, as well as a sponsor's core values.

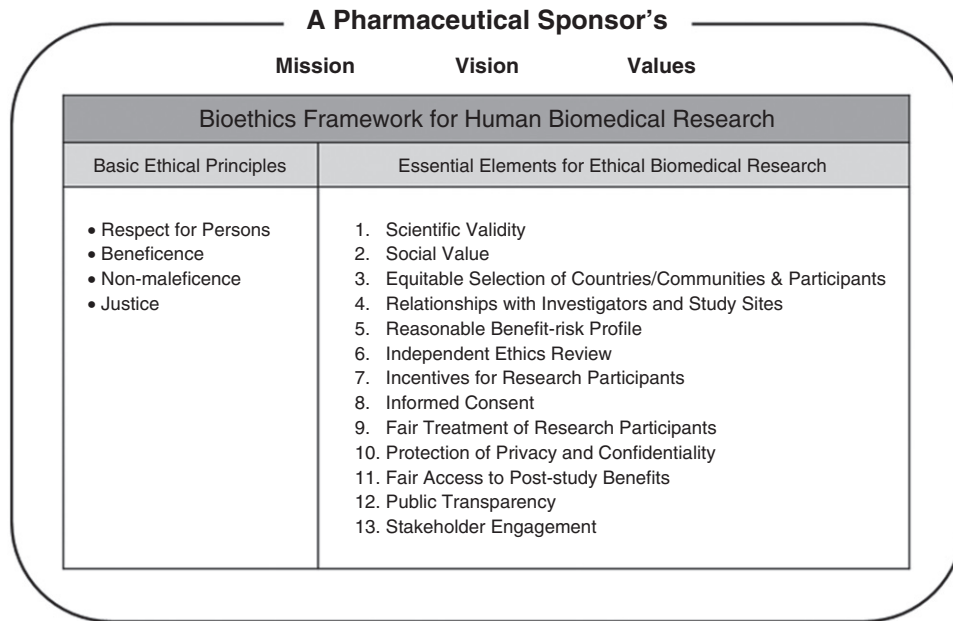
## Bioethics framework for human biomedical research

### Background

To construct the *Bioethics Framework for Human Biomedical Research*, a number of well respected resources<sup>1–15</sup> were evaluated for their relevance to the role of a pharmaceutical drug development sponsor. Principles or requirements that were regulatory in nature or related solely or primarily to investigators or ethics reviewers were eliminated, and the rest (including those that are shared responsibilities between or among sponsors, investigators and/or review boards) were synthesized and incorporated into the framework.

### Purpose

The framework is a tool for translating ethical aspirations into action – to help ensure human pharmaceutical biomedical research is conducted in a manner that aligns with consensus ethics principles, as well as a sponsor's core values. Specifically, it should be used to guide discussion and decisions regarding whether certain types of research should be pursued and subsequently how the research should be conducted. It can also be used as a reference to articulate the ethical rationale for a given decision, and to articulate bioethics principles and



**Figure 1.** Diagram of the framework. The framework resides within the context of an institution’s mission, vision, and values and comprises basic ethical principles and essential elements.

positions with third parties, such as research collaborators, business partners, clinical research organizations, or vendors. It is not, however, a stand-alone document and should be used in concert with clinical research requirements (such as regulations, International Conference on Harmonisation Guidelines, and company-specific policies and procedures) to evaluate the ethics of biomedical research that derives data from human research participants or human biological samples.

### Format

The framework consists of four basic ethical principles and 13 essential elements for ethical human biomedical research, and resides within the context of a sponsor’s mission, vision and values (Figure 1). The format of the essential elements incorporates the style of the CIOMS guidelines<sup>8</sup> in that each element has a high-level overview and a commentary for further explanation.

### Institutional context: a sponsor’s mission, vision, and core values

It is acknowledged that a bioethics framework must be consistent with an institution’s charter; therefore, a sponsor’s mission, vision, and core values should be part of the framework schema and referenced during bioethics deliberations.

This framework is motivated by the ethical concepts of what a person or institution should be, as well as what a

person or institution should do. ‘Being’ focuses on the motives and character of an individual or institution, while ‘doing’ focuses on the actions of an individual or institution and the possible consequences of the actions. A company’s corporate motives and character are formed by its mission, vision, and values (www.Lilly.com). Together these serve as the primary benchmark by which all company decisions and activities should be guided and measured.

A company’s mission articulates the fundamental purpose for existence – the calling or charge for the organization and each of its employees. The vision articulates the image of the future the company hopes to create if successful with the mission. The core values articulate the principles and qualities that the company founders esteemed and reflect the collective contemporary character of the company.

### Basic ethical principles

When making decisions, providing consultation or developing a bioethics position on a topic, one needs to appeal to values and principles that will serve as moral authority. Basic bioethical principles are considered a primary source of moral assessment or justification when considering what a person or institution should do in a given situation. Therefore, these are the foundational norms of the framework, and serve as its moral authority.

