



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Special issues raised by evolving areas of clinical research

Each study presents its own set of ethical considerations. Certain kinds of ethical issues are inherent in particular areas of clinical research, regardless of specific ethical questions associated with a specific study. In this chapter, some of the most common special areas of clinical research are presented, highlighting the ethical issues most frequently associated with each. Here are presented, also, some of the areas of research that are novel, contentious, or where the ethical thinking is simply still in flux. Investigators planning on conducting research in these areas will need to familiarize themselves with the ethical thinking about the studies they are contemplating, so the ethical thinking in the field can be well articulated and cited to justify study design.



1 Genetics research

Genetics is one of the fastest growing areas of clinical research. The pharmaceutical industry is eager to attach pharmacogenomic components to a vast number of their more traditional clinical trials. The mushrooming biotechnology industry is virtually synonymous with genetics research. Academic research is not far behind, either through collaborations with the pharmaceutical and biotech industries or through its own publicly and/or privately funded research (Goswami et al., 2019; Spector-Bagdady et al., 2019; Bell et al., 2016). Much of the genetics research fervor arises from public efforts engendered by the Human Genome Project, organized through the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH). More and more frequently, clinical research today includes a genetics component, regardless of what the primary study is about, because the value of relating human physiology and disease to inborn genetic determinants is increasingly recognized.

Given this ubiquity, and given the **RCR**'s inclusion of personally identifiable biospecimens and personal information, it is crucial that investigators

and institutional review boards (IRBs) recognize and are sensitive to the ethical issues most frequently encountered in human genetics research. This heightened attention to the inclusion at the time of study design or for potential future genetics studies is needed to determine how such studies can be addressed most appropriately and effectively in protocols and consent documents. A voluminous amount of rich and evolving literature exists on ethical issues in genetics research which we encourage investigators to read (e.g., Clayton et al., 2018; Shendure et al., 2019; Musunuru, 2017; Gurumurthy et al., 2016; Lester et al., 2016; Simmons and Quinn, 2014).

1.1 Variability in ethical standards, vocabulary, and regulations

One of the most frustrating problems for genetics researchers is the considerable variability in ethical standards, vocabularies, and regulations among states and countries. This variability requires that each protocol present the ethical arguments that support the study and refute convincingly all the expected arguments against it. The reasons for doing the study will be in the rationale section, with argumentation in the ethics section of the protocol. Clarification and definitions will be in the procedures section, and the regulatory compliance section of the protocol can identify the regulations and international guidance documents that govern the conduct and oversight of the protocol if it is to have an international component.

Consider the following problem. The prospect of ethnicity-based therapeutics is rapidly becoming a reality. Now that studies have shown that African-Americans with class III or IV heart failure and dilated ventricles benefit from being given isosorbine dinitrate plus hydralazine over placebo (Chang et al., 2018; Sharma et al., 2014; Ghali et al., 2007; Echols and Yancy, 2006; Taylor et al., 2004), a biotechnology company working with university investigators across the country and in different parts of the world wants to move this work forward. The idea is to genotype African Americans and persons of African descent with any heart disease. Objections within the company to this approach include concerns about discrimination. The company librarian is asked to do a search of state and federal legislation and legislation in several European countries to look for mention of genetic discrimination. The librarian comes back to the group frustrated and explains that this is going to be a very difficult search to run because genetics and genetic discrimination is defined differently across states and by foreign legislative bodies. Ultimately, the biotech group decides to limit the genotyping to only two U.S. states and two foreign countries in which the librarian can find state and national legislation that defines terms like genetic information and genetic condition comparably and has similar kinds of legislative protections against housing and/or employment discrimination based on utilization of genetic information.

1.2 Genetic studies or genetics study add-ons?

Is the genetic study independent, or is it a part of another broader protocol? Especially in light of the **RCR**'s new mechanism of "Broad Consent", this particular study design needs substantial thought in the study development stage. The question to be asked or the hypothesis to be tested determines the optimal design of a genetics study. Sometimes adding a genetics component to a larger study makes the ethical considerations more complex. The PI of the primary study might have his or her own biases for or against genetics studies, which could influence recruitment for the genetics component. Adding a genetics component to a larger study, however, may be an effective way to recruit sufficient participants into the genetics component. Although it could make the informed consent process longer, more cumbersome, and more difficult, integrating the two might make collection of samples much quicker and more efficient by integrating sample collection into other study procedures. This is a design issue that needs to be carefully thought through in collaboration with the investigators responsible for the related nongenetic primary research study. Through such discussion, mutual interests might be identified that would facilitate scientific progress as well as improve procedures for obtaining, maintaining, protecting, and analyzing samples for a genetics study. Such decisions have implications, also, for whether to include genetics study considerations in the consent and assent documents of the primary protocol or to append separate genetics research consent documents to the primary protocol. This question may be decided differently depending on whether the genetics research primarily involves genotyping, phenotyping, or gene expression studies.

For example, the fictitious Better Health Drug Company (BHDC) has made the scientific and commercial decision to add a genetics component to the majority of its drug development studies. This is in part because national regulatory agencies are beginning to ask for such data and partly because such data are needed to make the promise of personalized medicine a reality. Personalized medicine is expected to result from advances in pharmacogenetics and pharmacogenomics, which will lead to the creation of drugs targeted to patient groups and/or individuals with genetic characteristics that predict increased efficacy and reduced harmful side effects. The BHDC therapeutic division for gastrointestinal (GI) diseases and obesity is now working out procedures for complying with the new company initiative. First in the GI group's development pipeline is a trial of a new drug to be given to obese patients, postgastric-bypass surgery, that is hoped to both suppress appetite and reduce anxiety. The design of the genetics add-on component is that blood that is left over from a clinically required postoperative blood draw, which would otherwise be discarded, will be turned over to the company's Pharmacogenomics

Research Group (PRG). The PRG will then store it for its own studies. The PRG group's standard protocol and consent language have already gone through internal company review and review by the company's outside panel of pharmacogenetics/pharmacogenomics medical research consultants. The generic protocol and consent documents are approved for inclusion or attachment to any company protocol the PRG group deems appropriate. The GI group is now debating whether to incorporate the company-approved protocol and consent language into the primary protocol or to make it a separate add-on. Those in favor of incorporating the genetics add-on language into the primary protocol and consent think it will increase recruitment into the genetics component, which they support strongly. Others on the GI team are worried about those community investigators and members of the public who are particularly wary of genetics research, especially when a private, for-profit pharmaceutical company will be doing the research with samples it both controls and will be storing for long periods of time, if not indefinitely. These GI team members think by integrating the genetics add-on study into the main protocol they will jeopardize accrual to the primary study. It would be better, they argue, to make it a separate add-on, so those investigators and potential participants who don't want to participate can decline more easily, even though it will be made clear that the add-on is optional regardless of where the information is provided. Making the add-on separate, these team members continue, makes reading the information for the primary protocol less cumbersome and thus, less likely to scare off potential participants. They argue vigorously for separating the add-on from the main study.

