WHITE PAPER

THE ROLE OF LIMS IN MEETING BIOBANK REGULATORY REQUIREMENTS AND ENSURING OPERATIONAL QUALITY

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INTRODUCTION

Biobanks (which include both specimens and databases) contain a huge amount of personal health information, requiring firm regulatory oversight to guarantee privacy and ethical use of these materials. To facilitate the complex organization and interplay between biobanks and research and development, companies and institutions are increasingly using laboratory information management systems (LIMS), biobank management software which provides, at a minimum, data tracking and data exchange interface support. Because of the automation inherent in biobank LIMS, they have proven invaluable not only in the management of biospecimens, but also in the compliance to multiple and complex regulatory requirements both in the US and worldwide. In the US, they play an ever-important role in the Food and Drug Administration (FDA) approval process for new drug applications (NDAs).

Biobanks were initially developed at the time of the Human Genome Project (HGP) in the 1990s to enable researchers the ability to access biospecimens. The advancement of the use of biobanks remains one of the major outcomes of the HGP. Today, biospecimens are used to identify the genetics and other causes of disease in the search for medical treatments, personalized diagnostics and breakthrough drugs, and the samples stored in biobanks serve as the basis of translational science and drug development. A major goal for the use of biospecimens is to develop "personalized medicine" that improves individualized medical treatments by incorporating molecular and genetic information. This focus on personalized medicine is driving research and, in turn, the need for well-annotated sample preservation. The rapid expansion of large-scale genomic studies has also spurred the reliance on biobanks, as well as an increased interest in data mining. More recently, the biobank management software of biobank LIMS has been used to manage the multiple aspects of laboratory informatics. Such software management has rendered the use of unwieldy spreadsheets impractical as well as uncompliant to federal regulations.

Biobanks exist within academic institutions as well as hospitals, biotechnology and pharmaceutical companies. At last count, more than 620 biobanks were identified within the US alone, with an anticipated sample addition of 20 million a year. A 2015 initiative under President Obama, the NIH Precision Medicine Initiative, will ultimately create a biobank for the samples of more than one million Americans.[1] In addition, the Department of Veterans Affairs is currently creating a biobank and database of one million veterans, the Million Veterans

Program.[2] However, these expanding biorepository collections have presented an enormous logistical challenge for data management as well as for regulatory compliance. Virtually all biobanks are part of larger organizations, networks and consortia, and function as collaborative research efforts involving medical institutions, drug makers, biotechnology companies, biologics developers, and medical device manufacturers, among many others. Within these organizations, there are smaller biobanks and laboratories which have their own specific needs for operating at full operational efficiency while maintaining full regulatory compliance.

The importance and use of biobank LIMS will increase as data management and compliance demands grow, meeting the call for research studies of the highest possible caliber. A recent study indicated that more than half of all requests for biobank samples were rejected, usually because of a lack of scientific merit.[3] Thus, access to both samples and databases within biobanks is limited to studies deemed to have the most scientific merit, a process that ensures the highest quality research.

[1]https://allofus.nih.gov/ Accessed 8 March 2018.

[2]https://www.research.va.gov/mvp/Accessed 8 March 2018.

[3]https://www.americanlaboratory.com/913-Technical-Articles/189476-Trends-in-Biobanking/ Accessed 8 March 2018.

REGULATORY REQUIREMENTS FOR BIOBANKS

The US and the EU, as well as other countries, have a number of regulations in place to maintain donor confidentiality, patient privacy, and the safety of samples. In the EU, these general regulations are covered by the EU General Data Protection Regulation, while specific aspects of biobanking are governed by The Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine. The Council of Europe has issued inter-organizational recommendations on the research of human materials to be used in biobanking, with a particular focus on the 'secondary use' of stored biological materials, the primary purpose of biobanks. Although these are recommendations, not legal requirements, the text is linked to regulatory protocols which outline the requirements that apply to biobanks, including the need for independent oversight, regular audits, and procedures for transfer and closure of the biobank, among others. Internationally, a supplement to the Declaration of Helsinki, the World Medical Association Declaration on Databases and Biobanks regulates the collection and use of biospecimens.[4]

[4]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4856186/pdf/CroatMedJ_57_0207.pdf Accessed 8 March 2018.

