National Comprehensive Cancer Network

Your Best Resource in the Fight Against Cancer®

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

INITIAL PRACTICAL POINTS TO CONSIDER BEFORE ESTABLISHING A BIOREPOSITORY, DATA OR SPECIMEN BANK.

1. Why is the collection needed? Are there existing specimens and/or data that could be used for the same purpose? Note – the majority of biorepositories/specimen banks do not use all of the specimens available.
2. Who will use the biorepository? This should be understood and documented throughout the lifespan of the biorepository, database or specimen bank
3. What are the mechanisms for sharing biospecimens (locally, nationally and internationally)?
4. If DNA materials cannot be de-identified, can the specimens and materials be shared?
5. With regard to use of biospecimens, what information needs to be included in the informed consent document? Does it include transfer to other researchers locally, nationally and/or internationally?
6. What is the source of initial and long-term financial support for the biorepository? If federal funding ends, what financial resources will be used to support the biorepository? Has a budget been developed for the lifespan of the biorepository beyond the grant funding?
7. What resources will be available to store and share resources for the time you expect the biorepository to be active?
8. What are the milestones for measuring success?
9. How long do you expect the materials and information to be used?
10. Is there a plan for ending the biorepository and/or moving it to a new location?

It should be noted that lack of long-term physical and financial resources to support a biorepository will impact how specimens are received, stored, distributed as well as the use and results of the science.

NOTE – Biorespository, registry, databank, specimen bank, and repository are used interchangeably in this document.

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

1. Design

Point Of Interest	Comments
SCIENTIFIC AIM - What is the scientific aim of the repository (data and/or specimens)? Is it to create a: • Tissue/specimen repository or biorepository with linkage to data repository • Data Repository Only • Registry (e.g. Cancer Registry) • Who will control the repository (data or specimen bank)?	The repository's primary research mission, operational scope, and objectives should be well defined. A bank should have an established governance structure, as well as, policies, best practices, regulatory and procedural standards that are described within an IRB approved banking protocol. Research Principal Investigator (PI) should describe the use of human tissue for investigational, research, clinical (diagnostic, treatment predictors and therapeutic modalities), as well as for non-human subjects research purposes. Suggested resources: 1. Fred Hutchinson Cancer Research Center (FHCRC) – Repository, Registry or Databank Supplement form 2. University of Pittsburgh – Banking and Disbursement of Human Tissue and Other Biological Materials Application http://www.pittbiospecimencore.pitt.edu/ 3. NCI Best Practices for Biospecimen Resources at http://biospecimens.cancer.gov/bestpractices/ 4. Office of Human Research Protection (OHRP) Guidance on Research Involving Coded Private Information or Biological Specimens at http://www.hhs.gov/ohrp/policy/cdebiol.html 5. Fred Hutchinson Cancer Research Center (FHCRC) Repository - http://extranet.fhcrc.org/EN/sections/iro/irb/forms/063IRBform_RepositoryRegistryDatabank.doc http://extranet.fhcrc.org/EN/sections/iro/irb/forms/index.html
PURPOSE - For what purpose is the repository established? • Clinical – diagnostic, treatment, predictors • Research • Education • Single-purpose • Multi-purpose • Future use	Depending on the research, clinical and/or diagnostic purpose of the samples and/or data collected, the research investigator may need to comply with a number of regulatory requirements. For example: a. Food and Drug Administration (FDA) b. Department of Health and Human Services (DHHS) c. Clinical Laboratory Improvement Amendments (CLIA) d. Health Insurance Portability & Accountability Act (HIPAA) e. NIH Genomic Data Sharing Policy f. Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies g. Cancer Registry (federal and state laws may apply) It is important for the research investigator to describe in the protocol (and informed consent document related to the intervention or interaction with the subject) future use(s) of the samples so that certification requests (and the specific eligibility criteria that is required) for submission of data and/or samples to the dbGaP or for GWAS purposes are met. Most importantly, the informed consent document must adequately describe the plans to create genetic data that may be shared with other investigators in the future for broader use.

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	Suggested resources: 1. Repository Confidentiality Pledge https://extranet.fredhutch.org/en/f/irb/model-repository-access-confidentiality.html 2. Model Consent Form https://extranet.fhcrc.org/en/u/irb/informed-consent.html 3. IRB Pre-reviewed Specimen Data Sheet http://extranet.fredhutch.org/en/u/irb/submissionstotheirb/research-not-involving-human-subjects/_jcr_content/leftParsys/download_f2c7/file.res/Pre-Reviewed-Sources-De-identified-Human-Specimens.pdf 4. Statistical Supplement https://extranet.fredhutch.org/en/f/irb/statistical-supp.html 5. GWAS supplement https://extranet.fredhutch.org/en/f/irb/genomic-data-sharing-supplement.html 6. American Tissue Culture Center (ATTC) https://www.atcc.org/en/About/About_ATCC/Who_We_Are.aspx 7. NHGRI Points to Consider for IRBs and Institutions in their Review of Data Submission Plans for Institutional Certifications Under NIH's Policy for Sharing of Data Obtained in NHGRI-Supported or Conducted Medical Sequencing Studies (NHGRI MSP http://www.genome.gov/Pages/Research/SequenceMapsBAC/MedicalSequencing/MSPPtstoConsider03.12.08.pdf 8. Genomic Data Sharing (GDS) Policy (Effective 1-25-15) https://osp.od.nih.gov/scientific-sharing/policies/ http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-124.html 9. Genomic Data Sharing Policy-Institutional Certification https://osp.od.nih.gov/scientific-sharing/institutional-certifications/ 10. NIH Points to Consider for IRBs and Institutions in their Review of Data Submission Plans for Institutional Certifications Under NIH's Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS) https://osp.od.nih.gov/wp-content/uploads/GDS_Points_to_Consider_for_Institutions_and_IRBs.pdf 11. Compilation of Aggregate Genomic Data https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000501.v1.p1
BACKGROUND - What is the background supporting the creation of a data and/or specimen repository? • Research • State mandated reporting • Federally mandated reporting	Knowing how the resource will be utilized (inside and/or external to the institution has implications for how the informed consent document (if required) is written.

