Chapter

Harmonized and Quality Sample Handling in Biobank-Supported Multicenter Prospective Studies

Verónica Valdivieso-Gómez, Javier Garrancho-Pérez, Inés Aroca-Siendones and Rocío Aguilar-Quesada

Abstract

In the frame of multicenter research studies, biobanks ensure the harmonization and traceability of the prospective collection of quality samples. This is significant because pre-analytical variables must be carefully considered to guarantee the integrity of biomarkers to be tested and to avoid bias affecting the validity of the analytical results. According to a quality management system, biobanks contribute with documents and records; consumable preparation for collection, processing, and conservation; sample quality controls; and centralized management of sample handling, storage, and distribution. Traceability of samples is based on unique standard codes and the use of pre-assigned, pre-coded, and pre-labeled materials for sample collection, processing, and conservation. By using these supporting tools, quality derivatives are obtained based on common and evidence-based standard operating procedures (SOPs), with associated traceability information in relation with their collection, processing, conservation, and distribution. The biobank-supported workflow, specifically designed and implemented for each project, allows obtaining harmonized quality samples contributing to the quality of large and complex research projects and the corresponding validity of the analyses.

Keywords: multicenter prospective project, sample handling, traceability, workflow harmonization, quality-assured biobanking

1. Introduction

Professionalism is the current hallmark of biobanks [1], which are driven by standards and best practices. A biobank is "an entity that receives, stores, processes, and/or distributes specimens, as needed. It encompasses the physical location as well as the full range of activities associated with its operation [2]." Different types of biobanks have been proposed [3], although the definitive model will be the result of the activities performed in support of the particular needs of attended projects, including real or virtual collection, processing, conservation, and distribution.

Biobanks have been involved in large quality-assured prospective studies based on validated and standardized sample handling and storage protocols [4, 5]. When a prospective multicenter research project is designed, multiple variables must be considered such as the number and type of donations, recruitment sites and analytical laboratory locations, pre-analytical requirements of samples and derivatives

obtained, and processing and storage facilities. Attending to the complexity of the project, a specific workflow is implemented after process definition identifying every factor involved in (site, staff, equipment, method, materials, samples and transferences) and their corresponding checkpoints.

2. Harmonization of sample collection and derivative preservation

To guarantee the integrity of biomarkers to be tested and to avoid bias, pre-analytical variables must be carefully considered [6]. In fact, many studies are being conducted to elucidate the effects of pre-analytical variables on analytical profiles. In this sense, a study has been recently published to determine acceptable delays to fixation for formalin-fixed paraffin-embedded (FFPE) tissue samples [7]. In order to mitigate their impact in the complex frame of multicenter projects, biobanks contribute through supervised materials and sample handling and continuous and overlapped checkpoints.

2.1 Centralized preparation of consumables for sample collection, processing and preservation

With the objective to ensure the consistency in sample collection, stabilization, and preservation, specific kits with the consumables necessary for only a donation are defined in function of pre-analytical requirements of obtaining samples and derivatives (**Figure 1**). A careful selection of collection devices is critical here since differences in biomarker testing have been reported [8, 9]. Consumables such as modified cards (IsoCode cards or FTA cards) for blood spot collection, in addition to multibarrier pouches with desiccant packs for room-temperature transportation and future conservation, could be also included for traceability purposes [10]. For

