**Research Ethics and Quality Improvement**

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1. An investigator enters into collaboration with a pharmaceutical company to conduct a phase 1 clinical trial in children with malignant brain tumors. The investigator’s son-in-law owns $100,000 of stock in the same pharmaceutical company as an individual.

Which of the following statements most accurately describes this investigator?

A. He has a conflict of interest because his son-in-law owns the stock.

B. He does not have a conflict of interest because the stock is worth less than $250,000.

C. He does not have a conflict of interest because his son-in-law is not considered an immediate family member.

D. He has a conflict of interest because his son-in-law may transfer the stock to his daughter.

**Explanation**

A financial conflict of interest exists when two or more contradictory interests relate to an activity by an individual or an institution. The conflict lies in the situation, not in any behavior or lack of behavior of the individual. Conflicts of interest are situations in which financial or other personal considerations may compromise, or have the appearance of compromising, an investigator’s judgment in conducting or reporting research. In these situations, the researcher has interests in the outcome of the research that may lead to a personal advantage and that might, in actuality or appearance, compromise the integrity of the research. Financial interest by an investigator’s spouse or children is considered a conflict and must be disclosed according to US Department of Health and Human Services guidelines. The National Institutes of Health minimum threshold for disclosure is $5,000 in the previous 12 months when aggregated or when the investigator (including the investigator’s spouse or dependent children) has any equity interest in the entity*.*

2. A tenured, full-time professor on university payroll is invited to be a consultant with a startup biotech company. This biotech company has no relationship with the university. His consulting activity for the company occupies approximately 15% of his time and effort.

Under which of the following circumstances would the investigator be considered to have a conflict of commitment?

A. The university allows only up to 10% of time and effort for outside consulting.

B. 50% of his consulting time is spent supervising graduate students working on projects related to the product development for the biotech company as a part of their research theses.

C. He is not receiving any payment for his consulting services.

D. He does not plan to resign from the university when the company goes public after a year.

**Explanation**

Conflict of commitment is a situation in which a person has substantial professional activities and business interests outside his or her regular employment. Such external interests include consulting, lecturing, acting as an expert witness, public service, or service on a professional board or committee. Because the professor is on university payroll for full-time effort, effort beyond the permissible allowance according to university regulations, even if there is no financial benefit to the professor, is a conflict of commitment. The same holds true if the faculty member is planning a departure because he or she is still employed by the university. Supervision of graduate students is a faculty teaching responsibility, and it is inappropriate to use student effort to financially benefit a nonuniversity entity.

3. A fellow is conducting research on the cytotoxicity of a newly developed purine analog on leukemia cell lines. He assays five different drug concentrations and measures cell kill in triplicate. He runs out of culture media during the experiment and borrows culture media from a fellow researcher. He uses the borrowed media for the set of experiments testing the highest concentration of the drug. When assessing cell viability, he concludes that the highest concentration of the drug is most effective because there was a higher cell kill when compared with the other four concentrations. He publishes these results. However, several other groups cannot replicate his data. He then discovers that the culture media he borrowed for his experiment was serum free and thus may have affected cell viability.

What is this is an example of?

A. Falsification of results

B. Fabrication of results

C. Plagiarism of results

D. Honest error

**Explanation**

Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research or in reporting research results. Fabrication is making up data or results and recording or reporting them. Falsification is manipulating research materials, equipment, or processes or changing or omitting data or results such that the research is not accurately represented in the research record. Plagiarism is the appropriation of another person’s ideas, processes, results, or words without giving appropriate credit. Research misconduct does not include honest error or differences of opinion. In this case, the fellow did not manipulate the conditioning medium and therefore is considered to have committed an honest error.

4. A 12-year-old child is diagnosed with high-risk acute lymphoblastic leukemia (ALL). The treating oncologist discusses the treatment of high-risk ALL with the patient’s parents and offers them participation in a phase 3 clinical trial conducted by the Children’s Oncology Group. After considering the information presented, the parents give consent for their child to participate in the clinical trial but request that the treating physician not discuss participation in the clinical trial with the patient. The physician informs the parents that this is acceptable.

Why did the physician inform the parents that withholding this information from their child is acceptable?

