Mandatory Research Biopsies in Clinical Research

1. Summary of IRB Review Criteria

Institutional Review Board review of research subject to FDA regulations or regulations of agencies that have codified the Common Rule is focused on ensuring the protection of the individuals who volunteer to participate in research. Without the voluntary participation of human subjects or participants or volunteers—however they may be described—research that aims to provide new drugs, devices or other tools to better enhance the prevention, diagnosis and treatment of health conditions would not be able to take place.

Review by the IRB is guided by regulatory criteria which in their application can be broad, subjective and applied inconsistently. Those criteria are the following:

1. Risks to subjects are minimized
2. Risks to subjects are reasonable in relation to anticipated benefits
3. Selection of subjects is equitable
4. Informed consent will be obtained in accordance with 116
5. Informed consent will be appropriately documented or waived
6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data

Reasonable minds might differ as to whether a particular procedure serves to minimize risk; whether the research might provide benefits to the participants; whether subject selection is equitable given the geographical location from which recruitment efforts will occur; and so on.

Along the same lines, reasonable minds might differ whether something that is included in the research protocol, such as a mandatory biopsy, is necessary and integral in order for the investigator/sponsor to meet the scientific objectives outlined in the protocol.

2. ASCO Addresses Issue of Mandatory Biopsies in Research

In September of 2019, the Journal of Clinical Oncology published a statement by ASCO entitled: “Ethical Framework for Including Research Biopsies in Oncology Clinical Trials: American Society of Clinical Oncology Research Statement.” In the summary paragraph, the issue is stated as follows: “The widespread use of research biopsies that do not have the potential to directly benefit participants has come under scrutiny, with critics raising ethical concerns related to the adequacy of participant protections, informed consent, and participant understanding of the risks and benefits, as well as the scientific impact of research biopsies on drug development and treatment.”

The statement proposes six recommendations that fall within three major goals:

1. Maximize scientific utility,
2. Minimize participant risk, and
3. Improve oversight
With respect to maximizing scientific utility, the recommendations are:
(1) Improve the scientific rationale for and conduct of research biopsies
(2) Increase publication and dissemination of research biopsy safety and results

With respect to minimizing participant risk, the recommendations are:
(1) Promote best practices in the conduct of research biopsies
(2) Improve serious AE reporting for research biopsies
(3) Improve the informed consent process for trials requiring research biopsies

With respect to improving oversight, the recommendation is:
(1) Ensure that proposed research biopsies are adequately reviewed during the study development process

3. Mandatory Biopsies in Research

It is not uncommon for an IRB to review research that includes a mandatory biopsy. It may be difficult for an IRB to determine whether the biopsy is necessary for the research; or, whether it serves a purpose that is essentially secondary and not integral to the research objectives. This becomes more of an issue where the research may provide the only option for individuals who have exhausted standard of care options.

4. Mandatory Biopsies in Phase 1 Research involving Healthy Volunteers

Phase 1 research that seeks to recruit only healthy volunteers poses some challenges with interpretation and application of the IRB review criteria. First, in this type of research, there is no benefit to the healthy participants. Healthy volunteers in research are paid to participate in the research and that compensation has been subject to many different opinions in terms of how to describe the reason for the compensation. Is the compensation a benefit to participation in the research? Is the compensation intended as a type of reimbursement for the time spent to participate in the research? In addition, Phase 1 research in healthy volunteers poses a challenge in thinking about the IRB review criteria that requires an IRB to determine that the subject selection is equitable. When a protocol is only enrolling healthy volunteers, why would an IRB look more deeply into the type of subjects who will be recruited?

Phase 1 research in healthy volunteers may also include mandatory biopsies. As with any other research, these may be integrally related to the study endpoints—or not.

5. OHRP Guidance

In a compliance determination letter dated November of 2012 to the University of Michigan, OHRP opined:

“We determined that the consent form provided for a study indicates that subjects may be coerced into participating in open-ended, future research involving their biospecimens, in contravention of the regulatory requirements at 45 CFR 46.116.
Corrective Action: We acknowledge your statement that in future review of studies with a substudy, IRBMED will advise investigators to include an opt-out element in the informed consent process to be consistent with 45 CFR 46.116 to minimize the possibility of coercion or undue influence for subjects wishing to participate only in the main study. We acknowledge that your corrective action plan includes the following: education of IRB staff and IRB members to raise awareness of studies that require an "opt-out" consent provision when sub-studies are embedded within the main study; reminders to the research community to include an opt-out element in the informed consent when sub-studies are associated with the main study; and modification of your informed consent template to include instructions to manage opt-out provisions for sub-studies.”

At that point in time, OHRP appeared to be taking the position that if the main study was segregable in any way, that other procedures and sub-studies needed to be designed as optional in order to avoid the “the possibility of coercion or undue influence for subjects wishing to participate only in the main study.”

6. SACHRP has been asked to consider whether a guidance document on the issue of mandatory biopsies is an appropriate and useful topic for which SACHRP might provide useful guidance to Institutional Review Boards.

The inclusion of mandatory biopsies occurs in both pediatric and adult research. While it was highlighted by ASCO, it is not specific to oncology trials. It is not uncommon to see mandatory biopsies included in research approved by the NCI CIRB.

Under the current IRB regulations, an IRB would not be able to approve a research protocol involving mandatory tumor biopsies if, in doing so, any of the seven criteria noted above could not be met.

7. Some discussion questions for SACHRP:
   a. How would an IRB determine that a mandatory biopsy is not appropriate to be included as a mandatory procedure in the study?
   b. Does the type of study make a difference in terms of the appropriateness of a mandatory biopsy?
   c. Is the IRB criteria as written sufficient to enable an IRB to address a concern with a protocol that includes a mandatory biopsy that an IRB might determine poses unreasonable risks or otherwise is not appropriate or necessary for the conduct of the research?
   d. Does the ASCO guidance provide additional criteria?
   e. Does the ASCO guidance provide a meaningful tool to interpret and apply existing IRB criteria?
   f. What would a SACHRP guidance document on this topic address?