This is an example of the kinds of design considerations that should be well considered before the protocol goes to the IRB (Edwards et al., 2011, 2012).

1.3 Use and storage of genetic samples

Ethical issues related to the use and storage of identified, coded, anonymized, and anonymous samples were addressed in [Chapter 13](#). Protocols need to thoroughly explain where such genetic material samples are being used and stored specifically for DNA analysis. Regardless of whether genetic information is qualitatively different from other kinds of medical information, many in the field believe that it is. Investigators must take special care to protect DNA samples in ways often not required in studies with no genetics component.

Consider the following difference. Dr. Jenkins is a psychology professor at Sunset College. Her area of expertise is cognitive performance under stress and she has been conducting both animal and human studies in the area for many years. The majority of her human participant studies are pencil and paper tests that include the stressor of background noises of different kinds. Sometimes the background noise is pleasant, such as soothing music. Other studies involve more

distressing noises such as highway traffic, sometimes including a car crash. Usually, the pencil and paper tests are anonymous, but they do include a detailed demographic section so information can be stratified according to age, gender, and other variables of interest. Dr. Jenkins has been conducting one longitudinal study, however, for the past 17 years. In it she gives the same set of tests under the same set of background noise conditions to a cohort of participants. These data are kept with personal identifiers. Because Dr. Jenkins has been conducting much research over the last 20 years, her office is full of file cabinets. The ones in which she keeps anonymous data are unlocked. She keeps the identifiable data in a locked cabinet. The IRB has always considered this sufficiently protective.

Dr. Pearson, a faculty member in the same department, conducts genetic research. He is looking for genetic connections between genotype and persons of different personality types. Some studies divide persons into extroversion/introversion groups. Other studies differentiate these two groups further. Once a participant has tested into the extroversion or introversion group, the participant is tested into such types as uninhibited/shy, respectively. Dr. Pearson has been doing this research for many years. He has always kept his personality inventory data with identifiers because some of his participants continue to serve in studies year after year. Now that Dr. Pearson is taking blood and/or saliva samples to do genetic testing and is combining the genetic information with the personality data, his IRB is questioning whether or not his data storage procedures are adequately protective. The genetic material is coded and Dr. Pearson keeps only one list linking the code to the name of the participant. This list is kept in a locked drawer in his office. But now that there is identifiable genetic material that can not only be linked to the coded genetic samples, but also to the participants' personality data, the IRB thinks Dr. Pearson needs to come up with a more protective strategy for all the data.

A final point about storage and clinical research. Biobanking, and using samples from biobank for clinical research present concerns for protection of privacy and confidentiality. When considering developing protocols using samples from biobanks, these concerns and those raised related to concerns about appropriateness related to such matters as population effects should be well considered and discussed explicitly in the protocol (Shade et al., 2019; Antommaria et al., 2018; Pawlikowski et al., 2011).

1.4 Stem cell research

Stem cell research is considered by many as one of the great gateways for translational research (more fully discussed further in this chapter), into the eventual mainstreams of clinical medicine. Whether true or not, this is certainly an area of research that holds out great promise but at the same

time presents high ethical hurdles (Poulos, 2018; de Miguel-Beriain, 2015; King and Perrin, 2014; Fung and Kerridge, 2013; Sugerman, 2008). Whether a stem cell researcher is thinking about a study with embryonic or somatic stem cells or normal human body cells that are, or will be, reprogrammed into an embryonic stem cell-life state, controversies abound. These include such relatively straightforward ethical considerations as informed and voluntary consent and potential for harm or benefit of experimental interventions to the seemingly intractable ethical complexities of the destruction of embryos or their creation for research purposes. And then there can be the ethical procedural complexities of differing ethical and legal standards where stem cell lines are derived when such cell lines move through different institutions in different geographical locations or legal jurisdictions. Differences in funding source may create different oversight strategies and regulatory requirements.

Because there is the potential for so many, and such diverse, ethical complexities in stem cell research, after an investigator or group of investigators has started sketching out the technical aspects of a protocol, it might be wise to start on the Ethics Section of the protocol at that time, as well. In doing so, the ethical complexities in attempting to answer a particular scientific question or test a specific hypothesis involving research with stem cells may unfold in layers as the protocol develops. In that way, also, an investigator may be able to ascertain at an early stage of protocol development what ethical procedural steps may need to be taken to gain a head start of working through these ethical aspects of stem cell research (MacPherson & Kimmelman, 2019; Power & Rasko, 2011; Lo and Parham, 2009).

1.5 Risks to participants

The substantive risks to participants reside not in obtaining the genetic material for study but in the information generated from the study. When the information suggests potential or existing health problems, to whom that information is given, whether intentionally or accidentally, with permission or not, can have negative implications for a participant's ethnic group or other kind of community, job status, insurability, or family relationships. Discovery of genetics information may affect family dynamics, and it may put other family members at unknown risk. It is crucial that these risks be explicit in the consent section of the protocol and in the consent form (Tsosie et al., 2019; May et al., 2014).

Information that predicts the risk of disease may affect a research participant's or his or her family members' psychological status. For example, a study of Huntington's chorea, a disease that in an individual progresses to involuntary movement disorders and dementia, may involve testing of multiple family members. Some who are at risk will be positive for the genetic abnormality, while others will not. Both results have the potential for psychological impact. Individuals who are positive will have to adjust to the expectation of developing Huntington's disease if they live long enough. Those who are negative for the abnormality may suffer what is referred to as "survivor's guilt." To assist participants through these often difficult transitions, pretest and posttest counseling as well as both traditional nondirective genetics counseling and psychotherapeutically focused counseling may need to be included in a genetics protocol. Although genetics counselors are scarce, their lack of availability cannot excuse inadequate counseling when it is needed for study participants (Brett et al., 2018).

Genetics information may carry with it the key to uncovering more serious family secrets, such as discovering nonpaternity, as already mentioned in [Chapter 9 \(Mandava et al., 2015\)](#). Views differ on how to convey to participants the possibility of generating this information as part of the research process, with agreement, at least, that the possibility of finding such information should be clear in the consent and/or pretest counseling process ([Wright et al., 2019](#)). Although it is generally agreed that if misattributed parental status is revealed during the research process, the information ought not be provided to the participants. That does not mean that on rare occasions, when the information is important for clinical care or future reproductive planning, this information must never be conveyed ([Hercher and Jamal, 2016](#); [Garrett, 2015](#)). And some data suggest that some in the public are inclined to want such data disclosed ([Lowe et al., 2017](#)). It just means that the default position is not to convey such information. If an investigator believes that it is important to inform the participant, the investigator should consult with the IRB and other relevant institutional personnel about whether, and if so, how such information is best disclosed.