There are four basic bioethical principles that have been highly influential in human research ethics: (1) respect for persons, (2) non-maleficence, (3) beneficence,

and (4) justice. These four basic bioethical principles were incorporated into the framework as a reference for a sponsor to evaluate plans, actions, and possible consequences of pharmaceutical drug development.

Three of these, respect for persons, beneficence, and justice, were articulated in the Belmont Report<sup>16</sup>. Subsequent analysis of these principles by Beauchamp and Childress<sup>13</sup>, however, highlighted the need to separate out considerations that may have been blurred in the categorization utilized in the Belmont Report. Adding the principle of non-maleficence makes it possible to deliberate on bioethical issues in a more comprehensive and precise manner.

It is important to note that there may be interplay among the principles for any given ethical decision – such that any or all of them may be invoked during a decision-making process and any one of them may take precedence as the deciding factor in any particular decision.

The four basic ethical principles are described in the following sections.

### Respect for persons

This principle requires that individuals be treated as autonomous (or self-determining) agents who have the mental capacity to make voluntary decisions that are free from external constraints; and it requires that individuals are not treated as a mere means to an end.

- Respect involves acknowledging the value of persons and their decision-making rights, and permitting and facilitating them to act autonomously.
- Disrespect involves attitudes and actions that ignore, insult, demean, or are inattentive to others' rights of autonomy.
- Respect also involves treating an individual as an end unto him/herself and not as a mere means to achieve a specific end goal.
- One way to treat individuals as an end unto themselves is by applying the principle of proportionality, which requires that an action should be no more severe than necessary. With regard to biomedical research, this principle stipulates that research should be pursued only if (1) the research question or questions are of sufficient significance to warrant the use of human participants and/or tissues; (2) the research methodology is necessary to achieve the aims of the study; and (3) there are no acceptable alternative methodologies.
- The capacity for self-determination is subject to change across an individual's lifespan due wholly or in part to maturity, illness, mental or physical disability, or circumstances that restrict liberty. As such, those with limited autonomy can be considered

'vulnerable' and should be afforded extra protection until their decision-making capacity matures or is restored.

- The protection provided to vulnerable persons should be appropriate for the anticipated risk of harm weighed against the likelihood of benefit for the individual with reduced autonomy.

### Beneficence

This principle requires that individuals prevent or remove harm and do or promote good; in other words, beneficence is the obligation to act for the benefit of others.

- Beneficence has long been treated as a foundational value – and sometimes as the foundational value – in healthcare ethics.
- Harms to be prevented, removed, or minimized are the pain, suffering, and disability of injury and disease.
- The range of benefits that might be considered relevant is broad.
- Sometimes the benefit may be for the patient, while at other times it may be for society, or a combination thereof.
- This principle is satisfied in the research context by assuring that risks stand in reasonable relation to probable benefits.
- Research participants should not be asked or allowed to consent to more risk than is warranted by anticipated benefits.
- Vulnerable participants should not be exposed to research procedures or interventions with greater than minimal risk unless these procedures hold out prospect of direct benefit to the vulnerable person.

### Non-maleficence

This principle requires that individuals avoid inflicting harm on others or imposing undue risks of harm. Non-maleficence is reflected in the longstanding maxim, 'Above all, do no harm', which is included in many commentaries on healthcare ethics. Harm can be thought of as bodily harm, such as pain, disability, or death, or mental distress, or in some way interfering with or setting back another party's significant interests.

- Both intentionally and negligently causing harm are fundamental moral wrongs.
- It is morally impermissible to harm one person so that others may benefit, but it is not impermissible to allow reasonable risks of harm so that others may benefit.
- Research endeavors very often include some risk of harm. Therefore, an investigator is not obligated never to cause harm, but rather to strive to create a positive balance of goods over inflicted harms (see *Beneficence*).

- A standard of ‘due care’ requires that the goals of a research endeavor justify the anticipated risks of harm that will be imposed on a research participant.

## Justice

This principle requires that there should be fair, equitable, and appropriate treatment of individuals based upon what is due or owed to them.

- Injustice occurs when an undue burden is imposed or when a benefit to which one is entitled is denied without good reason.
- Since biomedical research is a social enterprise undertaken for the public good, it must be accomplished in a broadly inclusive and participatory way.
- Justice can be satisfied in the research context by ensuring that there is fair distribution of both the burdens and the benefits of research. In particular, justice is relevant for the fair selection of research sites and participants.

## Thirteen essential elements for ethical biomedical research

The 13 essential elements provide a meaningful way to apply the basic bioethical principles to daily activities and are a useful tool for evaluating whether human biomedical research fulfills bioethical standards in design, conduct, analysis, and disclosure. These elements are applicable to both medical research and research with human biological samples. For the former, most if not all of the elements will generally apply, whereas for research with biological samples nine of the 13 elements will generally apply (1, 2, 5, 6, 8, 9, 10, 12, and 13).

