Biobanking Framework: “One Size Fits All”

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Research

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Abstract

Background Biobanking has been identified as a key area for development in order to accelerate the discovery and development of new drugs. biobanks include not only a collection of specimens but associated -omics data, thus the need for databases that inventory samples, associated clinical and omics data. As access to human biospecimens is becoming less of a barrier to translational studies, it is becoming clear that annotation of human samples and complex databases is our next hurdle.

Purpose In this paper, we elaborate on the steps and processes that were considered in order to establish the Research Institute of the McGill University Health Center Liver Disease Biobank (RIMUHC-LDB) and highlight the success of our translational projects that sustain this biobank.

Results The workflow model is based on a two-tier approach: a “mother” protocol that requires participant’ signed consent form and a “companion” protocol which allows the use of biospecimens and data for research. The “companion” protocol is based on a review of the protocol by the biospecimen access committee (BAC) and approval followed by an expedited review by the research ethics board. Our workflow is open, in addition, to include different prearranged requirements for collection of biospecimen and data from different project. Following strict standard operating procedures and ensuring that biospecimens are processed in a short amount of time after procurement, we are able to provide high quality biospecimen and data. Also, integrated in our biospecimen procurement process is our Quality Assurance Program (QAP). Every 4 months two samples are randomly selected and screened. We regularly isolate RNA from these tissue samples, labeled Quality Assurance/ Quality Control (QA/QC), and assess their RNA integrity number (RIN).

Conclusions The biobank has enabled national and international access of biospecimen and data for genomic, proteomic and phenotypic research in addition to provide the biobank financial sustainability. Understanding the complexity of disease has and will always remain a challenge. As disease burden has shifted from acute conditions to chronic conditions, primarily seen in community and primary care (PC) rather than tertiary care centers, new approaches for forging relationships with local and regional community partners will become increasingly critical. A personalised PC Biobank along with disease-specific biobanks and industry biobanks (clinical trials) will ensure that the best personalised care is delivered to participants.

Background

Understanding and investigating human diseases is a multi-disciplinary field that requires validation through one of two avenues: human tissues and/or trials. Animal and cell models have allowed for a better understanding of disease and the development of markers for diagnosis and treatments however, (1) if we are to succeed in the war against cancer, we must work closely with human tissue samples of diseased and non-diseased participants, translational studies. There is growing hope that a focus on personalized medicine will speed up the translation of our rapidly increasing knowledge about disease

processes into new and useful therapies. (2–4) The collection and storage of human tissue for medical research is not a new concept. (5) Biobanking has been identified as a key area for development in order to accelerate the discovery and development of new drugs in addition to study disease development and processes.(6, 7) In Canada, the national policy on research ethics uses the term “biobanks” to encompass all “collection(s) of human biological materials that may include associated information about individuals from whom biological materials were collected”. (8) The number of biobanks worldwide is increasing especially hospital-integrated biobanks and this is only for the best as we advance towards precision and translational medicine. (9) It is difficult to assess the number of existing biobanks worldwide because a big number of biobanks are not registered and cannot be integrated within global statistics. Moving forward biobanks include not only a collection of specimens but associated -omics data, thus the need for databases that inventory samples, associated clinical and omics data. As access to human biospecimens is becoming less of a barrier to translational studies, it is becoming clear that the “quality”, “clinical” annotation of human samples and complex databases is our next hurdle.

In this perspective, we elaborate on the steps and processes that were considered in order to establish the Research Institute of the McGill University Health Center Liver Disease Biobank (RIMUHC-LDB) and highlight the success of our translational projects that sustain this biobank. We further elaborate on the challenges and issues faced running the biobank throughout the institution and integration with routine clinical care, in a specific participant population. Through the building of our RIMUHC-LDB, we have come to understand the importance of basic sample specifications but also as we use the samples across different projects and thus apply different “omics”, each sample has a plethora of data associated with it that can be more effectively used in combination than alone. The real value of a biobank is not only the “sample in the freezer” but its associated data and the integration of this data across a number of samples.

