Summary of Public Comments in Response to the First-Generation Guidelines for NCI-Supported Biospecimen Resources

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I. Background

Human specimens that serve as analytes for new and developing biomolecular technology platforms have emerged as a critical resource for basic and translational research in cancer, as they are a direct source of molecular data from which targets for therapy, detection, and prevention are identified and molecular taxonomies of cancer are derived. The reliability of molecular data derived from these new analysis platforms is dependent on the quality and consistency of the biospecimens being analyzed. As a result of the increased requirement for biospecimen quality, standardization of biospecimen resource operations using state-of-the-science approaches has become a pressing need across the research enterprise.[1] The lack of standardized, high-quality biospecimens is widely recognized as a significant roadblock to cancer research.

In 2002, the National Cancer Institute (NCI) initiated an intensive due diligence process to understand the state of its funded biospecimen resources and the quality of biospecimens used in cancer research. These efforts culminated in 2005 with the development of the First-Generation Guidelines for NCI-Supported Biorepositories ("Guidelines") featuring salient guiding principles that define state-of-the-science biospecimen resource practices, promote biospecimen and data quality, and support adherence to ethical and legal requirements. This first-iteration document was published in the Federal Register on April 28, 2006 (71 FR 25184), and on the Web site of the NCI Office of Biorepositories and Biospecimen Research (OBBR). The NCI requested public comments on the Guidelines both through the Federal Register and the OBBR Web site. The public comment period, originally set for a period of 30 days, was extended an additional 30 days through July 3, 2006. The NCI received public comments from a considerable number of respondents, including individuals and groups representing academic institutions, professional societies, private industry, healthcare systems, foundations, advocacy groups, and Federal Government agencies. Representatives from cancer centers and biospecimen resources constituted the majority of the respondents. The responses received ranged from general comments to detailed reviews of the Guidelines.

The Guidelines were subsequently revised, based on public comment and input from content experts, and renamed the NCI Best Practices for Biospecimen Resources ("NCI Best Practices").[2] The current NCI Best Practices do not comprise detailed laboratory procedures; rather they consist of principles by which such procedures should be developed by biospecimen resources. Recommendations contained within the document are intended to be adapted, as appropriate, based on the mission and scientific needs of individual biospecimen resources. Although adoption of the NCI Best Practices is voluntary, the NCI believes that the principles

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[1] The NCI defines a biospecimen resource as a collection of human specimens and associated data for research purposes, the physical structure where the collection is stored, and all relevant processes and policies. Biospecimen resources vary considerably, ranging from formal organizations to informal collections of materials in an individual researcher's freezer.

[2] The NCI Best Practices are available at http://biospecimens.cancer.gov/practices/.

outlined in this document support the goal of optimizing biospecimens for cancer research. The NCI Best Practices will continue to evolve as the field of biospecimen biology advances; as novel scientific, technological, and clinical practices develop; and as new ethical and legal policies and regulations emerge (e.g., National Institutes of Health (NIH) and Department of Health and Human Services policies). Therefore, input will be required from researchers, biospecimen resource managers, advocates, policymakers, and related stakeholders to ensure that future iterations of the NCI Best Practices remain "state-of-the-science."

II. Public Comments and NCI Response

A. Overview: Scope, Applicability, and Compliance

Many respondents commended the NCI for its efforts to standardize biospecimen resource practices, describing the Guidelines as "well reasoned," "comprehensive," and "an excellent first effort." Although the comments reflected agreement with the overall objectives of the Guidelines, respondents raised questions about the feasibility of their application. Some individuals were concerned about the broad definition of "biorepository" and questioned the feasibility of implementing the Guidelines for small, existing biospecimen resources that are not linked to clinical trials. Several respondents raised questions about determining compliance and the notion that future funding decisions may be predicated on compliance with the Guidelines.

Several commenters requested that the NCI remove any mandatory language to underscore the voluntary nature of the Guidelines and focus on providing "high-level" guidance while referencing relevant documents for specific standards.

