

Ethics of Mandatory Research Biopsy for Correlative End Points Within Clinical Trials in Oncology

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ABSTRACT

Clinical investigators in oncology are increasingly interested in using molecular analysis of cancer tissue to understand the biologic bases of response or resistance to novel interventions and to develop prognostic and predictive biomarkers that will guide clinical decision making. Some scientific questions of this nature can only be addressed, or may best be addressed, through the conduct of a clinical trial in which research biopsies are obtained from all participants. However, trial designs with mandatory research biopsies have raised ethical concerns related to the risk of harm to participants, the adequacy of voluntary informed consent, and the potential for misunderstanding among research participants when access to an experimental intervention is linked to the requirement to undergo a research biopsy. In consideration of the ethical and scientific issues at stake in this debate, the Cancer and Leukemia Group B Ethics Committee proposes guidelines for clinical trials involving mandatory research biopsies. Any cancer clinical trial that requires research biopsies of participants must be well designed to address the scientific question, obtain the biopsy in a way that minimizes risk, and ensure that research participants are fully informed of the risks, rationale, and requirements of the study, as well as of treatment alternatives. Further guidelines and discussions of this issue are specified in this position paper. We feel that if these principles are respected, an informed adult with cancer can both understand and voluntarily consent to participation in a clinical trial involving mandatory research biopsy for scientific end points.

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INTRODUCTION

Under what circumstances, if any, is it ethical to require that participants in a clinical trial undergo a biopsy for evaluation of scientific end points? With increasing frequency, cancer researchers are seeking to understand the biologic bases of response or resistance to novel interventions and to develop prognostic and predictive biomarkers that will guide clinical decision making. Such research often requires samples of tumors before, during, and/or after treatment to evaluate potential molecular predictors of clinical outcomes. Although for some questions, evaluation of correlative end points from a subset of clinical trial participants may be sufficient, for others, universal or near-universal participation in providing research biopsies may be required, making consent to one or more research biopsies mandatory for trial participation. However, the requirement for patients to consent to a research biopsy as a component of clinical trial participation has raised ethical concerns related to the risk of harm to participants, the adequacy of voluntary informed

consent, and the potential for misconception among research participants.

Progress in clinical research requires both scientific rigor and a strong partnership between research participants and clinical investigators. There is a need to understand and address the concerns that may arise regarding these issues so that the rights of patients and trial participants can be protected while also evaluating the potential for research involving biospecimens to move forward on a solid ethical foundation.

The ethical concerns described in this article reflect both the limited published literature on this subject and the positions considered in discussions of this issue within the Cancer and Leukemia Group B as informed by our prior experience in trial development. This position paper is intended to review the context of research biopsies in oncology clinical trials, present and evaluate the ethical concerns that we believe have led to controversy in this area, and propose a framework that provides a basis for both ongoing discussion and for ethical conduct of mandatory biopsies within clinical trials under select conditions.

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CONTEXT: CLINICAL NEED AND POTENTIAL FOR PROGRESS

There are more than 565,000 cancer deaths each year in the United States and more than 7.5 million annual cancer deaths worldwide.¹ For decades, systemic therapy of cancer was based primarily on administration of cytotoxic chemotherapy regimens according to cancer type and disease stage based on evidence obtained from phase III randomized controlled trials. With this strategy, and with the development of endocrine and biologic approaches for treatment of some cancers, there has been limited progress in controlling, and virtually no progress in curing, advanced stages of most solid tumors. The revolution in molecular biology now offers us the tools to begin to better understand the biologic bases for malignancy and to develop targeted strategies for cancer treatment. In recent years, such strategies have achieved major improvements in disease outcomes in several types of cancer.²⁻⁴ Even with the most effective new treatments, however, clinical response, progression, and survival are highly variable for reasons that often remain unclear.

Evaluation of tumor samples through research biopsies can potentially advance our knowledge and treatment of cancer in several ways. First, we may identify biomarker predictors of response or resistance that might lead to more appropriate selection of therapy for individual patients.⁵⁻⁸ Second, we may gain insight into how our treatments actually work and determine whether targeted therapies are in fact “hitting the target” and yielding a biologic response or, if treatments fail, why this might be the case.^{9,10} Third, we may identify additional biologic pathways that are important at baseline or in the presence of therapy and thereby identify additional therapeutic targets.^{11,12} The goal for this line of research is to move beyond the traditional clinical research model to more accurately and efficiently identify which patients respond to an intervention and which do not. Ideally, we can identify a subset of patients with a very high likelihood of response to a given therapy and search for modifications or alternatives for those with less chance of response, allowing us to move closer to a truly personalized model of effective cancer care.