### 1. Scientific validity

Human biomedical research must be scientifically valid in order for it to be considered ethically justifiable. If this criterion is not satisfied for a particular study or project, then the remaining essential elements become irrelevant.

#### Commentary

To be considered ethically justifiable, biomedical research on human research participants must be scientifically valid and operationally feasible. If the research cannot produce reliable and valid data, or is not reasonably feasible to conduct, then it has no scientific or social value and exposes participants to risks for no personal or social benefit, thereby making it unethical. Scientifically valid biomedical research on humans must be (i) based on adequate knowledge of the pertinent scientific literature,

(ii) preceded by adequate preclinical studies, (iii) methodologically sound, (iv) described in a detailed protocol, and (v) conducted according to well established quality standards (e.g., ICH Good Clinical Practices or adequate laboratory standards).

Specifically, a principle of proportionality should be applied, such that (i) the research question or questions are of sufficient significance to warrant the use of human research participants and/or collection of human biological samples or tissues, (ii) the research methodology is necessary and sufficient to achieve the aims of the study, and (iii) no acceptable methodological alternatives exist other than to use human research participants and/or human biological samples or tissues. Only the requisite amount of study data and samples necessary to test the scientific hypothesis and fulfill legal and regulatory obligations should be collected, used, and disclosed.

Once the first essential element of scientific validity is satisfied, then the other 12 essential elements can be assessed.

#### Basic ethical principles

- Beneficence
- Justice
- Respect for persons

#### Primary cross references

- Essential elements: 2, 5
- CIOMS guidelines: 1
- DoH principles (2013): 8, 12, 14, 21
- ICH E6: 5.4, 6.4

### 2. Social value

Human biomedical research must have anticipated social value, such that the research will contribute to generalizable knowledge and the expected discoveries will either directly or indirectly benefit people’s health and well-being.

#### Commentary

Biomedical research has instrumental value because it generates scientific knowledge that may lead to improvements in people’s health or well-being. Without anticipated social value, human research participants would be indiscriminately subjected to research risks without any promise of benefit to them or others, and valuable resources would be misused. With anticipated social value, the risks of research participation can be appropriately weighed against the potential benefits.

Although the process of translating science to the practice of medicine is complex, each study that involves

human participation needs to be evaluated directly for its social value. Human biomedical research should contribute to the common purpose of improving the quality and value of clinical care and should utilize learning from clinical care settings. Even early clinical studies should be evaluated in light of the data they will generate, and whether and how they will inform additional studies. Ultimately, a series of studies should contribute to generalizable knowledge that has potential to improve health and well-being.

Because of the pharmaceutical industry's mission to discover, develop, manufacture, and distribute drugs to improve patient outcomes, pharmaceutical biomedical research should not be an end unto itself. Pharmaceutical biomedical research should be pursued to answer scientific questions that are important and relevant to patients, healthcare providers, and payers. Studies that should be avoided are those that do not produce generalizable knowledge, do not address a significant healthcare issue, or are conducted for strictly commercial purposes. It is not ethically justifiable to conduct medical research with intent that the mere conduct of the study itself will induce the sale of a medical product. Off-label medical research is ethically justifiable provided it is conducted for the purpose of answering important and relevant scientific questions, and is not conducted to induce the sale of a medical product for off-label use.

#### Basic ethical principles

- Beneficence
- Justice
- Respect for persons

#### Primary cross references

- Essential elements: 5, 11, 12, 13
- CIOMS guidelines: 1
- DoH principles (2013): 6, 8, 20, 28
- ICH E6: No guidance

### 3. Equitable selection of countries/communities and research participants

Selection of countries/communities and research participants must be based upon their respective needs as well as research objectives. The selection of a country or community in which to recruit research participants should ensure that the burdens and benefits of the research will be distributed equitably. The selection of research participants must be based on scientifically and ethically justifiable inclusion and exclusion criteria.

#### Commentary

##### *Country/community location*

Research objectives must be the primary basis for selecting a country/community location for a clinical trial. Once a target population is selected based upon their ability to satisfy the research objective, then the sponsor is obligated to consider whether the country or community and study participants will be better off or at least not worse off at the conclusion of the study. To avoid the possibility of exploitation, certain criteria should be considered when selecting candidate countries or communities, including (i) the local prevalence of the disease under study, (ii) the relevance of the research to local or community health needs, (iii) the potential for the research to yield important scientific advances, and (iv) the anticipated benefits (e.g., knowledge gained) to justify risks to participants and the host country or community.

The primary benefits of pharmaceutical research are the research results (i.e., knowledge generated) and the product developed. A sponsor should only conduct clinical trials in countries or communities in which the benefits of research can be made reasonably available for research participants and the host country or community. Prior to initiating a trial in a country, a sponsor should (i) plan to disclose the research results in a public forum (e.g., clinical trial registry or medical journal or meeting) that is accessible to local professionals, and (ii) show evidence of a good-faith intention to make the product developed commercially available to the population of the host country or community in which the research is conducted. Research in a country or community where it is not possible to make the drug commercially available may still be justifiable if the research results will be disclosed through a locally accessible public forum and there is intent to make the product available through other means (e.g., utilizing non-profit organizations).