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INTENDED BENEFIT - What is the repository's intended benefit? • Investigators at the same institution • External collaborating investigators • National research consortium or initiative • International investigators • International consortiums	Depending on to whom the biorepository, database or registry is intended to benefit there may be additional regulatory, clinical, State or Federal requirements, certifications, and/or clearance needed. Examples of National Research Consortiums or initiatives – • National Cancer Institute Oncology Group Studies (e.g. Southwest Oncology Group (SWOG), Gynecologic Oncology Group (GOG), etc.) • National Marrow Donor Program (NMDP) • HIV Vaccine Trials Network For example, HIV laboratory research requires Biosafety Level clearance. See Section 6. STORAGE, ACCESS AND DISTRIBUTION
SHARING - With whom will the specimens and data be shared? • Will the specimens or data be shared with individuals only in your institution? • Will specimens or data be shared with individuals outside of your institution? Nationally? Internationally? • Is a usage agreement required to manage confidentiality and access to HIPAA unique identifiers or identifying information?	The research protocol and informed consent should describe who will be provided the data and/or specimens, how this will be provided, its uses and restrictions (Material Transfer Agreement (MTA)/Data Use Agreement (DUA) or Limited Data Set (LDS). It is important to think about the long-term plan and whether or not outside collaborators will want to utilize this material or data at a later date or if there is a requirement to share data either from journal requirements (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html) or by the funding source (such as: https://grants.nih.gov/grants/policy/data_sharing).
MAINTENANCE - Who will maintain the biorepository, database or registry? • Individual Investigator Maintained • Institution Maintained Repository • National Repository (that distributes specimens to investigators in US and internationally)	The research investigator is required to describe whom, how and under what circumstances the repository, database and/or registry will be maintained. This description should take into consideration present and future timeframes as this may change over time.

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MATERIAL COLLECTED - What type of human biological specimens (Biospecimen) and data will be collected? • Whole blood • Tumor samples • Data • Medical record information • Skin • DNA/RNA • Established permanent cell lines • Paraffin-embedded • Fresh • Urine • Fluids (CNS, pleural, synovial, cyst, saliva, bronchial, etc.) • Fluorescent • Human Leucocyte Antigen (HLA)	If the repository resides in an institution (e.g. a pathology lab or individual researcher's repository of biological specimens) oversight for transfer, use, employee safety, biosafety and clinical storage are the responsibility of the investigator and institution to ensure compliance with state, federal and international export/import laws. A research institution or hospital has various entities responsible for establishing and assisting repository gatekeepers with an appropriate collection process (i.e., IRB approval for research collection, Institutional Biosafety Committee, Privacy Officer, etc.) Standardized procedures should be applied consistently in collecting, storing and distributing biospecimens to ensure quality and avoid introducing variables into research studies. See Section 6. STORAGE, ACCESS AND DISTRIBUTION
SOURCE - Where did the material or data originate (source)? • Medical Record Department • Pathology Department • Another research repository • Cancer Registry • Publicly available tissue source [American Tissue Culture Center (ATTC)] • Operating Room – tissue or excess tissue • Leftover human specimens used for in vitro diagnostic device studies	The research investigator should describe where the specimen(s) and/or data originated. Leftover specimens are generally remnants from routine clinical care or analysis that would have been discarded. Does the research involve using an in vitro diagnostic device that uses leftover human specimens? If so, the repository is subject to FDA regulations. Either one of the following FDA guidance documents on consent may apply: • Guidance on In Vitro Diagnostic Device studies using leftover human speciments that are not indivudally identiable: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071265.pdf; OR • Guidance on IRB waiver or alteration of informed consent https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM566948.pdf The specimens are provided to the investigator(s) without identifiers and the supplier of the specimen has established policies and procedures to prevent the release of personal identifying information. The research investigator should seek clarification with the FDA if the supplier can also be the investigator or part of the Investigator's team. The regulation infers that the investigator and supplier be different people. 21 CFR 812.2(c)(3)

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2. Regulatory and Institutional Approval, and Accreditation

Point Of Interest	Comments
HUMAN SUBJECT RESEARCH - Is the activity human subject research? 45 CFR 46 (DHHS regulation) Whether the collection and dissemination of data and samples from the biorepository are considered human subjects research depends on several factors: • What types of specimens are being collected? • What data are being collected in conjunction with each specimen? • Is Personally Identifiable Information (PII) or Protected Health Information (PHI) being kept with the specimens or data? • Is there an Honest Broker process in place that codes the specimen and the PHI (maintaining a separate location for each), thereby preventing release of PHI? • Will PHI be released with the specimens? • Is the information associated with the specimens or data readily **i**dentifiable? Coded? HHS (defined) Readily Identifiable Information? • Is the data/information de-identified prior to distribution of the specimen? • Where did the specimens or data originate (clinical activity; research activity; autopsy specimens)? If you are testing the safety or efficacy of a device OR there are plans to do this in the future, the FDA regulations also apply. In this case, even if the biospecimen is de-identified or from a deceased individual it is considered human subject research. (21 CFR 812.3 (p))	Research investigator should describe the use of human tissue for experimental and research purposes for diagnostic, treatment and therapeutic modalities. In the protocol, the investigator should address the questions listed in this section. The institutional review board (IRB**)** may review this study using an expedited (IRB) review process or at a fully convened board. Depending on what the activity is it may also qualify for non-human subjects research. The research investigator should determine what de-identification methods will be used? *Applicable Regulations*: Food and Drug Administration (FDA) Department of Health and Human Services (DHHS) Health Insurance Portability & Accountability Act (HIPAA) Genome Wide Association Studies (GWAS) Cancer Registry (federal and state laws may apply) Applicable state or local laws *Suggested resources*: 1. International Society for Biological and Environmental Repositories (ISBER) at http://www.isber.org/ 2. Good Laboratory Practices (GLP) at http://www.oecd.org/document/63/0,2340,en_2649_34381_2346175_1_1_1_1,00.html 3. Clinical Laboratory Improvement Amendment at http://www.cdc.gov/clia/ 4. International Organization for Standardization (ISO9000) at http://www.iso.org/ 5. U.S. Food and Drug Administration (FDA) Quality System Regulation, 21 CFR 820 at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=820 6. 45 CFR 46 – Office of Human Research Protections – Human Subject Research regulations 7. International Air Transportation Association (IATA) athttp://www.iata.org/ 8. Occupational Safety and Health Administration (OSHA) at www.osha.gov/ 9. Biosafety in Microbiological and Biomedical Laboratories (BMBL) at www.cdc.gov/biosafety

