Chapter 2

CANCER TRIALS AND THE INSTITUTIONAL REVIEW BOARD (IRB)

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1. INTRODUCTION

The issues involved in clinical trials involving cancer patients are often unique. IRBs may be unfamiliar with aspects of such trials that differ from studies involving other types of patients such as healthy subjects and patients with infectious or chronic diseases. Often for cancer patients, there may be no effective treatment for example when metastases have occurred. Experimental treatments might be based on chemotherapeutic regimens that have been used in other cancers or in patients in the adjuvant setting but not in that particular cancer patient population.

Cancer patients are often willing to accept risks of treatment that other patients would not, even in the adjuvant setting. In a recent study, women with breast cancer who had completed adjuvant chemotherapy were asked knowing the discomforts and expenses that they had experienced, how much benefit would be necessary for them to be willing to take the chemotherapy if they had it to do over again. Roughly three quarters of the women said that they would be willing to take chemotherapy again for what might be considered modest gains, e.g. an increase in survival from 15 to 17 years.[1]

As oncologists, we are comfortable offering very toxic treatment to patients who we know might or might not even need the treatment. We

knowingly accept the fact that as many as 70% of patients with early stage breast cancer are cured by the operation and radiation therapy that they receive and don't actually harbor occult metastases. Nevertheless, we offer Stage II breast cancer patients adjuvant chemotherapy because we don't yet have the tools to determine which patients harbor metastatic cells. IRB members who come from a variety of non-oncological backgrounds don't necessarily share our view on this problem. In this chapter we will describe the issues that the IRB considers in reviewing cancer clinical trials and give some practical suggestions for improving the study and hopefully ensuring passage of the trial.

2. HISTORY OF CLINICAL RESEARCH

In 1966 Henry Beecher published a landmark article identifying at least 22 studies recently published in the medical literature that suggested serious ethical problems in the treatment of human subjects[2] Beecher's, as well as other scientists' and journalists' revelations about the risks of research that emerged during the 1960s and early 1970s led to increasing calls for government regulation of research. In 1974 Congress passed the National Research Act. Title II of the Act created the National Commission for the Protection of Subjects of Biomedical and Behavioral Research (National Commission). The National Commission worked from 1974 to 1978 and issued 17 reports. Perhaps the most well-known and influential of these reports, published April 8, 1979, was the Belmont Report, described below, which identified key ethical principles that should guide human subjects' research and which formed the basis for regulations issued by the Department of Health Education and Welfare (DEHW, now HHS) and the Food and Drug Administration (FDA). These regulations, originally published January 19, 1981, as "DHHS Regulations for the Protection of Human Subjects and FDA Regulations for Clinical Research and Informed Consent" and issued as 45 CFR part 46 and 21 CFR parts 50 and 56, were more consistent than earlier regulatory efforts and had a tremendous impact on biomedical research. Ten years later efforts to bring all government sponsored research under similar rules was finally realized with publication of the Common Rule in 1991, covering all research using human subjects sponsored by 16 federal agencies. The Common Rule retained most of the provisions of the 1981 regulations, including the requirement for prior ethical review of all studies and the establishment of Institutional Review Boards (IRBs) for this purpose with specific responsibilities.

The remainder of this chapter deals with the requirements of the CFR in regulating research and particularly role of the IRB in relation to cancer trials, but necessarily much of the information is generalizable to other types of studies as well.

As with most significant bodies of federal regulation, a government body exists to implement and enforce the regulations. Originally established in 1972, this entity was called the Office for Protection from Research Risks (OPRR); it was part of NIH and reported directly to the director. In 2000 that office was renamed the Office of Human Research Protections (OHRP). OHRP has continued the activities of OPRR and has issued guidance for research in specific settings.

3. BOUNDARIES BETWEEN PRACTICE AND RESEARCH

3.1 Basic ethical principles

The Belmont Report, issued in 1979, described fundamental ethical principles that should guide research involving human subjects. The Commission was charged specifically with providing guidance on: (1) the boundaries between clinical practice and research; (2) assessing risk and benefits as part of the process of reviewing human subject research; (3) fair selection of subjects; and (4) informed consent for research. Researchers and clinicians often have difficulty defining what constitutes research and what is clinical practice. One simple definition is that research is the collection of data from live human subjects for the purpose of producing generalizable knowledge. Thus, testing new medications or treatments for cancer patients with the intention to present the results to peers would certainly qualify as research. An example of a project that would not be considered research would be a quality assurance program such as a survey of infections in the hospital where the purpose is to improve the care at that particular institution without influencing other hospitals. Sometimes such quality assurance projects yield such interesting information that publication or presentation is valuable. In those cases, the IRB will need to review the project and create the parameters for the use of the data so that the rights of the participants are adequately protected. It is often wise to seek IRB approval for projects that might carry such promise.

