Chapter 5
Ethics and Single Subject Research

This chapter provides a broad overview of ethical guidelines for single subject research in biomedicine. As a starting point, a primer on ethical decision making is used to clarify major ethical views and their guiding principles. This is followed by a discussion of professional competence, which is the foundation of proficient decision making. Then, ethical issues involving patients' rights and methodological considerations are reviewed. In closing, single subject design research is described as playing a key role in ethical biomedical research.

Primer on Ethics

Traditionally, two major views have been used to guide ethical decision making [1]. The philosophy of utilitarianism assumes that actions are ethical to the extent that they maximize health and well-being. This view has generated the ethical principles of non-malfeasance, beneficence, and efficiency. In contrast, the Kantian ethical view assumes that individuals behave ethically when they respect the reasoning capacities of other people. Thus, the Kantian view emphasizes principles, such as justice, dignity, autonomy, and honesty. Although these views often suggest similar actions, occasionally ethical dilemmas occur in which one guiding principle conflicts with another, such as when respecting patient autonomy may lead to negative health outcomes.

Philosophical Perspectives

Two philosophical perspectives have traditionally provided the basis for ethical decision making across a wide variety of disciplines [1]. The philosophy of utilitarianism focuses on the consequences of decisions, whereas the philosophy of Immanuel Kant is primarily concerned with human rights.

The philosophy of utilitarianism assumes that actions are morally right to the extent that they foster happiness and satisfaction; wrong to the extent that they generate pain and suffering. To determine the morality of a decision, one must simply

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examine the positive or negative consequences of the decision. If one action provides greater benefits to an individual and society than another action, it is the more ethical alternative. Epicurus laid the groundwork for utilitarianism over 2,000 years ago, though his philosophy was largely ignored until being revived by David Hume in the 1700s [2]. Hume argued that the idea of fostering happiness as an overarching principle was relatively sensible, making the philosophy of utilitarianism so appealing. As he rhetorically questioned, "what need we seek for abstruse and remote systems, when there occurs one so obvious and natural?" [2]. Although Hume helped to revive utilitarianism, he contemplated the philosophy of ethics only in passing. Jeremy Bentham, and John Stuart Mill are best known for their contributions to utilitarian philosophy, and are best known for popularizing such phrases as the "greatest happiness principle" or the "greatest utility principle" [3]. Although Bentham, and Mill agreed that morally the goal of decision making should be to foster life satisfaction, they debated how satisfaction should be measured. In fact, the primary difficulty of the utilitarian philosophy is that when making decisions, it can be very difficult to predict their ramifications [4].

In stark contrast, Immanuel Kant argued that motives are more important than consequences when determining the morality of a course of action [1]. The premise of Kantian philosophy is that human beings are autonomous agents, capable of reasoning logically and worthy of respect and dignity. Individual people should be treated as valued entities in and of themselves, rather than merely as a means to some other end. At times, Kantian philosophy conflicts with utilitarianism, such as in situations where ignoring an individual's autonomy might lead to desirable consequences (e.g., disregarding a "Do Not Resuscitate" (DNR) order to continue a person's life). These types of ethical dilemmas force physicians or practitioners to question which guiding philosophy – Kantianism or utilitarianism – is most defensible. Fortunately, these philosophies conflict less than one might expect because respecting an individual's autonomy often allows them to make decisions that have beneficial consequences (e.g., allowing a patient to choose among various treatment options). Furthermore, both philosophies likely contain positive guiding ethical principles which help to facilitate clinical decision making.

Guiding Principles

Based on utilitarian and Kantian philosophies, several guiding principles have been articulated to guide ethical decision making (see Table 5.1) [1, 5]. Utilitarian philosophy is more closely aligned with the principles of non-maleficence, beneficence, and efficiency, whereas Kantian philosophy is more consistent with the principles of justice, dignity, autonomy, and honesty. Ethical conflicts occur when two or more guiding ethical principles suggest different courses of action. The remainder of this Chapter is devoted to considering how these ethical principles can guide complex decision making in single subject research in biomedicine.