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CLIA - Will information be used for clinical purposes, such as prevention, diagnosis or treatment?	Biospecimen collection, processing, management, and distribution should be carried out within a quality management system (QMS**)** that contains formalized quality assurance/quality control policies and written SOPs. CLIA certified lab required for use of information for prevention, diagnosis or treatment. A CLIA-certified lab must be used for the analysis of specimens collected in research that will be used for clinical decision-making.
OVERSIGHT COMMITTEE - Are there any local approvals to utilize the database, repository or registry, e.g. ancillary or oversight committee approvals, confidentiality pledge? • Are there user committees to approve the science of the bank? • Is there a pathology review committee? • Do you need to think about whether a certain amount of tissue needs to be kept for clinical purposes?	The type of oversight committee for each repository and the institution it resides in will vary but may include: • Scientific Advisory Board or Committee • Biospecimen Use Committee • Pathology Approval (Pathology Department Policy regarding access to tissue**s**) • Honest Broker Use Committee
TRAINING REQUIREMENTS - Are there specific training requirements beyond the standard human subjects research training? • Are the specific training requirements for the management, handling and storage of the tissue? • Are there other HIPAA requirements relating to tracking of the information?	Personnel involved with the operation and management of a biorepository resource should be provided with initial and on-going training on the applicable standard operating procedures, institutional policies and procedures and any State or Federal laws governing the resource. Confirm that biospecimens that have been collected have the appropriate biohazardous materials standard operating procedures in place. Occupational Safety and Health Administration (OSHA) regulations may then be applicable (29 CFR § 1910.1030 (f)(1)(i)). For international shipping the International Air Transportation Association (IATA) requirements should be reviewed. Biosafety in Microbiological and Biomedical Laboratories (BMBL) best practices should be followed as well as general safety regulations and procedures regarding chemical, electrical, fire, physical, and radiological safety (See International Society for Biological and Environmental Repositories (ISBER)). Updated standard operating procedures (SOPs) and training should be provided on a periodic basis.

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IRB - Have you submitted your protocol to your IRB for approval? • Protocol • Informed Consent • Data Use Agreement (DUA) (see also De-identified data set) • DbGaP Certification	The research investigator should review the requirements, documents and signatures required for submission to the IRB and/or other units/departments, for example Grants and Contracts if they are required to review and approve the Material Transfer Agreement (MTA). dbGaP Certification-If there are plans or a requirement to submit data to dbGaP (such as NIH funds being used to generate the data) this requirement should be considered at the inception of the repository to ensure the criteria necessary to certify the data are met. Most importantly, the consent form must adequately describe the plans to create genetic data and subsequently share for broad use.

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3. Consent

Point Of Interest	Comments
REQUIRED - Is informed consent required? See also Section 2 - Regulatory	IRB review required for research purposes. The research investigator should take into consideration the following; • Broad versus specific consent • Tissues/specimens are identifiable – Protected Health Information (PHI), Personally Identifiable Information (PII), Identifiable (45 CFR 46, 21 CFR 160, 164) • Data linked to identifiers – Linkages • De-identified data set • Anonymized • Other permutations of linkages with firewalls • Honest Broker • Tissues/specimens are de-identified • Expert Determination (De-identification) Method. (45 CFR 164.514(b)) • General requirements for informed consent are revised in the 2018 Final Rule (45 CFR 46.116) • Broad Consent in the 2018 Final Rule addressed in §46.111(a), (a)(5), (d 1-7)), (d)(2), (d)(7), (e), (e)(2), (f), (f)(2)) *Suggested resource*: Use NCI model consent Broad Versus Specific Consent, Consent Form Examples and Model Consent Language-Genome.gov http://www.genome.gov/27559024

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INCLUDED - What information should be included in the research consent? • Pre 2018 Final Rule requirements vs. 2018 Final Rule requirements • Immediate use • Future use • Use in the institution by the investigator only • Use by the investigator and others (internal and external) • Use of broad consent under the 2018 Common Rule • Withdrawal of consent • Incidental Findings • Return of Results (this plan should also be described in the protocol) • FDA information if plans to use the data or samples in future FDA regulated studies –consent should include a reference that the data or samples may be used in investigational drug or device studies in the future and include a statement that the FDA can inspect records for this study. • Any intellectual property interests that may come from a conflict of interest	The information needed will depend on what the purpose of the research is and what is the permitted use of the specimens/data. The type of consent will dictate additional considerations of validation of consent, management over time and process to update/obtain on-going approval Withdrawal of consent needs to be specified in original consent and the process to do so. There should be a plan indicated in the protocol that should be included in the consent document on whether or not incidental findings will be returned and how this information will be conveyed and/or managed by the investigator and possibly local treating physician. The potential for incidental findings should be discussed in the IRB approved consent. Under the 2018 Final Rule, §46.104(d)(8)(iii) Exempt research, the investigator does not include returning individual results as part of the plan. Describe what will be disclosed or not, based on CLIA status of test results (if applicable). If not a CLIA approved lab, special permission can be sought with IRB approval if there are incidental findings not previously anticipated that the subject should be aware of because of the clinical relevance. For In Vitro Diagnostic Device (IVD)/Investigational Device Exemption (IDE) research, the research investigator should address whether or not reports of mutations will be reported to the subject The research investigator should assess, at the earliest stage, whether or not including FDA information in the consent for the purposes of avoiding the issue of a waiver of consent for future studies. Some institutions are permitting future sample/data use (determining the use to be FDA compliant if the consent covers drug and device use “and” includes inspection of records). While FDA regulations do not recognize a waiver of consent except for Exception from Informed Consent (EFIC) or Emergency Consent (21 CFR 50.24), recent guidance from the FDA has been issued to provide enforcement discretion of the FDA regulations and allow a waiver of consent if certain criteria are met in minimal risk studies.

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CONSENT - Is informed consent required? • Was there written consent to use the specimens for biobanking research? • Were there any restrictions on the use of the specimens in the consent form? • Does the consent form contain language on future use? GWAS? dbGaP? (See Section 1 – Design (Purpose)) • Was there a waiver of consent to use the specimens or data for research? • If samples were collected under a consent form that does not explicitly authorize biobanking for future use, does the language or context of the consent form support a decision to allow biobanking? • Were data/biospecimens collected using broad consent as defined in the 2018 Final Rule?	Written signed consent required unless: • the research does not meet the definition of human subjects research • the research is exempt research from the DHHS regulations • the research has been granted a waiver of informed consent by the IRB • if FDA-regulated, research involves anonymous tissue specimens and FDA exercises enforcement discretion • under the 2018 Final Rule, if broad consent is obtained, secondary research uses of the subjects identifiable data and biospecimens consistent with the broad consent would not require additional consent • waiver of consent cannot be granted for secondary research using a subject's identifiable data or biospecimens if the subject refused to consent under broad consent Additional requirements for written consent: opt in or opt out provision for biobanking.