The paternity issue can become quite contentious when minors are involved in a study. Paternity of offspring is often contested by spouses or unmarried partners. In a divorce and/or custody dispute, it is not unusual for the father or putative father to demand evidence for or against paternity from the investigator through access to the minor child's records. Parents have been assumed to have the right of access to the research records of their minor children. If nonpaternity has been determined, how it will be recorded in the child's records is an important issue. Planning for such an event is recommended, including a refusal on the part of the researcher

to provide any information about nonpaternity. This information can be obtained outside the clinical research setting and researchers are not obligated to share such information. Some genetics researchers have taken the extra step of having their research covered by a Certificate of Confidentiality (see [Chapter 9](#)) to ensure that research records cannot be obtained by warring parties in divorce or custody proceedings.

1.6 Participant and family member conflicts

Information gained during a study may compromise relationships of a participant with other family members ([Mendes et al., 2018](#)). For example, even in genetics studies that do not involve family linkage analysis, information gained about a participant may have implications for other family members. A study participant may find out something about himself or herself that others think should be shared with other family members. Or the investigator may feel the research participant should convey certain information to other family members ([Hodgson et al., 2014](#)). These can be a privacy questions for the participant who does not want to share personal genetics information, which might have health implications for others in the family.

Another frequent scenario is a genetics study involving a family with certain members who do not wish to participate. This situation can produce family discord as some family members attempt to persuade others either to or not to participate in a family genetics study. Although investigators cannot take responsibility for what family members do or say to each other, the well-planned protocol may be able to avert such family discord. Perhaps not all family members need to be involved to achieve the scientific ends of the study. To the degree that this is true, it should be clarified in the consent documents. Family members who are to be involved in the recruitment process will need to be educated about refraining from pressuring other family members. Voluntary participation is the hallmark of ethical research, regardless of who does the recruiting. Plans for education of family members should be explicit in the recruitment section of the protocol. Investigators are advised to have an established mechanism to enable any person who feels coerced by other family members but who does not want to be a study participant to decline gracefully, with appropriate cover provided by the protocol. This can be as simple as the use of an exclusion criterion that gives the investigator the option of excluding a prospective participant if, in the opinion of the investigator, it would not be in the person's best interest. It can then be said honestly by both parties that the family member did not meet study eligibility criteria.

1.7 Minors in genetics research

The participation of minors in genetics research poses several interesting and important ethical concerns that should be addressed in relevant protocol preparation. The complexities of devising and implementing mechanisms for handling stored samples from minors was addressed in [Chapter 13](#). Simply deciding whether a minor ought to be a part of a particular study can produce much discussion and disagreement. For example, genetics studies that include minors will often involve testing for a particular disease. There is, however, much controversy about when and for what kinds of genetic diseases minors should be tested. Many professionals in the pediatric genetics counseling and research communities believe that minors should not be tested for any genetic condition with a late onset of disease, especially those for which there is presently no treatment or cure. This view is not always shared by parents of minors in families with a history of specific genetic conditions or by the advocacy groups that speak for such parents and families. A reason given for not testing minors for late-onset disorders is that such knowledge can result in what is often termed closed futures. This term refers to the denial of opportunities to participants with genes for a late-onset disease, resulting in a sort of defeatist approach to the minor's future. Alternatively, the information might cause a child to be nurtured in aberrant ways as a result of having this kind of knowledge about his or her future. The principle of autonomy asks researchers to assist persons in being as self-determining as possible in the face of potentially life-changing information. If knowledge of the genetics information is of no immediate benefit to the minor child, respect for his or her developing autonomy suggests that testing wait until the child can consent or decline independently. At the very least, these concerns suggest that if a minor child is included in a genetics protocol, he or she should have the opportunity to dissent privately from his or her parents. Also requiring consideration in the design phase is how minors will be given the opportunity to withdraw stored samples when they reach the age of maturity. Since this book was originally published, considerations around these issues have been evolving. Investigators engaged in pediatric genetics research should familiarize themselves on where the ethical thinking has been, where it is now, and what might be the implications for the future ([Botkin et al., 2015](#)).

1.8 Risks to communities

Even when genetics research presents no risk to a particular participant or family member, the research may present a risk to a group ([Goldenberg](#)

et al., 2011). Chapter 5 cited the example of the stigma attributed to Ashkenazi Jewish women that ultimately resulted from anonymous genetics research. This case, like many in genetics, resulted not only from a bit of serendipity but also from the way in which genetics research progresses. To find genetic variability that is clinically meaningful is difficult under the best of circumstances. The prospects for doing so increase, however, when defined populations with as little genetic variability as possible can be studied. Such a population is a gold mine for genetics research. Because such populations are scarce, the risk of stigmatization is high when an identifiable population is intensively studied. Published reports of newly discovered genes tend to involve particular populations first (Martin et al., 2017; Arcos-Burgos and Muenke, 2002; Biesecker, 2002); only afterward is the gene pursued in more heterogeneous populations. Therefore, when investigators plan studies of particular populations, especially those in which conditions such as alcoholism, cancer, or psychiatric illness have already been identified, ways to minimize or avoid additional negative effects of the research findings on the population need to be considered. Although the shape of the protective mechanisms is a matter of judgment (DeCastro et al., 2016; Manz, 2016; Arias et al., 2015; Weijer et al., 2003), mention of the possibility of community harm should be included in the consent process and documents, even if there is no apparent risk to an individual because the data are anonymous. If the group can be identified, there is the possibility for group harm. With a prospect of harm to certain groups of people, some individuals may not want to participate so that they, themselves, can avoid contributing to the risk.



2 Biologics

Research involving biologically active agents have been conducted for at least the last two centuries; today research with biologics is expanding rapidly. Biologics have brought about important breakthroughs for many years in many diseases. Whereas synthetic drugs have been developed from non-living chemicals (e.g., Yi et al., 2014), biologics are derived from living sources such as viruses, animals, and people. Many traditional drugs are administered by mouth; most biologics if administered orally would be destroyed by the digestive system, so they are most often administered through injection. Biologics hone in on specific cells, often intending to produce an immune response. These characteristics have implications for the ethical

considerations necessary during the design process. For example, if there is even the theoretical possibility that a participant could shed either administered virus or a new virus produced by the combining of the administered virus with virus harbored in the host, what provisions will be made for containing the participant until shedding has stopped? How long might such a participant need to be quarantined? If quarantine is needed, what social amenities (e.g., free telephone access) might need to be provided? In designing protocols with biologics, there may be ways the biological agent presents risks and/or benefits similar to or different from other drugs. Investigators, sponsors, and review boards will want to think about these differences and/or similarities carefully in the study design and review process. Consider the following example.

A group of researchers have been working with a pharmaceutical company on a biologic intervention for liver cancer and the agent is now ready for its move from the bench to its first in-human trial. Because the biologic is not expected to have any serious side effects—one of the advantages over standard chemotherapeutic agents—the company wants to get PK data in healthy humans before conducting tests in patient volunteers. The company's clinical research and development (R&D) team leader convenes a meeting of scientists and clinical research ethicists to consider whether the risks of this biologic are different than a standard chemotherapy agent, and if so, how such a difference(s) might affect the risks to healthy human research volunteers.