The Commission identified what it considered three basic ethical principles, although it acknowledged that other principles could also be important. These principles, respect for persons, beneficence, and justice are familiar from the realm of clinical ethics, but when applied to research additional safeguards and rules need to be considered.

3.2 Respect for persons

The principle of respect for persons requires that scientists recognize the individual worth and dignity of all potential human subjects and it encompasses two important concepts. First, respect for persons requires that scientists and caregivers honor the right of self-determination, or "autonomy", for persons in relation to both medical care and participation in research. That means that individuals who are competent to make medical decisions generally have the right to freely choose whether or not to participate in biomedical or behavioral research. Second, those individuals who are not able to make decisions for themselves, are non-autonomous, deserve additional protection.

In practice, respect for persons has its most direct applications to research in that it requires that autonomous subjects of biomedical or behavioral research be fully informed of the nature, risks, benefits and alternatives to research, and that they consent voluntarily to participate. Respect for persons also requires that individuals or groups with diminished autonomy be protected in the research setting, usually by designating special steps to be taken to limit risk and by designating a process for obtaining consent for research from parents, guardians, or legal representatives.

3.3 Beneficence

The principle of beneficence requires that those conducting biomedical and behavioral research maintain as their primary focus "securing the well-being" of human subjects. This means both that subjects should be protected from harm and that, where possible, the likelihood of benefit be maximized. Beneficence requires that the clinical researcher remain a clinician first. Where the roles of clinician and researcher conflict, the researcher should resolve the conflict in favor of promoting the well being of the patient.

Applying the principle of beneficence to research requires that investigators, IRBs and institutions always minimize risks to human subjects throughout the study process, maximize the possible benefits in relation to

risks, and ensure that no study proceeds where the risks remain disproportionate to the potential benefits. It requires the researcher, in relation to individual subjects, to withdraw a subject from a study or trial if the researcher believes continued participation would be particularly dangerous to that subject. IRBs can and will require criteria in most protocols to determine when and if subjects should be withdrawn.

3.4 Justice

The principle of justice requires that the researcher consider whether the risks and benefits of his or her proposed research are equitably distributed. True justice or fairness does not mean purely "equal" treatment. In medicine, public health and research there are well-accepted criteria for treating different individuals differently (e.g., only those with cancer ought to be considered candidates for chemotherapy, or only pregnant women need prenatal care), however it can often be difficult to determine what exactly is "equitable" distribution of the risk and benefits of research.

In practice the principle of justice is most clearly applied to subject selection. Researchers and IRBs must ask, "is the choice of subjects fair?" are any group of subjects being exploited or unjustifiably excluded from the research? This requires consideration of several sub-questions: 1) are the proposed subjects roughly representative of the population affected by this disease or condition? 2) Does the research address a significant health need of the study population? 3) Are any groups excluded from the study without clear medical justification, and if so, why? 4) Is any group chosen purely for convenience? And 5) will the groups chosen as potential subjects be able to benefit from the results of research if they are positive?

These and other applications of the three fundamental ethical principles will be examined further below.

4. APPLICATION OF THE PRINCIPLES

4.1 Informed Consent

The Belmont report, the Helsinki agreement and other similar documents have helped raise the general awareness of the critical nature of informed consent in human subject research. Beyond safety this is the most important issue that the IRB will consider in deciding whether or not to approve the research.

Many have wondered what really constitutes informed consent in this context. Although it is tempting to try and make the subjects understand the scientific basis of the protocol, this is not a practical or reasonable goal. Subjects need to be told in clear language the overall purpose of the study, the potential benefits and risks of their participation, and alternatives to participation. The informed consent form (ICF) must also be written in a language understandable to the patient. If subjects' primary language is not English, the IRB is likely to insist that the ICF be translated into the primary language of the subjects. The ideal way to accomplish this is to have the ICF translated into the second language and then translated back into English by another interpreter (called "back-translation") to ensure accuracy. It is reasonable for the IRB to require the investigators to translate the ICF into some of the major languages in the vicinity of the study site, but the PI should not be expected to translate the ICF for one or two patients who speak a very obscure language.

