Supporting the development of biobanks in low and medium income countries

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Abstract: Biobanks are an organized collection of biological material and associated data. They are a fundamental resource for life science research and contribute to the development of pharmaceutical drugs, diagnostic markers and to a deeper understanding of the genetics that regulate the development of all life on earth.

Biobanks are well established in High Income Countries (HIC) and are rapidly emerging in Low and Middle Income Countries (LMIC). Surveys among biobanks operating in a LMIC setting indicate that limited resources and short term funding tied to specific projects threaten the sustainability of the biobanks. Fit-for-purpose biobanks targeting major societal challenges such as HIV and Malaria provide an excellent basis for integrating biobanks with the available research communities in LMIC regions. But to become sustainable for the future it is important that biobanks become an integrated part of local research communities. To achieve this, the cost of operating biobanks must be lowered, templates must be developed to support local ethics committees and researchers must be given the opportunity to build experience in successfully operating biobank based research projects.

The B3Africa consortium is based on these conclusions and set up to support biobank based research by creating a cost efficient Laboratory Information Management System (LIMS) for developing biobanks and also contribute to the training and capacity building in the local research community. The technical platform called the eB3Kit is open source and consists of a LIMS and a bioinformatics module based on the eBiokit that allow researchers to take control over the analysis of their own data. Along with the technical platform the consortium will also contribute training and support for the associated infrastructures necessary to regulate the ethical and legal implications of biobank based research.

Keywords: biobank, low- and medium-income countries, biobank and cohort building, eInfrastructure, open source open source software, ethical, legal and social issues, bioinformatics.

Introduction

A biobank is a collection of biologic material and associated data obtained from a population or cohort of individuals/subjects and stored in an organized system. The associated data (which can be linked back to the subject who provided the sample) include epidemiologic, clinical, and lifestyle data. Biobanks are increasingly considered an important platform for medical and scientific research. They provide key resources for studying the etiology and molecular mechanisms of diseases and for developing potential diagnostic biomarkers. Biobanking also contributes significantly to the development of personalized drug treatment through translational research.

Biobanking facilities are well established in High Income Countries (HIC) with efforts from international organisations such as the International Society for Biological and Environmental Repositories (ISBER), the European, Middle Eastern & African Society for Biopreservation & Biobanking (ESBB), the Biobanking and Biomolecular resources Research Infrastructure (BBMRI-ERIC), the US National Institute of Health-National Cancer Institute (NIH-NCI) and the International Agency for Research on Cancer (IARC). These organisations have developed international guidelines and protocols which have contributed to this development[1], [2]. However, in many Low and Middle Income Countries (LMICs) the uptake of the available resources has moved at a slower pace. In many of these settings, standard guidelines and protocols to regulate the collection, management, sharing and use of biological samples for research purposes are not being utilized.

IARC launched the LMIC Biobank and Cohort Network (BCNet) in 2013[3] with the overall objectives to promote capacity-building in LMIC biobanks and to increase opportunities for training and funding. BCNet aims to raise awareness among stakeholders, communities, and decision-makers about the benefits of biobanking as an important infrastructure for research.

A situational analysis of infrastructures and facilities was conducted, in order to gather information on biobanking activities, research infrastructures and resources. Twenty seven institutions from sixteen LMICs participated, including twenty-two institutions from eleven African countries.

Results from the survey showed that, although information on biobanking activities in Africa is limited, biological resource management infrastructure is being developed[4]. Biobanks were introduced through specific programmes targeted at major health issues affecting the populations of these countries (e.g. HIV treatment programmes) and their sustainability is seriously threatened after the project ends.

Lack of access to electronic record management systems and organised databases has made it difficult for the linkage of biobank records to other health related services. In cases where electronic databases are available, they are not harmonised with locally used software to allow direct linkage to associated databases such as cancer registries, clinical and treatment records databases, etc.

The lack of harmonization amongst databases and procedures limits opportunities for research collaborations and less than 30% of the centres are involved in scientific research collaboration.