NCI Response

The title First-Generation Guidelines for NCI-Supported Biospecimen Resources has been changed to NCI Best Practices for Biospecimen Resources. The term "best practices" has replaced "guidelines" to emphasize that implementation is voluntary. Comments received about the Guidelines indicated that "biorepository" implies a physical structure only, whereas "biospecimen resource" more appropriately implies a physical structure and the biospecimens, data, and policies that form the resource. These comments also are reflected in the new title and the text.

Several recommendations in the NCI Best Practices can be broadly or narrowly applied, depending on the mission and scientific needs of the biospecimen resource and/or the study design.

The NCI has addressed general concerns about the perceived mandatory tone of the document by removing any mandatory language and clarifying that the document comprises best practices.

B. Economic Implications

Many respondents expressed concern regarding the cost of implementing the Guidelines, particularly for small biospecimen resources and existing collections. Several respondents asked whether the NCI would establish new funding mechanisms to support the implementation of the Guidelines, including maintenance and repair of equipment for existing biospecimen resources from completed studies that are no longer receiving research funding. Aspects of the Guidelines

that were cited as cost prohibitive include implementing a sophisticated security and information technology (IT) infrastructure and maintaining secondary freezers for emergency backup.

A number of respondents commented that it would be difficult for applicants to estimate costs associated with the implementation of the Guidelines. One respondent recommended that the NCI conduct a cost analysis to determine the financial impact of compliance before making it a condition of an NCI grant award. It also was suggested that the NCI prioritize aspects of the Guidelines to mitigate the cost impact of full compliance.

NCI Response

The NCI recognizes that there may be costs associated with implementing the NCI Best Practices for some biospecimen resources. During the first year of implementation, the NCI recommends that NCI-supported biospecimen resources establish an evaluation process to assess the costs associated with implementation.

As part of an educational outreach program, several public meetings will be held across the United States to inform members of the intramural and extramural research communities about the NCI Best Practices and provide a forum for questions and feedback. Each forum will include a session dedicated to biospecimen resource economics and related issues.

C. Technical Comments Regarding Biospecimen and Data Collection, Quality Control, and Biosafety

Several comments were received about the technical guidelines regarding the collection, processing, storage, and dissemination of biospecimens. These include suggestions to remove recommendations for biospecimen resources to collect biospecimen banking research data (e.g., ischemia time); requests for clarification of NCI's expectations about biospecimen disposal, the use of control biospecimens, and automated security systems; and comments on specific elements of the sample shipment guidelines.

Several respondents requested clarification about the collection of clinical data and noted that extensive annotation is not always necessary to serve the purpose of a biospecimen resource and may constitute a significant burden to many biospecimen resources. Another concern focused on whether the Guidelines document recommends that both clinical and biospecimen-associated data need to be stored by the biospecimen resource. Some groups suggested that a biospecimen resource should not be required to maintain clinical annotation in its own database as long as the clinical data are linked to the biospecimen. Other respondents requested clarification about the need for biospecimen resources to validate the clinical data collected. One respondent expressed the opinion that validation should be the responsibility of the collecting organization, not the biospecimen resource.

Several respondents commented on references to a minimal clinical dataset and requested additional information about how the NCI plans to work with biospecimen resources to establish this measure. One respondent emphasized the importance of allowing individual biospecimen resources to determine the need for collecting specific clinical data elements to ensure that these data are useful to the resource. Furthermore, it was noted that the proposed minimal clinical

dataset should not be required for existing collections, as it would be expensive to collect new data on archived biospecimens.

Comments addressing quality control generally focused on noting additional costs associated with implementing these measures. Respondents addressing biosafety requested that recommendations included in the Guidelines not exceed the requirements of the Occupational Safety and Health Administration (OSHA) and the Centers for Disease Control and Prevention.

NCI Response

The NCI Best Practices address the specific technical issues raised regarding biospecimen collection, processing, storage, and dissemination. The NCI best practices on biospecimen disposal and disposition are clarified in the context of standard operating procedures and principles for responsible custodianship. Shipping regulatory considerations and training recommendations have been streamlined.