The upper limit for the language of the consent form should be a 10^{th} grade reading level. Often, even simpler language should be used. If the subjects are likely to have lower levels of education, the language level should be adjusted accordingly. Consent forms that are overly complex or technical are likely to be rejected by the IRB and neither read nor understood by the potential subjects. If the investigators desire to try and convey complex topics such as the molecular biology of the new agent, this can easily be presented in additional documents supplementary to the ICF.

Researchers must also be aware that modern IRBs consider informed consent a process, not just a document. Leaving a patient encounter with a signed trophy will not satisfy this important requirement. In examining the validity of the informed consent process, the IRB will consider broadly two major factors: are the patients *adequately informed* about the study and is their choice *fully voluntary*. In addition to ensuring that the ICF is written in a level suitable for the reading level and education of the potential subjects, the IRB will check that all the requisite information discussed below is included in the ICF (and thus should be discussed in the process). To ensure that patients who enter the study do so voluntarily, the IRB will consider whether the study and the process of informed consent are designed to minimize potential coercive influences on the potential subjects. Specifically, the informed consent should include the overall purpose of the study, the nature and duration of the subjects' involvement, the risks of the study, and an explanation of what will be done to minimize those risks, and alternatives to study participation. Benefits of the participation, if any, and incentives should also be listed, but should not be overstated. IRBs will scrutinize benefits and incentives to determine both if the ICF paints too rosy a picture of the actual clinical benefits that are possible and to ensure that

neither the benefits nor the incentives (payments or other gifts to research subjects) are so valuable as to be coercive.

In determining whether the informed consent process is likely to result in subjects who are "fully informed," an IRB will first consider the type of study. There are clearly different standards for non-therapeutic trials, where the purpose of the research is simply to find out about the biology of the cancer, compared to a Phase I trial using an untested investigational agent, compared to Phase II and III trials evaluating safety and efficacy of new agents, or to trials comparing previously approved agents.

4.2 Non-therapeutic trials

There is a great deal to be learned about the biology of cancer. Patients who have clinically apparent disease are a potential rich source of biological information. Demographic, diet, and genetic information can provide important clues as to the etiology of tumors. Blood, urine and other biological specimens can provide material for protein, genetic and other studies. Fresh or preserved tumor and normal tissue specimens not needed for diagnosis or staging are also invaluable clues in the fight against cancer. Sometimes studies such as these are independent of treatment trials other times they are imbedded in therapeutic trials. The ICF must clearly state whether or not participation in the therapeutic portion of the study is contingent on participation on the non-therapeutic part. If this is the case, then participation in this portion of the study might be viewed as coercive, and must be dealt with carefully by the investigators.

The risks of participation in the information, specimen and tissue portions must be fully described. Often researchers focus on the actual physical risks associated with this portion of the study. Sometimes this is important. For example, if bone marrow samples are being taken or if an invasive procedure needs to be carried out that would not occur during the normal course of treatment. If the collection is relatively risk free, such as blood drawing of small samples (i.e., less than 450 ml from healthy adults), then the consent should focus on the implications of the sampling. It is not necessary to spend many paragraphs on bruising and infection, but rather on the significance of the information that might be obtained and potential uses of the information within the study or by others. If the information is not clinically useful, then the explanation might be simple. If for example, however, genetic information is the focus of the study, then the consent process should focus on what the risk to the patient and their family might be with respect to learning about the fundamental building blocks of their inherited genetic information. If the test is examining markers of tumor

status or progression, then issues regarding disclosure of experimental information might be relevant. The researcher must inform the patient as to whether or not the information will be available to the patient or the healthcare team. Will the information become part of the medical record? Might knowledge of the information change the planned clinical care?

4.3 Phase I studies

Phase I studies are designed to gather information about safety and answer biological questions. They are not designed to result in benefit to the subjects although occasionally there might be some therapeutic gain. Therefore, research subjects are true volunteers, allowing the research team to learn about the effects of drugs or biologic agents. For that reason, the IRB expects several additional items. First, the research protocol must make abundantly clear what steps are taken to minimize risks to the subjects in a more comprehensive manner than in trials with therapeutic potential. If the investigators manufacture the drug or biologic agent tested, then the protocol must present safety data with respect to good laboratory practices. Usually, if a pharmaceutical company manufactures the agent, the IRB will accept that the manufacturing process meets standards. Similarly, the ICF must be more explicit, and often more detailed. Subjects need to be told in simple language that there is no expectation that their participation in the research will help them in any way. The ICF must state that there are known and unknown hazards associated with the agent.

