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Material Transfer and Data Use Agreements

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Medical research often involves the use and analysis of various materials developed and held by one entity and provided to researchers in another entity pursuant to terms and conditions set forth in a Material Transfer Agreement ("MTA"). Such materials might include human tissue specimens, cell lines, plant varieties, bacteria, transgenic animals (which are frequently mice and other rodents), compounds, proteins, peptides, nucleotides, plasmids, vectors, antibodies, pharmaceuticals and other chemicals or biological substances.

Transfers of human biological materials and associated information are becoming more common as the analysis of large cohorts of data and/or specimens are proving essential to advances in medical care and treatment, especially in the area of personalized medicine.[1] This article will focus on the terms typically found in an MTA for the transfer of human biological materials and associated information.

A Data Use Agreement ("DUA") might also be required under certain circumstances, as discussed below.

Regardless of the nature of the material transferred under an MTA, one central element of the agreement is that the material is only to be used for *in vitro* or non-clinical research purposes or for data analysis and not for use in human subject research or in clinical care.

Material Transfer Agreements

When the provider has no intellectual property or other proprietary rights in the materials and is not under an obligation to protect the property rights of a third-party in the materials, the transfer of such materials, absent accompanying identifiable health information, generally carries few risks, and the terms of the MTA can be brief and relatively straightforward. However, the terms of the MTA become more complicated when the materials are unique, proprietary, hazardous or include human fluid or tissue, or if there are issues regarding liability or ownership of any results that derive from the material, or the associated information constitutes identifiable health information.

The National Institutes of Health (NIH), through the Association of University Technology Mangers (AUTM), has promulgated a variety of MTA templates to facilitate the transfer of materials into and out of the NIH, as well as transfers among non-profit research institutions, such as universities that are signatories to the Uniform Biological Material Transfer Agreement (UBMTA) and other MTA templates, depending upon the parties and the nature of the material to be transferred.[2-4]

The NIH Guiding Principles for such agreements inform these templates. However, except for some basic terms, the UBMTA will not be useful in situations where the proposed transfer is between a non-profit research institution and a commercial entity, so the MTA must be crafted to meet the special circumstances and requirements of the parties.[5] Nonetheless, universities and other non-profit institutions have certain inflexible requirements and only marginal flexibility with respect to intellectual property issues.

An MTA is not generally required for the transfer of human biological samples or data to a sponsor or third party pursuant to a clinical trial protocol, informed consent form, and HIPAA authorization, since the transfer and use of the materials will be governed by the terms of the applicable clinical trial agreement. However, the use of an MTA is generally

needed for the transfer of human biological materials and associated information obtained as (a) leftover (or "remnant") material collected in the course of medical treatment, testing or clinical research; (b) additional or "secondary" specimens collected in the course of conducting a clinical trial, with consent by the subject; or (c) voluntarily provided by a donor for banking and general research use[6].

Typical MTA Terms

An MTA addresses requirements relating to the transfer and use of the material, including establishing safety requirements, allocating risk and liability, and clarifying restrictions on use and further transfer of the materials. The following are terms that would typically be found in an MTA[8]:

- Description of materials to be transferred
- The name of the principal investigator recipient overseeing the use
- Description of the intended research use, considering the following:
    - If the description of the research is too broad, then there may be an implied grant of rights related to future research
    - If the description is too narrow, there is an increased risk of breach
- Restrictions on use of the materials
    - Only for use in a not-for-profit research project by the research team and for educational purposes
    - No further transfers
    - No commercial use or purposes
    - No use in humans or for any diagnostic or treatment purposes
- Requirements for return or destruction of the materials upon completion of the research
- Reporting obligations
    - A summary report of the research and findings to be submitted to the provider upon completion of the research
- Confidentiality provisions
- Compliance provisions
    - IRB
    - HIPAA (including security requirements to ensure appropriate administrative, physical and technical safeguards)
    - Export controls
- Publication rights and requirements
    - Acknowledge provider in any publication
    - Provide an advance copy for a reasonably short period for the provider to review and comment, but no approval rights
    - No restrictions or unreasonable delays in the publication of a thesis or dissertation by a graduate student who worked on a research project involving the materials.
- Disclaimer of warranties
- Indemnification
    - Recipient assumes liability, except for the provider's gross negligence or willful misconduct, e.g., an unlawful transfer of a third-party's material

- Intellectual property and licensing obligations
    - The provider or a third-party owns the material
- Intellectual property and licensing obligations (typical only when the provider is a commercial entity)
    - The provider owns the material
    - Use of data or report
    - Disclosure of resulting inventions to provider
    - Royalty-bearing or royalty-free license
    - Exclusive or non-exclusive license
    - Field of use
    - Terms of license negotiation (option and negotiation period)
    - Conflicting obligations (depending upon the source of the funding for the research)
    - Reservation of rights by recipient to continue to use and share inventions and data for research, education and other non-profit purposes
- Transfer to recipient at no cost or only in an amount necessary to reimburse the provider's costs to assemble, prepare and transfer the material.

