Mandatory Exploratory Biopsies:

A checklist for study reviewers and the study team

By Karl Schwartz (patient advocate)

The checklist provided here is based on the guidelines in Ethics of Mandatory Research Biopsy for Correlative End Points within Clinical Trials in Oncology. [1]

The purpose is to help reviewers and researchers to weigh and communicate the risk/benefit potential – the rationale for mandating biopsies, particularly exploratory biopsies, as a condition of acceptance in clinical trials.

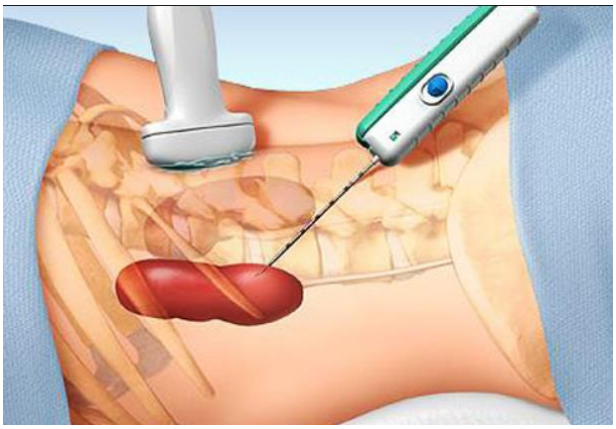
Procedures to reduce anxiety *during* the procedures may have improved. The risks of core needle, CT-guided biopsies are low (about 5%), and serious complications are rare (less than 1%).[2]

However, there are other burdens to consider (such as lost time and the expense of travel to have the extra procedures), as well as the impact of the requirement on timely study accrual and the potential of biasing the study results by including or excluding patients with higher or low risk disease based on the accessibility of the tumor.

Whether there can be sufficient justification for exploratory biospecimen-based correlative studies can be in the eye of the beholder. Certainly, not all of these can be fairly called “fishing expeditions.”

The reviewer’s assessments of the potential for the knowledge to be gained requires background in the science, but should also require of the scientist a directed explanation that is understandable to IRB reviewers, including patient advocates who are the liaisons with the patient community (the primary stakeholders).

For example, that a specific finding could apply broadly across many types of cancer or other classes of drugs, or is directed at a pivotal question of importance to patients will aid in the assessment. The justifications that are well stated and understandable to advocate reviewers will also help researchers to gain the public trust.



1 JCO, 2012: Ethics of Mandatory Research Biopsy for Correlative End Points Within Clinical Trials in Oncology http://bit.ly/1s0u1vx

2 JCO: Use of Research Biopsies in Clinical Trials: Are Risks and Benefits Adequately Discussed? http://bit.ly/2DqlsKu

MANDATORY EXTRA BIOPSIES		Notes and related questions.
Before Study	Y / N	Is the before-study-biopsy integral to the study - such as by establishing a tumor type or feature that's more likely to be sensitive to the mechanism of the study drug. *Can the screening be done with a panel assessment to identify a range of potentially actionable molecular changes?*
Only if archival tissue not available:	Y / N	For patients potentially eligible for this study (and for each cohort if multiple tumor types), provide as a ratio the number expected to have the tumor feature (?/100)
During study	1, 2, 3	Circle the number of mandatory biopsies and describe the associated endpoint (as integral, integrative, exploratory) *"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?) This should be addressed in trial protocols."*
On Progression (PD)?	No, Yes, Optional	Mandating biopsies on progression of disease (PD) may not be enforceable. Patients may opt out when coming off study due to PD.
Risk of procedures	1 - 5	In the column to the left, rate the risk on a scale of 1 to 5, with 5 being very high. - Does the consent describe risk of complications as a rate? - Does it describe the variation of risk based on tumor location and patient characteristics? - Does the procedure require general anesthesia? - Does a side effect of the study drug increase the risk of the biopsy procedure such as a bleeding risk? - Does mandating the biopsy introduce bias – selecting or excluding patients with higher or lower risk disease?

1 JCO, 2012: Ethics of Mandatory Research Biopsy for Correlative End Points Within Clinical Trials in Oncology http://bit.ly/1s0u1vx