Some studies raise questions of ownership interest in a valuable product developed using subjects' tissues (blood, tumor cells, etc). Subjects, researchers, institutions and funders may all make plausible ownership claims to products developed using such tissues and ICFs must describe whether or not the researchers intend to reimburse or otherwise compensate the volunteer if the study is successful and results in financial profit. This issue is often confusing for investigators as well as IRB members. CFR Section 46.116 regulations prohibit asking subjects to waive their rights in any way in a consent form "No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence." Investigators and research facilities are usually unwilling to share in the profit if the research results in a profitable product. In this situation, research subjects who provide such material cannot be asked to waive their rights to seek financial compensation. In this case however, the researcher can inform the subject as part of the consent process that there is no intention to compensate the

patient under any circumstance. It is then up to the patient to seek compensation through the legal system. Whether or not they are successful is up to the courts, not the researcher or the hospital.

4.4 Phase II and III studies

In Phase II and III clinical trial, there is an expectation that there might be some clinical benefit to the subjects as a result of their participation. The protocol and ICF should reflect this. In many cases, the test therapy will be compared to treatment that is considered the standard of care for the disease. The research design must describe the rationale for withholding effective standard treatment for those subjects who will receive the experimental arm. Decisions regarding study design with respect to the issue of parity or superiority studies must also be fully explained and justified in the power analysis.

The ICF must clearly state why the subjects are being asked to participate. The subjects must be told what standard treatment would be if they elect not to participate in the research and how likely that treatment would be to succeed. The document and informed consent process should then contain enough lay language information to allow the potential participant to understand why they should accept potential assignment to an unproven treatment arm. The ICF need not go into technical details, but should convey the rationale in a clear and succinct manner.

The second task of the IRB in evaluating the informed consent process is to ensure that subjects who participate do so voluntarily and free from undue coercion, and that they know they can withdraw from the study at any time. Cancer patients are often more vulnerable than non-cancer patients for several reasons and therefore susceptible to the influence of others. The diagnosis of cancer is extraordinarily stressful. No matter what we as clinicians know about the natural history of the disease, patients almost always view cancer as a threat to their existence in a very current and imminent manner. Additionally, because of the non-optional nature of treatment for most cancers, the patients have a need to please their caregivers and may mistakenly feel that entry into a clinical trial is their only option. Therefore, they might be willing to accept risks or recommendations in order to please the clinician or the staff that they would not otherwise accept. Cancer treatment is also very expensive. Often participation in a clinical trial will lower the cost of treatment to the patients who are underinsured or have high deductibles. This factor might also influence patients to accept risks that they would not otherwise. The significant financial benefit of participation (through lowered costs) is similar to the issue of payment to

subjects. The IRB will consider whether the financial implications of participation, like payment, will unduly influence the patient's ability to make an informed and non-coerced decision.

The ICF must also contain a number of procedural and administrative details. Subjects should be reminded that their participation is voluntary and that they can withdraw permission at any time. Withdrawal from the study might subject the patients to unexpected risks, e.g., if subjects withdraw during the nadir count portion of chemotherapy special protective measure might be required. Until data have actually been published, subjects should have the right to withdraw permission to use their data, to contact them in the future, or to bank their tissues, if these remain identifiable. The ICF should also contain accurate information on who is in charge of the study, who can be contacted with questions, where a subject should go with concerns about side effects of drugs or adverse events that occur during the study, and who to call if they have general questions about their rights as human subjects. Most institutions have developed language that can be used in ICFs to convey this type of information, but it is the responsibility of the investigators to ensure that the names and contact information are accurate.

5. ASSESSMENT OF RISK AND BENEFITS

Some degree of risk is inherent in almost all research on human subjects. Cancer trials are no exception. When an IRB reviews such clinical trials, their role is not to eliminate all risk but rather to ascertain that all foreseeable risks have been minimized and that the potential for benefit is maximized. The risks of the research must then be balanced and put into context of the clinical scenario. Once this is done, it is assumed that a competent adult can decide whether or not they are willing to accept the risks of the trial and elect to participate. For example, a greater degree of risk would be permitted for clinical trials involving patients who have no standard clinical option. Research using subjects with otherwise incurable malignancy would fall under this heading. On the other end of the spectrum would be basic science studies for which there is no foreseeable benefit to the patient. Under those circumstances, there would be little tolerance for risk.