Technical consideration in selecting and maintaining databases and cost implications with respect to acquisition, installation and management of Laboratory Information Management Systems (LIMS) were limiting factors affecting progress. Many do not have access to dedicated facilities to support the biobank LIMS or personnel with the relevant expertise.

On the other hand, biomedical research is producing a huge amount of big data generated from high-throughput experiments associated to biobanked samples. The lack of

infrastructures and software platform supporting storage and analysis of this data is creating a bottleneck in biomedical research[5].

The challenge of ethical, legal and social issues (ELSI) related to biobanking was also highlighted in this survey, as well as in previous reports[6], [7]. Although the different ethics and scientific committees have established various mechanisms to deal with ELSIs in scientific research, in most cases, the committees lack the experience and the regulatory framework to adequately review applications specific to biobanking or biobank projects. This situation creates a barrier for the effective use of biobank samples in these countries as well as international collaboration.

There is also the need to increase the level of participation of African researchers within Africa in a fair and transparent manner.

To address these anomalies, the Human Heredity and Health in Africa (H3Africa) Initiative project has developed a policy framework to promote fair collaboration between scientists in Africa and with the international community[8]. This policy particularly highlight key areas to focus on such as sample and data sharing as well as the importance of a data and biospecimen access committee.

In this article we present the solutions that are being proposed by the EU-H2020 B3Africa project. The project builds on the conclusions from the BCNet and other projects such as the H3Africa Initiative[8]. It proposes an innovative solution, integrating available open-source software, services and tools for biobanking, bioinformatics, ethics, regulation and training.

The main goal of the project is to create a collaboration framework that bridges European and African biomedical research and provides a technical platform (eB3Kit) that implements and integrates the necessary components of this framework including: biobanking, bioinformatics, education, training and dissemination.

Defining an ethical and regulatory framework

There are two basic notions of bioethics that can be considered universally accepted, the need for informed consent and ethical approval to allow a safe and legitimate handling of biological samples and data within research[9]. The B3Africa project builds upon these two notions as well as through a Model Data Management Policy (MDMP) based on the legal framework. The MDMP will provide a set of formal rules, criteria and priorities that should guarantee a consistent ascertainment of all requirements that should be fulfilled by the platform and by the users of the B3Africa platform.

Four main risks have been identified within the project; a) The B3Africa project encounters a complex legal landscape which is difficult to navigate. This creates a risk that the legal tools used are incorrect. b) Some of the prospective users of the B3Africa platform may be situated in states with underdeveloped bioethical legislation, where procedures that would be considered unethical elsewhere, remain legal. c) In states with underdeveloped bioethical legislation, it is likely that the governing infrastructure is also underdeveloped, for example institutional control and audit of biobanks, research ethics boards, etc. d) If the bioethical regulations are too strict, research in itself may be hampered, especially if all national laws of the participating states must be upheld in practice. The potential limitations for the future use of research data according to ethical regulation and guidelines, for example the (African Union) AU convention on cyber security and personal data protection, could lead to global national control, unless there is specific provision for data access for future scientific research.

Legal framework

All processing of biomedical data within the B3Africa project should adhere to two basic principles, *informed consent* and *ethical approval*, both in regards to processing within a state and for cross-border sharing. The legal implementations of the principles are carried out within each national legal order, by national authorities enacting administrative decisions applicable within the state. For sharing data between two states, there is a need to find a model for connecting the ethical approval from the sending state to the receiving state[10]. International administrative law provides two approaches that can be applied[11]. First, a common rule can be established for all entities to apply, together with an obligation for all to accept each other decisions (home state control). Secondly, the collaboration can be built on a conflict of law-approach, leaving each state to decide for themselves how to govern the issue at hand and to develop tools to connect to other administrative orders, for example via agreements in each individual case.