Table 5.1 Guiding ethical principles

Principle	Description
Non-malfeasance	Above all, researchers and practitioners must aim to do no harm to their patients and research subjects.
Beneficence	The goal of medicine should be to facilitate health, well-being, and other positive life outcomes.
Efficiency	When making decisions, one should maximize positive outcomes, while minimizing the time, effort, money, and other resources needed to meet those objectives.
Justice	Medical resources should be allocated fairly across individuals, regardless of personal attributes, including gender, sex, race, ethnicity, age, and socioeconomic status.
Dignity	Patients and research participants should be treated with respect, not merely as a means to some other end, such as finding evidence for a successful medical treatment.
Autonomy	To the extent that individual people have appropriate cognitive capacities for decision making, their medical decisions regarding treatment should be respected.
Honesty	Researchers should openly and accurately describe the nature of medical procedures and research protocols.

Professional Competence

Professional competence is the foundation of ethical practice. In particular, maintaining a high level of competence aids in guarding against malfeasance. It also helps to ensure awareness of effective treatment modalities, promoting beneficence. Further, sound knowledge of available treatment options and practice guidelines also helps to improve efficiency. Thus, professional competence is important for meeting ethical guidelines based on utilitarian principles.

Certification and Licensure

Gaining board certification is important for medical practitioners and physicians because it ensures a basic level of competency, as well as providing additional privileges and income [6]. Typically, the certification process entails completing medical school and a residency program, both of which are accredited. Then, one must successfully pass a certification exam in the United States, which varies from state to state, and can be oral, written, or both. Certification attests to the practitioner's competence, whereas licensure grants governmental authority to practice medicine [7, 8]. These same education and training principals should be modeled for expertise in research methodology. Ethical complaints can frequently lead to restrictions on or a loss of licensure, or a ban or lack of permission for conducting research.

Maintaining Professional Competence

Continuing education is often required in order to maintain competence and to meet requirements for the renewal of one's license. Requirements vary considerably based on state, ranging from 0 to 50 continuing education credits required per year, with a national average of 30 required credits annually [9]. In addition to continuing education requirements, other professional engagements facilitate sustained competence (i.e., reading professional journals, participating in oversight, review, and editorial responsibilities) [5].

Maintaining professional competence is vital to the successful implementation of single subject design studies for several reasons. Continuing education activities promote knowledge of new treatments and procedures, and ensure that physicians and practitioners are aware of which interventions have the greatest empirical support. Thus, sustained competence facilitates selection of the best treatment available. Additionally, due to the methodological sophistication of the single subject design, physicians and practitioners drawing upon this methodology must also keep abreast of the existing standards of conducting studies and analyzing data. A particularly useful method for sustaining competence of methodology and treatment effectiveness would be to become aware of recent, relevant single subject design studies, among other design options, within the field [10, 11].

Practicing Within an Area of Competence

The level of competence is best viewed along a continuum, and practitioners should only provide interventions within areas where they demonstrate a high level of competence. When a practitioner's level of competence could lead to suboptimal treatment outcomes, several alternatives should be considered. The practitioner could consider seeking additional training or supervision to obtain a desired level of competence. Otherwise, a referral to an appropriate source would be suitable.

Patient Rights

Although emphasized most directly from a Kantian ethical perspective, utilitarian philosophy can often be used to justify a strong position on patient rights. Respecting patient rights by providing informed consent, allowing freedom to discontinue treatment, upholding confidentiality, avoiding deception, and avoiding conflicts of interest, is essential to upholding the dignity and autonomy of the patient. Furthermore, assuring these rights most often allows patients the freedom to make decisions that likely improve their well-being.