Cancer clinical trials often involve the use of chemotherapeutic or biologic agents. These drugs might be standard combinations of approved drugs, new dosages or formulations, the use of non-accepted regimens, or the use of investigational agents. From a human subject point of view, the safety requirements would necessarily vary. If the agent being used is not a standard drug manufactured by an established company, then the IRB will need to monitor not only the application of the material and the ethical

nature of the study, but also the manufacturing process. Investigators need to satisfy the IRB that a safety system is in place to ensure that good laboratory practices will prevent chemical and biologic contamination. Additionally, they need to establish quality assurance programs to ensure that: 1) the material that is manufactured is the product intended; 2) the concentrations and doses are reliable and match those listed in the protocol; and 3) the product is sterile and non-pyrogenic. Biologic agents manufactured from living tissue or cell lines raise other concerns. Specifically, the IRB will be expecting to hear how molecular material and viral contamination or transmission will be tested for and prevented.

5.1 Selection of subjects

Historically, clinical researchers often chose subjects based on groups who were immediately available (ward or clinic patients), easy to follow for periods of time (incarcerated or institutionalized adults and children), or unlikely to question the type of care they received (uneducated, poor or minorities). As a result, the burden of research fell disproportionately on the poor, minorities, and those with limited autonomy. Such patients might have been easy to enroll and follow, but they often also had less capacity to understand the potential risks and benefits of participation in trials and may have not have freely chosen to participate. Although it could be argued that for some patients, participating in trials was the only way to access care, this cannot justify exposing only needy patients to the risks of research and may, in fact, interfere with the voluntariness of their choice.

In many ways the Tuskegee Syphilis study provides a classic example of a study which enrolled poor, uneducated subjects who were denied real choice in entering or continuing in the study and suffered various harms as a result of their participation. In that study, poor black men with a diagnosis of syphilis were observed without treatment over a period of decades. When inexpensive and highly effective antibiotic treatment for syphilis became available, the men were denied treatment. In addition they were never clearly informed of the purpose of the study or the nature of their disease. As a result, most subjects experienced the long-term complications of syphilis and some transmitted the disease to their spouses, partners, and children. The subjects in Tuskegee were African-American, poor, unable at the outset to obtain treatment outside the study, largely uneducated, and unlikely to question the "treatment" they received.

Recruitment of subjects in developing countries is a more current example where the benefit of treatment argument can be made but is often surpassed by other considerations of equity in risk sharing. This is discussed more fully below.

In order to avoid exploitation of subjects, investigators' protocols must justify their selection of subjects as equitable, based on the particular condition studied and the risks and benefits of treatment. The investigator must make it clear to the IRB that no particular population or class of subjects will bear an undue burden of the risks. Unless the study involves a disease or condition that is unique to a patient population such as homeless people or patients of a particular race or ethnicity, the methods section must include a plan to offer participation in a fair and equitable manner.

Subject selection also raises another issue. While some studies have unfairly singled out specific groups to bear the risks of research other studies have unjustifiably excluded groups of potential subjects. Besides depriving these potential subjects as individuals of the advantages of participation such as access to free medications or drugs that have clinical promise otherwise not available to them, exclusion can pose larger societal problems. If a group of subjects, such as fertile women, is systematically excluded from research, then information regarding the benefits and risks of the drugs tested are not available to those patients. For example, if a drug is only tested in post-menopausal women, even if it is found to be effective, it might not be used in pre-menopausal women because of the lack of data on safety and efficacy. Similarly, drugs for diseases such as hypertension have been shown to have differing efficacy depending on the race of the patient. If the clinical trial does not include enough subjects of different racial backgrounds, then those patients are deprived of the benefits of the research. Until recently there were very few clinical trails on the safety and efficacy of numerous drugs in children. Consequently, physicians treating children often had little empirical data to guide safety, efficacy, and dosing for children.

The research plan submitted to the IRB must take these factors into consideration. Some funding agencies will require a plan to recruit a percentage of patients from particular racial or ethnic groups. In multi-institutional trials this can be accomplished by including hospitals and clinics in a variety of settings. In single institution studies the plan may be more complex. If subject selection for a particular trial cannot be sufficiently diverse to broadly reflect the population that could benefit from the drug, the researcher must explain and justify the less diverse plan. For pilot studies with limited funding, recruiting patients that don't exist in that community might not be practical. This too should be carefully described and justified.

6. SPECIAL SITUATIONS

An important assumption of the modern approach to research on human subjects is that a competent patient has the capacity to understand the implications of participating in the study. Furthermore, there is an expectation of a lack of coercion. There are clearly circumstances, however, when potential subjects might not have the capabilities to understand the research or have the same ability to make voluntary choices regarding participation. The implications for the IRB are considered below.