The initiative

The RIMUHC-LDB was initiated based on the need of putting in place a strategic systems medicine program focused on liver disease including non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and liver cancers such as hepatocellular carcinoma, neuroendocrine tumours, cholangiocarcinoma and colorectal cancer liver metastases. We started with the idea of a more specialised biobanking, a disease- specific hospital-integrated biobank. Our objectives were to:

1. 1. establish standardized procedures including obtaining informed consents, sample acquisition, clinical annotation, histopathology annotation, study design and data sharing without re-inventing the wheel;
2. 2. coordinate inter-professional meetings to review incoming data and support its integration with clinical care and;
3. 3. support and maintain multinational collaborations.

The goal of the RIMUHC-LDB is to integrate clinical management of liver disease with high-end research analysis to identify new biomarkers for the diagnosis, staging, and eventual treatment of liver disease. The RIMUHC-LDB embraces a “personalized” or “precision” medicine approach, generating vast amounts of clinical data on participants to identify biomarkers related to disease progression and response to treatment. We followed a fit-for-purpose or fitness for intended purpose collection which meant that the collection would be done in line with prearranged analytical or relevant criteria for an intended project within the biobanks goal. (Fig. 1) We also ensured that the biobank can cover other fit-for-purpose requests if future collaborations were to be established with the biobank. Based on the idea of supporting translational research, we ensured that the ultimate goal of the biobank was to support research primarily around liver disease and secondly to general research.

Methods

The workflow model

We have developed an infrastructure for participant oriented research by streamlining logistical (acquisition of biological specimens, histopathology evaluation, clinical annotation), regulatory (informed consent, protection of participant privacy, incidental findings) and scientific (study design to account for tumor heterogeneity, bioinformatics for analysis of multifactorial data) components, whilst maintaining high quality standards (SOP driven) such that overlap and redundancy can be minimized and the value of data increased through comparison. Although, we follow *Best Practices from ISBER (4th edition)* in our procurement and storage of biospecimens, the process is a living entity, changing in a structured manner to allow research to flow and not be hindered. It generates vast amounts of clinical data on participants to identify biomarkers related to understanding disease, disease progression and response to treatment. Figure 2 provides an overview of the RIMUHC- LDB. Our workflow and integration of the different prearranged requirements from different project includes (1) approval by the Research Ethics Board (REB) to conduct the banking of specific biospecimens in order to use the material for research; (2) obtaining informed consent from participants prior to biospecimen collection; (3) implementation of a “double” coding (pseudo-anonymization) system to preserve participant privacy (4) coordination of efforts with operating room staff, surgeons, head nurses and pathologists to ensure no delays in biospecimen collection; (5) processing of samples with clear time lines from the operating room or pathology suite; (6) supervision of process by pathologist, such that the specimen is released as swiftly as possible; (7) Transfer of biospecimens to the laboratory for processing; (8) collection of detailed clinical and biospecimen information in the form of a standardized Clinical Research Form (CRF); (9) review of processed samples by pathologist through the establishment of standardized study pathology form; and (10) establishment of a database to manage specimen and clinical data. This workflow model allowed us to run the biobank activities based on our clinical flow. The biobank workflow was integrated within the clinical requirements and standard of care procedures. We worked with the clinical team to ensure there was training and education associated the concept of biobanking, and the clinical team collaborated with us without compromising participant care.

The process

In 2011, when we initiated our biobank, the process of review for a biobank project was not yet well defined in our Institutional Review Board (IRB). Therefore, we had to put together a framework based on different resources available at ISBER (10) and the Canadian Tumour Repository Network (CTRNET). (11) With the goal of supporting translational research we needed to integrate any future methodologies and use of the biospecimens into the protocol while maintain the interest of the participants confidentiality. For this reason, we decided on a two-tier approach, described below. Briefly, the “mother” protocol which focuses on collection and the “companion” protocol for the actual research component on the biospecimens.