As we now understand, cancers from the same tissue of origin (ie, breast cancer, colon cancer, lung cancer) may in fact represent different diseases on the molecular level.^{4,13-15} In addition, there are numerous examples of single molecular differences that determine the likelihood of response to a given therapy. Recent examples include identification of *K-ras* mutations, which result in cetuximab resistance in colorectal cancer, and PI3Kinase mutations, which convey trastuzumab resistance in HER-2–positive breast cancer.^{4,16} To improve outcomes in oncology, we ultimately need to understand the appropriate molecular diagnosis for each patient. Failure to understand important biologic differences among otherwise similar cancers using the traditional clinical trial model can result in overestimation of the impact of treatment for one subset of patients and underestimation for another subset.^{4,17} This approach risks potential treatment toxicity and inappropriate use of health care resources on patients who can't truly benefit and failure to recognize the value of drugs that may be highly effective in a small subset of patients with a specific molecular diagnosis.¹⁸

WHAT IS A RESEARCH BIOPSY?

In considering this issue, it is important to differentiate between the different types of biopsies that may be proposed in the context of clinical trials and to clarify the steps in biomarker-based research. First, we must distinguish between a clinical biopsy and a research biopsy (Table 1). A clinical biopsy is a procedure through which a sample of tissue is obtained through an invasive procedure for purposes directly related to the care of the patient or research subject based on established techniques and evidence. In contrast, a research biopsy is a procedure through which tissue is collected for research purposes only, with no proven role in clinical management of the patient.

In oncology, both clinical and research biopsies are frequently performed to evaluate tumor tissue biomarkers, defined as any molecular feature of a cancer that conveys clinically important information of prognostic value (such as the likelihood of recurrence after local resection), or predictive value (such as the chance of response or

Table 1. Biopsy Classification

Type of Biopsy	Role in Patient Care	Role in Research
Clinical biopsy	Direct benefit to patients is established	There may or may not be a research component of a clinical biopsy
	The results will be used directly to guide the care of the patient undergoing the biopsy	A portion of the biopsy sample not needed for clinical use may be used for research or may be stored for potential future research
Research biopsy for correlative science	Direct benefit to patients is not established	The biopsy will be used to assess the correlation between molecular features of a tissue and patient disease type or treatment outcomes
	Results will not be used to impact the care of the research participant in any way	The research purpose may be: A. Exploratory: used to identify potential novel biomarkers B. Predefined: intended to evaluate or validate one or more known biomarkers
Research biopsy for integral biomarker study	Direct benefit to patients is not established	The biopsy will be used to determine whether a patient is eligible for a clinical trial or to assess one or more biomarkers that will be used to guide intervention within the trial
	Results will be used to directly guide the care of the patient within a clinical trial	One of the purposes of the trial is to assess or validate the biomarker(s)

resistance to a given therapy).¹⁹ The identification and validation of biomarkers that accurately predict a patient's response to cancer treatment is a rigorous scientific process that requires well-designed clinical trials.¹⁹ In general terms, biomarker research progresses from an exploratory phase, in which biomarkers are observed to be correlated with an outcome of interest, to prospective validation studies designed to confirm the clinical utility of a previously identified biomarker. A validated biomarker can be defined as a tissue-specific molecular feature of a cancer (such as the presence or amount of a specific protein or amplification or mutation of a specific gene) that has proven value as a clinical test in standard practice to guide patient management. Examples include estrogen receptor and *HER-2* testing for breast cancer and identification of mutations in *c-kit* in patients with gastrointestinal stromal tumors. Any biopsy performed to determine the status of a validated biomarker, whether within or outside of a trial, can be considered a clinical biopsy, and the primary ethical considerations relate to the risk of the procedure for the individual patient and the potential benefit to the patient from analysis of the biospecimen.

In considering the ethics of research biopsies, there are two primary types of research to be considered. The most common are correlative studies, in which the goal is to establish the association between a molecular feature of the cancer and a clinical outcome of interest. Correlative studies may convey vital information about which subsets of patients in a clinical trial are most likely to respond to a given intervention. These types of analyses are often a secondary goal of a trial that is designed to evaluate outcomes across a broader population of patients in the traditional research model. In correlative studies, the scientific evaluation of the tumor tissue sample will have no impact on the management of the trial participant and therefore no chance for direct benefit to participants.

In integral biomarker trials, the utility of the biomarker may not yet be firmly established, but a research biopsy is required to address the central question of the trial. Integral biomarkers include those that either determine patient eligibility for trial participation or those whose results dictate a specific therapeutic arm within a trial. For integral biomarker studies, even though the use of the biomarker to guide therapy is experimental, there may be a chance of direct personal benefit to study participants.