6.1 Prisoners

Prisoners were used as research subjects millennia ago by Persian kings. Researchers in the U.S. used prisoners in pellagra studies in the late 1800s and malaria studies in the early 20th century. During World War II, U.S. prisoners participated in numerous medical experiments and received public praise for their "contribution to the war effort."[3] As pharmaceutical research expanded dramatically after WWII, many prisoners became research subjects. Some prisons even had special units dedicated to drug company research.[3] By the end of the 1960s an estimated 85% of new pharmaceuticals were tested on prisoners.[4,5] There were many potential advantages to researchers and pharmaceutical companies for using this captive population. Prisoners were stably housed and easy to follow throughout the study period. Conducting studies in prisons could be less expensive than among the non-incarcerated.

Participation often provided tangible benefits to prisoners also. Participation was rewarded with early parole or better treatment and privileges. Better food, housing, health care, and safety were also often available to prisoners in drug trials. The material benefits of participation often made for easy recruiting, even for studies that involved treatments or procedures that the non-incarcerated population would not accept. Prisoners, however, also faced risks from inclusion in trials including: the risks of unproven drugs, the possibility that the drugs would be less effective than those already approved, harms to healthy prisoners from drugs taken in non-therapeutic trials, or procedures associated with therapeutic or non-therapeutic trials.

Even when prisoners were not directly harmed in studies, however, their participation could rarely be described as fully voluntary. Prisoners are subject to coercion on many levels. They are deprived of freedom of movement, assembly, employment, and communication with the outside world. The health care provided to them has historically been poor to non-

existent and they are prevented, by their confinement, from choosing alternative health care providers. In recognition of their greatly reduced autonomy, and the potential coercive nature of both therapeutic and non-therapeutic trials in prisons, a subchapter of the Code of Federal Regulations[6] specifically addresses the additional protections necessary for prisoners as a "vulnerable group." The IRB is legally bound to only approve research that meets the strict requirements of Subpart C.

Briefly, with respect to cancer trials, prisoners can only participate in clinical research if there is a reasonable expectation of personal benefit to them as a patient with a disease. They may participate in non-therapeutic trials only if the study is investigating questions about being a prisoner or about a select population that is incarcerated. These rules therefore narrow the scope of research that prisoners may be enrolled in. They may not be included in any clinical trials that do not contain a therapeutic arm. This would include studies regarding the biology of tumors, markers, etc. However, if the study is a comparison of potentially therapeutic treatment arms and there is also a tissue collection portion of the study that will likely be approved unless the specimen collection is deemed to carry an excess risk. A good barometer is whether a competent non-prisoner would be willing to contribute tissue under the same circumstances.

A critically important interpretation of the rule is that prisoners cannot participate in a therapeutic trial that has a placebo arm. The reason is that they might be randomized to the non-therapeutic arm and therefore not receive the same treatment that they would ordinarily be offered. Although researchers might argue that for some cancers no treatment might be best or that no proven, effective treatment exists, this argument is unlikely to succeed under the current narrow interpretations of this rule.

IRBs reviewing studies that include prisoner subjects must also meet certain requirements themselves, including having a member with expertise in prisoner issues[6] who is not affiliated with the prison system **46.304 (b)** "At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.". If researchers are considering prisoners as research subjects for a cancer trial, they also need to comply with any administrative and other requirements of the correctional system itself. Often these requirements can be far more time consuming than standard IRB approval and must be factored into the proposed timeline for a clinical trial. Although the requirements for enrolling prisoners as research subjects add a measure of complexity to conducting a clinical trial, they are critically important to ensuring protection of prisoners as a class and as individuals. Such requirements were established to protect

against repetition of abuses in the past. Researchers or IRBs that violate these rules have faced sanctions in the recent past.

7. INTERNATIONAL STUDIES

Given the ease of communication and travel in our modern times, multi-national studies have become quite common, especially in Europe. Many trials now include patients in both Europe and North America. When the study population includes subjects of similar socio-economic backgrounds, then the experimental design is generally simpler to construct.

The issues are different when scientists from industrialized countries conduct clinical trials that will primarily involve subjects in developing countries. IRBs are accustomed to assessing clinical trials within the framework of the Belmont Report. Studies in poor nations raise issues of beneficence, respect for persons (informed consent), and justice in ways that differ from studies conducted solely among patient populations in industrialized countries.