Biologics, as opposed to chemical drugs, are being used more and more in clinical practice, calling for more scholarship related to ethics considerations raised by this use. It is already appreciated that there are serious justice issues related to the costs of biologics research and use in clinical practice (e.g., [Dulai et al., 2016](#); [Zheng et al., 2014](#)). These justice concerns call for large-scale public debate but also should be part of an IRB's review of any new trials for biologics. Investigators should take this ethics consideration in account and justify these costs in their protocols.



3 Vaccine trials

Although vaccines may be the least expensive and most effective intervention for infectious disease outbreak, there continue to be a variety of ethics issues that produce barriers to vaccine development research. These include the ethical complexities of deciding who should comprise a study population (and whether or not to prioritize health care providers), randomization strategy, and comparator arm intervention selection ([Kahn et al., 2018](#); [Folayan et al., 2016](#); [Rid et al., 2014](#)). The ethical and logistical difficulties in running vaccine trials have long been known and discussed, but

the Ebola outbreak, the Zika virus, and most recently the novel coronavirus, or COVID-19 (Zheng et al., 2018), have brought these discussions to a head. When infectious outbreaks occur for which there are no proven vaccines but there are those in the experimental pipeline, studies to rapidly test such vaccines and get those that work deployed is an ethical mandate. That there is a social mandate for such research does not, however, lessen the ethical and logistical complexities of designing and running such trials. One way to meet this need is to have protocols written, in draft, in advance so such protocols can be refined according to the dynamics of the infectious outbreak, reviewed by relevant bodies, and then initiated as quickly as possible. An additional, important consideration, in the design of vaccine trials that is often left out of research considerations of population involvement is pregnant women. As the Zika epidemic has shown, however, justice and beneficence calls for researchers to work to involve this ethically complex population. If the COVID 19 pandemic has brought anything about clinical research into sharp focus, it has been the need for vaccine trials. It's likely COVID 19 will not be overcome until we have a vaccine. The race is on.

In the meantime, while the vaccine research itself is being designed and developed, studies, often of a qualitative nature, can be conducted to learn more about stakeholder engagement and vaccine use. Gathering this type of information is just as important as the development and testing of the vaccines, themselves (Rockcliffe et al., 2018; Morain et al., 2017). In such conditions as COVID 19, standard lengths of time to develop and implement vaccine trials are likely to be shortened. So knowing how new vaccines will be accepted in the many and varied populations where they are needed can be useful to dissemination of new vaccines as they become available.



4 Psychiatric research

Psychiatric research has been a magnet for controversy regarding research ethics since the mid-20th century. The first presidential ethics commission, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978), out of which came The Belmont Report (see Appendix 11), and a series of authoritative reports now embodied in the federal regulations that govern research on human participants in the United States. One of the Commission's reports also produced recommendations, specifically considering

studies of individuals with mental illness that were not implemented at that time ([National Commission's Report and Recommendations on Research Involving Those Institutionalized as Mentally Infirm, 1978](#)). Another presidential ethics commission, the National Bioethics Advisory Commission (NBAC), submitted its report and recommendations 20 years later for the ethical conduct of research involving psychiatrically ill participants ([National Bioethics Advisory Commission, 1998](#)). These authoritative documents and a wealth of additional literature, some of which has already been cited elsewhere in this book, should be reviewed and digested when considering this highly specialized and often contentious area of clinical research (e.g., [Foulkes et al., 2019](#); [Racine and Bracken-Roche, 2019](#); [Bracken-Roche et al., 2016, 2017](#); [Tsao et al., 2008](#)).



5 Capacity to give consent: Adults

One of the most difficult and important ethical issues in research involving individuals with psychiatric illness or cognitive-impairing neurologic conditions ([Prusaczyk et al., 2017](#)), such as Alzheimer's disease, relates to altered mental status and poor judgment that are a part of these disease processes and relates to the effects of these conditions on decision making. As a result of severe stroke or coma, a patient's clear lack of capacity requires that a surrogate make the decisions for that patient in the clinical setting and if that individual might become or be a research participant, that individual will need a research surrogate. In the case of severe stroke or coma, there is ordinarily no disagreement about whether or not the individual is decisionally capable. The individual's lack of decisional capacity may be quite obvious. That is sometimes not the case for psychiatric illness or less cognitively-impairing other disorders. Psychiatric symptoms wax and wane over the course of an individual's disease and simply having a diagnosis of Alzheimer's disease does not indicate whether a particular individual may have a moderate case or not.

Some in the research field take the position that if participants cannot provide their own informed consent, they should be excluded from research altogether. Others believe such individuals ought to only be involved in expected-direct benefit research. Some believe that if one is decisionally capable of providing consent but who might be anticipated to lose that ability during the study that individual ought to be allowed to be involved in research only if they are willing and able to assign a research surrogate prior to study entry. There are those in the research community, however, who

believe that both approaches raise concerns. These include ethical concerns for increased stigmatization and pose therapeutic problems on the basis that such protective mechanisms may exacerbate feelings of powerlessness and paranoia in an individual prone to such problems. There will also be concern that summarily excluding adults who cannot give their own informed consent is likely to make whole groups of adults research orphans, slowing progress towards treatments for the conditions that have rendered these individuals unable to give their own consent. Whether an autonomy-driven approach or a more protective, beneficence-driven approach is proposed in a protocol considering involving research participants unable to give fully informed consent to all aspects of a study will depend on the ethical perspective of the investigators and review bodies responsible for the trial. Any approach will present its own set of ethical complexities, and whichever approach is taken will need to be justified in the body of the protocol, particularly in the Ethics Section ([Chapter 10](#)).

Controversy also surrounds the dispute about how capacitated a decisionally-impaired individual has to be to provide ethically and legally valid consent. The ethical and legal notion of consent is that it is decision specific. Assessment of a participant's ability to provide ethically and legally valid consent needs to be built into any protocol where participants can be expected to have questionable capacity. Although processes for such assessment are becoming increasingly refined, they are and can be expected to continue to be a subjective determination, as discussed in [Chapter 5](#).

Protocols involving participants with psychiatric and/or medical conditions that present a possibility of decisional impairment, or the possibility that participants could lose decisional capacity during study progress, will need to address the capacity issue with specificity. Discussion of how capacity is to be assessed should be built into the protocol. Where additional protections ought to be built into the proposed study, such protections may include consent monitors, nonresearch-affiliated physician advocates, and nonresearch-affiliated individuals performing the capacity assessments as well as research surrogates.

Other possible protections include the increased demand for more patient advocates joining IRBs. Progress on this point has been slow. Nonetheless, programs to train and place patient advocates on IRBs and to create institutional policies and practices for including greater numbers of patient advocates and/or former research participants on the review bodies should be considered.