Biomarkers studies may not be exclusively dependent on research biopsies. In many cases, correlative research and even evaluation of an integral biomarker can be conducted on the basis of tissue from clinically indicated biopsy samples or surgical specimens. It is possible, however, that such samples may not be available for all patients or in all settings. In addition, there are many instances in which important research questions cannot be addressed with clinically indicated biopsies. Examples of these include testing of the validity of new biomarkers or trials that require a biopsy during therapy or assessment of tissue from a metastatic site where there is no proven role for a clinical biopsy.²⁰ As noted previously, optional research biopsies may be sufficient in some settings, but optimal progress in the field of biomarker research may at times require the conduct of clinical trials in which all participants undergo a research biopsy. Many feel that these trials are justified in the context of inadequate outcomes in many cancer settings and the increasing understanding that individual tumor biology can better guide therapy.²⁰⁻²³ The potential for harm, however, has raised questions within both individual cancer research centers and within the National Cancer Institute-funded cancer co-

operative groups. The science of oncology is presently at a crossroads in this area.

ETHICAL CONCERNS OVER MANDATORY RESEARCH BIOPSIES WITHIN CANCER CLINICAL TRIALS

The use of tissue samples for research is not controversial. In addition, the practice of obtaining research biopsies from informed voluntary participants, independent from any other clinical or research considerations, is also not particularly controversial.^{24,25} However, substantial ethical concerns may emerge when clinical trial designs establish a connection between participation in a clinical trial and the requirement that all participants undergo a mandatory research biopsy. This connection between the decision to participate in clinical research and the decision to undergo a biopsy solely for research purposes may be viewed as an unfair limitation of patient autonomy. Some have even argued that the requirement that patients subject themselves to a research biopsy to gain access to an experimental intervention potentially represents a form of coercion.^{24,26}

Part of the concern over mandatory research biopsies stems from the risk of the procedure itself. Although for any biopsy, for research purposes or otherwise, there is always some question of safety, in the clinical context, this risk is balanced against the prospect of direct benefit from the information obtained from the biopsy. For research biopsies, the participant undergoes some risk (including the possibility of very rare life-threatening complications), which will vary depending on the location of the tumor and the nature of the biospecimen required by the study, with no prospect of direct benefit in a correlative study, and at best uncertain benefit in an integral biomarker study. Some make a distinction between trials with mandatory biopsies with at least some chance of direct benefit (such as an integral biomarker study where intervention is guided by the biomarker),²⁶ whereas others draw no clear distinction.²⁴ Regardless of whether there is potential for direct benefit from the research biopsy or not, most would likely agree that the location of the tumor and the level of risk involved in the procedure are relevant factors that should be taken into account when deciding whether a mandatory biopsy design is acceptable.

Given that a research biopsy conveys some risk and little to no chance of direct benefit, it is clear that patients should be given the opportunity to make a voluntary informed decision about whether or not to participate in such research. However, the bundling of this decision with the decision to participate in a clinical trial raises longstanding concerns regarding why patients enter clinical trials and the adequacy of informed consent.^{27,28} In this context, the requirement for biopsy to participate in a trial can be seen as a direct limitation of patient autonomy.

Although altruism motivates some patients to enter clinical trials,²⁹ it is well established that the majority of patients choose to enter clinical trials out of hope of direct personal benefit.^{30,31} A patient may be strongly motivated to participate in a clinical trial to obtain access to a promising new, though unproven, intervention, and such trial participation is sometimes viewed as the best choice of treatment for a patient.³² These observations lead some to conclude that requiring subjects to undergo a research biopsy as a condition for trial participation may be coercive.^{24,26} This view hinges in large part on both the availability (or lack thereof) of alternative treatments or clinical trial

options and the perception of the patient considering trial enrollment. Although this is a controversial and perhaps extreme view, most would agree that some patients seeking access to a novel intervention may feel compelled to enroll in a clinical trial because of the vulnerability created by their illness and the limitations of standard therapy and that they therefore deserve special protection from exploitation in research. Whether such protection should preclude studies with mandatory biopsy or merely inform the standards for how and when they are included in clinical research is a matter of debate.

It must be noted that not all potential studies with mandatory research biopsies raise similar levels of concern. Integral biomarker studies for which the trial simply cannot be conducted as designed without a research biopsy to guide therapy according to protocol are less problematic than studies that require biopsies purely for scientific purposes. Similarly, a distinction can be made between correlative studies that are purely exploratory and those that are designed to test a strong scientific hypothesis. Consideration can also be given as to whether the correlative science question is a secondary end point, rather than the primary end point of a trial. Trial size is typically based on recruiting the minimum number of patients to address the primary objective, leading some to observe that if a study is not statistically powered to definitively address a secondary correlative science question, then there is no scientific rationale to justify requirement of biopsy in all research subjects.