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CONSENT WAIVER OF AUTHORIZATION - Is there a waiver of HIPAA authorization requested or needed? • Is there PII linked to the specimen or data? • Does the PII constitute PHI? • Was there a written HIPAA authorization signed? • Did the Privacy Board grant a HIPAA waiver? • What is the plan for revocation of authorization should this happen? Consider implications for dbGaP submissions if consent is waived. • Can the research question be answered with consent or is the need for consent prohibiting the research from moving forward? • Does the research request meet the regulatory requirements to be waived? • Is the study minimal risk or greater than minimal risk. • Is the research retrospective analysis of existing specimens or data? • Is there valid justifications to waive consent?	The requirements to obtain a waiver to use Protected Health Information (PHI) for research without authorization must satisfy the criteria in 45 CFR 164.512. Applicable regulation: 21 CFR 160, 164 The use or disclosure of PHI involves not more than a minimal risk to the privacy of the individual based on the presence of at least one of the following: • An adequate plan to protect the identifiers • An adequate plan to destroy identifiers at the earliest opportunity consistent with the conduct of the research – unless there is a health or research justification to retain the identifiers or retention is required by law, or • Adequate written assurances that the PHI will not be reused or disclosed to any other person or entity except as required by law. HIPAA requires no more than minimum necessary PHI be disclosed for the intended purpose of the research. The research could not be practicably be conducted without the waiver; and the research could not be conducted without access to and use of the PHI. The research investigator (or regulatory office supporting the research investigator) should review the new interpretation of the Omnibus rule regarding secondary use under primary authorization. New interpretation of the HIPAA Privacy Rule (164.508 (c) (1) (iv) (see excerpt below from HIPAA presentation at March 2013 NCCN directors meeting) New interpretation in Omnibus rule (does not change actual rule) • Description such that individual would understand that their PHI could be used for future research including collection of information after the study • All elements of authorization remain including information as to whether or not there is an expiration • May rely on consent obtained prior to the effective date if ◦ Reasonably described future use ◦ Included authorization

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GWAS - Will the data be used for any Genome-Wide Association Studies? If so, the informed consent document is required to contain language that addresses GWAS. • Certification required by IRB /Privacy Board • Proposal and application to the NIH 2018 Final Rule, additional element of informed consent includes disclosing whether the research is known to or might include whole genome sequencing (§46.116(c)(9)).	GWAS policy applies to genome-wide association research utilizing genetic material and data collected both prospectively and retrospectively. The research investigator should review the NIH policy extending GWAS to genomic data due to funding agencies and/or journal requiring dbGaP submissions. See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-13-119.html Prospective studies – for studies intending to utilize genetic materials (data or specimens) collected in the future, in which GWAS is included within the study design at the time of the research participants provide consent, the consent form and process must comply with the requirements of 45 CFR 46 and any other applicable law. Retrospective studies – for studies utilizing existing specimens or data (e.g. genetic materials), the IRB is expected to determine whether or not the consent under which the existing genetic materials and data were obtained is consistent with the submission of data to the NIH GWAS repository and the sharing of that data in accord with the GWAS policy.
PEDIATRIC - Will pediatric specimens or data be collected? • Is follow-up/longitudinal data being collected? • Will consent be required at age of majority or can it be waived at age of majority?	The research investigator should describe in the research protocol the plan to consent through assent, collect, use, and store pediatric participants' data and/or specimens. Should the research design also involve longitudinal data analysis on the data and specimens collected and the participants reach legal age, the protocol should describe the method to re-consent the now adult participants after reaching the age of majority or if a waiver of consent will be sought for continued use of the data and/or biospecimens. The research investigator and IRB will need to consider the future use of the stored biospecimens as no more than minimal risk if not identifiable. If identifiable and greater than minimal risk then the research may need to re-contact the participant and re-consent for the continued storage and research of their specimen/data.
OBTAIN INFORMED CONSENT - Who will obtain informed consent? • Investigator • Clinical research nurse, • Operating Room staff or personnel, • Laboratory personnel? Will informed consent be obtained using a paper copy or an electronic informed consent (eConsent)?	The IRB approved research protocol and informed consent document should describe how and by whom the specimen/data will be collected. This description should describe the use of a Delegation Log. Suggested resource: eConsent - see https://www.fda.gov/downloads/drugs/guidances/ucm436811.pdf

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ACCESS TO INFORMED CONSENT - Who should see or have access to the informed consent? • Investigator • Clinical research nurse, • Operating Room (OR) staff, • Laboratory personnel • Data or specimen biorepository personnel • Grants and Contracts - individuals who negotiate Material Transfer Agreements (MTAs) • HIPAA Privacy Officer or Privacy Board Is a Business Associate agreement needed (for a person or entity that performs certain functions or activities on behalf of, or to a covered entity)? • IRB	The research investigator should describe in the research protocol who is permitted to review the consent for purposes of: • Confirming the data and/or specimen was obtained with the appropriate consent • Determining whether or not the consent permits further use – broad or defined research • Determining whether or not the specimen/data can be shared inside and outside the institution • Identifying whether or not the sample may be retained or destroyed once the research has concluded. For purposes of possible perceived or actual conflict of interest related to determining if the consent is correct, the research investigator may want to describe a procedure to address this issue through the use of a third-party. The research investigator will be required to describe how the informed consent documents are stored, where and for how long. Example of a commercial electronic medical record is EPIC – See http://www.epic.com Examples of a commercial electronic clinical trial management systems are: Oncore Enterprise Research (Forte Research Systems) – See http://forteresearch.com/enterprise-research-oncore/
STORAGE - How will the consent document be stored? • In the study file? • In the electronic medical record • Clinical Trial Management system? What form will the consent be stored • Electronic • Paper Are there confidentiality or privacy concerns? Is there an identification risk? E.g., sensitive samples or data (HIV, Psychiatry research?)	The research investigator will be required to describe how the informed consent documents are stored, where and for how long. Example of a commercial electronic medical record is EPIC – See http://www.epic.com Examples of a commercial electronic clinical trial management systems are: Oncore Enterprise Research (Forte Research Systems) – See http://forteresearch.com/enterprise-research-oncore/

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EXCESS TISSUE CONSENT - Will the biological material or data be obtained through an informed consent (based on routine clinical care, excess tissue and/or at the time of informed consent for clinical research trial or study)? • Excess tissue to be banked following diagnostic and clinical uses completed • Specimens banked for future, yet to be determined research	The research investigator should determine if there is clinical consent and/or alternative consent process in place, e.g., clinical sample and/or excess tissue consent versus a research informed consent.