The *“mother” protocol*

Biobanking has been in practice for over 150 years, thus we did not wish to reinvent the wheel but evaluated existing best practices. Integral to our RIMUHC-LDB is ensuring the best quality specimens are banked and available for a multitude of research projects. This includes i. Participant recruitment; ii. Biospecimen procurement; iii. Biospecimen clinical annotation; iv. Multinational participation. Equally important to note is that some aspects of our biospecimen management are governed by our local (hospital) regulations, as well as regional and national/federal regulations. We found that working closely with our IRB allowed us to build a rapport and ensure we included their policies and procedures in our protocol from the beginning. Building a rapport and “circle of trust” with different members through “inclusion” allowed us to work effectively and efficiently. We started with an initial protocol that explained the RIMUHC -LDB with an introduction of our goals, including our expectations to provide access to other researchers and organizations (ie Pharma) to use biospecimens from the RIMUHC-LDB. The “mother” protocol is specific to liver disease and includes biospecimens collected from participants with liver disease. We provided details whenever possible as this demonstrated our transparency and build trust with our IRB. The protocol includes three possible sources for biospecimens: 1) All participants seen at the hepato-pancreato-biliary (HPB) clinic and scheduled for any interventional procedure at the hospital including biopsies, blood tests, intra-arterial interventions etc.; 2) organ donors who have provided research consent (livers not good for transplant would be collected) and 2) recipient explanted livers. To obtain biospecimens from donors, our institution’s ethics approval letter and a copy of the RIMUHC-LDB protocol is forwarded to Quebec Transplant (QT), our provincial transplant organization who have already incorporated a research study clause on their organ donor consent forms. Following the internal review with QT, a letter is sent to us confirming registration of the biobank with QT. All tissue specimens would only be collected from the liver and any prior primary cancer surgeries would be collected prospectively as well as retrospectively from paraffin blocks located in pathology departments of different hospitals around the province. The “mother” protocol also allows for serial blood, urine, saliva and fecal specimens collection. This represents the “mother” protocol that allows us to collect biospecimens from participants towards future liver disease research or future research. Ethics approval from the MUHC Centre of Applied Ethics was provided for the RIMUHC-LDB protocol along with the research consent form. Once finalized

this “mother” protocol allows us to consent and collect biospecimens from our liver disease participant group.

The *“companion”* protocol

The next step is access to the biospecimens for different research projects. Working closely with the IRB we generated a template for a “companion” protocol, which provides access to all biospecimens in the RIMUHC-LDB. These protocols enter into a two-step approval process. Step one: after completion of the template protocol, it is sent to the Biospecimen Access Committee (BAC), comprised of 7 members (director, layman, nurse, lawyer and two scientists) and defined in the “mother” protocol. The BAC committee will meet, review and discuss the requests. Once requests have been approved, the protocol is sent to our MUHC-Centre of Applied Ethics for institutional approval. The MUHC-Centre of Applied Ethics had also created a special committee, *Cells, Tissue, Genetics and Qualitative Research*, to expedite the review process for these protocols. It is important to note that integrated into the “companion” template is an appendix for a Material Transfer Agreement (MTA) which is reviewed and executed by the RI-MUHC Contract’s office and a material release form, overseen by the Biobank, once the specimens have been released. The goal of the “companion protocol” was to streamline and decrease the bureaucracy for accessibility to biospecimens or data from the RIMUHC-LDB. “Companion protocols” do not require a full board REB review since all “companion” protocols follow a template that was reviewed and approved by IRB which expedites the review process for access.

Results

Participant recruitment

In order to have enough biospecimens/participants, you have to identify the best place to identify your participant population. Our RIMUHC-LDB therefore starts within the HPB Clinic at the Cedar Cancer Centre. Focused on liver disease, the Biobank relies primarily on the clinicians/surgeons who treat these participants. Without this interaction/collaboration, participant recruitment would be minimal and impossible. Based on their primary evaluation, the clinicians inform the clinical research associate (CRA) which participants to approach. A clinical research associate (CRA), is a health-care professional who performs many activities related to medical research, particularly clinical trials. We decided, given the background experience and training of CRAs, it is crucial to have the following expertise as the first contact with the participants. During the consenting, we emphasize on informing the participant that proteomic and genomic information will be generated and used for research on the provided biospecimens. Ethical and legal aspects related to genetic information and how this information is given back to the participant is relatively new to the participants. Participants will have the choice to either sit in the waiting room to read through the consent or take a copy of the consent with them to read at their convenience. In any case, participants will have sufficient time to read, consider and discuss their participation into the RIMUHC-LDB with friends and family members. If any questions arise, they also have access to all contact information to help them in their decision in participating. The participant will

