# Attributes of Exemplary Research

## Issues Surrounding Biospecimen Collection and Use in Clinical Trials

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The ASCO statement on exemplary attributes for research sites was introduced in May 2008 in *Journal of Clinical Oncology*.[1] The initial statement was followed with a bimonthly series beginning in July of the same year in *Journal of Oncology Practice* focusing on providing expert advice regarding pertinent clinical research topics. The concept of exemplary attributes has since become the foundation of many ASCO initiatives and been referenced in several publications, including the recommendations of the 2010 Institute of Medicine report regarding cooperative group clinical trials.[2] Now, 2 years later, authors of the series remain committed to helping oncologists make clinical trial participation a key component of their practices. The series is aimed at assisting research sites in their efforts to exceed Good Clinical Practice guidelines by achieving all, or some, of the designated exemplary attributes:

- Diversification of clinical trial mix
- High accrual activity
- Participation in the clinical trial process
- Formal maintenance of high educational standards
- Quality assurance
- Multidisciplinary involvement
- Clinical trial awareness programs

We have chosen to commemorate the 2-year anniversary of the series with a particularly compelling topic: the ethical and regulatory concerns surrounding biospecimen research. As we seek to translate our understanding of cancer biology and genetics into novel preventive, diagnostic, and therapeutic interventions, we recognize an increased need to ask our patients to consent to use of their tissue or other biologic samples for biospecimen or correlative research. Numerous ethical and potentially legal questions have subsequently emerged, to which definitive answers are challenging. This article reviews several of the major concerns that may arise, addresses them on the basis of expert opinion, and references resources to assist research sites as they navigate this promising field. It should be noted that although research is addressed in this article, biospecimens and the complexities surrounding them increasingly exist in standard medical care, and more treatments are based on molecular decisions.

### ASCO Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Sites

The ASCO statement addresses the minimum requirements for sites conducting quality clinical trials as well as the attributes of exemplary sites. Both minimum requirements and exemplary attributes were determined based on a review of the literature, current regulatory requirements, and consensus among community and academic clinical researchers. To conduct quality clinical research, sites should meet the minimum requirements. However, it should be noted that the exemplary attributes are voluntary and suggested as goals, not requirements. Not all attributes will apply to all clinical trial sites, and many sites may be able to conduct high-quality clinical trials without accomplishing all attributes.

### Step 1: Talking With Patients

Given the importance of biospecimen research in addressing both current and future research questions and prevailing societal concerns over privacy of genetic information, it is essential that communication about biospecimen collection be thorough, open, and honest. Biospecimen research involves the collection of tissue or fluid samples for analysis of participants' genetic or other molecular features that may affect cancer risk, prognosis, response to therapy, or adverse effects of treatment. The science of oncology is undergoing a transformation from an era in which new drugs or treatment approaches are tested across broad populations of patients to an era in which drug testing will be focused on important molecular features of cancer to study the way patients respond to treatment. Results from this research will enable determination of who will benefit from a given intervention and who will not. The study of the association between molecular features of biospecimens and clinical outcomes is termed correlative science, and increasingly, correlative science is transforming patient care in oncology. However, our continued progress in this area relies on patients' willingness to donate tissue or other biologic samples for research. A recent court case between the Havasupai Native Americans and Arizona State University highlights the importance of ensuring that those who consider research understand, agree to, and are confident in the process.[3]

The challenge of collecting adequate numbers of biospecimens to address the oncology research questions of today is complicated by the relative lack of understanding about the need for and purpose of such research among the general pop-

ulation and many in medical practice. It often falls on the clinician treating a patient's cancer to explain the importance and nature of this correlative science research. Additionally, it is critical that clinicians and their staff give all patients, regardless of culture, the opportunity to participate in biospecimen and medical research. Participation by patients of all ethnic and racial backgrounds helps to ensure that future medical advances benefit all patient populations. This article offers some suggestions for keeping the discussion about biospecimen research as simple as possible for all involved.

First, it is important to explain the rationale for collecting biospecimens and discuss how scientists use the information collected from many patients to address important questions that may help prevent or treat cancer. Patients have a right to know how their participation in such research may help future patients. It is also important to fully discuss the risks and uncertainties surrounding biospecimen research and the data produced from it. One of the central challenges in this area is that researchers want to collect biospecimens now to address questions that will arise in the future, storing the tissue in biobanks. How tissue, fluids, and data collected today may be studied in the future is often not fully predictable at the time that clinicians request samples from patients. It is important that discussions with patients acknowledge these uncertainties as well as the potential for biobanks to create rapid access to stored samples as future research questions emerge.