A. There is a real chance that their child could benefit from participating in the clinical trial.

B. The child was asleep and needed to start treatment immediately.

C. Based on the child’s poor grades in school, the child is unlikely to understand the information.

D. The institutional review board allows assent to be waived for children younger than 14 years old.

**Explanation**

Legally, children are not able to provide informed consent before they turn 18 years of age. For such patients, clinical trial participation requires informed parental permission, and a parent or adult guardian would sign any informed consent documents. However, in some circumstances, assent also may be required, indicating that the minor agrees to take part in the research. Federal regulations require that assent be obtained and documented from minors capable of providing it. If a potential research subject is not thought capable, assent need not be solicited. However, the term *capable* is subjective, and assessment of which children and adolescents have this capability may not be straightforward. To take part in the assent process, participants younger than 18 years old must be mature enough to understand the trial and what they are expected to do. Minors develop this maturity at varying ages. Institutions vary as to whether they provide age-based guidelines for when assent is required.

5. An investigator is writing a clinical trial protocol for treating children with a new alkylating agent. The agent is known to cause hemorrhagic cystitis in 15% of adult patients treated at higher dosages of the drug. Because it is unlikely that that the adult maximum tolerated dosage would be tolerable in children, the investigator decides that it is not necessary for any specific monitoring for hemorrhagic cystitis or prevention measures.

In doing so, which research principle is the investigator violating?

A. Respect

B. Beneficence

C. Justice

D. Protection of a vulnerable population

**Explanation**

The Belmont Report outlines the research principles of respect, beneficence, and justice. Respect for persons involves recognition of the personal dignity and autonomy of individuals and special protection of those with diminished autonomy. Beneficence entails an obligation to protect people from harm by maximizing anticipated benefits and minimizing possible risks of harm. Justice requires that the benefits and burdens of research be distributed fairly. The case vignette described above is in reference to the research principle of beneficence.

6. An investigator sets up a collaboration with a clinician in a different city to study a new marker of bacterial infection in patients who present with febrile neutropenia after treatment with chemotherapy. The researcher asks the clinician to provide him with leftover samples from routine blood cultures to test for this marker and asks the researcher to maintain a link to the specimen for later correlation of the biomarker and true infection. However, the researcher neither comes in contact with any of the patients nor receives any protected health information on the subjects.

Based on this information, which of the following statements is most accurate?

A. The study does not represent human subjects research.

B. The institutional review board (IRB) cannot require that the clinician obtain written informed consent.

C. The IRB can waive the requirement for informed consent.

D. Only the researcher’s IRB of record needs to review the clinical trial.

**Explanation**

The US Department of Health and Human Services regulations allow the IRB to waive the requirement for obtaining informed consent or parental permission or to approve a consent procedure that leaves out or alters some or all of the elements of informed consent otherwise required under [45 CFR 46.116(a) and (b)](http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#46.116). Waiving the requirement for obtaining informed consent or parental permission means that the IRB has determined that investigators need not obtain the subjects’ informed consent to participate in research. In this scenario, because no protected health information is being transmitted, the study is minimal risk, and only leftover samples will be used, the IRB may waive obtaining informed consent. However, because patients potentially can be identified through a code, it is considered human subject research requiring IRB review. Lastly, both the clinician and investigator are participating in the research, and therefore both institutions’ review boards will need to review the study and determine whether informed consent can be waived.

7. A pharmaceutical company has developed a grape-flavored formulation of acetaminophen. The pharmaceutical company wants to find out whether the grape-flavored acetaminophen is more palatable than the existing strawberry-flavored acetaminophen. The two flavors are administered to all children with fever on the pediatric ward. The parents were given an anonymized survey at the time of discharge to complete their child’s preference of flavor. The pharmaceutical company collects this information to decide which flavor of acetaminophen to market.

Based on this information, which of the following statements is most accurate?

A. This study requires full institutional review board (IRB) committee review because the children are being administered a drug.

B. Written informed consent is required because the children are subjects in a clinical trial.

C. The IRB can waive consent but mandate that the patients be compensated for participating in this study.

D. The IRB may determine that this study is exempt from review because acetaminophen is an approved drug, the change in flavoring does not alter the safety of the drug, and the survey is anonymized.

**Explanation**

Research activities in which the only involvement of human subjects falls into one or more of the following categories are exempt from IRB review:

 research conducted in established or commonly accepted educational settings, involving normal educational practices

 research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior

 research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or through identifiers linked to the subjects

 research and demonstration projects that are conducted by or subject to the approval of department or agency heads, which are designed to study, evaluate, or otherwise examine public benefit or service programs, procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs

 taste and food quality evaluation and consumer acceptance studies

It is best that even clinical studies that fall within these categories be presented to the IRB so that the IRB can make the determination that it is exempt from review.

8. A group of institutions collaborate to conduct a phase 2 clinical trial. An independent Data and Safety Monitoring Board (DSMB) is set up to monitor the conduct of the clinical trial. Which of the following is *not* a responsibility of the CSMB?