CAN MANDATORY RESEARCH BIOPSIES BE ETHICAL IN SELECT CANCER CLINICAL TRIALS?

The specific issue at hand is whether an informed adult patient can ethically be asked to decide for themselves whether or not to participate in a clinical trial that includes a research biopsy, and if so, what the requirements and regulation of such research should be. All ethical research requires a meaningful scientific question, a research protocol that is well designed to answer the question, informed consent on the part of trial participants, and respect for research participants at all stages of study design, conduct, and analysis.³³ We contend that it is possible for a cancer clinical trial to require research biopsies from all participants in accordance with these principles under select circumstances.

First, to include a mandatory biopsy in a clinical trial protocol there must be a strong scientific rationale for doing so. The potential risk to the participant can only be justified by the likelihood of social benefit as a result of the research. A critical part of trial design and independent review by cancer center protocol committees and institutional review boards must be the consideration of the specific scientific hypothesis that dictates a need for a mandatory research biopsy. If the correlative research is purely exploratory, or the scientific question can be addressed through optional biopsies from a subset of trial participants, then mandatory biopsy should not be required. Similarly, if the trial is powered for a clinical end point and there is insufficient statistical power to address a correlative question, then there is likely insufficient rationale to make research biopsies mandatory. Whether the correlative component is a primary or secondary end point of the trial is not ethically relevant, so long as the study is otherwise adequately designed to be able to address the question deemed to require mandatory biopsy.

Second, there must be stringent efforts at all stages of research design and conduct to minimize the risks of the research biopsy to

study participants. Accepting some degree of personal risk, without direct personal benefit, has long been accepted for research biopsies and for many common mandatory components of trials, including blood draws and imaging studies. In general, the concept of accepting some personal risk in exchange for scientific benefit has been viewed as ethically permissible in major codes of ethics, including the Belmont Report and Declaration of Helsinki.³³⁻³⁵ There has been limited study of the safety of research biopsies, and more research in this area is clearly needed.²¹ Despite this, there is a large body of experience with performance of clinical, nonresearch-related biopsies, which are typically an identical procedure differing only in the purpose and processing of the biospecimen.^{36,37} For select disease sites, such as prostate cancers, studies of repeat core biopsies done for clinical indications have shown rates of serious complications approaching 0.1%.³⁸ In general, patients seem willing to accept some degree of risk in the interest of contributing to cancer research.³⁹ The least invasive method of biopsy collection should always be considered, and the risks of any procedure must be minimized, monitored, and carefully explained to ensure informed consent of potential trial participants.

One of the major concerns that we considered was whether mandatory research biopsies establish a barrier to access to the experimental intervention and in some sense may therefore cause harm to the patient who does not agree to undergo a research biopsy. In our view, such a claim would rest on the problematic premise that access to an investigational agent in a clinical trial is likely to be beneficial. Although in many cases, access to an investigational agent does prove beneficial for some trial participants, for many trials there is no benefit,⁴⁰ and in rare cases, outcomes with experimental therapy may be inferior to standard care.⁴¹⁻⁴⁵ By definition, an experimental intervention has unclear safety and efficacy. Although coercion implies undue pressure to persuade someone to accept something (eg, consent to a research biopsy) that is against their values or interests to gain something they need (eg, access to therapy), in effect depriving them of their autonomy, this may be falsely applied in the case of concerns over mandatory biopsies within clinical trials. If the intervention is not proven to be safe or effective for the patient's condition, then the ethical problem is not coercion, but rather the false understanding among potential research participants regarding the need for access to the intervention. Similarly, there is no established right to access to experimental interventions that would be infringed by a trial design with mandatory research biopsies.⁴⁶ The solution to this problem is not to make research biopsies optional, but to ensure that potential participants understand the nature of and uncertainties surrounding the experimental intervention in particular and the difference between standard care options and experimental options in general.⁴⁷

Although including a mandatory biopsy in a clinical trial should not be viewed as coercion, we must still recognize that patients frequently enter trials to obtain access to experimental therapy, even when adequately informed of the unproven nature of the intervention. We must therefore continue to take steps to insure that this motivation does not lead to exploitation. Patients considering a trial with a research biopsy must be clearly informed that the biopsy is for research purposes only, and any potential harm must be described. Biopsy protocols must specify collection of tissue in the safest way possible and should monitor for safety and tolerability of the research biopsy by the same strict criteria used to monitor for adverse effects of experimental medication. Finally, trial participants must be informed of alternatives to trial enrollment and of their ability

to drop out of the trial before the biopsy, if they choose. It must be recognized that including mandatory research biopsies within a trial may have an impact on trial accrual and that patients' right to withdraw from a study risks the possibility that some participants will drop out after randomization in randomized control trials. For open-label studies of new interventions, unequal drop-out rates in the arms of the trial could lead to bias in the study results. These factors must be weighed against the scientific benefits of requiring biopsies from all participants.