6 Minors

Since the first edition of this book, the numbers of clinical trials including minors has increased substantially. When pediatric participants are involved in a study, the level of ethical complexity increases. Adding minors to any protocol, as discussed in [Chapter 5](#), adds a whole new set of ethical questions ([Shakhnovich et al., 2019](#); [Binik, 2018](#); [Neill, 2005](#)). These include the growing autonomy rights of adolescents with implications for greater design attention to matters of assent and dissent by the minors ([Sibley et al., 2016](#); [Waligora et al., 2014](#); [Hein et al., 2015](#); [Bloomfield, 2015](#); [Wendler, 2006](#); [Ungar et al., 2006](#)). More is known about parental thinking and knowledge of the research process involving their children ([Harvey et al., 2017](#); [Denhoff et al., 2015](#); [Hoberman et al., 2013](#)) than was known when this book was originally published. There has been a deepening of considerations about the vulnerability of young children, neonates and preterm newborns ([Megone et al., 2016](#); [Schreiner et al., 2014](#); [Abdel-Rahman et al., 2007](#)), and making research decisions for children when time is of the essence ([Jansen-van der Weide et al., 2015](#)).

Of particular concern may be the appropriateness of surrogate (e.g., parental) decision making. For example, while the care and attention devoted by parents to their ill children are ordinarily presumed to be in the best interest of the child ([Crane et al., 2018](#); [Bos et al., 2017](#); [de Vries et al., 2011](#); [Kimberly et al., 2006](#)), there may be concerns about the quality of care that some parents may be providing. Ill children are likely an enormous sadness for parents and, also, may be a burden on their families. Some children may have parents with similar problems that raise a concern that such a parent or parents could be less than optimal decision makers for their children in research, e.g., parents with substance abuse disorders. Such problems, or others such as impoverishment, in parents who would be the ones to make research decisions for their minor children create concerns about the motivations of parents who enroll their children in research, especially research that has little or no expectation of direct medical benefit and for which there is some sort of payment ([Fernhoff, 2002](#); [Wendler et al., 2002](#)). When participants will be paid, serious thought is required to decide the specifics of compensation (e.g., what kind, how much, to whom, such as payments to the parents, child, or both). These issues need to be presented clearly in a protocol for the reviewers to consider. Justifications for conducting the study need to be thorough. Concerns about the appropriateness

of administering drugs, especially psychotropic drugs, to children mandate a particularly high level of justification for such studies. Rescue end points should be specific.

Although many of the ethical questions about if and how minors ought to be involved in clinical research remain, these questions and concerns are magnified because of the increased numbers of protocols that call for the inclusion of minors. These matters require thoughtful attention given that this area of research can be expected to expand rapidly over the next several years as a result of the interests of parents, physicians, physician-investigators, the pharmaceutical industry and academic institution investigators, and the U.S. FDA in increasing the inclusion of minors in research.



7 Recruitment and retention of women, minorities, and other vulnerable and/or potentially vulnerable populations

During the second half of the 20th century the traditional perspective that vulnerable individuals must be protected from the harms and burdens of research participation shifted to one in which all individuals, particularly women and those from minority populations, should have access to the potential benefits of research. This philosophical turn-about was given practical shape by the NIH Revitalization Act of 1993, which required establishing guidelines for inclusion of women and minorities in clinical research. The guidelines call for all NIH-funded clinical trials, especially at the phase III level, to collect sufficient data to elicit information about participants of both genders and diverse racial and ethnic groups. The influence this guidance has had on changes in clinical research populations is immeasurable (e.g., [Nielsen and Berthelsen, 2019](#); [Myles et al., 2018](#); [Kurt et al., 2016, 2017](#); [Neelotpol et al., 2016](#)). Prior to 1993, it was common for women to be excluded from clinical trials, even of medical interventions that, if approved, would be taken by women as well as men. There was a general lack of appreciation of the possibility that differences in female and male chemistry and physiology might result in substantial differences in the ways therapeutic interventions affected each gender. Couple this lack of attention to differences in treatment impact with the variability in women's bodies resulting from menstrual cycles—it was just considered easier to study men. As data mounted that significant differences in drug metabolism and outcome existed between the sexes, however, data also

accumulated pointing to differences in health patterns across racial and ethnic groups. These scientific awakenings were taking place within a social context of attention to injustices towards women and minority populations in other sectors of society. The resulting 1993 act literally changed the face of clinical research, regardless of funding source. Progress has been swift in some ways and in other ways it has been slower. Today, women, even women of reproductive potential, are regularly included in clinical trials. The shift from excluding women completely to only excluding women of childbearing potential to including all but pregnant women (see discussion in [Chapter 5](#) and in the next section of this chapter) has been accomplished quite completely. Of note here is that pregnant women are no longer included in the **RCR** as an example of a population that is potentially vulnerable (like the removal of “handicapped” or physically disabled individuals) to coercion or undue influence.

For studies in which a fetus would need to be protected from an experimental agent, protocols and consent documents include clear and explicit language on requirements for birth control. Also, an increased equalitarianism has surfaced when scientifically appropriate. When relevant, birth control is required for both female and male study participants. This attention to gender issues in reproduction can be seen in other ways as well, such as discussions of egg and sperm banking in relevant protocols.

The swift shift to a reasonable and fair balance of the benefits and burdens of research participation that can be seen between males and females, however, has not been achieved as successfully concerning inclusion and retention of minority populations. Recruitment and retention of minority populations in research continues to exist at lower levels than would be hoped for on the basis of fair access and percentage representation in the general population. There appear to be multiple reasons for the reduced numbers of minority participants. Fear and mistrust on the part of minority communities of the majority-dominated research community account for much of the problem. Few discussions of problems in recruiting minorities escape reference to the lingering effects of the Tuskegee Syphilis Study on lower numbers of African-American research participants (see [Chapter 15](#)). It is unlikely, however, that mistrust is the only cause of low minority recruitment. Researchers are working to learn better techniques for community outreach. The 1993 act specifically requires the creation of outreach programs to recruit the populations covered by the act. As researchers gain knowledge of which outreach strategies work best ([Wong et al., 2019](#); [Lunn et al., 2019](#); [Winter et al., 2018](#); [Wallington et al., 2016](#); [Friedman et al., 2015](#); [Brown et al., 2014](#); [Arean et al., 2003](#); [Meinert et al., 2003](#);

Swanson and Ward, 1995) it can be anticipated that the numbers of minority participants will increase.



8 Involvement of pregnant women or fetuses

As was noted in [Chapter 5](#), the ethical involvement of pregnant women or fetuses in research is a highly controversial topic. The DHHS regulations described in 45 CFR 46 (Appendix, No. 15) that relate to involvement of pregnant women or fetuses have now been revised in the **RCR**. The revised regulations, in Subpart B, describe circumstances under which Common Rule agency-funded research may involve pregnant women, fetuses, and neonates; and after delivery, the placenta, the dead fetus, or fetal material. In the case of pregnant women, a fetus, or a neonate, research can be performed when risk has been minimized and there is an expectation of direct medical benefit to the pregnant woman or the fetus. When there is no direct benefit expected to either, research in the US under Common Rule agencies can be carried out when risk to the fetus is no greater than minimal and the expectation of utility of the information to be gained is important and cannot be obtained in any other way. If research benefit may be expected solely for the fetus, consent of the pregnant woman and the father, if available and capable, must also be obtained.