Investigators may consider many reasons to consider the option of conducting clinical trials in poor countries. The costs of conducting studies may be far less, the numbers of subjects with a particular disease may be higher, or recruitment might be expected to be easier. One rationale for permitting such trials is that without the clinical trial, the population in that country would likely not have access to the medications or treatments that would be available with participation. Similarly, some researchers (and funding agencies) have argued for inclusion of non-treatment (placebo) control arms in international studies, even where an effective treatment is available in the industrialized home country of the researchers[7-9] because the "standard of care" in the developing country might be no treatment at all. Both sides in these debates have claimed to be acting out of beneficence. In favor of these studies, researchers argue that some of the subjects may benefit directly from the study's active regimen that would not otherwise be available, while the entire population will benefit if research identifies inexpensive, effective alternatives to regimens used in industrialized countries. Those opposing such studies argue that it is unethical to give a placebo to subjects where a known, effective regimen exists, because the researchers will knowingly be exposing some subjects to worsening of their condition or even death. They argue that poor subjects should never be used as a "means" to discovering less expensive treatments where their participation will definitely harm them.

Therefore, in the absence of extraordinary circumstances most IRBs will find a protocol using a placebo or non-treatment control arm that could not

be conducted in US unacceptable in a developing country.[7-9] Although it might be true that without the trial there might be no treatment, it is generally considered an injustice to treat certain subjects in a way that would be viewed as below the standard of care in this country.

For international studies to meet the standard of respect for persons, the issue of informed consent will be critical to the IRB. Keeping in mind the concept of informed consent as a process, not a document, careful attention must be paid to regional, cultural and religious considerations. At the very least, the informed consent process must be conducted in a language familiar to the subjects. A beautifully constructed ICF in English will not be acceptable in a non-English speaking country. In order to pass this test, the ICF must be translated into the native language and then translated back into English to ensure accuracy. Cultural, religious and idiomatic sensitivities are critical. Additionally, investigators in international research face a daunting task of explaining the concept of research and uncertainty in simple lay language to potential subjects whose education and literacy levels may be very low and the local understanding of biology and the scientific method may be very limited. In some cases oral consent might be needed and so a mechanism for accomplishing this will be expected by the IRB.

The lack of access to care makes subjects in developing countries especially vulnerable to coercion. In order to get treatment for their cancer, such patients might be willing to accept risks that patients in this country would not. A study that includes payment to subjects for their participation will be a red flag for the IRB.

The issue of justice is particularly important in relation to selection of subjects, including the choice to conduct studies in a developing country. Fundamentally, research in developing countries should address health problems that are important to the local population and provide potential benefit for that population in the future. If adequate numbers of patients with the target disease could be found easily in the researchers' home country, then his or her choice to use subjects in a developing country should be subject to closer scrutiny. An IRB will ask, are these subjects being chosen merely to lower research costs or to recruit subjects for dangerous or unpalatable studies? If the answer to either question is "yes," then the study should not be allowed to proceed. Additionally, according to international standards (WMA Declaration of Helsinki, paragraph 30 and clarification) "every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study." Furthermore, Helsinki requires that the plan for ensuring access must be included in the study protocol so that review committees can consider its adequacy. In practice this could mean, at a minimum, that if a new therapy is found safe and efficacious, all subjects who can still benefit from it should

have immediate access to it at the conclusion of the trial. Where such access is impossible, as where subjects have died or recovered, researchers should consider offering the new treatment at an affordable cost to community in which the research is conducted. For similar reasons, non-therapeutic trials will be subject to close scrutiny because subjects ordinarily do not benefit directly.

In summary, international studies can be done, but important issues need to be addressed carefully with the IRB. Issues of safety of the subjects treated in local settings need attention as well.

7.1 Terminal patients

Despite our best efforts, our treatments will fail some patients. As experienced oncologists we recognize that at some point patients will have exhausted all therapy with curative intent. Such patients might become the subject of clinical investigations. For this group, Phase I drug studies, tumor sampling, and end of life research might be contemplated. While there is a great deal to be learned from these patients, there is also the risk that their inclusion in non-therapeutic research might diminish the quality of the remainder of their lives. There is, however, an opportunity to conduct studies that could not otherwise be done.