The B3Africa project will employ both strategies to safeguard compliance with relevant law set out above, the home state control approach and the conflict-of-law approach, in a model adapted to the project. A common understanding of the principles of informed consent and ethical approval will function as threshold-principles, basic requirements that all parties must follow in their internal work. These requirements should thus be upheld by all and will be implemented in the project via the Model Data Management Policy (MDMP) and the Data Model, explained below. When collaboration cross-borders, each transfer of data must be governed by an individual legal tool, for example a data transfer agreement. Standard versions of data transfer agreements, especially targeting transfer of medical data, may be drafted in the project, for the parties to use or to adapt according to their own needs. In developing of this part of the framework, inspiration will be taken from other relevant international research projects and infrastructure, such as the work within the common service ethical, legal and societal issues of BBMRI-ERIC (http://bbmri-eric.eu), IARC (http://www.iarc.fr) the H3Africa project (http://h3africa.org) and the RD-Connect project (http://rd-connect.eu).

Model Data Management Policy (MDMP)

The MDMP is based on the B3Africa legal framework and will provide a set of formal rules, criteria and priorities that should guarantee a consistent ascertainment of all requirements that should be fulfilled by the platform and by the users of the B3Africa platform. This policy will be implemented as part of the B3Africa final product, the eB3Kit and will pave the way for managing the use of the eB3Kit in control and regulated environments beyond the project's life time.

The model will be based on common standards regarding informed consent and ethical approval. The definition of the concepts will be determined by the applicable law on site. If the applicable law does not regulate these issues, the minimum requirements set out within the legal framework of the project will be applied. For all the European users it will be based on the EU Data Protection Directive (and in due time, the General Data Protection Regulation). Central features of the MDMP are an *Adoption Committee* that is tasked with evaluating adoption requests from potential users. In order to enter the platform, each user needs an *Organization membership* as well as *Individual membership* for the person conducting the analysis. An application for an organizational membership is done via a standardized application form in which the requester provides information regarding the organization, (contact information, aim and purpose, if the organisation is private or public, means of funding, forms of supervision over the organisation, etc.). Once the B3Africa platformeB3Kit has been adopted by an organization or group, the individual requesters is

also asked to provide information. Only accepted members can request store, management and analysis services. Before data is uploaded, standardized documents with the approvals by ethics committee or institute research boards for the research project, consent information from sample donors whose samples have generated the data, and, if applicable, for authorization of use of non-consented data must be uploaded.

Technology Description

B3Africa will provide a curated platform for open-source software in the biobank domain built upon the *BiBBoX* (biobank software in a box). Within *BiBBoX* software components are pre-installed and configured ready to go with minimal IT effort. The *BiBBoX* core module will cover the core functionality necessary to operate a biobank and the repository will also contain docked software tools such as a bioinformatics module based on the eBiokit[12]. In addition APIs and interfaces will be specified to integrate open source software solutions in the areas electronic health records (EHR), patient and study management, imaging and data integration and analysis. The first version of *BiBBoX* is already accessible at http://bibbox.org/.

BiBBoX architecture

The *BiBBoX* system architecture is built on top of a virtual machine and docker containers, see figure 1. A lightweight central component (green part in figure 1) will provide functionality for the deployment of software tools, a central ID und user management and a user interface based on the Liferay portal (www.liferay.com).