##### *Research participants*

When selecting potential research participants, study inclusion criteria are used to determine who may be enrolled in a study, while exclusion criteria are used to determine who may not be enrolled in a study. Both inclusion and exclusion criteria must be scientifically and ethically justified. Scientific inclusion/exclusion criteria are derived from scientific and medical knowledge, such as known genetic differences between populations or epidemiological data, and should be the primary basis for determining eligibility for participation in biomedical research. Ethical inclusion/exclusion criteria are derived from moral norms such as fairness and non-maleficence.

Equity requires that no population, group, or class of persons bear more than its fair share of the burdens of participation in biomedical research. Likewise, no group participating in biomedical research should be deprived of

its fair share of the benefits of such research. If inclusion/exclusion criteria are scientifically and ethically justifiable, then no population, group or individual may be excluded from a study being conducted in their locale if they satisfy inclusion criteria.

Unfortunately, there are historical cases in which vulnerable populations, such as the uneducated, poor, or those otherwise powerless to defend their own interest have been used for high-risk research or research that yields no direct benefit to them or their communities. Conversely, in an effort to protect them, vulnerable populations have also been unfairly excluded from promising research. The exclusion of some populations from promising research has resulted in a gap in information about the proper means of diagnosis, prevention, and treatment of diseases in these populations. It is unjust to exclude vulnerable research participants (such as children and incapacitated individuals) from studies for a disease that affects them simply because of the participant's vulnerability. However, vulnerable participants do require added protection. The protection provided to vulnerable persons should be appropriate for the anticipated risk of harm weighed against the likelihood of benefit for the individual with reduced autonomy. Therefore, individuals who are physically, mentally, or developmentally (e.g., children) incapable of providing informed consent should not be included in a study unless their condition is a necessary characteristic of the research population.

#### Basic ethical principles

- Justice
- Respect for persons
- Beneficence

#### Primary cross references

- Essential elements: 5, 8, 11
- CIOMS guidelines: 10, 13, 14, 15, 16, 17
- DoH principles (2013): 13, 17, 20, 28, 30
- ICH E6: 1.61, 2.2, 4.8.14

## 4. Relationships with investigators and study sites

Collaboration with study personnel is predicated by their ability to comply with a single global standard. The collaboration must be conducted in an objective manner that i) fosters fair opportunity for qualified sites to participate in industry-sponsored research and ii) mitigates conflicts of interest and potential bias in trial design, research participant selection, informed consent, and collection, interpretation, and disclosure of data.

### Commentary

In order to ensure quality research and protect the rights and well-being of enrolled research participants, it is the sponsor's responsibility to apply a single global standard to the conduct of human biomedical research. Medical research involving human participants should be conducted in accordance with i) consensus ethics principles derived from international ethics guidelines, such as the Declaration of Helsinki<sup>10</sup> and CIOMS International Ethical Guidelines<sup>8</sup>, ii) the International Conference on Harmonisation Good Clinical Practice (ICH GCP) Guideline (E6)<sup>6</sup>, and iii) applicable laws and regulations of the country or countries where a study is conducted.

It is a sponsor's responsibility to collaborate only with investigators with appropriate scientific and ethical training and professional qualifications, and adequate facilities to conduct studies in compliance with this single global standard. If an investigator and site meet these qualifications, they should be given fair opportunity to participate in a study. Prior to enrolling research participants, the sponsor has a responsibility to provide investigators and support personnel with appropriate training to conduct the study. This training should include an explanation of ethical expectations, as well as study requirements.

The sponsor's responsibility to mitigate conflicts of interest and circumstances could introduce potential bias in trial design, participant selection and enrollment, informed consent, and collection, interpretation, and disclosure of data. To this end, the promise of payments of money or other rewards to consultants and investigators should not be so large as to unduly influence the above factors or a prospective investigator's decision to participate in a research study, enroll inappropriate participants, or to engage in protocol violations. Therefore, sponsors should make payments to investigators only for legitimate, reasonable, and necessary services and in amounts that are no more than the fair market value for the services performed. To mitigate conflict of interest, an individual must be disqualified from serving as an investigator for a particular trial if s/he (or their immediate family) has direct ownership interest in the test article (drug or device) to be studied in that trial.

To facilitate honest and respectful relationships with investigators, sponsors should clearly communicate to investigators that i) the clinical judgment of clinician investigators will be respected and given due consideration, ii) they will have access to data collected at or derived from their study site(s), iii) they may publish results from their study site(s), and iv) there are specific criteria for scientific authorship.

#### Basic ethical principles

- Non-maleficence
- Justice

### Primary cross references

- Essential elements: 12
- CIOMS guidelines: 20
- DoH principles (2013): 3, 4, 10, 14, 18, 22, 36
- ICH E6: 5.6, 5.9, 5.18.3

## 5. Reasonable benefit–risk profile

The potential benefits and risk of harms of the research must be reasonably balanced; potential benefits should be maximized and risk of harms minimized to the extent possible.