be able to bring back a signed copy of their informed consent at their next follow-up appointment at the HPB clinic. Every time a participant is approached for biobanking, a visit is created in our electronic medical records which will permit us to write the informed consent process and attach a copy of the signed consent form provided with a bar code. This process will help other healthcare workers taking care of the participant be aware of his participation and help us communicate clinical information and other updates to the CRA. In addition, the structure of the consent is in the form of a opt-in option. The participants have the option to decide, at the time of consent, what biospecimen to donate to the RIMUHC-LDB. As for transplant biospecimens, the consent process is overseen by QT. During their informed consent process for organ donation, the family or next of kin, as per Quebec Transplant and provincial policies, will sign for organ donation and at the same time will consent for research related to organ donation. When consent is obtained, QT will contact the CRA on call and will let them know about possible biospecimens available for the biobank.

Return of research results and incidental findings

Incidental Findings (IFs) are defined as “unforeseen findings concerning a research participant that have potential health or reproductive importance. They are discovered during the course of research but are outside its objectives”. Individual Research Results (IRRs) are defined as “results discovered during the course of research, which concern an individual participant, and have potential health or reproductive impact”. (12) The LDB has implemented a framework for the return of research results and incidental findings. In the LDB consent form, participants were asked to express their preference regarding the feedback of individual research results. The consent form reads: “If research using your samples reveals information we were not looking for (i.e. incidental findings) and which clearly indicate a significant health problem that can be treated or prevented, then you will be informed by providing us a name of a physician who will transmit the information to you” and “I would like to be informed, through my physician, about incidental findings that indicate a significant health problem. (YES/NO).” The participants were also asked to designate a physician to mediate the return of significant health information, who according to Quebec laws, is the only person qualified to report incidental findings to the patient. As such, the ‘mother” protocol includes a procedure for the feedback of individual research data, and the roles of the Research Ethics Board (REB), Keyholder, and Principle Investigator (PI) in this process. (12) The double coding system is an important means of privacy protection but could also present a hurdle to the feedback of individual research data to participants. Therefore, the LDB protocol also outlines clear procedures for the assessment of individual research data, re-identification of participants, and communication to participants and designated physicians. Therefore, the Biobank will only contact the physician indicated on the consent and it is their decision how to proceed with the findings.

Biospecimen procurement

The importance of the team is further appreciated as the next steps involve teamwork between the CRA and the Manager of the RIMUHC-LDB. A list, with surgical dates is provided to the manager. This then triggers a domino effect. Since a large portion of samples banked are from cancer participants, the tissue

must be released by a pathologist, to ensure participant care/diagnosis comes first. The quality of the sample is directly related to the amount of time between procurement from the participant to processing. To minimize this time, the manager and CRA work closely with the surgeon, head nurse and pathology technician, such that they are paged once the specimen is procured and brought immediately to the pathology suite, where the pathologist, is waiting to clear the specimen for biobanking. To date we average approximately 30–45 minutes from the participant, to release by the pathologist and snap freezing and/or available as fresh sample for research. To ensure the highest quality biospecimens, biospecimens are banked in the following order of priority: snap frozen in liquid nitrogen in both the presence and absence of OCT and stored at -80^{o}C, isopentane freezing (sample kept on ice for 5–10 min then processed in isopentane at -45^{o}C and stored at -45^{o}C) and formalin fixed paraffin -embedded (FFPE). It is important to note that bloods are collected for all participants prior to surgical procedure (just after anesthesia), which includes plasma, serum, buffy coat and PAXgene. In the case of biopsies, the first specimen is for pathology and the subsequent for biobanking. Standardized collection, annotation, storage and retrieval of biospecimens are followed. Although we follow strict SOPs, when sufficient material is available, we test new developing operating procedures (DOP's). The flow of activities allows us the flexibility to introduce these DOP's without compromising the existing SOP's thus integrating new technologies allowing for multidimensional profiling studies to be conducted. Once validated, we convert these procedures to SOP's.