In the US, regulations include the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule established in 1996, the Federal Policy for Protection of Human Subjects (Common Rule) for informed consent, and Part 11 of Title 21 of the Code of Federal Regulations (21 CFR Part 11; Protected Health Information [PHI]) Food and Drug Administration (FDA) guidelines, which pertain to electronic signatures used to indicate review, verification, and approval. Additionally, biobank LIMS provide management for adherence to CAP, the laboratory accreditation program of the College of American Pathologists. All federal regulations are legally enforceable.

Comprehensive audit trails are also strongly recommended, as they may come under FDA review, and audit trails that are maintained for the purpose of maintaining patient privacy are regulated by the HIPAA Privacy Rule. However, no federal regulations oversee audit trails that are maintained for other purposes, although the FDA maintains several audit compliance programs (Good Lab Practice Program [GLPP], IRB Program, Clinical Investigator) on a state-by-state basis and has the power of enforcement.[5] Moreover, complete audit trails are essential for the legal establishment of biological sample ownership.

A recent proposed change to US regulations includes an update that all samples, including those originally obtained for clinical use, should be obtained following informed consent specifically allowing their use for biobanking.[6] In addition to federal regulatory requirements, access to biobanks generally involves peer review approval and scientific review, as well as approval from institutional review boards.

[5]Section 3. Recommendations for biobanks. International Agency for Cancer Research (IARC) Publications: 2018, pp. 11-54.

[6]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5526496/pdf/pbio.2002654.pdf Accessed 8 March 2018.

THE ROLE OF LIMS IN MEETING REGULATORY REQUIREMENTS FOR BIOBANKS

One of the major challenges to biobanking pertains to the regulatory requirements and strict adherence to these requirements. Broadly, these requirements help to ensure the integrity of the samples, patient privacy and consent, and security of donor information. The three major federal regulations involved in US biobank compliance are Part 11 of Title 21, Protected Health Information (PHI) and HIPAA privacy rules (Privacy Rule), and informed consent. The latest biobank management software has been designed to deliver purpose-built functionality and to address the unique regulatory needs pertaining to sample

collection, recording, storage, and tracking, and address each of these classes of regulations. These compliance requirements are complex and multifaceted, to cover the many functions of the biobanks themselves. A well-designed LIMS restricts unauthorized access to sensitive data and follows regulatory guidelines including HIPAA and 21 CFR Part 11.

The FDA considers Part 11 of Title 21 PHI to be applicable to a number of records maintained in electronic format, including:

- Those that are maintained in electronic format in place of paper format.
- Those that are maintained in electronic format in addition to paper format and are used to document regulated activities.
- Any records that are submitted to the FDA.
- Any electronic records that use a signature as the equivalent to handwritten initials or signatures to designate that a document has been reviewed, verified, and approved.

To add to these regulatory complications, Part 11 applies not only to the specific nature of the electronic document, but also to the processes involved, including creation, modification, maintenance, archiving, retrieval, and transmission of these electronic documents.

Biobank facilities are required to properly disguise patient identifications in accordance with HIPAA regulations. To stay in compliance with federal law, each biobank must have a comprehensive policy in place to ensure the safe and secure transfer of data, while also protecting patient privacy. Obtaining and recording informed consent for the collection and maintenance of samples for biobanks entails its own set of challenges. In the most general sense, informed consent discloses information to prospective participants; this information concerns the research goals, risks, and benefits. However, the informed consent process is really an ongoing exchange of information, as the full range of research deriving from biobank samples is frequently not known; this is especially true in the development of genomic research. Complete and regularly-updated informed consent documents are essential in order to remain in compliance with the Office for Human Research Protections (OHRP) 45 CFR Part 46, the regulatory arm of Health and Human Services. The OHRP is authorized to oversee and enforce regulatory compliance.

In addition to established federal regulatory requirements, biobank facilities should also maintain audit trails and detailed logs for each sample. The FDA follows Current Good Manufacturing Practices (CGMP) guidelines in deciding if data integrity (completeness, consistency, and accuracy of data) has been maintained and will review these audits to make

this determination on a state-by-state basis. In a broader sense, high-quality audit trails also help to maintain high-quality sample collections. A complete audit will contain the details of sample processing and storage and will contribute to the integrity of data used in larger collaborative studies.

Biobanks and their associated databases are increasingly essential to research and to the assessment and documentation of critical biological samples. The development of biobank management software addresses the varying needs of research and commercial facilities. Large laboratories often use their own servers and associated computers to support LIMS, a costly and time-consuming enterprise and one requiring dedicated IT. However, smaller laboratories increasingly rely on more economical internet-enabled LIMS software for cloud-supported on-demand services.