### Commentary

#### *Benefits*

Sponsors and investigators need to consider potential benefits for both society and individual research participants. While interventions in biomedical research are designed to answer a specific research question that may benefit a population of people, some interventions may also benefit individual research participants. The potential for therapeutic benefit can be a motivating factor to participate in research, but so also might be the desire to contribute to science. Therefore, when assessing the benefits and risks of a clinical trial, it is important to keep in mind that well informed volunteers who are capable of assessing the benefits and risks of a study should not be precluded from participation for altruistic reasons or for modest remuneration. For vulnerable participants, like children or incapacitated individuals, the sponsor and investigator need to ensure that the intervention or procedure is responsive to the health needs or priorities of the group and that the relation of the anticipated benefit to the risk is at least as favorable to the participant as that presented by available alternative therapeutic approaches.

#### *Harms*

The health and safety of research participants enrolled in biomedical research must prevail over all other interests. The harms involved in biomedical research are not limited to physical harms, and may include social, economic, and psychological harms. To the extent possible, sponsors should avoid imposing nonclinical harms and burdens on research participants. It is the responsibility of both sponsors and investigators to ensure that risk of harms of the research is minimized and that it is reasonable in relation to the potential benefits. Sponsors and investigators need to identify and clearly communicate the type of harms, the probability that harm will occur, and the magnitude of the harm if it were to occur.

Sponsors should design a study in which control groups are not exposed to unreasonable risk of serious or irreversible harm. Usually this means that research participants in

the control group of a clinical trial should receive an established effective comparative intervention for the disease or disorder being evaluated. However, there are ethically defensible reasons to use alternative comparators, such as placebo or ‘no treatment’ when i) there are scientifically sound methodological reasons to use a placebo control, ii) withholding an established effective intervention will not result in irreversible disease progression, prolonged non-trivial disability, or undue suffering, and iii) research participants are part of a robust informed consent process, and provide voluntary informed consent.

### Basic ethical principles

- Non-maleficence
- Beneficence

### Primary cross references

- Essential elements: 1, 8, 11
- CIOMS guidelines: 8, 9, 13, 16, 17
- DoH principles (2013): 8, 14, 16–21, 28, 33
- US Code of Federal Regulations: 45 CFR §46.405
- ICH E6: 2.2

## 6. Independent ethics review

Research protocols must be reviewed and approved by one or more independent ethics review committees prior to enrolling participants in a study, and at least annually during the course of the study.

### Commentary

In pharmaceutical biomedical research, there are different types of independent reviews, such as internal protocol review committees (PRCs), external institutional review boards (IRBs) or ethics review boards (ERBs), conflict of interest committees, and data safety monitoring boards (DSMBs). An independent ethics review of biomedical research protocols is necessary to scrutinize the ethical merits of the protocol in an unbiased fashion. This work may or may not include consideration of conflicts of interest and public accountability. Independence indicates that the review is conducted by a group of people separate from the individual or team that developed the protocol.

Biomedical research imposes risks on research participants for the benefit of society and an independent review of a protocol’s ethical requirements helps assure members of society that the interests and well-being of research participants will be protected. It is prudent for sponsors to conduct an internal check of ethics (such as by a protocol review committee) prior to sending a protocol to an external ethics review committee in order to assure that the proposed study meets internal ethics standards. To provide



ongoing participant protections, an external ethics review committee conducts further review during the study as necessary; for example, to review any changes that significantly affect the conduct of the trial and/or increase the risk to participants. This type of external ethics review must be conducted for each study site in which the study will be conducted, except in cases where a centralized ethics review committee is used.

### Basic ethical principles

- Respect for persons
- Non-maleficence
- Beneficence

### Primary cross references

- Essential elements: 4, 5, 9, 12
- CIOMS guidelines: 2, 3
- DoH principles (2013): 23, 30, 32
- US Code of Federal Regulations: 45 CFR §46.101
- ICH E6: 5.11

## 7. Incentives for research participants

The promise of payments of money or other rewards should not be so large as to unduly influence a prospective participant's decision to join a research study or persuade them to take undue risks.

### Commentary

It is generally considered ethical to recompense participants for their time and inconvenience when participating in a research study, as well as for lost earnings, travel costs, and other expenses they might incur. Further, it is considered ethical for them to receive medical services at no cost if the services are deemed necessary for study participation and/or as a direct result of study participation.

Just as the promise of payments of money or other rewards to investigators should not be so large as to unduly influence enrollment of research participants, it is considered unethical to offer payments or other benefits to participants that are out of proportion to the burdens of participation. The promise of payments or benefits that are out of proportion to the research requirements may induce an individual to participate in a study against his/her better judgment. Such inducements could invalidate the informed consent process and are therefore regarded as an 'undue inducement'. It is often difficult to determine the line between appropriate recompense and undue influence to participate in research; thus, monetary payments and in-kind recompense must be evaluated by an independent ethics committee, taking into account the cultural norms and traditions of the population in which

the research is being conducted. When biomedical research interventions present more than minimal risk with no prospect of direct benefit to the research participant, then research sponsors, investigators, and ethical review committees must take special care to ensure that monetary payments or other benefits are proportional to the research burden. Under no circumstances should payments be provided to research participants specifically for assuming the risk of the research.