Additionally, the **RCR**, consistent with the changes for Subpart A, has the same goals where applicable in Subpart B. These include ways of promoting individual autonomy by changing requirements for consent and adding the use of “Broad Consent” where appropriate. Included also are the **RCR**’s Subpart A changes to reduce administrative burdens and streamline IRB reviews. Nonetheless, even these newest of US regulations will continue to be stretched as technology in the area of fetal surgery, for example, moves swiftly forward ([Riggan et al., 2019](#)).

In the case of the neonate, the anticipatable benefit must be the enhanced prospect of survival to viability. In all cases, the potential benefit must be obtainable only through the research proposed. For research after delivery involving the placenta, the dead fetus, or fetal material, the research must adhere to any applicable federal, state, or local laws. In addition, if information associated with the material is recorded so that living individuals are identifiable, these individuals are considered research participants, and all pertinent regulations apply. Research of this kind presents substantial religious, cultural, philosophical, and political controversies and continues to produce controversy over how we think of pregnant women as vulnerable,

potentially vulnerable, or not (van der Zande et al., 2017; Krubiner and Faden, 2017; Sheppard, 2016; Churchill et al., 2013; Lange et al., 2013; Wendler, 2012a). Further, these debates can be expected to continue for the foreseeable future. Thus, when a proposed study involves pregnant women, the fetus, or any of the materials described (Fourniquet et al., 2019), the ethical considerations involved in such study designs ought to be well articulated in the protocol.



9 Community-based participatory research

The requirement for community involvement discussed in the preceding section reflects just one aspect of the discussion on ethical considerations regarding research and its effects on community or communities. Growing concern about how a community or communities ought to be involved, treated, and protected in the research setting has led to the reasonably new research area of community-based participatory research (CBPR). CBPR is community-driven, community-organized, community-focused, and community-managed clinical research. Unlike traditional clinical research that is investigator- or sponsor-initiated and focuses on their interests, even in the studies that ask questions about particular communities, CBPR reverses this process. Community-based or participatory research addresses concrete problems and issues of interest to the community that are generated from within the community through partnerships with researchers and, thus, presents unique ethical challenges to the conduct of trials (Crigger, 2017; Tamariz et al., 2015; Marshall and Rotimi, 2001).

Much of this research is ethnographic or applies other qualitative methodologies. It frequently focuses on services and educational aspects of community activities and addresses problem areas that communities, themselves, have an interest in studying. The focus is often on research that can be used to influence public policy. Research agenda priorities are commonly set by the urgency of the community's need to address a particular aspect of its services.

For researchers embarking on community-based research, the design phase can be expected to be much longer than for traditional clinical and biomedical research studies. A lot of work will be required to familiarize the researcher with the community in which he or she chooses to work (Souleymanov et al., 2016). A special characteristic of this kind of research is the source of control (e.g., the community as driver), which involves a lengthy process of community organization and agenda creation. IRB members may need education about how to review such

protocols (Jamshidi et al., 2014; Anderson et al., 2012; Flicker et al., 2007). The role of each partner in the collaboration needs to be clarified and agreed upon before a protocol is drafted. Funding mechanisms can be cumbersome and also need to be well defined early in the design process. Nonetheless, one can expect to see the call for more CBPR as communities become more attentive to their own research needs and researchers become more interested in the fascinating clinical research opportunities CBPR can offer.



10 Surgical research

Although we addressed some of the ethical issues related to surgical research in [Chapter 11](#), here we address other aspects of this ethically complicated clinical research area (Roberts et al., 2019). Norms and practices for clinical research involving surgical interventions are changing nonetheless. Most IRBs review fewer surgical protocols than they do drug or biologics protocols. This may be due in part because of the differences between regulatory processes for the approval of pharmaceuticals and those for devices. It is likely, also, that it is due in part to the differences in ethical complexity in the design of drug versus surgical trials. A final part of why there may be fewer surgical trials than there are drug trials is because of the differences between the traditions of progress in drug development and the ways in which surgical practice has always moved forward, which has been through surgical innovations, a primarily unregulated aspect of surgical practice. But all this may be changing. Concerns about misinterpretation of findings in some surgical trials (Brody et al., 2013) may produce greater scrutiny of surgical study design and conclusions.

While US drug development has long come under the intricate architecture of regulatory oversight, surgical progress has continued to move forward through the traditions of clinical surgical innovation (Biffel et al., 2008; McCulloch et al., 2009; Schwartz, 2014; Hutchison et al., 2015). Although the imposition of regulatory oversight has been creeping into surgical progress, that progress has been slower than it was when regulatory oversight moved into other areas of clinical care (Blencowe et al., 2015; Horng and Miller, 2003). While there have been increased conversations about when might it be appropriate for an innovative surgical practice to be tested, if at all, in a surgical study, conceptual confusions in this domain remain (Birchley et al., 2019). And while blurred lines between what some might

consider research and what others define as innovative surgery can be expected to continue, even where surgical research is being developed and implemented, the disclarity in language and understanding of surgical research requirements appear as complex internationally as in the US (Boult et al., 2011). That is because surgical procedures, per se, are not regulated and regulatory bodies are appropriately hesitant to appear to be seeking authority to regulate medical practice.

A group of orthopedic surgeons at a community teaching hospital come back from a surgical conference having learned about a new technique for repairing complicated ankle fractures. They want to apply the new procedure, but some are not convinced that it will be better than presently used techniques. Because surgical procedures themselves are not regulated, some of the surgeons just want to invite the surgeon who presented the information at the meeting to their hospital to train them so they can start using the new technique, which is pretty much the way new ways of advancing surgical practices has always occurred. Others want to set up a formal test of the procedure so that, once all the surgeons have been trained, as eligible patients are identified, they are invited to participate in a randomized trial of the old technique versus the new. The chief of surgery asks that his group think it over and to come back for a meeting the following week prepared to defend one option or the other.

If the authors had written this example so that the surgical research study had been about a sham surgery research study design, the debates around such a study design could be expected to be even more difficult and perhaps contentious as for the example given (Savulescu et al., 2016; Cooper & McNair, 2015). But just the mere contemplation of whether or not any surgical practice should be tested in the research context will be expected to be a complex ethical area for surgeons and IRB in the coming years.



11 Emergency medicine research

Research in emergency medicine is an area of study that has acquired over the last decade its own set of regulations. This expansion of regulations resulted from the identification of an improper practice for obtaining consent that was endemic throughout the emergency medicine research community. In many emergency medicine studies, the consent mechanism judged to be outside the bounds of ethical justification and regulatory compliance was referred to as “deferred consent.” The practice was that investigators enrolled individuals into emergency medicine studies who were unable to provide their own consent and had no one to consent for them.