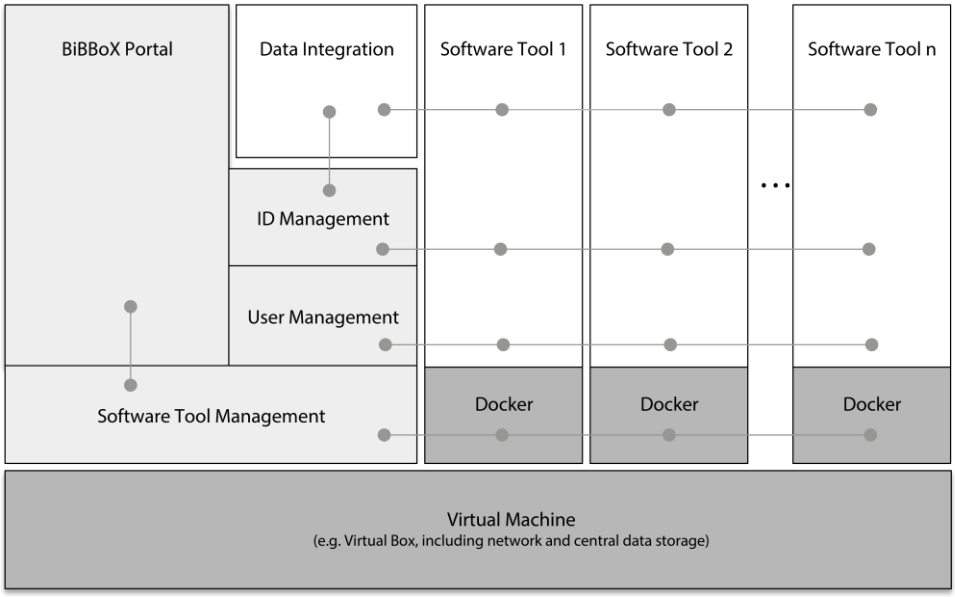

Figure 1: The BiBBoX System Architecture, central component in green, integration software in blue and docked software in white.

Data exchange between software tools and ID management will follow the MIABIS recommendations.

The Minimum Information About BIobank data Sharing (MIABIS) was developed in 2012 by the Biobanking and BioMolecular Resources Research Infrastructure of Sweden (BBMRI.se). In 2013 a working group was formed under BBMRI-ERIC to continue the development of MIABIS through a multi-country governance process. MIABIS is the “de facto” biobank information standard for BBMRI-ERIC community and has been widely accepted within Europe and beyond.

The minimum information guidelines consist of a collection of components with associated attributes representing relevant concepts from biobanking and biomedical research and can be used to integrate the most relevant building blocks of the biomedical research ecosystem (https://github.com/MIABIS/miabis/wiki).

MIABIS has been implemented in several projects and e-infrastructures as BiobankCloud (http://www.biobankcloud.com/), RD-Connect (http://rd-connect.eu/), BioMedBridges (http://www.biomedbridges.eu/), BCNet Catalogue (http://bcnetcat.iarc.fr/), BBMRI-ERIC Directory (http://bbmri-eric.eu/bbmri-eric-directory-2.0), among others.

B3Africa platform will implement MIABIS as part of the data model for representing and sharing biobank and research data which will lead to a wider and more efficient use of valuable bio-resources.

Based on previous requirement analysis work [13], [14], we specified core functionality for the *BiBBoX* and identified an initial set of core modules for the first *BiBBoX* release.

BiBBoX core module

The *BiBBoX* core module consists of software tools for the organization of samples and related data in the context of a collection / study protocol. It includes functionalities for sample acquisition and sample metadata management, sample processing, sample storage, sample and data retrieval/distribution (provided by BIKA http://www.bikalabs.com/) as well as data integration and cataloguing. In particular the following functionality will be supported:

Organize Collections, Studies and SOPs: Each collection has to be based on a specific study design, follow well-documented rules, and describe responsible stakeholders (including their roles), sample types, data formats, ontologies and business processes. The *BiBBoX* core module will provide functionality to handle all this information in a version-controlled manner and will provide a user management system that defines users and what actions they are entitled to perform in the system.

Sample Acquisition and Sample Metadata Management: Each sample and aliquot in a collection is related to a specific patient / donor and to a medical / study event. Basic information about patient / donors and medical / study data objects will be available in the *BiBBoX* core module, at least global unique identifiers for patients and medical/study events will be provided for each sample and aliquot. For sample acquisition in the field we plan to integrate the ILRI monitoring system as software component[15].