Integrated in our specimen procurement is our Quality Assurance Program (QAP). Every 4 months two samples are randomly selected and screened. We regularly isolate RNA from these tissue samples, labeled Quality Assurance/ Quality Control (QA/QC), and assess their RNA integrity number (RIN). Furthermore, to have a comprehensive inventory on the histopathology of our biospecimens, we prepare blocks from every formalin tissue, section and stain with hematoxilin and eosin (H&E). The slides are then uploaded using the Aperio system and screened by our pathologist. We thus maintain a digital inventory of all banked biospecimens.

Biospecimen clinical annotation

The samples are only of value if they are appropriately annotated. We use the AtiM software (CTRNet) to record and keep track of our biospecimens, which is integrated into our hospital database (behind the firewall) allowing clinical information to be directly fed into the RIMUHC-LDB database. Histological evaluation by pathologist is important to confirm diagnosis and to grade the biospecimen (ie. Tumor type, NAFLD, NASH, etc). As part of our SOPs for the collection of clinical data we have generated Clinical Research Forms (CRF) to ensure we record all critical parameters associated with each participant. In addition, we have developed Pathology Review Forms (PRF), which allows a standardized method of recording of diagnosis.

Access

For researchers to access biospecimens from our RIMUHC-LDB, the researcher submits a request along with a "companion" protocol that will explain the objectives and use of these biospecimens as well as its

impact towards research (described above). This is an expedited process with no consent form is required. The “companion” still requires science review with the Research Ethics Board. We require that requesters have the expertise to perform the required experiments, as well as provide evidence that necessary funding is available to perform these experiments. Requesters that provide protocols with previous ethical review must provide us with a copy of their approval that will also be attached to the MTA as well as a copy of the “companion” protocol. This is the basis for local, national and international collaborations. The RIMUHC-LDB will require requesters to notify the RIMUHC-LDB of any clinically relevant data so that participants may inform as per the biobank policies but also ask the requestor return research data associated with the specimens provided.

Discussion

Foreseeing the future of the RI-MUHC LDB and understanding disease complexity

Understanding the complexity of disease has and will always remain a challenge. Participants arriving at the clinic, rarely arrive with a full medical background. Information is collected in pieces through communication of physicians and this is usually amongst surgeons, oncologists and other specific specialties. Rarely, you will see any communication between the surgeon and the family physician of the participant. And this is due to, in this case, the number of participants with no family physician and the family physician not involved in the current care of participants when diagnosed with diseases such as cancer, NALFD and NASH. In the case of NAFLD and NASH, once diagnosed, follow-ups and treatments are taken care by hepatologists who are located in tertiary care centers. The concept of personalised medicine is very closely aligned with the ideas of participant-oriented research however when participants are banked at the onset of disease in a tertiary care center, only a portion of the picture is captured. Therefore, understanding and investigating human diseases is increasingly multi-disciplinary (3) requiring collaboration with immunologists, neuroscientists, psychologists, epidemiologists, sociologists, clinical specialists, and other scientific colleagues. The current care model often focuses on acute illnesses, but several guidelines have recommended directing increased attention to chronic diseases, participants of which are the most frequent visitors to doctors. (13) The current focus and investments in health research has been put towards public education in ways to prevent the onset of disease as opposed to how initial symptoms such as cardiometabolic factors lead to chronic disease. As disease burden has shifted from acute conditions to chronic conditions, primarily seen in community rather than tertiary care centers, new approaches for forging relationships with local and regional community partners will become increasingly critical. In addition, current studies have focused on the prevalence of certain cardiometabolic factors within specific, small communities as opposed to larger settings such as primary care, known as *Family Medicine Groups (GMF)* in Quebec, where, in Canada, these chronic diseases account for 80% of visits and more than two-thirds of medical costs (14, 15) and 65% of all deaths. (16) Therefore, the generation of evidence at the PC level requires substantial networks of PC practitioners and investigators, as well as interesting and innovative solutions, one of which may be to consider a PC biobank.