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4. Confidentiality And Privacy

Point Of Interest	Comments
PROTECTION OF THE DATA - What protections are in place for the confidentiality of the data? • Is there a separate code that links PHI and the specimen? • How are the linkages maintained? • Where is the data to be housed? Is it encrypted? • Password protected? • Locked cabinet? – who has the key or access when needed? • Locked freezer? – is there a business continuity plan in place if there is a power outage? • Consider sensitivity of the information Physical and electronic protections: • How will data and specimens be obtained/transferred/shared? • Are there data degradation concerns over time? • What format of the data will be used and available over time (years)? • How stored? • What are the preservation techniques used? • Who has access and how is access provided?	The researcher should provide the IRB with a protocol that outlines strategies to maintain confidentiality of identifiable data, including controls on storage, handling, and sharing of data, robust description of information technology plan to ensure that the data is protected and that the opportunity for a breach to occur is minimized. The research investigator should identify in the protocol for the IRB what encryption process will be used. *Suggested resource*: Health Insurance Portability and Accountability Act (HIPAA) 45 CFR Part 160, 45 CFR part 164 Subparts A ad E (45 CFR 46.111(a)(7) and 21 CFR 56.111(a) (7) http://www.hhs.gov/ocr/privacy/hipaa/administrative/privacyrule/

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

CONFIDENTIALITY AND PRIVACY - What does the study consent indicate regarding the researcher's agreement about how the participant's identifiable private information and specimen will be handled, managed, and disseminated? Releasing/distributing data and specimens: • Who can release under what conditions • Description of <u>what</u> information and specimens CAN be released and what information will not be released • Time frame, if applicable • Description of <u>who</u> can release information and specimens • Description of to <u>whom</u> information on the data and specimens can be released too • Description of <u>how</u> information and specimens will be released. • Limits of confidentiality and provisions regarding what is released with patient authorization and consent – and with waivers. • Limits of confidentiality and provisions regarding what is released with patient authorization and consent – and with waivers. • Certificate of confidentiality should be covered in this section. • Who has access ◦ Password protection ◦ access control ◦ encryption options • What can be released and what is required for release ◦ Data Use Agreement (DUA) ◦ Material Transfer Agreement (MTA) ◦ Confidentiality agreements	The research investigator should be familiar with the regulatory definitions of privacy and confidentiality as listed below: Privacy is the control over the extent, timing, and circumstances of sharing oneself with others. Confidentiality relates to the DATA/information about a person.

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

WAIVER OF HIPAA AUTHORIZATION - Is there a Waiver of HIPAA Authorization? *See also* Section 1, 2 and 3 • What is required? • When can this be used? • Does the consent address the issue of withdrawal	...

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

5. Collection and Analysis

Point Of Interest	Comments
SAMPLES COLLECTED - What types of samples are being collected? See Section 1 - Design Are there issues around integrity for future use (e.g., size, amount, thawing and re-freezing)?	Check the IRB approved protocol and/or any agreements if they indicate the specific sample(s)/data collected? The researcher (or designated laboratory personnel) should follow standard operating procedures for the collection, processing and specimen and data integrity. A plan to check the internal laboratory procedures are working for quality control and quality assurance purposes is also needed.
LOCATION - Where are the samples collected? • In clinic, the Operating Room, at a facility away from where they will be collected? See Section 1. • Are there multiple individuals handling the collection and processing? A Chain of Custody document should be used to document points of contact and processing. • Are these individuals required to be on a delegation log?	Are there additional approvals needed for the collection site? Are there concerns regarding availability of personnel if samples need to be collected after normal working hours or on weekends? If there are multiple individuals involved in the collection process, what are their roles? For example, OR staff coordination and communication with laboratory staff.
AMOUNT - How much will be collected? • Enough for the single research project or will samples be stored for future research projects? • Will the samples be used only at the institution where they are collected or will there be future use through outside collaborations? • Who decides the allocation of the specimens and amounts? • Can an investigator request samples from the same bank several times with priority above other investigators? What are the governance rules? Are they specified in the protocol?	Confirm that the amount meets statistical needs and there is appropriate short-term and long-term quantities available, if needed. Identify whether changes to the IRB protocol is needed for future use research. Check with grants and contracts or similar entity on the need for a Material Transfer Agreement (MTA).

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

VERIFICATION - What is the process to confirm whether or not the sample or data is correctly identified? • What are the reference ranges – are they defined or undefined? • How is the label created – barcode? Written? Typed? • What is the proof of performance test models? Do you need them? • Are these uniform or standard reference ranges?	The research investigator should have written policies and/or standard operating procedures on the process to verify whether or not the sample and/or data has been identified correctly. Is the label, barcoding appropriately sized? For example, will it fit on a small aliquot tube.
CONFIRMATION - Chain of Custody • Is there one? • Is it a standard template or do you need a more detailed document? • Is this in an electronic format or paper? • Is it available for out of normal business hours should a sample/data be collected?	The investigator should confirm that all personnel involved in the collection and handling of the samples/data have been trained on how to use of the Chain of Custody form and the essentials of the information to be collected and maintained for this purpose. If fresh samples need to be distributed to the research investigator quickly, does the chain of custody cover that process? What records, tests, analysis of the fresh sample must occur by repository staff prior to the release of the sample to the research investigator? Are any clinical safety tests necessary prior to use of the fresh sample (e.g., HIV status)?
CHAIN OF CUSTODY • How is the chain of custody for all biospecimens entering the repository tracked and documented? • Are all shipments accompanied with a manifest?	Sample Chain of Custody documents can be found at: http://www.testamericainc.com/data-solutions/electronic-chain-of-custody/
RECEIPT - • Are all biospecimens inspected upon receipt? • Are all specimens appropriately coded/de-identified, as appropriate?	The research investigator should develop SOPs to describe this process.
INVENTORY - • How are storage activities documented and managed? • Freeze/thaw cycles • Are audits conducted to verify that actual specimen locations correspond to documented locations?	...

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

HONEST BROKER - Is there an honest broker system? • Does there need to be an Honest Broker? • What is the governance for the Honest Broker system? • Are the activities of the Honest Broker described in the repository or research protocol or in institutional policies? • Is there a custodian or caretaker of the specimens (custodianship of the data or biospecimens)? • Is there an informatics system used to assist in the Honest Broker activities for specimens and data? For example –I2B2?	*Suggested resources*: 1. University of Pittsburgh Tissue and Research Pathology Services (TARPS) http://www.upci.upmc.edu/tarps/brokeserv.cfm 2. SACHRP Report www.hhs.gov/ohrp/sachrp-committee/recommendations/2011-october-13-letter-attachment-d/index.html *Suggested resource*: I2B2 - https://www.i2b2.org
ANALYSIS – PROCESS - What is the process for analysis of the samples and/or data? • Does an assay (bioassay) need to be developed or is there one already in existence? Do one or more individuals need to be trained on the conduct of the specific assay? • Has the process for analysis been validated or assessed prior to the start of the study? • Are there bloodborne pathogens concerns? • Will proteomics be done? • Is there associated data being collected? • Is there a need for standardized training? • What reagents are needed? • What are the controls or derivatives? Is there randomization? • What is the process for documenting, interpreting and reviewing the results?	The investigator should consider Good Laboratory Practices, CLIA Certification, Authorized personnel, Trained personnel, Vendors, Controls and Randomization as applicable.
ANALYSIS – INCIDENTAL FINDINGS – Have there been any incidental findings? • Review how incidental findings should be handled • Nature of findings • Outcome – reported to subject? Local treating physician	The research investigator should describe in the research protocol if they intend to report incidental findings back to the research subject and the mechanism of reporting any to the IRB if found. The research investigator should ensure the research protocol and consent address the possibility of having incidental findings – whether they will be provided to the research subject.