Sample Processing: In a typical biobank environment various kinds of procedures are carried out on samples, e.g. preservation procedures, generating aliquots and more complex processing such as deviation of the original material. To ensure that the fate of all of the sample material is known, each aliquot and sub-sample will be tracked and their relationship to the parent sample will be recorded. Even if all of the sample material has been consumed, this needs to be recorded, so that the processing history is known.

Sample Storage: After processing and validation samples are moved to a (long term) storage. The *BiBBoX* core module will assist users to organize shelf spaces and to find stored samples again when they need to retrieve them. The system will track sample locations and monitor freezing and thawing cycles, as well as disposal of them. For bigger biobanks automated systems and storage robots will be supported.

Data Integration and Cataloguing: The *BiBBoX* core module will provide functionality to import and integrate external data objects and generate a catalogue of physical and data objects available in the biobank. A catalogue will include metadata elements collected in the sample acquisition process including sample availability and

access conditions. In addition biobanks metadata describing storage and quality parameters will be included. We plan to implement the catalogue functionality based on the Molgenis platform[16] providing both sample level and aggregated information as well as search functionality.

Sample / data retrieval and shipping, retention and destruction: The *BiBBoX* core module will provide functionality to manage samples in transit between source and destination, for both receiving samples and redistributing them to authorized recipients. Shipping is related to the whole chain of custody and storage inventory and the sample access management. In addition also a retention schedule for samples and data defining how long samples and associated sample records will be supported.

Administrative, business and management support: The *BiBBoX* core module will support administrative tasks of the biobank operation, including workflow and customer management. For this we will provide functionalities, which allow managers and auditors to monitor the biobank operation.

Docked bioinformatics module

The BiBBoX integrate a bioinformatics modules based on the eBiokit[12] which is a self-contained computing platform providing users with access to popular bioinformatics software and services. The local storage allows researchers to conduct advanced data analysis in a user friendly environment and access local copies of commonly used databases. Combined with extensive in-built tutorials this system allows non-specialists to process data generated from a biobank collection.

Data analysis is often a significant bottle neck in modern life science and the bioinformatics component in the eB3kit provides research institutions with the means to more efficiently distribute the work load. Junior researchers can perform routine operations and screening while simultaneously learning the basics of bioinformatics. Research institutions can then either use the eB3kit bioinformatics toolkit as a foundation for further specialization in bioinformatics or use the data produced as a basis for collaboration with research groups specialized in bioinformatics.

Education and capacity building

The eB3kit will contribute to establishing an open-innovation ecosystem in Africa and Europe. In doing so it is important that researchers in Low and Middle Income Countries have the infrastructure and know-how to participate in the co-creation and exploration of ideas. To bring a real added-value to the institutes and countries in which it will be implemented, the eB3Kit will therefore be supported by an extensive education and capacity building effort where different enabling factors have been considered.

First, the project recognizes the paramount importance of having the B3Africa concept validated by biobanks from both continents. This implies an active involvement of a different range of actors from involved biobanks, providing complementary technical, scientific, ethical, legal and political perspectives. Different actions are planned to engage those actors: ethics and legal issues meeting, stakeholder forums, technical jamborees.

In addition, the eB3kit will be installed and tested in real-life settings (use case), using a step-wise approach. Three centers involved in H3Africa were first selected to take part of the use case work package.

- National Health Laboratory Services - Stellenbosh University Biobank, Cape Town, South Africa
- Institute of Human Virology, Abuja, Nigeria
- Makerere University College of Health Sciences, Kampala, Uganda

The involvement of those three centers represents a great added-value for both the B3Africa and the H3Africa projects, as it reinforces synergies and complementarities. Since the beginning of the B3Africa project, the International Livestock Research Institute (Nairobi, Kenya) already partner of the project, has also volunteered to act as use case for non-human biobank setting.

