Annex S2: Background and References for Ethical Considerations in CKDu Research

Ethical guidelines for biomaterial collection and analysis for CKDu

There are major problems in establishing a CKDu diagnostics, incidence and prevalence, progression and causal factors that include demographic, sociocultural, environmental and genetic. With a sharp increase in cases requiring analysis of blood and kidney tissue for diagnosis and a concomitant increase in research requiring blood, urine and other materials for testing, there are a surfeit of biomaterials that could be available to researchers desperately seeking definitions, etiologies and interventions with which to address the disease. The potential availability of these rich biomaterials from diverse countries holds the promise of establishing a global definition or identification of subtypes, identification of etiological factors and approaches to prevention and treatment.

There are significant issues associated with the collection, storage, utilization and future re-utilization of biomaterials. We review these below:

Bio repository /Biobank

"Biorepository", "Biobank", "Specimen bank/repository" and "tissue bank/repository" are the terms used for "libraries" within which such biological materials as blood, tissue, biopsy specimen, and biological fluids, DNA and RNA are collected, processed, stored and distributed either for clinical or research purposes (Atherton, 2017; "Biorepositories and Biospecimen ", 2016; Dash et al., 2012; Watson & Barnes, 2011). Whatever they are called the maintenance of biomaterials require exacting procedures, expensive equipment, review of requests for access and a committed staff. Bio banks can be classified as disease-centric, case control, and tissue bio banks, clinical trials, population based bio banks for genetic research, cellular, e.g. cord blood, stem cells ("Biobanks for Europe," 2012; Institute, 2017; Watson & Barnes, 2011).

Biobanks are repositories that collect bio-specimens in various ways:

- Almost 75% of total contributions to biobanks in the United States are remaining or "left over" from clinical care and surgical intervention in hospitals and other clinical settings where organ donation, laboratories and pathology departments are present (Henderson et al., 2013).
- The remaining percentage involves a variety of kinds of research that include clinical trials and descriptive studies conducted by universities, research institutes and pharmaceutical companies
- Biobanks are available in every continent and usually consists of two type of data, individual demographic descriptors and bioparameters as well as the biomaterials themselves (Artene et al., 2013; Institute, 2017; Meslin, 2009).

The major issues associated with biobanks, whether in a single institution, multiple feeder institutions or national includes the following:

- Standardization of collection procedures
- Consistent inclusion criteria
- Proper stage and maintenance
- Linkage of demographic, bioparameters and biospecimens
- Procedures for access by qualified researchers
- Informed consent from the individuals who provided the biometerials

IRB/ERC Approval

(1) Approval of the use of biospecimens resulting from surgical or clinical care for research or speciments to be collected as a part of research require an IRB (or an Ethical Review Committee) should approve the research(Williams & Wolf, 2013).
(2) Notice of proposed Advanced Rule-Making (ANRMP), proposed that "as the research involving biological specimens begin with an initial "interaction with individual." Such research falls under

the human research regulatory framework known as Common Rule" and thus requires written consent to conduct the study (Williams & Wolf, 2013).

(3) The exceptions to the written consent are as follows (Williams & Wolf, 2013):
   - The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals
   - The investigators cannot ascertain the identity of the individuals

(4) There are certain other conditions that don't fall within the exemptions but can be conducted without the participant's informed consent if the IRB finds that the study meets certain IRB criteria that include:
   - The study involves no more than the minimal risk to the subjects.
   - The waivers will not adversely affects the right and welfare of the subjects.
   - The research could not practicably carried out without waiver or alteration
   - Whenever appropriate, the subject will be provided with additional pertinent information after participation ("HHS.gov Office for Human Research Protections," 2009)

Informed Consent:

There is a wide variation in nature of consent, across countries with regards to biospecimens. Some countries accept **"general consent**", whereas others required **"signed consent"** and yet others required **"informed consent"** (Maschke, 2006; Riegman et al., 2008). In United States, **informed consent** can be obtained with opt-in or opt-out options. **Opt in** requires the research staff to generate the written consent of the donors, in which they agrees to participate in the research project. **Opt out** translates the inaction of the donors, after being informed about the implications of their agreement, as a sign of consent.

Before collecting specimen participant should be well informed about the nature and the extent of collection and use of their samples in a study, the outcome of the research, where the samples will be analyzed, both the risks and benefits of the research (Hoeyer, Olofsson, Mjorndal, & Lynoe, 2005).

Only, after voluntary consent, can the specimen be collected or if collected as a part of clinical care, be used for non-clinical research. To maintain the autonomy, privacy and personal integrity of the participants some ethicists have suggested that there should be an opportunity to withdraw consent, but there has been no proposal as yet to determine what can be withdrawn and at what point of the study can the subject withdraw (Helgesson & Johnsson, 2005).

Consent for future research

While consent for a specific project is clear, the ability of researchers to use samples for an as yet unspecified research is less clear/ The broad or blanket consent gives permission to use the biosamples for future and as yet unspecified research as long as confidentiality and privacy are well maintained (Hawkins, 2010). **Broad consent** refers "to a process by which individuals donate their samples without any restrictions". **Blanket** also called as "general consent " refers to a process by which individuals donate their samples for a broad range of future studies, but are subject to specified restrictions" (Wendler, 2013). It also requires the need of re-contacting and re-consenting to use the samples in new study other than the earlier proposed one (Maschke, 2006).

Nature of Consent:

IRBs have debated the use of a universal standardized consent form to ensure the reliability and the validity of the procedure. Others have suggested that the consent structure should be specific to the population respecting their culture and religious beliefs (Artene et al., 2013).

Confidentiality and Protection of information:

The major issue with bio banking is the risk of a breach in the confidentiality and privacy of the individual that can lead to social stigmatization and discrimination (Cambon-Thomsen, Rial-Sebbag, & Knoppers, 2007). This is most common with genetic research, in which genetic information is linked with clinical data of the participant. To ensure the privacy of the participant, The American Society of Human

Genetics has identified the ways of identification of samples for research purpose (Godard, Schmidtke, Cassiman, & Ayme, 2003; "National Cancer institute Best Practices for Biospecimen Resources," 2007)

- Anonymize/deidentify the specimens so that they cannot be linked to their sources.
- Coding and encrypting the biosample and associated data
- Biological specimens that were originally collected without identifiers cannot be linked to the donors.

Competency of the Study Participants:

- Dual consent both from guardian as well as from children is required in the case of children from the age 12 until they reach maturity (Hein et al., 2015)
- In case of incompetent individuals, such as those suffering from mental illness, a guardian must sign the consent and the ethical board must be consulted in all cases to protect the privacy and confidentiality of the person.

Summary of suggested procedure:

(1) Ensure through IRB/ERC review that the protocol for the appropriate selection of subjects and the procedures for collection, transportation, storage and maintenance and analysis will result in a quality project, worth doing.
(2) For specimens collected as a part of clinical care, written informed consent must be used to grant permission for such use
(3) For specimens collected for research purposes, written informed consent needs to be required
(4) For individuals who have provided written consent for a specific project, an additional consent (or an additional paragraph on the consent form), which provides consent for specified additional projects (blanket consent) or for use in unspecified additional projects
(5) Special consent is needed for biosamples to be sent out the country
(6) Biosamples and associated data should be de-identified to reduce as much as possible the risk of loss of confidentiality.

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