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

CLIA - Is the processing done in a CLIA certified laboratory? • Does it need to be? • What is the purpose of the research? See Section 2.	...

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

6. Storage, Access and Distribution

Point Of Interest	Comments
STORAGE – CONDITIONS - How are the samples stored? • Do they require specific temperature conditions, e.g. -70 Degree Freezer, Liquid Nitrogen, Room Temperature? • How are the storage activities and conditions documented and managed?	
STORAGE – LOCATION - Where are the samples stored? • Laboratory, pathology department, other site? • Off site – outside of institution, in a different location from where they were collected? • Is there Chain of Custody plan that tracks the samples or data stored at multiple locations?	The research investigator should conduct (or utilize individuals in the Quality Control/Quality Assurance unit) frequent audits to verify what actual specimen locations correspond to documented locations.
STORAGE - VALIDATION OF EQUIPMENT AND CONSISTENT AMBIENT CONDITIONS - How is the equipment used for storage assessed, checked or validated? • Is there a Quality Control (QC) process in place? See Section 8 • Are there process validation studies routinely conducted? • Do the refrigerator/freezers have monitored alarm systems in case of out of range temperatures or equipment failure?	

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

ACCESS – PERMISSION -Who is granted access? • How is this determined? • Is there a Biospecimen Use Committee or governance body? • Do all people with access need to be listed on the IRB protocol on on the delegation log? • Do these individuals require specific training? • How frequent should the training and on-going training be?	The researcher should determine and document in the IRB protocol, standard operating procedures, chain of custody, delegation log and other documentation (as appropriate) for has access to the specimens and data (identifiable, de-identified).
ACCESS – PERMISSION - What level of access is permitted? • Limited, full and/or conditional? • Is this assessed periodically? By whom?	The researcher should determine the mechanism by which the individuals who have access to the meta data should be limited, full and/or conditional. The researcher should determine on a periodic basis whether or not the current individuals and their access levels are appropriate.
ACCESS – TRAINING - What training is required for individuals granted access to the data or samples? • Is this documented? • Is there on-going training required? Documented?	The researcher should ensure all individuals are appropriately trained to conduct the research and follow required training – institutional or other as required. For example: • Responsible conduct of research training • HIPAA training
DISTRIBUTION - What is the process for distribution of the data or samples? Is there a Biospecimen Use Committee or other oversight process on the distribution and use of samples? Does the process assure verification of appropriate approvals/agreements? For example: • IRB approved protocol • Material Transfer Agreement (MTA) • Limited Data Set (LDS) agreement • Others?	The investigator may need to consult with Grants and Contracts administration or the unit responsible for drafting a Data Use Agreement (DUA), Material Transfer Agreement (MTA) or agreements required by the institution sending the samples/data out and/or receiving the samples/data. The approval process for distribution of samples to researchers should be defined and address issues such as prioritization, the amount that may be distributed and that to be retained by the repository, Prioritization should address internal research requests/uses versus external collaborations and requests from commercial / for-profit organizations. It is very likely the IRB will be consulted to determine if this information can be sent and under what circumstances, e.g. identified and/or de-identified (Not Human Subject Research)

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

DISTRIBUTION – SHIPMENT - What are the physical transportation/receipt requirements? • Are there additional protections needed? E.g., biohazardous materials? • Are the hazardous concerns identified and addressed in an SOP or policy? • Determine whether there are State, Federal or International restrictions on transportation • International Air Transport Association (IATA) shipping requirements, manifest documentation and training • Proper approvals in place (IRB, MTA, Simple Letter Agreement (SLA) (for NIH)) distribution, etc.) • Documentation of who/what/when • If individually identifiable samples are shipped, consider HIPAA requirements	*See Appendix – Biospecimen Glossary* In sending samples out to other sites or institutions the research investigator should assure the integrity of the specimen including any temperature concerns, the collection standards required both at the site where it was collected and the recipient site (if there are requirements to be met before receipt), SOPs (if they are required), best practices for all samples so that data integrity concerns are minimized, histological preparation, the type of container used (will it withstand shipping (and weather) conditions and any national or international shipping requirements (e.g. for hazardous, blood products etc.) The IATA has specific requirements regarding how samples are to be sent internationally. For example, there must be a shipping manifest that includes a list of sample identification (ID) numbers and a description of the samples shipped. Certain networks or coordinating data repository centers also require a feedback questionnaire in each shipment that asks researchers about the quality of the samples received. IATA: http://www.iata.org/Pages/default.aspx Export Control: https://www.treasury.gov/resource-center/sanctions/Programs/Pages/Programs.aspx
DISTRIBUTION – RECEIPT • Are all biospecimens inspected upon receipt • Are all specimens appropriately coded/de-identified	The research investigator should have identified procedures in place to handle the receipt and processing of specimens and data. Issues around loss of specimen integrity, inappropriate identification and/or loss should also be appropriately documented and handled per the SOP or protocol.
DISTRIBUTION – INTERNATIONAL -What is the shipping process for international sites? • IATA considerations • Export Control requirements and any federal export restrictions.	The research investigator should consider flight or shipping times that may impact the quality and integrity of the samples. Different time zones and temperature differences with the northern and southern hemisphere are important to consider when shipping and receiving samples to and from foreign sites. In the reverse, the research investigator should consider whether or not samples sent to the US from a foreign site met with the shipping requirements both in packaging, time in transit and delivery.
DISTRIBUTION – PERMISSION TO LEAVE INSTITUTION - Does the institution have a policy on the samples or data being retained by the research investigator should they leave the institution?	The research investigator should determine if the samples or data will remain with the institution or not if they leave the institution. Discussion with appropriate individuals should be considered (Chair, Department, Office of Research, Office of General Counsel). See *US v. Catalona*

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

7. Retrieval, Maintenance and Planned Destruction

Point Of Interest	Comments
RETRIEVAL – Is there a documented procedure for determining what specimens and/or data will be retrieved and by whom? • What if the request is outside normal business hours? What happens when an "unmet" user situation occurs? • How is this adjudicated? • By whom?	The research investigator should have in place a plan or procedure on who may retrieve the specimens and when. There should be identified procedures on the format and documentation related to the request and permission granted. Generally, there are four approaches to retrieving samples for individuals who have requested access: 1. first come, first served, 2. priority customers of the network, collaboration, group and/or those who have contributed to the repository, 3. prioritization based on merit related to the research proposal, and 4. prioritization based on a set policy of the repository. The research investigator should design a plan on the retrieval and distribution of the specimens and/or samples at the beginning of the protocol so that there will be a limited opportunity for dispute resolution should there be a complaint. Additionally, the research investigator should consider how an "unmet" user should be handled. In most cases, there are three scenario's where an "unmet" user concern arises: 1. the request is for extremely rare tissue or highly sensitive data; 2. the request cannot be met simply because the volume, amount or magnitude of the data/specimens requested is too large; 3. there are rate limiting constraints to getting the data/specimens to the requested user, for example, there is insufficient time or the preparation requirements cannot be met.