BCNet, from which the B3Africa project could largely draw on, has also been identified as an important source for use case centers. With twenty-one members from seventeen countries (seventeen centers from thirteen African & Middle East countries, along with centers from two European countries and two Asian countries), this dynamic network represents great opportunities for testing and dissemination of the eB3kit. Equally, the eB3kit will provide a concrete solution to some of the challenges reported by BCNet members. Initially, four BCNet members will be take part in the use case work package:

- Breast Care International, Peace and Love Hospital, Kumasi, Ghana
- Medical Research Council, International Nutrition Group, Banjul, The Gambia
- National Cancer Institute, Vilnius, Lithuania
- Wroclaw Research Centre, EIT+ Biobank, Wroclaw, Poland

Furthermore, key professionals involved in the implementation of the eB3Kit will be trained. Courses and tailored learning materials will be developed based on a detailed learning needs assessment. Inputs from B3Africa partners in charge of developing the eB3Kit will be requested in order to take into account the specificities of the various tools included in the kit (technology and various components, required knowledge and skills, available learning resources, etc.). Professionals at use case institutions will also be consulted in order to take into account the various profiles of those responsible for the implementation of the eB3Kit ("focal points"), as well as end users of the kit. Besides knowledge and skills specific to eB3kit components (tool-specific), other competencies (core competencies) will be considered for an effective and sustainable use of the eB3Kit. Available learning resources/opportunities within B3Africa and related partners (i.e. H3Africa, ESBB, ISBER, BBMRI, etc.) will be identified, in order to maximise synergies between existing laboratory capacity building initiatives. Over the first years of the project, training initiatives will target the use case institutions listed above.

Finally, learning materials developed throughout the implementation of the project will be produced as standalone generic resources organised as a standardized learning environment such as the eBioKit used in the Pan African Bioinformatics Network for H3Africa (H3ABionet). Resources will be more widely disseminated through awareness raising actions on project activities and results, as well as dissemination of project deliverables and outcomes to relevant stakeholders, including at the policy level. Besides communication activities of the B3Africa project, a course will be organised towards the end of the project and will target professionals from other biobanks interested in the use the eB3kit.

All the above will enhance the ability to conduct training for new and/or developing biobanks and therefore strongly contribute to create a sustainable network of biospecimen repositories infrastructures interacting and sharing knowledge between Europe and Africa.

Maximizing the social and economic impact of biobanks in Africa

The surveys among biobanks operating in a LMIC environment show that biobanks have so far mainly been created to support specific programmes targeting major health issues in the countries hosting the biobank[4]. Such programmes may be successful in achieving their aims and also set a precedent for effective biobank management in the region. But experience in the field show that these benefits may quickly be lost unless the

biobanks evolve into a sustainable infrastructure embedded in the local research community (figure 2).

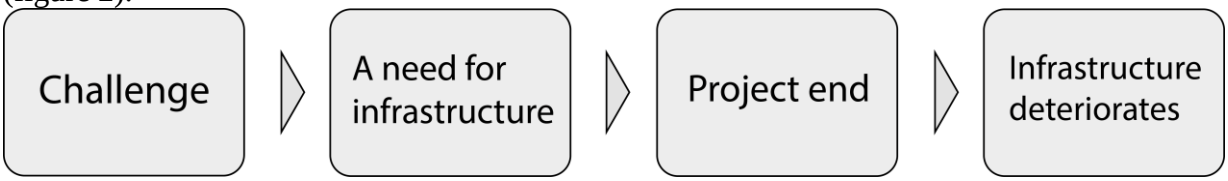

Figure 2, the life cycle of a biobank if sustainability is not achieved.

To ensure sustainability it is important for projects like the B3Africa project to take a holistic perspective towards biobanking and its role in research. Research is not a continual flow of progress from point A to point B but rather an endless number of research cycles where ideas are conceived, tested and hopefully contribute to the shared knowledgebase of society. Biobanks contribute to this process by facilitating the efficient management of biological samples and associated data. In a fit-for-purpose biobank this task is well defined and the project justifying the creation of a biobank can be expected to handle the research tasks outside simple storage and management.