The IRB members who are not oncologists might not have the same appreciation for the condition of these patients that a seasoned oncologist would. The IRB should frame decision making in the context of the Belmont Report principles, respect for persons, beneficence and justice. Dying patients clearly must be afforded the same rights and dignities that apply to patients who have therapeutic options available to them. Their willingness to accept risks however might be higher. The distinction between experimentation and treatment with therapeutic intent is more critical for them than for any other group. While these patients may be motivated by altruism, their desperate situation makes them susceptible to misunderstanding regarding the boundaries between clinical care and experimentation. IRBs ought to ensure that non-therapeutic, or Phase I trials with little likely benefit are accurately described to terminal patients to ensure that entry into a 'trial' is not confused with effective treatment.

7.2 Tissue and gene banking

Remarkable progress has been made in the understanding of the biochemical and metabolic nature of cancer. Advances in molecular biology and protein chemistry have resulted in extraordinary opportunities to gain

information. These advances almost always require the acquisition of biologic material from humans with cancer. While this material is especially valuable, the rights of the patients submitting this material must be respected.

Cancer studies might involve collection of a variety of different tissues, including blood or serum, fresh tissue, or archived tissue. Such samples might be obtained prospectively (i.e., the investigator might be looking for fresh tissue or blood from patients diagnosed with a particular cancer) or might want tissue already collected. The samples might be removed as part of a therapeutic procedure or might only be collected for the purpose of non-therapeutic research. Some of these issues have been covered in the section on non-therapeutic research.

Federal regulations govern some aspects of collection of such materials. Section **46.110** of the Code of Federal Regulations provides guidance for exempt studies that use tissue that already exist. Such studies must use tissues that have been stripped of all personal identifiers. For this research, it is not possible to collect any further information on the patients. Information stripped of identifiers can be stored in a properly secured tumor bank. The use of these specimens must not jeopardize the rights of the subject in any way. It is up to the IRB, not the investigator, to determine whether or not the research is considered exempt.

If the samples do not already exist (i.e., they are to be collected), then the research might approved through the expedited process if the tissues will be collected as part of routine care, or are obtained through non-invasive methods. Section **46.110** of the CFR includes a list that describes the types of samples that are appropriate to this regulation. The investigator must bear in mind that the ability to obtain tissue through an expedited protocol is a separate question from the need for informed consent from the patient. As a general rule, if any information might be obtained that could affect the patient or the patient's family, then specific consent will need to be obtained.

The investigator must also ensure that the study meets the requirements of current federal privacy and security regulations, promulgated as part of HIPAA. Researchers who are not part of the patient care team may not review patient charts looking for subjects. The IRB application must describe the method of recruitment. Separate HIPAA regulations will apply to this process. HIPAA permits waiver of some requirements for appropriate circumstances. Clinicians who are treating the patient must recruit these patients not researchers who are not entitled to review protected health information (PHI). Individual patients may contact the researchers without going through their own physicians if there are IRB approved advertisements. If it will be important to collect additional tissue samples or

to gather follow-up information from the subjects, then specific consent and HIPAA-specific authorization must be obtained.

Many hospitals have established tumor and tissue banks. These serve as an invaluable resource to researchers looking to study cancer. Some institutions have constructed their surgical consent form to allow for the storage of excess tissues that are not needed for the purpose of making a diagnosis or other pathologic assessment. Such resources need to be approved by the IRB. They must be carefully managed and the identity of the subjects protected.

When research involves stored samples the important issue is whether or not the patients need to give permission to use the tissues. As stated above, some research will qualify as "exempt" under federal rules, and the patients do not need to be contacted. An example of such research would be a study looking for tumor markers in archived tissue. The tumor bank can supply samples from patients with a particular disease, but cannot disclose personal identifiers. However, as a general rule, if information on genetic material is being investigated, then the IRB will expect that permission from the patient will be sought due to the sensitive nature of the study, and the possible implications for the patient's family. For example, if the research is to find genes that result in susceptibility to cancer, then it would be highly relevant to the family. If the research is looking at genes (or other factors) that would predict the response to a particular therapy such as chemotherapy, then the patient would have an interest in knowing that their tissue (or blood cells) was being examined. A separate issue is the potential financial aspects of the research. This has been covered above.

8. CONCLUSION

Decades of quality research has led to improved patient survival and quality of life. It is our hope and society's expectation that continued research will result in even more successes. Unfortunately it is our failures and poor outcomes that often dictate policy. As Mark Antony stated regarding the slain Caesar "The evil that men do lives after them; The good is oft interred with their bones".[10] Our obligation to our patients is to conduct safe and ethical research. It is the duty and responsibility of the IRB to ensure this. While the rules might seem onerous, a clear understanding of the ethical underpinnings and a pot of hot coffee are the tools needed to reach the goal.

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