A Closer Look at Certain Terms

Intellectual property issues flow from the definition of the material to be transferred, with inventorship in the U.S. generally governed by U.S patent law. Material is defined as the physical substance being transferred plus the following:

- **Progeny,** which are understood to be descendant copies of the material produced by the recipient as a result of replication, such as cell division, or copying the DNA. Progeny are, essentially, unchanged copies of the original material that was provided.
- **Unmodified Derivatives,** which are subunits or products expressed by the material, such as subclones of unmodified cell lines, purified or fractionated subsets of the material, proteins expressed by DNA/RNA, or monoclonal antibodies secreted by a hybridoma cell line. Unmodified derivatives can also include unmodified portions of the original material fixed as tissue sections.

In addition to retaining ownership of the original material, the provider typically owns all Progeny and Unmodified Derivatives, as well as the original material included in any Modifications. A "Modification" is usually defined as substances created by the recipient that contain or incorporate the original material; e.g., when a derivative of the original material is embedded in a recipient-owned expression vector and using a recipient-owned promoter, resulting in genetic modifications or manipulation of cells extracted from the material. Modifications can include crosses, breeding varieties, cell fusions, and subclones. Modifications could constitute an invention, which might be owned by the recipient, by the provider, or jointly, depending upon the facts and the circumstances. The recipient also owns any substances created through the use of the original material or Modifications but which are not Progeny, Unmodified Derivatives or Modifications. If government funding is involved, attention must also be paid to obligations under the Bayh-Dole Act and its implementing regulations[6-8].

The UMBTA defines "commercial purpose" as:

> The sale, lease, license, or other transfer of the MATERIAL or MODIFICATIONS to a for-profit organization. COMMERCIAL PURPOSES shall also include uses of the

MATERIAL or MODIFICATIONS by any organization, including RECIPIENT, to perform contract research, to screen compound libraries, to produce or manufacture products for general sale, or to conduct research activities that result in any sale, lease, license, or transfer of the MATERIAL or MODIFICATIONS to a for-profit organization. However, industrially sponsored academic research shall not be considered a use of the MATERIAL or MODIFICATIONS for COMMERCIAL PURPOSES per se, unless any of the above conditions of this definition are met. (Article I, Section 10)[4]

Privacy Issues

Increasingly, the transfer of human biological material is accompanied by associated information or other data (collectively, "Data") about the individual from whom the specimen was obtained. These Data might include age, gender, ethnicity, treatments, study arms, treatment dates, admission and discharge dates, disease-stage parameters, environmental factors, community risks, and other clinical, genealogical and lifestyle information relating to the biospecimen that could, potentially, lead to the identification of the donor of the specimen, either directly or in combination with other available information.

The disclosure of individually identifiable health Data meeting the definition of protected health information ("PHI") is governed by the requirements of the Health Insurance Portability and Accountability Act of 1996, as amended ("HIPAA"), the Health Information Technology for Economic and Clinical Health Act, and regulations promulgated under each by the Department of Health and Human Services (collectively referred to herein as the "Privacy Rule"). In addition, there might be state and local regulations or funding agency policies that apply to the use and disclosure of clinical data.

In general, the Privacy Rule requires patient authorization for uses and disclosures of PHI for research purposes. However, if a Data set has been fully de-identified by removing all 18 types of identifier information with respect to the individual, the individual's relatives, employers or household members in accordance with the requirements set forth in 45 CFR 164.514(b)(2)(i) ("De-identified Data"), it is no longer PHI, and therefore does not require HIPAA authorization to be disclosed or used for other purposes.

The Privacy Rule also permits use and disclosure of PHI for research purposes without HIPAA authorization in the following circumstances: (a) with documentation from an institutional review board (IRB) or privacy board waiving the requirement for patient authorization (45 CFR 164.512(i)(1)(i)); (b) pursuant to a data use agreement for use of a "Limited Data Set," as further discussed below (45 CFR 164.514(e)); (c) for use or disclosure for activities preparatory to research (45 CFR 164.512(i)(1)(ii); and (d) for research on decedents' information (45 CFR 164.512(i)(1)(iii).