Informed Consent

Informed consent is the process by which a patient learns about the nature of treatment options and chooses a desired intervention. Informed consent is routinely

documented via a standard informed consent form that is included in the consenting process. These include a description of alternative treatment options available, the procedures to be utilized, the potential risks and benefits of treatment, the cost and expectations of treatments, and the patient's rights. However, the mere act of signing a consent form is generally insufficient for informed consent. Foremost, it has been suggested that subjects rarely read consent forms in their entirety and often fail to comprehend the technical medical jargon that is used [12]. Secondly, medical ethicists have argued that informed consent should instead be viewed as an interpersonal process, which can be supplemented with written documentation [6, 13]. The physician or practitioner should provide an overview of the most important points of the study or treatment procedures. Then, allow the patient to ask questions until satisfied with the desired level of knowledge that is obtained. This helps to ensure that the patient is neither overburdened by excessive detail nor left uninformed.

In cases where the patient does not have the capacity to make an informed decision, the guardian or surrogate must provide the informed consent [1, 5]. Parental guardians must provide informed consent when a child is to receive a medical procedure or participate in a research study. Under such circumstances, children are recommended to also provide their assent, or agreement to participate. In some circumstances, adults with particular physical or cognitive disabilities may also have legal guardians, who similarly make medical decisions; however, laws vary by state in the United States and depend on the severity of the disability. Additionally, for people who are incapacitated, a surrogate, such as a friend or family member, may be appointed to make medical decisions. This situation may occur when a patient is unconscious or in intense physical or emotional pain, though such circumstances are rare in single subject trials.

One aspect of single subject studies in which informed consent concerns are particularly salient involves the use of blind treatment phases. Methodologically, it may be advantageous if a patient does not know whether he or she is receiving a placebo, an active medication, or an alternative active medication. Similarly, dosage information may not be disclosed. However, this situation poses a minor ethical dilemma, as methodological concerns involving beneficence may conflict with Kantian principles, such as dignity, autonomy, and honesty. Providing the patient with full knowledge would compromise the methodology, likely decreasing internal validity, whereas keeping all information non-disclosed would violate informed consent. The typical compromise is to inform the patient of the types of conditions (or dosages) that will be used without describing when the phases will be implemented, while simultaneously providing an explanation for why keeping the participant uninformed (i.e., blind or masked) to the intervention may be in the best interest.

Valid informed consent is also instrumental for maintaining treatment adherence, which is consistent with the ethical principles of beneficence and efficiency. A key decision in single subject research is the selection of the patient. Because single subject studies can be laborious, it is important to choose a patient who is likely to complete the duration of the study [10, 14]. A valid informed consent process ensures that the patient is informed of the risks and benefits prior to beginning the

study, which decreases the odds of discontinuation later. When informed consent is merely viewed as signing a consent form, patients are likely at greater risk of attrition, due to undesirable procedures and risks that were unanticipated.

Discontinuation

The right to consent to treatment is accompanied by the right to discontinue treatment at any time. Such a view is consistent with the Kantian perspective of promoting autonomy and dignity, in addition to the utilitarian perspective of non-malfeasance. As noted, adequate informed consent procedures can guard against discontinuation.

Additionally, the choice of the patient can play a key role in guarding against dropout [10, 14]. Specifically, a patient should be selected who has a high probability for compliance with treatment changes, as well as compliance with completing outcome assessment measures.

Ultimately, the single subject design is well suited for handling side effects, adverse reactions, and other reasons for non-compliance. One strength for using the single subject design concerns the ability to flexibly modify the criterion levels, until the desired effect is obtained. For this reason, studies using the single subject design have often been noted to have lower rates of patient attrition [14].