### Basic ethical principles

- Justice
- Non-maleficence
- Respect for persons

### Primary cross references

- Essential elements: 5, 6, 8, 9, 13
- CIOMS guidelines: 7
- DoH principles (2013): 7, 9, 15, 22, 26, 34
- ICH E6: 3.1.8

## 8. Informed consent

Voluntary informed consent of prospective research participants must be obtained prior to conducting human biomedical research. In the case of an individual who is not capable of giving informed consent, the consent of a legally authorized representative may be obtained on behalf of that individual.

### Commentary

Informed consent is a decision to participate in research by an autonomous individual who has received and understands the necessary information about the research and has arrived at a decision to participate that is free from coercion, undue influence, inducement, or intimidation. Because the decision to volunteer for a study must be free from real or perceived controlling constraints by others, individuals must be informed that they are free to withdraw from the study at any time and for any reason.

The informed consent process is designed to respect an individual's autonomy and protect an individual's freedom of choice. Respecting autonomy also recognizes the social nature of individuals, including social practices and the impact individual choices may have on others. The process requires that an individual be adequately informed of the purpose, methods, and possible risks and benefits of a study, in a manner that fosters autonomous decision-making. This requires presenting the information (oral and written) in a language and at a literacy level that is appropriate for the participant population. It also may require incorporating local customs, norms, and beliefs, as appropriate,

into the informed consent process. Because of a sponsor's unique understanding of an investigational product and a given study design, and sometimes unique appreciation of stakeholder needs, a sponsor should draft an informed consent form that sites may then tailor to their needs. In so doing, the sponsor is taking ethical responsibility for the quality and consistency of the information disclosed to research participants, rather than delegating this task to an investigator.

There are two types of informed consent. The first type (autonomous) is provided when a person has the mental capacity to make voluntary decisions that are free from external constraints. The second type (surrogate) is provided by a legally authorized decision-maker and occurs when an individual is incapable of making such a decision for him/herself (e.g., incapacitated adults). In this case, a surrogate is enlisted to provide consent by following the individual's previously stated preferences for the given circumstances. If this is speculative, then the surrogate must decide what would be in the best interest of the individual.

Since children do not have the cognitive ability to adequately comprehend various aspects of risks and benefits associated with research participation, they cannot provide legally valid informed consent. Therefore, studies involving children must obtain parental or guardian permission (to which informed consent considerations generally apply) and, when appropriate, the child's assent to participate.

If personal information or biological samples will be used in a manner that is inconsistent with the original study intent, then there is an obligation to consult with the applicable IRB(s) to determine whether renewed informed consent is required, consistent with applicable federal law in the United States or other jurisdictions where research will occur.

### Basic ethical principles

- Respect for persons
- Non-maleficence
- Beneficence

### Primary cross references

- Essential elements: 1, 2, 5, 7, 13
- CIOMS guidelines: 4, 5, 6, 14, 15
- DoH principles (2013): 7–9, 24–32, 34, 37
- US Code of Federal Regulations: 45 CFR §46.116; Subpart D §46.402 and §46.403
- ICH E6: 4.8.1 to 4.8.15, 5.18.1

## 9. Fair treatment of research participants

Research participants must be treated fairly and with respect along the continuum of study activities – from

recruitment and enrollment through study completion and post-study responsibilities.

### Commentary

The ethical treatment of research participants actually begins when the study is being designed and ends with any relevant post-study responsibilities. Along this continuum of the study process, all research participants must be treated fairly such that similar cases will be treated in a similar manner. The well-being of patients must be a priority for sponsors and investigators. This entails protection of life, health, dignity, integrity, and rights, including the right to self-determination.

Candidate research participants should have fair access to participate in medical research; therefore, trial criteria must be publicly disclosed (e.g., ClinicalTrials.gov). Participants should be recruited in a manner that (i) is consistent with the scientific goals of the study, (ii) is clear and accurate, (iii) does not promise inappropriate inducements, (iv) is appropriate for local customs and norms, and (v) respects privacy and confidentiality. Study sites should promote fairness in study enrollment. Studies should use an equitable set of inclusion/exclusion criteria, which should be based on scientifically and ethically justifiable criteria and not arbitrary factors such as age, race, gender, social worth, or socioeconomic status. If inclusion/exclusion criteria are scientifically and ethically justifiable, then no population, group or individual may be excluded from a study if they satisfy inclusion criteria.