A. Review of interim and cumulative data on adverse events

B. Review of the roster of IRB members who approved the protocol

C. Adherence to clinical trial protocol

D. Review of interim and cumulative data on efficacy according to predetermined statistical considerations

**Explanation**

The DSMB is an independent group of experts that advises the study investigators. The primary responsibilities of the DSMB are to periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy and make recommendations about the continuation, modification, or termination of the trial. Items reviewed by the DSMB include interim/cumulative data for evidence of study-related adverse events; interim/cumulative data for evidence of efficacy according to preestablished statistical guidelines, if appropriate; data quality, completeness, and timeliness; performance of individual centers; adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities; adherence to the protocol; factors that might affect the study outcome or compromise the confidentiality of the trial data (eg, protocol violations, unmasking); and factors external to the study such as scientific or therapeutic developments that may affect participant safety or the ethics of the study. The DSMB should conclude each review with their recommendations as to whether the study should continue without change, be modified, or be terminated.

9. A clinical trial offers $500 to a patient for participation in the optional pharmacokinetics component of the clinical trial that involves obtaining three blood samples.

Which of the following determinations is the IRB likely to make?

A. A payment of $500 will have undue influence on the patient to participate in the optional pharmacokinetic studies.

B. A payment of $500 is reasonable given that it is important to learn about the pharmacokinetics of the experimental agent.

C. A payment of $500 is acceptable if the payment is in the form of gift cards.

D. A payment of $500 is acceptable only if the patient’s annual family income is less than $30,000 per year.

**Explanation**

The IRB should determine that the risks to subjects are reasonable in relation to anticipated benefits and that the consent document contains an adequate description of the study procedures as well as the risks and benefits. It is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug, biologic, or device development. Payment to research subjects for participation in studies is not considered a benefit; it is a recruitment incentive. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to ensure that neither is coercive or presents undue influence. All information concerning payment, including the amount and schedule of payment, should be set forth in the informed consent document.

10. Which of the following is not considered a vulnerable population in clinical research?

A. Pregnant women

B. Native Americans

C. Prisoners

D. Children

**Explanation**

Certain groups including pregnant women, children, fetuses and neonates, decisionally impaired individuals, prisoners, and students are considered vulnerable as determined by the US Department of Health and Human Services and have special rules regarding their participation in clinical research. Native Americans are not one of those groups.

11. A researcher needs 1 mL blood from patients for his studies, which can be obtained by venipuncture at the time of a clinically indicated laboratory blood test.

Which of the following most accurately describes this intervention?

A. A minimal risk procedure

B. A slight increase over minimal risk procedure

C. A greater than minimal risk procedure

D. None of the above

**Explanation**

The regulatory definition of *minimal risk* is that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

12. Which of the following is *not* a criterion for authorship recommended by the International Committee of Medical Journal Editors (ICMJE) ?

A. Conception or design of work or acquisition, analysis, or interpretation of data of work

B. Providing funding to conduct the research

C. Drafting the work or revising it critically for intellectual content

D. Final approval of the version to be published

E. Agreement to be accountable for all aspects of the work

**Explanation**

Authorship confers credit and has important academic, social, and financial implications. Authorship also implies responsibility and accountability for published work. The ICMJE recommendations are intended to ensure that contributors who have made substantive intellectual contributions to an article are given credit as authors but also that contributors credited as authors understand their role in taking responsibility and being accountable for what is published. These recommendations include substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

13. Which of the following is not an established component of process improvement?

A. Adopting a systematic approach

B. Adhering to a single method or approach

C. Using data

D. Aiming for improvement

**Explanation**

Process improvement is defined as a data-driven, system-level discipline designed to achieve appropriate, consistent, and efficient delivery of established clinical measures by changing human performance. The methods by which human performance can be changed are numerous, and several approaches are often used to yield improvement rather than emphasizing one approach over all others. Other components of process improvement include a reliance on data, an aim to improve, leveraging the input of customers or stakeholders to set priorities, and adopting a systematic approach.

14. Which of the following best characterizes the lean approach to process improvement?

A. An emphasis on nutrition and healthy lifestyle in healthcare

B. A focus on eliminating waste

C. A plan-do-study-act cycle

D. A goal for reducing variation

**Explanation**

The lean approach to process improvement emphasizes waste reduction. Numerous kinds of waste have been identified in the healthcare process, such as transportation waste (unnecessary movement of products or resources), time waste (needless pauses before next step in the process begins), or talent waste (not harnessing or leveraging the strengths of those around you). The reduction in variation approach better characterizes Six Sigma, although there are commonalities between these approaches. Yet another approach is the plan-do-study-act cycle.