Confidentiality

The right to confidentiality ensures that information provided by the patient in the medical or research context is protected from third parties. This is consistent with a Kantian view of promoting patient dignity. Additionally, the right to confidentiality is important from a utilitarian perspective because without confidentiality rights, patients may fail to divulge important medical information, sometimes leading to negative health consequences. Confidentiality is not an absolute right, as specific conditions vary by state and by profession [5]. Typically, confidentiality rights may be limited under exigent circumstances, such as when a patient describes intending to do great harm to oneself or another, generally founded on utilitarian principles of protecting the general welfare.

Although the basic protections of confidentiality apply to any research or medical context, the question of when to breach confidentiality can be difficult, posing an ethical conflict between participant rights and considerations of beneficence [15]. This type of dilemma has become increasingly salient in recent years, due to the growing body of evidence suggesting that many medications, psychiatric and otherwise, can trigger suicidal and aggressive behavior [16]. The decision to breach confidentiality requires the close consideration of evidence that impending harm would otherwise occur. Because single subject design research involves repeated observations the ability to detect side effects or dramatic changes in behavior is improved

[10, 14]. To the extent that observable evidence is available that harm will occur, the informed investigator will have an easier time determining whether a confidentiality breach, or some other intervention, could occur.

Deception

The question of when deception can be appropriately used in research has long plagued biomedical ethicists. According to Kantian philosophy, honesty is fundamental for respecting the dignity and autonomous decision making of medical patients. Utilitarian philosophy assumes that any action, including deception, is moral to the extent that it fosters positive outcomes. Although honesty is essential for informed decision making and the integrity of the medical profession, there may be limited circumstances under which deception would be permissible from a utilitarian perspective. Typically, deception, or a lack of full disclosure, occurs when blind or masked treatment or placebo conditions are used. As described under the section on informed consent, ethical dilemmas can often be avoided by providing the patient with information upfront that (1) a placebo may be used and (2) the patient will be blind or masked to the treatment conditions. Occasionally, deception may be permissible when these two criteria are absent, though this option is more controversial from an ethical perspective [17].

Conflict of Interest

A conflict of interest occurs when an investigator's perspective is biased by a secondary role or relationship [5]. Single subject studies often require direct and frequent contact with the patient. Under these circumstances, the potential exists for personal relationships to develop that cross professional boundaries, whether these are classified as friendships, romantic relationships, or business partnerships. Investigators should guard against forming these dual relationships, as they can compromise the integrity of the research being conducted, have the potential for damaging the integrity of the profession, and can hinder one's ability to provide the best medical care possible.

Additional conflicts of interest can occur when an investigator has a vested interest in a particular intervention. As discussed in Chapter 3, if a team of researchers have devoted a substantial portion of their careers to a particular treatment or stand to gain financially from the success of a treatment outcome, they will be prone to social-cognitive biases that can impact the conclusion or validity of the study. A similar problem can occur when the investigator has previously received gifts from pharmaceutical companies or other suppliers.

Methodological Considerations

Although ethical and methodological aspects of research are often considered separately, they are deeply intertwined. Ethically, research should be conducted

effectively and efficiently, which has direct ramifications for the choice of a research patient to be studied, choice of treatment outcomes, choice of interventions, use of control conditions, and monitoring of withdrawal reactions.

Choice of Patient

Investigators should take great care in selecting a research patient for a single subject study [18, 19]. According to the ethical principle of efficiency, resources for research are necessarily limited, and time devoted to a study that is eventually unsuccessful could have been better spent elsewhere. Similarly, the principle of justice holds that resources should only be allotted with balanced consideration. Consistent with other ethical guidelines, an ideal patient would be one who willingly and enthusiastically gives informed consent to participate in the study, as this increases the probability that the patient will complete the investigation. It may also be useful to assess personality variables, such as agreeableness, conscientiousness, and self-efficacy, which are known to predict treatment adherence [20]. Similarly, evidence for past side effects or adherence issues in response to similar interventions would suggest a poor prognosis for completing a similar trial [21].