While a participant is enrolled in a study, sponsors and investigators are obligated to support and provide for (respectively) the well-being of the research participant, as it directly relates to the research study. Once a study is completed, investigators need to arrange for any appropriate follow-up care. Sponsors should provide for treatment of any injury or impairment suffered as a direct consequence of a properly administered research intervention. Finally, research participants have the right to withdraw from the study at any time and for any reason without fear of reprisal. This right must be clearly stated in the informed consent document.

### Basic ethical principles

- Respect for persons
- Justice

### Primary cross references

- Essential elements: 3, 7, 8, 10, 11, 13
- CIOMS guidelines: 11, 19, 21
- DoH principles (2013): 7-9, 15, 22, 26, 34-36
- ICH E6: 5.8.1, 5.8.2, 5.18.1

## 10. Protection of privacy and confidentiality

Safeguards must be instituted to protect privacy and confidentiality in the collection, use, and storage of a research participant's personal information and biological samples. Participants must be informed as to how their personal information and biological samples may be used or shared and how the sponsor/investigator will ensure security of such information and samples.

### Commentary

Clinical trials may involve the collection, use, and storage of personal information and samples that could cause harm or distress if disclosed to a third party. Sponsors and investigators must utilize methods to collect and store personal information and samples in a manner that provides protection of privacy and confidentiality. During the informed consent process, the investigator must inform the prospective research participant about the precautions that will be taken to protect privacy and confidentiality. Potential research participants also should be informed regarding how their data and samples may be used and shared, as well as whether, under what conditions, and how research results of relevance to their health and well-being will be provided to them.

### Basic ethical principles

- Respect for persons
- Non-maleficence

### Primary cross references

- Essential elements: 1, 8, 9
- CIOMS guidelines: 18
- DoH principles (2013): 7–9, 24
- ICH E6: 2.11

## 11. Fair access to post-study benefits

Any product/intervention developed or knowledge generated because of a clinical trial must be made reasonably available for the benefit of the participants, population, or community in which the research was conducted.

### Commentary

If there are reasons to believe that research benefits are unlikely to be reasonably available to the research participants, or patient population, community, or country after the conclusion of the research, then it is not ethically justified to conduct research in that population, community, or country. This essential element is particularly relevant for populations, communities, or countries in which resources are limited and research participants

may be vulnerable to exploitation by sponsors and investigators.

The issue of what type of benefits can be made reasonably available is complicated and should be made on a case-by-case basis. However, there are four general categories.

### *Generalizable knowledge*

It is the sponsor's responsibility to publicly disclose research results that are significant to patients, healthcare providers, or payers in a timely fashion and in a venue that is relevant to the country or countries, and communities in which the research was conducted.

### *Product developed*

If the investigational drug achieves regulatory approval, the sponsor must follow through on a good-faith intention to make the product developed commercially available to the population of the host country or community in which the research is conducted, or must make the product available through other means (e.g., utilizing nonprofit organizations).

### *Continued access to an investigational product*

Sponsors should support and collaborate with the investigator and other parties (e.g., investigator institutions, ethics committees, and local regulatory bodies) to determine when research participants should receive the benefit of continued access to an investigational product. Decisions regarding whether it is appropriate to offer continued access to an investigational product should be based upon the following conditions: i) the disease or condition being studied is serious or life threatening, ii) the patient is benefiting (with no undue risks) and discontinuation of treatment might adversely affect the patient's health or well-being, iii) there are no other suitable treatment options for the patient, and iv) sufficient efficacy and safety data exist in order for the sponsor to make a reasonable assessment of a favorable benefit–risk balance. The nature and duration of continued access to be offered should be delineated, to the extent possible, prior to initiation of a clinical trial (i.e., during the study design process) and described in both the study protocol and the informed consent form. This should include provisions, if any, that will be made for continued access in the case of early termination of the trial or drug development program by the sponsor.

### *Off-trial access to an investigational product*

Requests for off-trial access to an investigational product (also known as expanded access or compassionate use) before an investigational drug is commercially available

may be considered only for serious diseases or conditions for which there are no commercially available therapies and the available safety and efficacy data support such use.

### Basic ethical principles

- Justice
- Beneficence

### Primary cross references

- Essential elements: 2-5, 8, 9, 12, 13
- CIOMS guidelines: 10, 21
- DoH principles (2013): 8, 15, 22, 26, 34–37
- ICH E6: 2.2

## 12. Public transparency

Public transparency must be ensured by: i) disclosing information regarding potential conflicts of interest, ii) publicly registering information about planned and ongoing clinical trials, and iii) disclosing results that are significant to patients, healthcare providers, and payers, whether the results are favorable or unfavorable for a given product.

### Commentary

#### *Conflict of interest*

In human biomedical research, there are multiple areas in which the potential for conflicts of interests exist, such as payments from sponsors to investigators and healthcare professionals. It is incumbent upon sponsors and investigators to disclose real or apparent conflicts of interest so that scientific peers and the public can take this into account when evaluating the study design and results. As such, the informed consent document should include information regarding potential conflicts of interest, such as funding, sponsors, and institutional affiliations.