Later, when the participant was able to consent and/or an appropriate surrogate was available, consent for the completed procedures plus permission to continue were sought. Regrettably, this is a term still used in other parts of the world, making the language of emergency medicine confusing (Woolfall et al., 2013, 2015).

Nevertheless, when the US federal government realized, roughly 30 years ago, that this was a widespread practice in emergency medicine research, guidance letters were mailed to thousands of investigators to inform them that deferred consent is not only unacceptable, there is no such thing. Consent must be prospective and continuing until terminated. Needless to say, this “cease and desist” directive brought emergency medicine research to a virtual halt. Although the U.S. FDA regulations were a bit more liberal than those of the U.S. DHHS, it became immediately apparent that for emergency medicine research to progress, regulatory relief and clarification were required.

Regulatory relief came in 1996 in the United States in the form of FDA regulatory guidance and clarification in the form of a two-part process for formal community engagement in the design process for emergency medicine research in the form of a waiver of informed consent for emergency research (Coats and Shakur, 2005; Shah and Sugarman, 2003). Part of meeting the new regulatory requirements in emergency medicine research were two intriguing innovations. When such an informed consent exemption is being sought, an emergency medicine study must include a public disclosure process for the study being envisioned and what is called a community consultation (CC) to ensure that those who might be included—by either disease group or geographical area—have the opportunity to voice any comments or concerns they have about such a study. The IRB must document the PI’s consultation with representatives of the community or communities in which the study will take place and from which the study participants can be expected to come. The regulatory guidance has information about what will not be accepted as meeting the community consultation requirements. Final determination of what meets the standards for community consultation and public disclosure is left to the discretion of the investigator and the review bodies. Although these are seemingly reasonable and innovative approaches to assuring emergency medicine research is conducted at high levels of ethical standards, there have been significant difficulties, in large part related to confusion and disclarity about how these innovations ought to be implemented (Holsti et al., 2015; Dickert et al., 2014). Even though other aspects of the consent waiver process have proven

complex, efforts have been made to come up with solutions that allow emergency medicine research to move forward (Wendler et al., 2017), with success rates just starting to be documented in the literature (Brienza et al., 2016).

There is, however, a growing consensus and urgency around the importance of planning and being able to implement high quality studies, including randomized controlled trials, in emergency medicine research is essential (Kohrt et al., 2019; Razzak et al., 2019; Ellenberg et al., 2018; Alirol et al., 2017; Chiumento et al., 2017; Schopper et al., 2015). Effective implementation is a challenge for investigators and IRBs; data on the impact of research under the new regulations are just beginning to appear in the literature (Henry et al., 2017; El-Menyar et al., 2016; Neuman et al., 2015; Halila, 2007; McClure et al., 2003). This literature will be particularly important in delineating where the thorniest ethics concerns are and providing the opportunity for the most important ethics thinkers in emergency medicine research ethics to offer their opinions. It is this literature that should guide investigators and IRBs as we have more emergencies that call for tight, well designed and implemented studies.

From an ethics perspective, emergency medicine research presents many complex ethics issues. Progress in medicine rests on the performance of clinical research but research in emergency medicine may be among the hardest studies to design, conduct, and bring to fruition. Many emergency medicine studies will have to be designed before the emergency occurs, making perhaps an impossible prediction with the kind of precision relevant protocols will demand (Pretz et al., 2009). The ethically complex matter of needing to conduct emergency medicine research in Low and Middle Income Countries (LMIC) calls for much thought that is just beginning to coalesce (Kwok et al., 2019; Aarons, 2018; Bain et al., 2018; Tansey et al., 2017). When the research is to include minors the ethical considerations needed to perform emergency medicine research can be even more difficult to untangle, although even here useful data are beginning to accumulate (Roper et al., 2018).

Emergency medicine research covers a wide swath. Disasters, man-made or natural, are likely to produce many injuries and create the setting for emergent disease. As climate change produces conditions conducive to increasing frequency and intensity of disasters, research data in all these areas of clinical medicine will be needed even more than such studies have been needed in the past (Saxena et al., 2019).



12 Prisoners

DHHS regulations at 45 CFR 46, Subpart C, lay out constraints on research involving prisoners (Appendix, No. 15). For research governed by the DHHS regulations, Subpart C applies when any participant is or becomes a prisoner. This last point may not be well-appreciated by researchers and review bodies. It seems that some have not understood this aspect of the regulations, rather interpreting the regulations only to apply to those incarcerated at the time of study entry. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term covers those sentenced to such an institution under criminal or civil statute and individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution, such as institutions housing individuals deemed too psychiatrically impaired to stand trial. The term also covers individuals detained pending arraignment, trial, or sentencing. When a study includes a participant(s) who meets the definition of prisoner, special composition of the IRB is required. With the exception of prisoners, IRB members must not have association with the prison(s) involved. Also, at least one member of the IRB (or one of the reviewing IRBs) must be a prisoner or a prisoner representative with appropriate background and experience to serve in that capacity. There are additional conditions that must be met for research involving prisoners related to avoidance of undue influences on prisoner informed consent, fairness of participant selection, immunity from arbitrary intervention by prison authorities or other prisoners, parole board actions concerning study participation, and specific details about poststudy follow-up care. These constraints and the additional logistical complexities they bring to research involving prisoners have resulted in little prisoner research since the regulations were created.



13 Epidemiological research

The ethics of epidemiological research and review are evolving (Piasecki et al., 2017). Epidemiological research is research designed to study processes, characteristics, or other facets of particular populations or phenomenon. Epidemiological studies are among the oldest and most common human participant research studies. Historically, this area of research has attracted little attention or controversy. The ways in which epidemiological

studies are carried out, however, especially regarding restrictions on researcher access to study populations, have tightened markedly and ethical consideration of the complex kinds of study tools is increasing (Kramer & Soskoine, 2017; Piasecki et al., 2017; Caughlin and Beauchamp, 1996; Horner, 1998). The kinds of databases that researchers automatically have access to without a requirement for study-specific consents from participants have declined (Baig & Alzahrani, 2019). The days are over when researchers would obtain the names, addresses, and other contact information of family members from a proband (primary research participant) and contact these family members directly. In light of the QA and QI issues discussed in Section 15 of this chapter, the sun may be setting on days when it was possible to simply access patient charts without institutional review and oversight for epidemiologic studies. IRBs now commonly require that investigators provide probands and/or database registry administrators with researcher contact information and request that the proband and database registry administrator do the contacting. With the advent of HIPAA, epidemiological research is likely to become increasingly complicated.