For a biobank to become sustainable it must strengthen the local research community enough to justify its costs. The B3Africa project achieves this by not only focusing on a technical solution for tracking samples and associated information but also to support researchers all the way from the ideation stage to knowledge generation. Such an integration into a local research community cannot be limited to technical solutions but must also incorporate social and legal factors in order to ensure its integration into the local community into the program. The B3Africa project therefore consist of a combination of the open source software package called the eB3Kit and a social integration program aimed towards enabling communities adopting the software(figure 3).

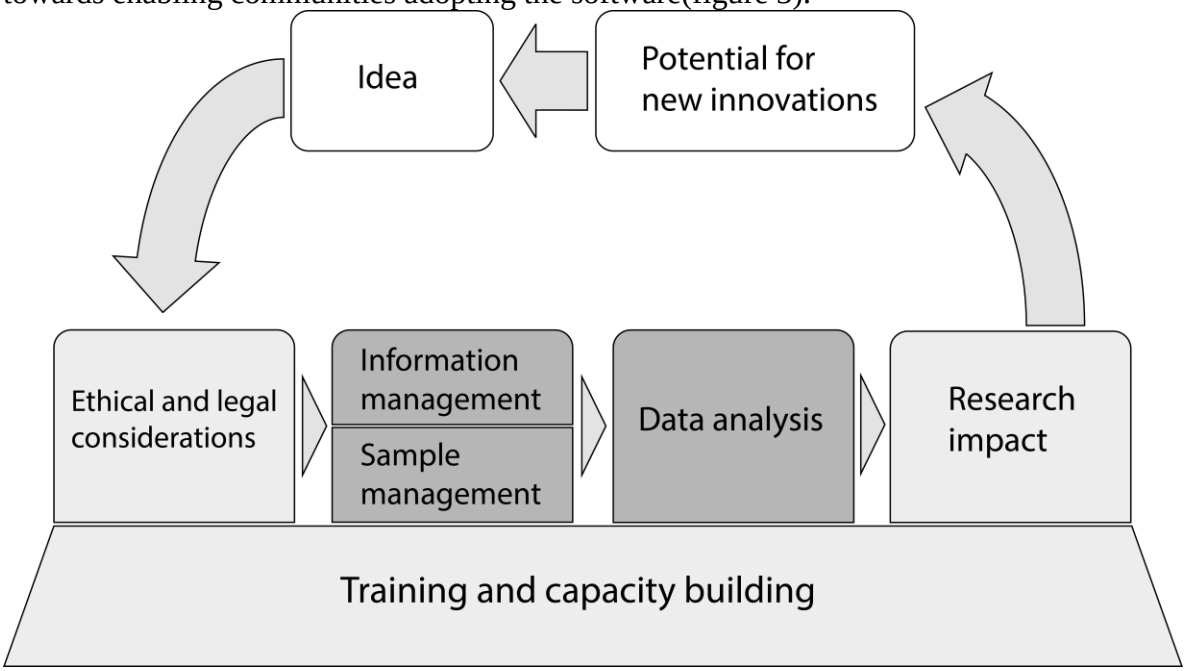

Figure 3,the B3Africa project is built upon a technology platform in the form of the eB3Kit (blue) and social components (green).Together the components contribute to strengthen African and European research communities in LMIC by reducing the thresholds in the research cycle..

The successful completion of the B3Africa project will therefore not only be reliant on production and availability of a high quality open source LIMS in the form of the eB3Kit, but also on its successful integration into local research communities across the Europe and Africa. Major initiatives such as H3Africa and BCNet provide a valuable opportunity to embed biobanking as a natural component of research in a LMIC setting. But smaller local

initiatives serve as a complement to major programs as they can draw upon earlier experience and implement them in local research communities[17]. The eB3Kit provide the information technology necessary to provide the services of a biobank in a robust and cost efficient management. Combined with the training and ELSI components this allows the small scale creation of biobanks that can be integrated into the global biobanking networks through the regional networks initiated by H3Africa and BCNet.

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