A tailored, purpose-built biobanking LIMS incorporates features that facilitate regulatory compliance while addressing varied needs. To be compliant, systems must ensure consent management, patient privacy, and documentation; a typical biorepository LIMS consists of:

- A visualization tool, which allows users to physically identify biosamples within the freezer and their precise location within plates and boxes.
- A patient consent management tool, which provides access to digitized consent forms and links these forms to the associated biosample.
- A defined system of recording sample and subject information while adhering to HIPAA regulations.

Manual spreadsheets notebooks do not meet federal requirements for biobank compliance. To transfer and save legacy data, manual data from spreadsheets and lab notebooks can be converted to .csv and .xls files. Once this transfer takes place, easy and simplified tracking of sample location and freezer inventory follows.

Together, these features manage sample storage, documentation, maintenance, and chain of custody in a secure and compliant manner.

CLOUD-BASED SAAS LIMS ENSURE OPERATIONAL QUALITY WHILE MAINTAINING REGULATORY COMPLIANCE FOR SMALLER LABS

For optimal operational quality, LIMS must fulfill several functions simultaneously in a smoothly integrated manner. LIMS are tailored to address the specific and often unique needs of the

biobanking industry, which range from small-scale research to pharmaceutical development. All biobanks share commonalities, however, which include the collection, storage, and tracking of biosamples.

In 2011, the first internet-enabled LIMS software specifically scaled to fit the needs of small laboratories was introduced. This product provides access to laboratory management software from remote servers in a process known as software as a service (SaaS), a method that had been in use for other applications for a number of years. More recently, SaaS has been commonly delivered by cloud computing, an IT method in which "...third-party data storage providers offer computing power as an outsourced service. The cloud-based SaaS model.... allows research organizations to pay for software rather than full license, while reducing the maintenance cost associated with the in-house equipment."[7] The cost-saving features also include the minimal installation charge and absence of IT maintenance costs to service either hardware or software. The decision to convert to a SaaS cloud-based LIMS is guided by the specific concerns of the individual laboratory, including security, operational, as well as regulatory needs. Operationally, requisition, shipping and receiving, lab inventory management, data retrieval and traceability needs can be easily met using cloud-based LIMS.

[7]https://www.labvantage.com/advantages-of-a-dedicated-lims-for-biobanking/ Accessed 9 March 2018.

Initial concerns over data security have been addressed by correcting technical issues, which included difficulties with interfacing instruments such as bar-code readers. Private or internal cloud services also function to ensure complete security with the use of encrypted LIMS data. In addition, cloud-based backup and recovery solutions provide protection from unanticipated disasters. Operationally, cloud-based LIMS provides easy access to data using a secure login ID from any internet connection. This simplicity of access facilitates collaboration between laboratories. Cloud-based LIMS allow secure access and sharing of data with collaborators; they are hosted on a variety of multi-layered application level security systems. Secure and reliable client and collaborator transmission is ensured by encryption and, based on user group and user role, unauthorized access to sensitive data is restricted.

Today, LIMS are configured for the specific applications concerning biobanking, such as the instrumentation of a particular laboratory, and LIMS software is highly affordable for small laboratories. Users of the cloud-based system say that its main advantage lies in its ability to either scale up or down services, on the basis of fluctuating user demand; these adjustments

were not easily achieved when each user worked with a single server. Cloud-based LIMS provides a completely configurable and scalable biobanking solution. Using cloud-based SaaS systems, small academic laboratories are also able to bypass university server departments when software upgrades are required; new application software is generally accessible via the cloud. SaaS users also note the greater efficiency of the biobank LIMS and the greatly decreased down time. Finally, data encryption allows cloud-based LIMS the ability to protect health information following HIPAA guidelines, maintaining HIPAA compliance in regulated laboratories.

CONCLUSION

Because of the diversity of biobanks and the range of functions they support—from small -scale tissue biopsy analyses, to large-scale pharmaceutical screening and population-based translational studies—LIMS that have been designed with purpose-built functionality is best able to meet complex compliance requirements while improving operational quality. For smaller labs, cloud-based SaaS LIMS provide a cost-effective means to provide individualized services while also fulfilling specific operational, security and regulatory laboratory needs.

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