Regarding clinical data collection, the NCI Best Practices offer flexibility in terms of the type and amount of data that should be collected and acknowledge that the data collected are dependent on the types of biospecimens collected and the study design and objectives. In addition, the NCI recognizes that clinical data collection and management are not always the responsibility of the biospecimen resource. The NCI Best Practices do not recommend that biospecimen-associated data and clinical data be stored together in the same database, only that clinical data could be linked to biospecimens as study requirements dictate.[3] Furthermore, the NCI Best Practices emphasize that applicable privacy statutes and regulations as well as human subjects protection regulations should be followed in collecting and managing clinical data.

Regarding clinical data validation, the NCI recommends that data collected with biospecimens should be of the highest quality possible. The NCI Best Practices state that "…a method for validating the clinical data collected…" should be employed, but no method is prescribed. The biospecimen resource should develop the method or verify that an appropriate validation method is in place.

References to a minimal clinical dataset have been removed. Although the development of a minimal clinical dataset is an important initiative that would allow comparisons of data collected from multiple biospecimen resources, the NCI plans to provide recommendations on this topic in a future iteration of the NCI Best Practices in consultation with the research community.

D. Informatics

Several respondents voiced strong concerns about the informatics section of the Guidelines. For example, respondents cited the requirement to meet Capability Maturity Model Integration (CMMI) Level 3 as "too stringent" and "out of reach" for small biospecimen resources. Other

[3] *Biospecimen-associated data***.** Any data associated and collected with a biospecimen, including research data, phenotypic data, clinical data, epidemiologic data, and biospecimen resource data (NCI Best Practices working definition).

respondents commented that the requirement to eliminate local, unsecured, ad hoc databases such as Microsoft Excel® and Access® and arrange for external hosting to ensure proper data security is unnecessary and would be very difficult to justify for small biospecimen resources.

Several respondents expressed serious concerns about the requirement for biospecimen resources to have caBIG™ silver level–compatible informatics systems. Respondents stated that this is premature given that caBIG™ is still under development. Multiple respondents commented on experiences with caTISSUE Core, a biospecimen management software tool being developed through caBIG™. These respondents found caTISSUE Core to have limited functionality.

Other respondents noted with concern the need to use Cancer Data Standards Repository (caDSR) naming conventions, which is a requirement for achieving caBIG™ silver-level compatibility. These respondents argued that until the caDSR naming conventions are established, they should not be part of the Guidelines. Finally, several respondents questioned how the NCI would verify caBIG™ compliance for individual biospecimen resources.

NCI Response

The NCI encourages compliance at CMMI Level 3, which defines a level of operation widely accepted for effective software development and maintenance. It is a useful standard for organizations to consider when assessing the requirements for effective management of biospecimens.

Regarding informatics system security, the NCI Best Practices have been amended to reference the National Institute of Standards and Technology Special Publication 800-30 “Risk Management Guide for Information Technology Systems.” Biospecimen resources that consider themselves too small to implement appropriate security measures may not be appropriate repositories for maintaining data. Application hosting is widely used and should be considered where economic or technical capabilities of a biospecimen resource cannot support adequate IT security.

The purpose of encouraging caBIG™ compatibility at the silver level for NCI-supported biospecimen resources is to promote electronic sharing of research data to integrate biospecimen resource systems with other sources and types of data, including genomic and proteomic information and clinical research results. Common data elements (CDEs) provide a means toward semantic continuity and data comparability across studies over time. To achieve caBIG™ compatibility, CDEs constructed according to best practices defined by the caBIG™ Vocabulary CDE workspace and registered in the NCI caDSR must be used.

Although applications like caTISSUE Core are developed within caBIG™, use of these specific tools is not envisioned as the sole route to achieving caBIG™ compatibility. Biospecimen resources are encouraged to collaborate with their software developers to make their systems interoperable with others by following caBIG™ compatibility guidelines (see Appendix 1 of the NCI Best Practices).