#### *Disclosing clinical trial information and data*

Because biomedical research is fundamentally a social enterprise, there is an ethical responsibility to publicly disclose information about a clinical trial itself, as well as the results of a trial. Important public health benefits related to clinical trials can be realized only when this information is made publicly available. Further, those who made the effort and assumed the risk to participate in a study (research participants, investigators, communities) deserve to know the results and how their participation might affect the advancement of healthcare.

However, scientific disclosures must not jeopardize the sponsor's ability to secure and enforce its intellectual property since protection of intellectual property is foundational for scientific innovation. Working closely with

relevant company experts (e.g., patent attorneys), sponsors must appropriately balance the need to protect intellectual property with the need to disclose positive, negative, and inconclusive results. Unless a delay is necessary to protect intellectual property rights, sponsors should disclose publicly human biomedical research results that are significant to patients, healthcare providers, or payers – whether favorable or unfavorable to a given product – in a timely, accurate, objective, and balanced manner in order for customers to make informed decisions about products.

Disclosure of medical research results can be made through public clinical trial registries or through scientific publication (including scientific journals and congresses). In any venue, sponsors and investigators must protect the privacy and confidentiality of research participants. Prior to disclosure, sponsors of medical research are responsible for receipt and verification of data from all research sites.

### Basic ethical principles

- Beneficence
- Justice

### Primary cross references

- Essential elements: 4, 5, 8, 10, 11
- CIOMS guidelines: 2, 3, 10
- DoH principles (2013): 6, 22, 34, 36
- ICH E6: 5.22

## 13. Stakeholder engagement

To understand and respect issues that may affect the rights and interests of human biomedical research stakeholders, it is necessary to work collaboratively with and through groups of people affiliated by special interest, expertise, customs/beliefs, geographic proximity, or similar situations.

### Commentary

Stakeholder engagement is fundamental to showing respect for those who are or will be touched by a pharmaceutical company and its products. Because human biomedical research is meant to have social value (essential element #2), it cannot be viewed as something that is done to people, but rather as an undertaking that is done with and for people. The latter idea rests on an important concept that research is a joint endeavor or partnership among biomedical research collaborators – that is, a partnership among those who sponsor, conduct, participate in, and could benefit from the research. Ultimately, the success of a study depends on the degree to which collaborative partners feel another party is trustworthy, and trustworthiness is at least partially determined by the

degree to which a partner feels respected. Stakeholder engagement promotes respect and engenders trust in a research project's purpose and conduct.

By engaging and consulting with stakeholders it is possible to do the following and thus to satisfy the other essential elements:

- (1) gain insight as to whether the research questions are relevant and responsive to the health needs of the target population, community, and/or country (essential elements 2, 3);
- (2) determine whether a trial is scientifically and ethically justified (essential element 1);
- (3) determine whether the anticipated balance of benefits and risks for the study is acceptable (including whether post-trial plans are satisfactory) (essential elements 5, 6, 11, 12);
- (4) demonstrate respect for and protect a group's rights and interests by identifying, understanding, and incorporating stakeholder norms, beliefs, customs, and cultural sensitivities into research designs, conduct, and analysis, as appropriate (essential elements 4, 6, 7, 8, 9, 10, 11);
- (5) improve operational factors such as recruitment and retention, and the informed consent process by resolving problems related to the use of difficult, unfamiliar, or culturally unacceptable concepts and practices (essential elements 8, 9, 10).

Stakeholder engagement may include discussions with the sponsor's internal stakeholders, such as bioethics, quality, compliance, clinical operations, patient safety, employees affected by a related healthcare problem, etc., and external stakeholders, such as community representatives or leaders, advocacy groups, advisory boards, patient groups, health authorities, ethics review boards, investigators, and those who regulate the conduct of biomedical research. Stakeholder partners must be selected carefully to ensure consultants can both fairly and accurately represent the target population's rights, interests, needs, and values.

Stakeholder engagement can be fulfilled through both formal and informal mechanisms, depending on a trial's characteristics. If this is integrated with other trial and implementation activities, it should facilitate quality research and improve the conduct of a study and subsequent outcomes. When stakeholders are consulted early and throughout clinical planning and study design and conduct, plans can be adapted to maximize anticipated benefits and mitigate risks.

### Basic ethical principles

- Respect for persons
- Beneficence
- Non-maleficence
- Justice

### Primary cross references

- Essential elements: 1-12
- CIOMS guidelines: No guidance
- DoH principles (2013): 25
- ICH E6: No guidance

## Transparency

### Declaration of funding

The preparation, review and approval of Lilly's *Bioethics Framework for Human Biomedical Research* were completed by Eli Lilly and Company.

### Declaration of financial/other relationships

L.E.V.C. and M.K. have disclosed that they are full-time employees and equity holders of Eli Lilly and Company. D.G.T. has disclosed that he is an equity holder and retired employee of Eli Lilly and Company. R.J.L. has disclosed that he is a paid consultant for Eli Lilly and Company.

CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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