Conclusion

PC brings healthcare closest to where the people live and work and putting in context the participants' complementing with the understanding of the community's social and cultural fabric. We foresee a PC biobank complementing disease specific biobanks in tertiary care that will allow us to get closer to a degree of personalization which can be enabled by the new technological developments in past few years. In the pursuit of finding a vaccine for COVID19, the research community has been able to closely connect with the population more than ever before. There is a global commitment and collective action recognising that no country or jurisdiction alone can resolve this crisis, future pandemic crisis or even the impact of chronic disease. In addition, this pandemic has been able to communicate and provide education of research concepts such as biobank, big data access and clinical trial to the general population about the importance for researchers of all disciplines to access readily accessible data. A personalised PC Biobank along with disease-specific biobanks and industry biobanks (clinical trials) will ensure that the best personalised care is delivered to participants. Our concept of personalised care "Bench to participant" will soon enough be converted to "From Bench to PC", as the concept of a PC based biobank surfaces in tertiary care, processes to start by developing this framework has already been initiated and PC health professionals are in support of increasing the use of genomics in their practices. We believe the next big leap in Biobanking will be its integration into the primary care setting.

Abbreviations

PC: Primary Care

NAFLD: Non-Alcoholic Fatty Liver Disease

NASH: Non-Alcoholic Steatohepatitis

RI: Research Institute

MUHC: McGill University Health Center

RI-MUHC LDB: Research Institute of the McGill University Health Center Liver Disease Biobank

GMF: Family Medicine Group

MTA: Material transfer agreement

H&E: Hematoxilin and Eosin

PRF: Pathology Review Forms

SOP: Standard Operating Procedures

QAP: Quality Assurance Program

RNA: RNA integrity number

FFPE: formalin fixed paraffin -embedded

AtiM: Advanced Tissue Management Application

CTRNet: Canadian Tissue Repository Network

OCT: Optimal cutting temperature

CRF: Clinical Research Forms

DOP: Developing operating procedures

QT: Quebec Transplant

CRA: Clinical Research Associate

REB: Research Ethics Board

PI: Principal Investigator

IRB: Institutional Review Board

BAC: Access Committee

ISBER: International Society for Biological and Environmental Repositories

HPB: hepato-pancreato-biliary

Declarations

Ethics Approval

The biobank was approved by the McGill University Health Center (MUHC) Center of Applied Ethics. The REB number associated with the study is SDR-11-066.

Consent for publication

The manuscript does not contain any individuals' data.

Availability of data and material

There is no data for availability

Competing Interest

The authors declare that they have no competing interests

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Authors' Contributions

Ayat Salman: original drafting, correction, review and design of work

Anthoula Lazaris: Review and correction

Peter Metrakos: Supervisor, Co-corresponding Author, Review of article and corrections