If the study is being used to promote generalizable knowledge, rather than simply improve individual patient care, then a patient must also be chosen who represents a prototypical case [18, 19]. Factors that should be considered are demographic characteristics, level and type of symptoms, co-morbid diagnoses, and past response to interventions. Choosing a patient that will enhance the external validity of the study is vital to making the best of the researcher's and patient's time and, therefore, important to ethical decision making.

Choice of Treatment Objectives

In single subject studies, the patient should play a vital role in determining the desired treatment objectives [5]. This role is important from the Kantian perspective of honoring the patient's dignity and autonomy. Similarly, according to utilitarian philosophy, the patient should play a key role in determining which outcomes are desirable, and therefore worth pursuing.

At this point in the planning process, the patients may need to evaluate their priorities [5]. Foremost to this evaluation is that not every treatment objective is worth pursuing. For example, a patient who is overweight may not desire to take medication, exercise, or make changes in diet to achieve mild weight loss. Similarly, many patients might object to multiple cosmetic surgeries to correct minor physical defects. Thus, the patient can play a key role in determining which problems should be treated, and at what cost.

Secondly, patients often present with multiple health complaints, which may require prioritizing which treatments should be vigorously treated first. As longevity continues to increase, the problem of co-morbid diagnoses is likely to become more commonplace in the primary care setting [22]. The practitioner and patient should

weigh several important variables when prioritizing treatment objectives. These include the level of danger associated with each condition, the distress and discomfort associated with each condition, and the expense and discomfort of treatment [5]. Utilitarian philosophy assumes that when making these decisions, one should consider the fecundity of each option, or the ability of successfully treating one condition to provide gains in other domains. For example, a patient presenting with chronic back pain, obesity, high blood pressure, and depressive symptoms might benefit most from treating the back pain first, if doing so would facilitate making changes in the other problems. Specifically, with decreased back pain, the patient might then be able to exercise more, helping to improve weight and blood pressure, and possibly decreasing depressive symptoms. Targeting a different problem first would have likely been less useful in facilitating overall positive functioning.

Choice of Interventions

Upon determining treatment objectives, the practitioner and patient must agree upon initial strategies for treatment interventions [5]. Again, the patient can play an important role in the decision making process, but here is a lengthier list of factors to be considered. Specifically, physicians and practitioners must call upon their expertise and knowledge of treatment alternatives. This is one of the reasons that professional competence, including continuing educational requirements, plays an important role in biomedical ethics [7, 8]. If a professional level of competence is lacking for treating a particular condition, the practitioner should provide the patient with an appropriate referral.

Upon weighing the available evidence to determine which treatment options are most viable, the physician or practitioner should carefully evaluate patient variables, including demographic characteristics known to impact treatment outcomes and past tolerance of similar treatments. If a patient has attempted to use a similar treatment in the past, the reasons for a lack of success should be explored, and different treatment alternatives should be considered [5, 18].

Additionally, when weighing treatment options, it is important that the physician or practitioner be unbiased by conflicts of interest. Pharmaceutical and medical supply companies regularly offer researchers and practitioners gifts in an effort to impact treatment decisions. These efforts have been highly successful [5, 23]. In order to prevent ethical dilemmas from occurring, physicians and practitioners should avoid accepting gifts because it may impact treatment decisions and the validity of the research study.

When several treatment options are available that have similar rates of success, the patient and practitioner should consider which treatment options are most efficient. Factors to consider include the cost of treatment, number and frequency of doses, typical amount of time required for successful treatment, amount of physical effort or discomfort likely to be experienced, and probability of major side effects.