E. Ethical, Legal, and Policy Issues

Respondents commented on several aspects of the ethical, legal, and policy (ELP) guidelines. Comments addressed the applicability and enforceability of various recommendations included in the ELP section of the Guidelines. For example, one respondent noted that the need to obtain informed consent is based on the decision of local institutional review boards (IRBs). Several other respondents noted that Federal regulations do not always require informed consent for collecting biospecimens. In addition, many respondents criticized the sample informed consent form included in the Guidelines and suggested replacing it with a list of essential elements.

Respondents requested further clarification about (1) obtaining informed consent for the use of biospecimens from children participating in research who reach legal age during or after a study, and (2) aspects of the guidelines pertaining to discontinuing participation in a research study.[4]

Some respondents inferred that the guidelines regarding biospecimen access suggest that all investigators should have equal access to any biospecimens and associated clinical data stored in NCI-supported biospecimen resources. Others remarked that some of the access-related recommendations included in the Guidelines do not apply to certain types of biospecimen resources.

Some respondents requested expansion of the privacy section of the Guidelines because of the importance of this issue and its potential impact on public trust. Others requested that additional information be included about mechanisms for protecting privacy, such as encryption, controlled access, repository personnel nondisclosure agreements, and honest broker systems. In addition, some respondents suggested referencing the Health Insurance Portability and Accountability Act (HIPAA) Security Rule and providing additional guidance about the development of HIPAA authorization forms.

Respondents requested expansion of the custodianship discussion because of the importance of this issue and the relative lack of clarity in this area.

Regarding the intellectual property section of the Guidelines, respondents questioned the necessity of material transfer agreements (MTAs) for biospecimen transfer. Other respondents noted that (1) many biospecimen resources currently have effective agreements in place; (2) materials also are shared under cooperative research and development agreements (CRADAs) or collaboration agreements; (3) biospecimens for many studies are collected under protocols approved by collaborators' IRBs and are beyond the control of the receiving biospecimen resource; and (4) sharing requirements on research resources developed by end users of biospecimens may lead to diminished use of the resources.

Several respondents expressed concern that the sample MTA form provided in the Guidelines requires indemnification as a default condition of transfer. One respondent indicated that

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[4] While the NCI views the terms "research participant" and "human subject" as equivalent, the latter term is used when discussing the regulation at 45 CFR Part 46 Subpart A (the Common Rule).

although allocation of liability should be required, the approach to doing so should not be mandated.

NCI Response

The NCI Best Practices clarify the relevance of the ELP section to biospecimen resources and distinguish between mandates based on Federal regulations and additional NCI recommendations. For example, the NCI Best Practices incorporate a clearer discussion of when informed consent is necessary under Federal regulations. References to all relevant Federal regulations and guidance documents have been added as well as a specific statement that informed consent may not be required or may be waived in some instances. In response to the public comments, the NCI Sample Consent Form formerly found in Appendix 1 has been deleted. The NCI Best Practices emphasize that the authority to determine the adequacy of informed consent resides with the Office for Human Research Protections (OHRP).

The section describing reconsent of children who reach legal age during a study or afterwards now states that such reconsent issues may be best addressed by IRBs at the time the board reviews the initial protocol. In addition, OHRP guidance on this issue is available via the "Informed Consent" link on the Frequently Asked Questions Web page of the OHRP site at http://www.hhs.gov/ohrp/faq.html.

The term "withdrawal of consent" has been replaced with "discontinuation of participation" in the NCI Best Practices to be consistent with usage in 45 CFR Part 46. As clarified in the NCI Best Practices, the NCI suggests that if participation is discontinued, any remaining identifiable biospecimens and associated clinical data should be withdrawn from the biospecimen resource; however, distributed samples and clinical data and the research data generated from such samples need not be withdrawn. Furthermore, investigators who obtain individually identifiable biospecimens from a biospecimen resource are conducting human subjects research under 45 CFR Part 46. If the research participant discontinues participation, the investigator is required to withdraw the participant from the research study. Specific actions that a biospecimen resource or recipient investigators, as appropriate, could take if a human subject discontinues participation are also specified.