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Figures

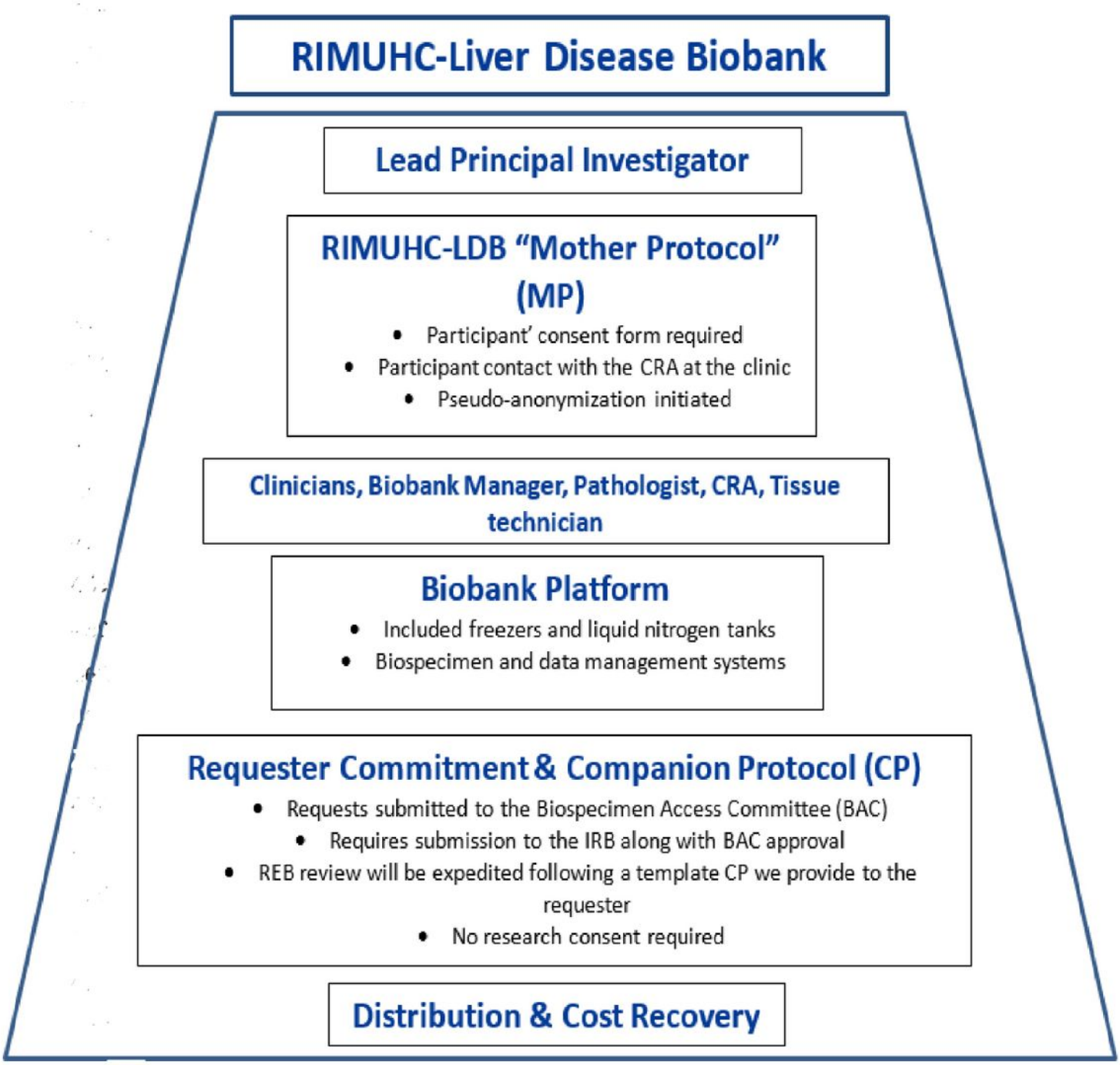

Figure 1

RIMUHC-LDB Overview (original figure)

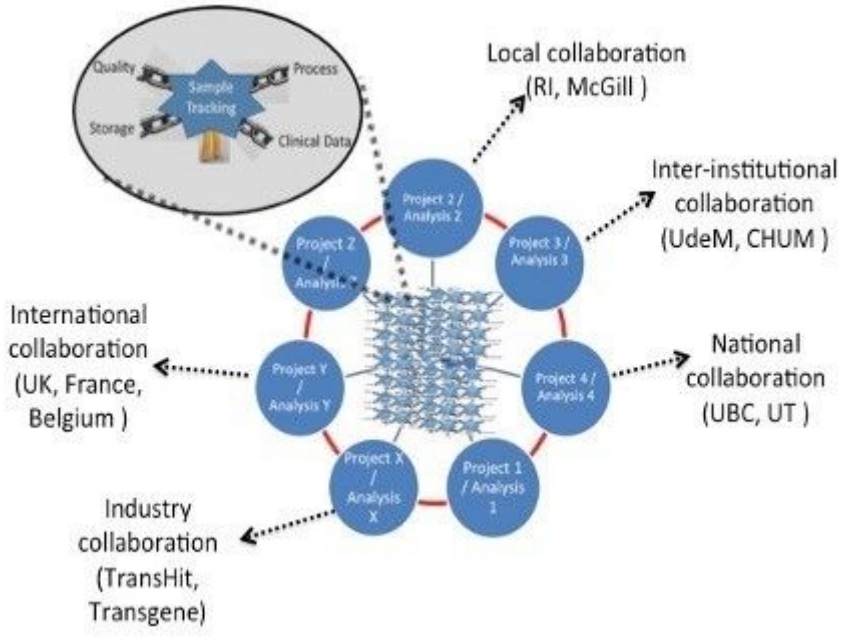

Figure 2

Fit for intended purpose collections (original figure)

Supplementary Files

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- TranslationalMedicineCoverLetterSalmanetal20200601.pdf