Choice of Control Conditions

To improve the internal validity of a study, the investigator generally must include some control phases within the study design [1, 5, 18, 19]. The choice of the particular type of control phase will affect how results are interpreted and also have an impact on patient care. Several options are available, including a no-treatment control, a placebo condition, or a treatment as usual or usual care (TAU) condition. According to the principle of non-malfeasance, treatment should not be denied if it is known to be effective. Thus, no-treatment control conditions and placebo conditions should only be used in treatment studies where the treatment alternatives have only questionable effectiveness. At the same time, researchers should not shun the placebo, for a number of presumably effective treatments have been later shown to work no better than the placebo itself; furthermore, unlike actual treatments, placebos are not likely to have any side effects – an important consideration, particularly within the context of polypharmacology. A placebo condition is generally superior to a no-treatment control condition because it controls for perceived treatment gains due to self-fulfilling prophecies; however, an appropriate placebo is often lacking, particularly for studies involving non-medication interventions.

When no-treatment control conditions and placebo conditions are unethical, TAU conditions provide a useful alternative. For example, in a single subject study examining blood pressure, a patient may present with the problem of only partial success on a current medication. In an A-B-A-B-A-B alternating design, the current medication could be used in the TAU control condition (A) and a new medication could be used in the experimental condition (B). Thus, there would be a useful baseline for examining the effects of the new medication, and the patient's health would not be jeopardized by using a placebo or endure a no-treatment phase.

In instances where a patient presents with a newly diagnosed medical condition and has either been receiving no medical intervention, or a substantially inferior treatment, and several known effective treatment options are available, use of the no-treatment control, placebo control, and TAU control conditions is not advised. Instead, the researcher may wish to conduct a study comparing two or more known effective treatments to determine which is most suitable for a particular patient (e.g., an A-B-C-B-C-B-C design, where A represents a baseline monitoring phase and conditions B and C represent known effective treatment options).

Withdrawal Designs

Investigators must closely monitor patients whenever they are withdrawn from a particular treatment, as the removal of many interventions can allow the recurrence of previous symptoms or cause withdrawal reactions [16, 24, 25]. Although strict withdrawal designs (A-B-A) are used infrequently, most single subject studies will

require a patient to repeatedly withdraw from a treatment to a baseline phase (e.g., switching from B to A and an alternating A-B-A-B-A-B design) or withdraw from one intervention to begin another (e.g., A-B-C-B-C-B-C). If during a withdrawal phase severe prior symptoms recur or new symptoms appear, it may be necessary for the health of the patient to reinstate the treatment that was being used prior to the withdrawal phase, and consider modifying the methodology of the study. For medications known to cause withdrawal reactions, the physician or practitioner would be advised to slowly taper off dosages, rather than abruptly switching from one phase to the next.

Research Context

In addition to considering how to conduct single subject research ethically, researchers may also wish to examine how single subject research ethically fits within the greater context of epistemology in science. Single subject research can provide valuable evidence for the effectiveness of biomedical interventions, in and of itself, or as an adjunct to Randomized Controlled Trials (RCTs). According to utilitarian philosophy, the purpose of science should be to foster health and well-being, and single subject research should be a necessary component of the skilled researcher's repertoire in meeting this goal.

Facilitating Research

According to utilitarian philosophy, primary care practitioners should aim to improve the health and well-being of society as much as possible. RCTs have traditionally been used to promote scientific knowledge in biomedicine. Although research is valuable in promoting societal well-being, no single methodology is applicable to all research scenarios [10, 11]. The greater acceptance of all research methodologies, including epidemiological studies and single subject research, would ensure that biomedicine is maximizing its research potential. Primary care practitioners have generally contributed to societal well-being on an individual basis, but single subject research allows practitioners to contribute to public health on a much larger scale by providing a means for sharing treatment outcomes. Thus, the use of single subject research is necessary for enhancing research options available for biomedicine, and also for providing a means for a greater number of investigators to make valuable contributions to science.

Although single subject studies should be valued as a research methodology in their own right, they also have the potential to make important contributions to science when used adjunctively amidst RCTs. When embedded within RCTs, for example, single subject research has been shown to improve treatment adherence, decrease side effects, and facilitate treatment outcomes [10]. To the extent that this methodology improves patient care and aids research, it should be valued from a utilitarian perspective.

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