One topic that merits special consideration in these discussions with patients is genetic research, which frequently raises questions of personal identity and confidentiality. First, it is important to differentiate between types of genes involved in research. The focus could be on heritable genes that affect an individual's risk of developing cancer (such as *BRCA1* or *BRCA2*), heritable genes that may affect an individual's drug metabolism (such as *CYP2D6*), and tumor-specific genes—which may or may not be heritable—that may affect the response of the tumor to therapy (such as *KRAS* or *HER2*). In addition to distinguishing the type of genes under investigation, there is a need to discuss precautions taken to protect patient confidentiality. Typically, researchers are using biospecimens that have been stripped of identifiable information, but a biobank may retain a code enabling linkage of the sample, results, and personal identity of the patient. The code is stored separately, with multiple safeguards to preserve privacy. However, it is important to acknowledge that although current technology is incapable of identifying individuals solely by genetic material alone, such technology may emerge, potentially making de-identified specimens and their associated data identifiable in the future. Much like fingerprints, biospecimens may one day be traceable back to the individuals who donated them. A growing trend is to share data derived from individual studies through Web-based warehouses, such as the Database of Genotypes and Phenotypes, which introduces another level of complexity.[4] This sharing of data is usually desired by researchers and patients alike, but both the advantages and possible risks need to be explained. Conversations about biospecimens should address precautions taken to protect confidentiality and explain who will have access to any personal identifiers associated with donated specimens.

It is also important to discuss with patients whether they will directly benefit from donating specimens and the nature of any risks involved. In most cases, when a biospecimen is used for correlative science, meaning that a molecular feature of the sample will be studied in correlation with clinical outcomes, there will be no direct benefit to the individual patient, because it takes many patients, and time, to realize practice-changing outcomes. In some cases, a biospecimen may be collected as part of a clinical trial and used to determine course of therapy within the trial. This type of trial, in which a biospecimen is central to the purpose of the study itself, is termed an integral biomarker trial. By definition, there is some potential for direct benefit in such trials, but the uncertainty of benefit from using a biomarker to guide therapy must be made clear to patients. In contrast, if a biospecimen is collected for research purposes only within a clinical trial, the patient must be informed that he or she will not directly benefit from research involving the biospecimen. This must be distinguished from any portions of the trial that do provide potential for direct benefit to the participant. If collecting the specimen requires a procedure that is beyond what would be conducted for routine clinical care, it is important that the patient be aware of the additional procedures and understand the potential for increased risk. These procedures could range from additional blood draws to invasive biopsies. When possible, protocols should aim to reduce the need for excess procedures that involve risk to participants and no or minimal chance of direct benefit. If a sample obtained for clinical purposes can also be used for biospecimen research, this is typically preferable.

A practical challenge for clinicians who wish to offer their patients the opportunity to participate in biospecimen research includes the need to explain the rationale for research, review any risks and benefits, and discuss the matter in a manner that fosters patient understanding. Accomplishing this can be challenging, considering the time pressures of the average clinical visit. To educate patients and families in the most clear and efficient way, clinical researchers may consider a team approach. In some settings, the oncologist introduces the option of clinical research during a routine appointment, a clinical research associate or nurse provides follow-up to answer additional questions, and a patient advocate or support group continues to facilitate the process through education or by serving as a patient navigator. This approach not only provides the patient with several ways to learn and process information but also empowers the patient to make an informed decision with reduced fear of disappointing his or her physician, which may occur when the physician is both the clinician and the only point of contact regarding trial participation.

Several resources exist to assist in educating patients about genomic research. Many educational materials can be ordered free from the National Cancer Institute, including the helpful brochure "Providing Your Tissue for Research: What You Need to Know."[5] Patients seeking slightly more advanced information may benefit from the free educational materials published by the Research Advocacy Network, which include English and

**Recently Released Resource**

- Peppercorn J, Shapira I, Collyar D, et al: Ethics of mandatory research biopsy for correlative end points within clinical trials in oncology. J Clin Oncol 28:2635-2640, 2010

Spanish versions of brochures such as "Why Is It Important for Me to Consider Donating My Tissue for Research?"[6] After the initial discussion of genetic research with a patient, the informed consent process provides another forum for the patient to learn more about the proposed research.

## Step 2: Informed Consent

There are many considerations that must be addressed during informed consent. The informed consent form must include information specific to regulatory compliance and the use of biologic specimens in each trial. In the United States, the Office of Human Research Protections regulates federally funded research with human participants and publishes guidance documents regarding these regulatory requirements, which are accessible through its Web site.[7] Many of these considerations are also addressed in the "National Cancer Institute Best Practices for Biospecimen Resources,"[8] which is a voluntary guidance document available online through the National Cancer Institute (NCI) Office of Biorepositories and Biospecimen Research.