Regarding biospecimen access, the NCI Best Practices incorporate NIH guidance that promotes the sharing of biospecimens within the research community. The NCI Best Practices indicate that NCI-supported biospecimen resources should offer equitable and appropriate access to investigators while following applicable Federal, State, and local regulations for the protection of human subjects and their privacy. Furthermore, the NCI Best Practices suggest general principles that are relevant for defining access principles. It will be the responsibility of investigators and biospecimen resources to determine reasonable access guidelines specific to their resource.

The privacy section of the NCI Best Practices has been expanded to include discussion of the HIPAA Privacy Rule, Privacy Rule Authorization, and additional mechanisms that could be used to protect research participant privacy. A reference to the HIPAA Security Rule also has been added in Section B.5.6, Ethical and Legal Issues Pertaining to Informatics Systems.

Regarding custodianship, the NCI plans to provide additional recommendations in a future iteration of the NCI Best Practices in consultation with the research community and relevant regulatory authorities.

The NCI Best Practices indicate that agreements other than MTAs are appropriate as long as they are consistent with the NIH Research Tools Policy and the NIH Data Sharing Policy. Generally, MTAs are agreements between specific institutions, not individuals, thus requiring an institutional signature. However, institutions determine to whom they will delegate the authority to sign such agreements based on institutional policy.

While an institution and its collaborators may each have their own intellectual property policies, it is anticipated that as research resources, biospecimens will be shared in a manner consistent with the NIH Data Sharing Policy and the NIH Research Tools Policy. The MTA provides an opportunity to communicate to biospecimen end users that sharing research data with the community has a highly desired outcome.

The intent of an MTA or other appropriate document (e.g., contract, CRADA, collaboration agreement) is to ensure that all involved understand the terms of the material transfer. A clinical protocol does not typically document the material transfer obligations of each institution and therefore would not be considered a substitute for an MTA or other agreement. The MTA in Appendix 2 of the NCI Best Practices is intended to provide example terms to consider when transferring biospecimens among institutions and is based on the NIH Simple Letter Agreement (SLA). The liability/indemnification term in the MTA in Appendix 2 is similar to the term found in the SLA.

F. Glossary

Commenters noted that definitions appearing in the glossary were unclear and sometimes inconsistent with usage in other guidance documents. Respondents suggested that terms used in the section pertaining to ELP issues needed clarification relative to the pertinent regulations.

NCI Response

Terms and definitions used throughout the NCI Best Practices have been reviewed for consistency and clarified by an NCI working group. Wherever possible, standardized definitions from Federal documents and/or the NCI Thesaurus[5] are used in the NCI Best Practices. Where such sources were not available or appropriate, definitions were selected from widely used texts, such as Black's Law Dictionary[6] or Taber's Medical Dictionary[7]; reports specific to biorepositories, such as the International Society for Biological and Environmental Repositories (ISBER) Best Practices[8] and RAND Corporation's *Case Studies of Existing Human Tissue*

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[5] National Cancer Institute Thesaurus. NCI Web site. Available at http://nciterms.nci.nih.gov/NCIBrowser/Dictionary.do.

[6] Garner B, ed. Black's Law Dictionary. 8th ed. Eagan, MN: Thomson West; 2004.

[7] Venes D, ed. Taber's Cyclopedic Medical Dictionary. 20th ed. Philadelphia, PA: F.A. Davis Company; 2005.

[8] International Society for Biological and Environmental Repositories (ISBER). Best practices for repositories I: Collection, storage, and retrieval of human biological materials for research. *Cell Preserv Technol*. 2005;3:5-48.

Repositories[9]; or relevant Web sites such as the OSHA site. In some instances, definitions were drafted specifically for the NCI Best Practices by the NCI in consultation with appropriate experts. In some cases, two definitions are listed for a single term to convey both a general and a biospecimen resource–specific meaning or to provide definitions from two Federal regulations. Where two definitions are listed, the first definition contains the meaning most relevant to the NCI Best Practices.

[9] Eiseman E, Bloom G, Brower J, et al. Case Studies of Existing Human Tissue Repositories: "Best Practices" for a Biospecimen Resource for the Genomic and Proteomic Era. Santa Monica, CA: RAND Corporation; 2003.