Although requiring a research biopsy may limit trial accrual, this is a scientific trade-off comparable to other burdens and limitations considered in clinical research. Survey of patients with cancer suggests that up to one third of potential trial participants may be reluctant to enter a study involving mandatory research biopsies, but close to 50% report it would not impact their willingness to enter a trial.³⁹ Given that participants may refuse biopsy once enrolled in the trial, how this will be managed (eg, will a patient be allowed to continue to receive experimental therapy?) should be addressed in trial protocols, and the proper response may vary for different studies and scenarios. For example, for integral biomarker studies in which biopsy results will be used to guide experimental therapy in some way or in studies that require the research biopsy before initiation of therapy, it may be reasonable (and/or necessary) to exclude those who refuse the biopsy from further trial participation, whereas for studies in which a biopsy for correlative purposes is indicated midtherapy, patients who refuse the biopsy should likely be allowed to continue on trial therapy in some cases. The impact of mandatory research biopsies on trial accrual is an important but distinct question from whether such studies are ethical.

Finally, it should be noted that although optional biopsies rather than mandatory biopsies are frequently preferable, mandatory biopsy design may be more ethical in terms of balancing risk to participants with likelihood of scientific benefit in some cases. If a scientific question is unlikely to be adequately addressed from a subset of trial participants, then the risk of the optional procedure yielding no scientific benefit cannot be justified. An informed patient entering a trial with a mandatory research biopsy design that is adequately powered to address the scientific question may be better served.

POSITION

It can be ethical to include mandatory research biopsies within clinical trials for correlative science and integral biomarkers studies. This is not meant to imply blanket approval of all study designs that employ mandatory research biopsies, and further debate on this issue is needed and encouraged. However, under the following conditions, the designation of a research biopsy as a mandatory component of a clinical trial can be consistent with both pursuit of good science and appropriate protection of human research subjects.

First, there must be similar rigorous evaluation of the rationale for mandatory (vs optional) biopsy in the trial development and independent review process, as is commonly used when considering the rationale for administration of an investigational agent within a trial. Investigators, sponsors, and institutional review boards must make an affirmative judgment on a protocol-by-protocol basis that mandatory biopsies are indicated to achieve an important scientific objective.

Second, meaningful efforts must be taken to insure that patients are adequately informed that biopsies are required and are for research purposes only.

Third, there must be adequate monitoring to insure that the necessary procedure is performed safely and that adverse events are reported appropriately. The safety of research biopsies in the study population should be considered in formulating the trial inclusion and exclusion criteria.

Fourth, when possible, research samples should be obtained at the time of routine clinical procedures to minimize inconvenience and discomfort for patients.

Finally, separate research biopsies should only be required when no clinical sample that can adequately meet the scientific goals of the study is available.

In conclusion, in the era of molecularly targeted therapies and continued poor outcomes for many types of cancer, there is a pressing need to improve our understanding of the biology of cancer and to improve outcomes for future patients. The promise of personalized cancer care rests on our ability to truly understand and respond effectively to the biologic differences between patients. In addition, given the reality of constrained health care resources, there is a need to determine which patients may benefit from an intervention and which should be treated with an alternative strategy. There are moral dimensions to both our need for better treatments and better use of health care resources. On the other hand, there is a need to acknowledge that patients with cancer seeking access to investigational therapy are frequently under duress from their illness and may be interested in trial participation primarily due to expectation of direct personal benefit. Any study using research biopsies in this population must be well designed to address the scientific question, obtain the biopsy with minimal possible risk, and ensure that research participants are fully informed of the risks, rationale, and requirements of the study, as well as of treatment alternatives. In addition, the scientific justification for a mandatory biopsy design as opposed to optional biopsy or use of clinical specimens for correlative end points must be carefully considered in trial design and review. We feel that if these guidelines are respected, an informed adult with cancer can both understand and voluntarily consent to participation in a clinical trial involving mandatory research biopsy for scientific end points. Such trials may be necessary to ultimately defeat cancer, and our patients can be valued and respected partners in this effort. Finally, we acknowledge that there is a need for ongoing discussion of this important research issue.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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