An additional topic unique to biospecimens that may be addressed in consent forms is custodianship, which involves proper maintenance of patient specimens and privacy. Consent forms should outline how patient privacy will be maintained for the use of specimens collected and banked, such as de-identification. Procedural concerns must also be explained, such as timing of specimen collection, where the specimens will be stored, what will happen to the specimens, and who will have access to them. The topic of future use should also be addressed if specimens or results will be used in future evaluations. The issues surrounding future use are still under debate. Although it is agreed that consent documents should address future use, it is often difficult to fully explain the scope of what that use may encompass. Therefore, the terms of future use often vary among institutions. Trials performed in the past in which consent for the future use of biospecimens was not obtained now face challenges regarding whether specimens can be used for research beyond the scope of what was included in the original consent forms. Intellectual property should also be explained in the consent process; patients should be clearly informed that they will not receive financial gain from any new treatments developed through research conducted on their specimens. It may be helpful to inform patients that thousands of specimens may be needed to lead to the development of new products. Therefore, their specimens, though vital in the process, are not individually responsible for the development of new treatments in most cases. As previously discussed, potential risks associated with participation must also be addressed, including risk of physical harm and any risks related to privacy and confidentiality.

In recognition of the complexity of informed consent documents and the challenges faced by researchers in consenting patients for participation in biospecimen research, the NCI asked its Group Banking Committee to develop a harmonized informed consent document, patient educational materials, and institutional review board information materials, all pertaining to the collection and banking of biospecimens for research use. The Group Banking Committee Regulatory Working Group, which consists of patient advocates and representatives from each NCI Cooperative Oncology Group, will release these documents in the near future.

Although these documents will be designed for NCI-funded trials, similar guidance documents have also been produced by the pharmaceutical industry and may be helpful for industry-funded or investigator-initiated trials. The Pharmacogenetics Working Group (PWG) is a voluntary working group of pharmaceutical companies created to address ethical, regulatory, and legal issues associated with pharmacogenetic research. Pharmacogenetics is a subset of biospecimen research involving the study of germline genetic differences among individuals that influence metabolism, response, and/or resistance to pharmacologic interventions. The PWG has published several documents, including one article outlining the elements that should be included in informed consent documents for pharmacogenetic research.[9]

## Disclosing Research Results

Many patients who participate in research express a desire to receive results regarding testing that is performed on their donated specimens. Policies regarding this issue vary among trials, sponsors, and even locales in which the study is being conducted. In the case of a trial with inclusion criteria requiring that a patient express a specific biomarker for eligibility, the attending physician is usually informed of the results and is responsible for relaying the results to the patient, thus confirming his or her eligibility for trial participation. In the case of a trial in which specimen collection is for correlative or exploratory use, individual results may not be shared with the treating physician or patient. Exploration of genomic or phenotypic predictors of treatment responsiveness or specific disease subsets within a trial are increasingly the examples we see in research. Study reports may include information on biomarker expression, response data, and outcomes, but this is aggregate information rather than information specific to individual participants. When research involves experimental biomarkers that have not yet been validated for clinical use, additional ethical issues regarding sharing specific patient information must be tackled before clinical utility can be studied appropriately in randomized clinical trials.

It is good practice to inform patients when general outcomes of studies conducted with their specimens become available in publications. This may be accomplished through discussion with their research teams, annual reports sent to research participants, notification when outcomes are published, or Web sites established for this purpose. Listing outcomes on specified Web sites can be a helpful way of conveying this information, because it ensures that patients with Internet access can obtain the information even if they no longer receive treatment or follow-up at certain research

## Upcoming Events

ASCO plans to offer online educational opportunities in which content providers to the series will discuss these topics in more detail. Visit www.asco.org/ClinicalTrialResources for more information, and obtain tools and resources related to topics in the article series. Access the entire Attributes of Exemplary Research series at http://jop.ascopubs.org.

## Feedback Request

Suggest future topic ideas for the series and provide your feedback by sending an e-mail to researchresources@asco.org.

sites. This may help patients recognize tangible value in donating specimens and facilitate their continued desire to participate in research. It also fulfills a promise made in consent forms, described as sharing important information learned from trials. The PWG has published a detailed overview of the laws and regulations governing this topic. The article is entitled "Returning Genetic Research Results to Individuals: Points to Consider."[10]

Ultimately, it is the responsibility of investigators to follow specific procedures for each trial they conduct. Study protocols, addenda concerning correlative trials, and consent forms should include all information necessary to inform patients, meet institutional review policies, and collect specimens. Because pharmacogenomics and biospecimen collection constitute a rapidly evolving field, there are efforts to help facilitate understanding and standardize policies where possible.

The collection of biospecimens for the conduct of correlative science research now and in the future is becoming an ever-important aspect of oncology. Widespread participation on the part of community-based oncologists and patients is important to both achieving an adequate number of samples and helping ensure that results are generalizable to the broadest population of patients with cancer. This is a complex subject potentially involving invasive procedures for research purposes only and presenting the need to consider and discuss privacy and confidentiality concerns amid a shifting technologic landscape. In many cases, there will be no direct benefit to patients from donation of biospecimens for research. This needs to be made clear, particularly when a specimen is collected within a clinical trial or when the only person discussing the issue with the patient is the treating physician. With attention to these important ethical issues, this crucial research can move forward on a strong foundation of human research participant protection and patient education.

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