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

MAINTENANCE OF SYSTEMS - Are the data security systems current and up-to-date? • Review of data security systems • Are routine tests conducted on the system prior to or post new releases or bug fixes? • Protection against unauthorized access. How is this determined and tested? • Is there an Environmental Monitoring System? • Is there a central alarm system? • Are personnel on-site 24 hours a day, seven days a week, or is the system monitored by an alarm company or from within the institution? • Are there back-up freezers available?	Good quality control means the investigator has polices and standard operating procedures, which indicate how the security systems are periodically evaluated for maintenance purposes. The researcher should have a "validation" protocol and conduct an assessment at least annually on each freezer and/or equipment used for storage. It is strongly suggested that if the specimens are housed in a freezer, that it have around-the-clock monitoring, weekly checks, and at least annual quality maintenance review. There should be back-up systems available should the primary equipment fail.
DESTRUCTION - Is there a documented procedure for determining what specimens and/or data will be destroyed or retained? • Does the protocol stipulate if and when this will be done? And, how? Are the specimen and data destruction processes appropriate? • Approved procedures should be in place • Documentation of withdrawal and/or destruction • Safe and approved methods in place • Random audit of data and specimens that have been destroyed	Documentation of date, reasons for destruction of specific tissue and attendant data sets. Employee/staff have had safety training and approved procedures related to destruction of specimens.

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

8. Quality Assurance, Quality Control and Quality Improvement

Point Of Interest	Comments
PLAN - is there a plan to conduct quality assurance and quality control reviews? See Section 10	Depending on where the research investigator is sending, analyzing, storing or sharing the data and/or specimens there should be a plan or protocol to conduct periodic QA/QC and QI reviews. How frequently should the reviews be conducted? Ideally the location for which the samples will be stored and analyzed is accredited.
CONDUCT - Who conducts the QC/QA and QI reviews? • Is this person trained? • Does this person have permission to conduct such a review? E.g., HIPAA training, biohazard certification, etc.	The QA/QC and QI reviews should be performed by a trained individual either within the institution or outside (consultant, etc.) with knowledge and experience of biorepository activities and best practices. *Suggested resources*: College of American Pathologists (CAP) Accreditation Biorepository Checklist - See http://www.cap.org/apps/docs/laboratory_accreditation/lap_info/biorepository_accreditation_program_checklist_sample.pdf International Society for Biological and Environmental Repositories (ISBER) – Best Practices for Repositories. See http://www.isber.org/?page=BPR
QUALITY ASSURANCE - What types of activities are involved in quality assurance? • Standard Operating Procedures (SOPs) • Equipment qualification • Equipment maintenance • Equipment calibration • Software testing/validation • Personnel training • Maintaining personnel training records • Data/documentation maintenance, storage and archival – coded data or specimens, integrity of the specimens, etc. • Safety: chemical, biological, fire, etc. • Inventory management/tracking review – Chain of Custody • Periodic and annual internal and external audits • Oversight and review of key indicators of quality (e.g. are goals being met) Are there standard precautions guidelines?	Quality Assurance is the planned and systematic activities implemented in a quality system so that quality requirements for the collection of biospecimens and data is fulfilled.

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

QUALITY CONTROL - What types of activities are involved in quality control? • Histologic and/or pathological review of samples upon receipt and/or at time of distribution to ensure quality • If materials are provided to source sites to assist with collection and shipping are they inspected prior to sending?	Quality Control are the observation techniques and activities used to fulfill the requirements for quality assurance.
QUALITY IMPROVEMENT - What types of activities are involved in quality improvement? • Comprehensive CAP accreditation (CAPA) program • Customer satisfaction • Vendor review/assessment	A comprehensive Corrective Action and Preventative Action (CAPA) program should include a mechanism to report deviations/incidents (as well as defining ahead of time what falls into each category), root cause analysis activities, corrective action plans and effectiveness checks. This program should only include preventative action initiatives.
QA/QC or QI RESULTS - Mechanism for reviewing the QA/QC/QI results?	There needs to be a process to audit review findings, and to report them to the research investigator/biorepository holder and any other individuals.
ACCREDITATION - College of American Pathologists Biorepository Accreditation Program • Is the biorepository CAP accreditated?	The Biorepository Accreditation program is designed to improve the quality and consistency of facilities that collect, process, store, and distribute biospecimens for research.

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9. International Research

Point Of Interest	Comments
INTERNATIONAL SITE - Will research be conducted at a foreign site?	To conduct research, including the collection and analysis of data and/or specimens a research investigator should be familiar with international regulations, laws and requirements. There are foreign sites where human research and/or personal rights require compliance with additional elements of approval; for example, the original biospecimen donor's consent must be available. Further, contractual agreements between the United States biorepository or biobank and the participating international site are strongly advised and in some cases mandatory proof of compliance with associated regulations and laws are required. For example, considerable differences may exist in terms of storage and documentation needs, or requirements to inform donors of relevant research results. Ethics committee involvement may be required prior to program approval; however, discrepancies can be avoided by contractual provisions and/or agreements. Investigators should review the requirements and seek information from ethics committees they are submitting the research project to in order to meet any compliance obligations. *Applicable regulations:* European Medicines Agency (EMA) – See http://www.ema.europa.eu/ema/ Food and Drug Administration (FDA), See http://www.fda.gov/ WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects– See http://www.wma.net/ *Suggested resource:* *International Compilation of Human Research Standards* See http://www.hhs.gov/ohrp/international/intlcompilation/intlcompilation.html This document lists of over 1,000 laws, regulations, and guidelines on human subjects protections in over 100 countries and from several international organizations. Many of the listings have embedded hyperlinks to the source document. These laws, regulations, and guidelines are classified into six categories: 1. General, i.e., applicable to most or all types of human subjects research 2. Drugs and Devices 3. Research Injury 4. Privacy/Data Protection 5. Human Biological Materials 6. Genetic 7. Embryos, Stem Cells, and Cloning