15. What are the 6 dimensions of quality care according to the Institute of Medicine?

A. Safe, timely, effective, efficient, equitable, and person-centered

B. Safe, transparent, effective, efficient, equitable, and person-centered

C. Safe, timely, effective, low-cost, equitable, and person-centered

D. Safe, timely, effective, efficient, cutting-edge, and person-centered

**Explanation**

In their landmark report *Crossing the Quality Chasm,* the Institute of Medicine outlined 6 major domains of high-quality healthcare, which can be remembered using the acronym STEEEP. These are a good guide for teams to use in developing organizational and project-based aims.

* Healthcare must be **safe**. This means much more than the ancient maxim “First, do no harm,” which makes it the individual caregiver’s responsibility to be more careful (a requirement modern human factors theory has shown to be unproductive). Instead, the aim means that safety must be a property of the system. No one should ever be harmed by healthcare again.
* Healthcare must be **timely**. Unintended waiting that does not provide information or time to heal is a system defect. Prompt attention benefits both the patient and the caregiver.
* Healthcare must be **effective**. It should match the science, with neither underuse nor overuse of the best available techniques. Every elderly heart patient who would benefit from beta-blockers should get them, and no child with a simple ear infection should get advanced antibiotics.
* The healthcare system must be **efficient**, constantly seeking to reduce the waste—and hence the cost—of supplies, equipment, space, capital, ideas, time, and opportunities.
* Healthcare must be **equitable**. Race, ethnicity, gender, and income should not prevent anyone in the world from receiving high-quality care. We need advances in healthcare delivery to match the advances in medical science so the benefits of that science may reach everyone equally.
* Healthcare must be **patient-centered**. The individual patient’s culture, social context, and specific needs deserve respect, and the patient should play an active role in making decisions about his or her own care. That concept is especially vital today, as more people need chronic rather than acute care.

16. Which of the following is true about the types of measures used in quality improvement efforts?

A. Process measures are the only ones that really matter.

B. Balancing measures determine whether the intended change produced any unintended consequences.

C. Outcome measures tell us whether we are doing the right things to make the intended change.

D. Outcome measures are easier to collect than process measures.

**Explanation**

The major types of measures relevant to quality improvement endeavors are process, outcome, and balancing measures. Outcome measures reflect where we are ultimately trying to go, the things we most want to improve. They tell you whether changes you are making are actually leading to improvement in the overall system performance. Examples of outcome measures:

* For your personal improvement project: percent of the time you arrive punctually
* For diabetes: average HbA1c level for population of patients with diabetes

Process measures let us know whether we are doing the right things to get us to our overall outcome of interest. To effect the outcome measure, you have to improve your processes. Examples of process measures:

* For your personal improvement project, number of days per week you wake up early for work
* For diabetes, percentage of patients with HbA1c level measured twice in the past year

Balancing measures reveal whether the changes we are making to one part of the system are causing unintended changes (positive or negative) in other parts of the system. They are often measures that are not directly related to the aim. Balancing measures can influence whether your interventions are likely to be sustainable. Examples of balancing measures:

* For your personal improvement project, level of fatigue due to the earlier wake time
* For diabetes, amount of extra time spent with each patient with diabetes that cuts into time with other patients

17. A pediatric fellow is planning a project intended to decrease the incidence of acute chest syndrome among patients with sickle cell disease who are already admitted to the hospital for other reasons. The fellow discussed with her mentor whether the project proposal should be submitted for review by the institutional review board (IRB). The mentor explains that, at their institution, quality improvement activities do not need IRB review, but research projects must be submitted to the IRB.

Which of the following is *not* a relevant consideration in determining whether the project is research or quality improvement?

A. The aim to create new knowledge for the individual institution versus discovering new and generalizable knowledge

B. The chosen method, which will include repeated plan-do-study-act cycles

C. The intent to publish the results in a peer-reviewed hematology journal

D. The efforts to hold biases and confounders stable over time, rather than control for them with, for example, randomization

**Explanation**

The distinction between quality improvement projects and traditional research projects can be confusing, but, over time, the relevant distinctions between these two activities have become clearer. The first pertains to intent. Researchers intend to discover new knowledge that would be generalizable to others, whereas quality improvement aims more to create new knowledge that would be applied to local practices and local systems of care. Second, research often involves a single experiment or trial, often done over a large amount of time, controlling for as many biases and confounders as possible. In quality improvement, the methods involve short, repeated cycles of intervention, each time layering on something new, while keeping biases and confounders otherwise stable, even if not controlled. In research we collect as much data as possible from this single experiment, whereas in quality improvement we collect just enough data to allow us to plan the next cycle. Those who are unsure of whether their project is best characterized as research or quality improvement are encouraged to consult their local IRB.