2 JCO: Use of Research Biopsies in Clinical Trials: Are Risks and Benefits Adequately Discussed? http://bit.ly/2DqlsKu

MANDATORY EXTRA BIOPSIES		Notes and related questions.
Burden: psychological, physical, economic	1 – 5	Rate the burden on a scale of 1 to 5, with 5 being very high. Economic burden: time from work or need to pay for care of family on day(s) of procedure(s) Are biopsies done on same day as a usual or non-invasive study procedure? Will there be assistance to pay for time off work or for travel? *Who is responsible to pay to treat complications from the procedure – the study sponsor, the patient, or the patient's insurance company?*
What are the eligible patients' other choices?	Unmet need / Standard can be effective	If there is no effective usual approach, the participants may consent to required biopsies done for exploratory purposes because they believe the study intervention is their only chance.
Stated purpose in protocol	Integral / Integrative / exploratory (mechanistic / dose-related / safety)	Tumor biopsies that are integral to the study may increase the prospect for benefit by selecting patients more likely to respond to the study drug. Integrative biomarkers have a high prospect to benefit future patients. The prospect for knowledge gained from exploratory objectives is less certain and requires a thorough and well written explanation.
Is the biopsy study related to a primary endpoint?		Reference primary endpoint here.
Assays	Validated / CLIA	Are the assays used to evaluate the specimens validated (provide reproducible findings?)
Scientific justification		Provide a score (rate with 5 being the highest) and a brief comment on the scientific justification for the correlative research - and integrative research if it is a close call.

1 JCO, 2012: Ethics of Mandatory Research Biopsy for Correlative End Points Within Clinical Trials in Oncology http://bit.ly/1s0u1vx

2 JCO: Use of Research Biopsies in Clinical Trials: Are Risks and Benefits Adequately Discussed? http://bit.ly/2DqlsKu

MANDATORY EXTRA BIOPSIES		Notes and related questions.
Marker type	Mechanistic? Dose / safety? Resistance? Prognostic? Correlative?	Is it known yet if the study drug can be efficacious for the study population? This should be considered if the purpose is to understand resistance to efficacy, mechanism of efficacy, or prognosis. *Is studying this correlation putting the cart before horse?* *What happens if the on-study biopsy finding strongly suggests that the dose of the study drug is not sufficient to be clinically efficacious? Is the participant informed?*
Sample size (Power)	N=? (per subtype)	Is the size of the study sufficient to find an answer to the biopsy-related purpose?
Heterogeneity of eligible tumor types		Justify confidence in the findings with consideration of the heterogeneity of tumor types and treatment histories.
What's the next step?		What specific finding (cutoffs etc) would warrant a clinical or research application?
Reporting		Please specify in the protocol a commitment to report the results of the required exploratory biospecimen-related research. Indicate if the participants will receive aggregate results (should this be standard?) and individual results if the findings are validated to be clinically useful.

Background for the public:

Exploratory biospecimen studies *look for associations between tumor features and certain outcomes – such as response (or resistance) to the study treatment. There may be billions of tumor features. Identifying which matter is very challenging. Thus, any associations that may be found cannot guide the care of patients in the near term.*

Associations do not prove causality – that A caused B.
(The rooster crowing at dawn does not cause the sun to rise.)

So it follows the purpose of exploratory biopsies is for science: the knowledge that may be gained. The findings cannot help the patient taking part in the study. So, it also follows that the study team must make the case to the ethics review board (the IRB) that the knowledge to be gained offsets the risk and burden of the biopsy procedure.

1 JCO, 2012: Ethics of Mandatory Research Biopsy for Correlative End Points Within Clinical Trials in Oncology http://bit.ly/1s0u1vx

2 JCO: Use of Research Biopsies in Clinical Trials: Are Risks and Benefits Adequately Discussed? http://bit.ly/2DqlsKu

JCO, 2012: Ethics of Mandatory Research Biopsy for Correlative End Points Within Clinical Trials in Oncology

Summary:

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.

Some Key Points:

Evaluation of tumor samples through research biopsies can potentially advance our knowledge and treatment of cancer in several ways.

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.

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.

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.

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

1 JCO, 2012: Ethics of Mandatory Research Biopsy for Correlative End Points Within Clinical Trials in Oncology http://bit.ly/1s0u1vx

2 JCO: Use of Research Biopsies in Clinical Trials: Are Risks and Benefits Adequately Discussed? http://bit.ly/2DqlsKu

conclude that requiring subjects to undergo a research biopsy as a condition for trial participation may be coercive.[24,26]

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.

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**.

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.

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.

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.

Related questions:

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.

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 [which can bias the study]

1 JCO, 2012: Ethics of Mandatory Research Biopsy for Correlative End Points Within Clinical Trials in Oncology http://bit.ly/1s0u1vx

2 JCO: Use of Research Biopsies in Clinical Trials: Are Risks and Benefits Adequately Discussed? http://bit.ly/2DqlsKu

1 JCO, 2012: Ethics of Mandatory Research Biopsy for Correlative End Points Within Clinical Trials in Oncology http://bit.ly/1s0u1vx

2 JCO: Use of Research Biopsies in Clinical Trials: Are Risks and Benefits Adequately Discussed? http://bit.ly/2DqlsKu