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CONDUCTING THE HUMAN SUBJECT RESEARCH INTERNATIONALLY	The research investigator must review the need for IRB approval or equivalent protections of the human participant for which data and/or specimens will be collected. If the research project is federally funded (DHHS/NSF) then the international site should obtain a Federal Wide Assurance (FWA). See http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html The research investigator should consider the following challenges with: • Consent/translation of the research in the language(s) or dialects of the international site • Norms and cultural differences between US and other countries and regions within those foreign countries • The logistics of fulfilling PI responsibilities, for example, how to address a-request to withdraw from participation and/or the collection and storage of data and specimens, return of results or handling possible incidental findings. Data security and privacy protection - same risks as with the national exchange of material and data. However, the European Union Data Protection Directive (Directive 95/46/EC) was repealed effective 25 May 2018 and replaced by the General Data Protection Regulation (GDPR) applicable as of 25 May 2018. The GDPR is in the form of a regulation rather than a directive. The GDPR is broader in its scope stipulating that any organization in the world which processes personal data of EU residents becomes liable to the GDPR provisions. There may exist restrictions of data transfer to those foreign countries of which the standard of data protection are not comparable to those pertaining to other foreign countries *Suggested resource*: *International Compilation of Human Research Standards* See http://www.hhs.gov/ohrp/international/intlcompilation/intlcompilation.html This resource lists the documents and links for each country related to privacy and confidentiality concerns regarding human subject research. If the international site has Human Research Protection Program accreditation by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) there is an evaluation instrument used to assess whether the institution is meeting the accreditation standards - See Evaluation instrument Standard I.3. http://aahrpp.org/apply/resources/annual-report-documents/evaluation-instrument-for-accreditation

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

WHO OWNS THE SAMPLE WHEN IT IS COLLECTED AT A FOREIGN (NON-US) SITE - Property rights	Research investigators will need to review the regulations and laws related to property rights in the foreign country they are collaborating with or conducting the research in. In general, the donor of a given biospecimen is usually also the owner of that sample. However, divergent regulations could be remedied by appropriate stipulations in contractual agreements. Generally, the donor's personal rights would supersede existing property rights, irrespective of who actually owned the biospecimen. In order to address supranational and international rights of all parties (human subject donors, investigators and institutions) there needs to be an explicit contractual agreement to protect interests of the parties. The research investigator should consult with their legal and/or technology or development office. *Suggested resource:* *International Compilation of Human Research Standards* See http://www.hhs.gov/ohrp/international/intlcompilation/intlcompilation.html
MATERIAL TRANSFER AGREEMENT (MTA)S AND CONTRACTS – When is it needed?	The research investigator should review the Uniform Biological Material Transfer Agreement (UBMTA) Federal Register - See https://grants.nih.gov/grants/guide/notice-files/not95-116.html or consult with their grants and contracts office or their technology transfer office for information on when and how to execute a materials transfer agreement or contractual agreement with a foreign site, both in the sending and receipt of information/specimens. Specifically, in some foreign sites, describing the particular requirements of the exchange(s) can only be done via a contract or agreement. This contractual requirement is to address any legal issues that are part of the dispositive law (those facts that settle an issue). *Suggested resource*: For biospecimens research in Europe - *V010-02 Biobanking EUCoop – Legal Basis of EU-wide biobanking cooperation*. Generic text produced in BMB-EUCOOP may help avoid conflicts and unwanted loss of rights (http://www.tmf-ev.
COMMERCIALIZATION AND INTELLECTUAL PROPERTY RIGHTS - consideration Is there a plan to patent?	Depending on the country, there are differences in what can be commercialized and/or claimed as intellectual property (IP). The research investigator should consult with legal and/or their local technology and development office. For example, there may be ethical reservations regarding certain types of materials such as gametes and embryonic stem cells and certain legal restrictions may exist that cannot be contractually disregarded.
CONFLICT – Alternative Dispute Resolution (ADR)	In cases where there is a dispute regarding ownership, activity or control of data and/or specimens, the research investigator should be aware that the laws and regulations that address legal conflicts/disputes vary greatly between countries. Alternative Dispute Resolutions (ADR), which is a means of settling a dispute outside the courtroom, would usually be preferable to taking a dispute to court.

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EXPORT CONTROL – Is there a partial or complete prohibition of commerce or trade with a particular country?	Embargoes are considered strong diplomatic measures imposed in an effort, by the imposing country, to elicit a given national-interest result from the country on which it is imposed. Embargoes prohibit the research investigator from sending or receiving data and/or specimens from the embargoed country. For a list of embargoed countries see the US Department of State – Country Policies and Embargoes, see: https://www.bis.doc.gov/
CRIMINAL LAW – violation and prosecution	The research investigator should consult with his/her institutional legal counsel or subject matter experts on the research project if there is a possibility of concern related to the conduct of the research in the foreign site. Matters regulated by criminal law include neglect of duty, negligent injury, privacy violation and the possibility of confiscation. For example, national differences exist in the case of a state's entitlement to biomaterial confiscation and these cannot simply be alleviated by contractual agreements. Whether donors should be informed is a topic of ongoing discussion. Related to benefit sharing of results there is national difference across countries. The involvement of donors in the pecuniary (monetary penalties or fines) and /or non-pecuniary outcomes of research on their biomaterials are often not clear cut in law or regulation and therefore, not yet legally binding in some countries. However, researchers remain under morally binding ethical obligations.

POINTS TO CONSIDER ON THE BEST PRACTICES FOR THE DESIGN, IMPLEMENTATION AND MANAGEMENT OF REPOSITORIES, REGISTRIES, AND DATABASES

10. Accreditation

Point Of Interest	Comments
ACCREDITATION - Will accreditation be sought? • Is it required for the creation, maintenance of the biorepository? • College of American Pathologists (CAP)	The institution or organization should assess and determine if accreditation is sought and the rationale for doing so. Most institutions or organizations seek accreditation in order to have standard operating procedures for biorepositories to help ensure consistent handling of biospecimens, quality samples available for research that include drug discovery, personalized medicine, and genetic diseases that will yield valid results. Further, accreditation will require timely and routine review of practices, as well as establish standardized criteria to maintain biospecimen quality to enhance the quality of research outcomes. *Accreditation resources*: • CAP Biorepository Program Checklist – See http://www.cap.org/apps/docs/laboratory_accreditation/lap_info/biorepository_accreditation_program_checklist_sample.pdf • CAP Laboratory General Checklist http://www.cap.org/apps/cap.portal?_nfpb=true&_pageLabel=accreditation
CAP Accreditation: • what are the steps for becoming accrediated by CAP? • What are the basic requirements of CAP accredutation	In order to seek CAP Accreditation the organization or institution must download and complete an application form. The CAP website (http://www.cap.org/apps/cap.portal?_nfpb=true&_pageLabel=home) describe the basic requirements that require a quality management program, laboratory safety plan, document control plan, competency assessment program, laboratory director oversight documentation, and specific requirements for a laboratory information system, if applicable.
Clinical Laboratory Improvement Amendments (CLIA) Certification—Note – CLIA Certification does not necessarily go together with CAP Accrediation.	For more information - http://www.cdc.gov/clia/