Data Use Agreements

To create a Limited Data Set from PHI so it can be disclosed for research purposes, the disclosing covered entity must remove 16 of the 18 directly identifying items that must be removed to create De-identified Data. These 16 items are:

- Names
- Postal address information
- Telephone numbers
- Fax numbers
- Electronic mail addresses

- Social Security numbers (SSN)
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate/license numbers
- VINs or license plate numbers
- Device identifiers and serial numbers
- URLs
- IP address
- Biometric identifiers
- Full face photographic images and any comparable images

Two types of Data do not need to be removed to create a Limited Data Set:

- Date information, including admission, discharge and treatment dates, age, birth date, and date of death
- Limited geographic information such as town, state or nine digit ZIP code

A Limited Data Set can include a link to allow the disclosing covered entity to re-identify the individual using a code that could be derived from direct identifiers, such as SSN or medical record numbers. (De-identified Data may contain such a link field, but it may not be derived from direct identifiers.)

A Limited Data Set should include only the minimum identifying information necessary to achieve the objectives of the disclosure. However, even with 16 identifiers removed, a Limited Data Set is still PHI.

For PHI disclosed for research purposes as a Limited Data Set pursuant to a Data Use Agreement ("DUA"), no informed consent authorization is required. In addition, approval of the disclosure or of the DUA by an IRB or other privacy board is not required under the Privacy Rule (although local IRB policies may require otherwise).

Data Use Agreement Terms

To comply with the Privacy Rule, a DUA must include the terms set forth in 45 CFR 164.514(e)(4)(ii). A DUA between a Covered Entity (e.g., a clinical research site) and a recipient (e.g., another research organization) must:

- Establish the permitted uses and disclosures of such information by the Limited Data Set recipient, consistent with 45 CFR 164.514(e)(3).
    - The DUA may not authorize the Limited Data Set recipient to use or further disclose the information in a manner that would violate the requirements of the regulations if that disclosure were made by the Covered Entity that created the information.
- Establish who is permitted to use or receive the Limited Data Set.
- Provide that the Limited Data Set recipient will:
    - Not use or further disclose the information other than as permitted by the DUA or as otherwise required by law;

- Use appropriate administrative, physical and technical safeguards to ensure the confidentiality, integrity and security of the information;
- Report to the covered entity if it becomes aware of any use or disclosure of the information not allowed by the DUA;
- Ensure that any agents to whom it provides the Limited Data Set agree to the same restrictions and conditions that apply to the Limited Data Set recipient with respect to such information; and
- Not re-identify the information or contact the individuals from which it came.

In the context of a clinical study, a DUA is not generally required for the transfer of study data to a sponsor or third party, since the subject has authorized the transfer and use of the data in a HIPAA authorization, and the terms of use are governed by the clinical trial agreement. However, a DUA is required for the transfer of clinical Data collected in the conduct of the clinical study, in the form of a Limited Data Set, if the transfer is outside of the scope of the study's informed consent form and HIPAA authorization.

Conclusion

The use of human specimens, other materials, and associated Data in research can lead to discoveries and inventions of great scientific and commercial value. In addition, certain transfers and disclosures are subject to government regulations. The parties to a transfer or disclosure should therefore agree on a clear statement of the terms and conditions of the transfer or disclosure.

The terms of an MTA depend on the source of the material. If the material is to be transferred between two non-profit institutions or between a governmental agency and a non-profit institution, the terms can generally be covered with a UMBTA template. However, when a commercial entity is involved in clinical or pre-clinical research, particularly as the source of proprietary material, there arise challenging intellectual property issues and publication issues that must be resolved, which usually means crafting a customized agreement. Human biological material and associated clinical Data may be transferred for use in the research:

- Pursuant to an MTA if (a) the Data is limited to De-identified Data, (b) with documentation of IRB waiver of authorization, (c) if the use meets the requirements for activities preparatory to research, or (d) if the use meets the requirements for research on decedents' information
- Pursuant to a DUA if the Data constitutes a Limited Data Set
- Pursuant to the applicable clinical trial agreement if specimens and Data are transferred pursuant to a clinical trial protocol, with appropriate informed consent and HIPAA authorization

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