For example, Dr. Samuels is a community geriatrician who regularly admits her patients to the Downtown Teaching Hospital. She has been sensing that an increasing number of her patients have been having infectious complications after cardiac surgery. She wants to conduct a study of the hospital's infection rates in cardiac surgery patients over the age of 65. She approaches the physician in charge of resident research projects, Dr. Yee, and suggests the project. Although interested and expecting that the project is doable, Dr. Yee is unsure how to manage the transfer of hospital information about patients other than those under Dr. Samuels' direct care. Dr. Yee tells Dr. Samuels that he will contact the hospital's HIPAA compliance officer and get back to her.



14 Translational research

Translational research is the “buzz word” for research today but it is a relatively new area of investigation. There was little thoughtful discussion of the ethics of translational research until well into the new century (Mandal et al., 2017; Rubio et al., 2010). Translational research moves from the laboratory bench, into the clinical research setting, into clinical care at the patient’s bedside, and back into the research setting. Translational research is designed to move basic research findings into therapeutics and to accelerate the flow of insights from clinicians that are shaped into questions answered at the bench and within the clinical research environment.

Investigators can expect to see funding for translational research growing at a dizzying pace over the next several decades. One of the primary ethical concerns about this research relates to the types of contractual agreements that are attached to many of the studies and the concerns the agreements raise for continued free exchange of scientific information. That is, translational research is characterized by the kinds of public/private collaborations that can produce serious conflicts of interest for investigators and institutions. Another ethical concern raised by the push for translational research is that there will be a reduction in funding for undirected basic research. Because so much of medical and scientific progress results from serendipitous findings, directing scientific inquiry towards therapeutics may have an effect opposite to that which the proponents of translational research seek. By attempting to move basic research too quickly into areas that have a specific therapeutic focus, the natural meandering of scientific interest may be constrained, and the possibility that scientific surprises can emerge will ultimately be reduced. A final and related concern mentioned is that the push of translational research will result in moving science so quickly from the bench to the bedside and in so doing participants may be harmed in ways that might have been avoided had the process been slower. A glaring example of how this problem might evolve is discussed in the presentation of the research focused on brain tissue transplants in Parkinson's Disease in [Chapter 15](#). Moreover, there are other concerns to contend with as the push for translational research grips the research community. These include developing ethical processes for partnering with sick patients ([Mamzer et al., 2017](#)), minority communities ([Estape-Garrastazu et al., 2014](#)), establishing frameworks for mentorship in translational research ([Abedin et al., 2012](#)), and developing ways in which to evaluate how well a translational study performed ([Trochim et al., 2011](#)). These ethical issues, and the many others embedded into the performance of translational research may require a complete rethinking of the ethics of clinical research in the age of translational science ([Hostiuc et al., 2016](#); [Bærøe, 2014](#)).



15 Quality assurance and quality improvement research

Research for quality assurance (QA) has been around for a long time. Only in this century has such research garnered much attention; particularly about whether or not it is the kind of research that should be reviewed by an IRB ([Bellin and Dubler, 2001](#); [Casarett et al., 2000](#)). The questions being raised since QA/QI research came up on the research review radar are about

how much oversight QA research ought to receive, how QA is the same or different from quality improvement (QI) research, and how different, ethically, is QA/QI research from traditional clinical trials research (Stiegler & Tung, 2017; Finkelstein et al., 2015). Quality assurance research has never been considered academic research in the scholarly sense. It has mostly been conducted in hospitals and other health care delivery organizations and/or systems to ensure that the quality of care provided is safe and adequate. Historically, QA research was most frequently of the retrospective chart review variety or involved anonymous patient satisfaction surveys. With the economic implications of the need for resource conservation of the past 40 years for hospital care, QA projects evolved into quality improvement research projects. QI is now the byword of evaluating and continually upgrading standards in health care organizations. As the need for increasingly sophisticated methods of assessing and improving quality have grown, the kinds of studies conducted to produce information about QA and QI have become more sophisticated (Ienca et al., 2018; Weinfurt et al., 2017; McKinney et al., 2015; Taljaard et al., 2014; Patsopoulos, 2011). This has translated into many QA and QI projects that increasingly resemble academic-level, quantitative research. The more such methodologies have evolved, the more attention has been brought to placing QA and QI projects under some sort of oversight system.

For those interested in performing QA and QI projects, some of the literature just cited can assist investigators and IRBs in deciding whether QA or QI research should receive IRB oversight and whether it requires a participant's consent. Consent issues in this area of research promise to present ethical challenges to the investigator and the review bodies that will ultimately, we predict, take responsibility for oversight of this area of research. Some of these issues are presented in these questions:

- Are there plans to present the QA/QI project findings at an academic meeting or to publish them in a journal?
- If QA and QI projects are required as part of a hospital's ongoing accreditation processes, can patients simply decline to give consent?
- Will written consent be required?
- Might some less obtrusive means for showing respect for those to be involved in the research, such as information sheets, be sufficient for deciding that all patients must be willing to participate in projects designed to increase the quality of care for all patients?

These and other ethical issues related to QA and QI research are only just beginning to be discussed in the 21st century.



16 Bioterrorism

Since the terrible attacks on the World Trade Center, Shanksville, PA, and the Pentagon on September 11, 2001, the United States and the rest of the world have been irreversibly changed. Fear and concern about more terrorist attacks have become commonplace (Ploug, 2018; Poland et al., 2009). Talk of terrorism has become the stuff of everyday life and now we are making distinctions between foreign-sponsored terror attacks and those resulting from home-grown terror, including the possibility for rogue scientist-inspired terror (Shapiro, 2015; Flower, 2014). For Americans, whatever sense of isolation we may have felt from the horror of terrorism that others around the world have experienced for generations is gone. A sad recognition for the need for clinical research into protection from terrorist attacks has set in, and much attention has focused on bioterrorism. This realization has been accompanied by attention to the ethical considerations raised by this new menace in our midst (Cairo et al., 2011; Moreno, 2003). Old concerns about the ethical conduct of military research (Dubov, 2014; Moreno, 2001) have resurfaced. New concerns have emerged about how such research will be conducted in public and private sectors (Evans et al., 2015; Strauss, 2014; DeRenzo, 2003; Fleischman and Wood, 2003; Meslin, 2003). Many hospitals, public health authorities, and state and local governments are developing plans for bioterrorism response requiring studies to predict how well such plans might work. This is an area of clinical research that can only be expected to expand in the immediate future and the years ahead. It may be prudent for researchers, research sponsors, and research review bodies to begin thinking about the ethical issues related to such clinical research. One of the concerns about bringing such protocols forward is that there will be an urgency attached to them that might reduce the time for design and review needed to assure that these scientifically and ethically complex protocols receive the required degree of thoughtful preparation. The other side of this ethical concern is represented by the ethical complexity of involving minors in such research. There will be those who believe minors should be treated similarly to adults while others will continue to take a protectionist approach (Gutmann, 2013). Regardless, clinical research in bioterrorism presents deep ethical concerns about potential participants and society. That such research is needed, at all, is difficult to contemplate but an ethical, regulatory, social, and logistic challenge that has to be faced pro-actively.