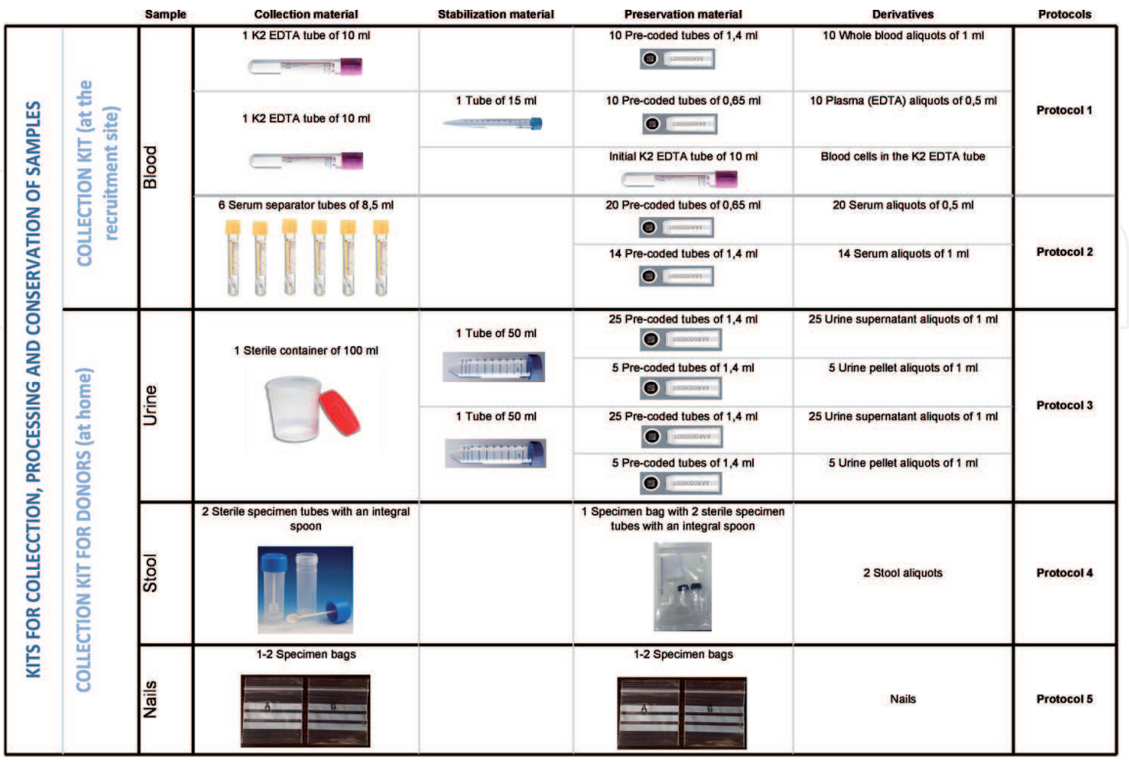

Figure 1.
Consumables included for sample collection, stabilization, and preservation in representative kits, classified by the corresponding protocol and derivatives obtained.

noninvasive samples (nails, stool, etc.), kits targeted to donors may be designed for a more accessible collection at home, with the appropriate consumables to guarantee the integrity of samples until they are receipted by the biobank or analytical laboratory. When processing is performed by a different center from the recruitment site, two kits are prepared in independent boxes for collection and processing, especially when the sample collection is made by the donor on his own.

Materials included in the kits are classified in several bags according with the downstream protocol. Expiration date and batch numbers for consumables must be considered during the purchasing process in relation with the recruitment rates and the validity of the results, respectively. Additionally, expiration date is identified for each kit according to the most recent expiration date from the consumables, and it is used as a reference to track and replace expired consumables by the biobank when the recruitment rate is not the expected.

2.2 Sample processing and quality controls

Evidence-based standard operating procedures (SOPs) are elaborated for sample processing taking the sample requirements provided by the testing laboratories into consideration. The number and volume of samples necessary for analytical assays and the type of derivative, anticoagulant or preservative must be identified in order to choose the most appropriate and approachable option of prospective collection of samples providing high-quality biomarkers useful for downstream applications [11]. Additional requirements from guides [12] or previous scientific publications [13] are also taken into account in relation with specific sample collection and derivative stabilization. Preservation delay and resources available for long-term storage will influence the selection of the collection device as well. In fact, room-temperature storage alternatives have been proposed [14]. When the same sample allows obtaining different derivatives (i.e., blood for plasma, buffy coat, and RBCs), protocols will adjust the number and type of collection tubes or devices to minimize the quantity of sample collected from the donor. On the other hand, the number of aliquots of liquid samples must be set in function of the different analyses to be performed avoiding unnecessary freeze-thaw cycles.

These pre-analytical conditions of samples and derivatives will determine where each process (collection, initial sample processing, provisional cryopreservation of derivatives, long-term storage, testing) will be performed depending on the recruitment site, the biobank, and the analytical laboratory locations and facilities. Accordingly, transportation of samples at the corresponding temperature should be organized [15] following the international recommendations.

Obtaining of specific derivatives such as nucleic acid isolation may be centralized in the biobank or testing laboratories in order to avoid bias. In the same sense, reactive batches must be controlled. When possible, automation of processes must be implemented to avoid traceability errors and decreasing hands on time. Samples should be handled following validation of standard operating protocols by using samples not belonging to the particular project, specifically collected and approved for this purpose by an ethical committee.

The quality of samples must be evaluated after processing by means of a comprehensive analysis of quality indicators [16]. Because of the current lack of qualification tools for each type of derivative and pre-analytical variable, numerous studies are trying to identify new markers to assess the fitness-for-purpose of samples. Thus, new scores and indicators have been proposed for the quality of samples in relation with the impact derived from the pre-analytical phase [17–23]. In the same way, participation in external quality assurance (EQA) schemes like the EQA program developed by the International Society for Biological and Environmental

Repositories (ISBER) focused on sample processing and testing evaluation [24]; it is a highly recommended complementary tool for the internal quality control (IQC). Biobank collaboration through international working groups focused on standardization of sample processing, and biological sample quality control will contribute to the implementation of the last innovations in the field as well.

2.3 Monitored storage of biological samples and distribution

In relation with sample conservation, derivatives are long-term stored in the most appropriate conditions to maintain their original characteristics, being very important for the sample stability the selection of the temperature storage [15]. When samples are receipted in the storage facilities, aliquots are immediately revised to check the shipment temperature; the number, integrity, and volume of each aliquot regarding the expected; and incidents reported, maintaining the cold chain. Racks and boxes are previously prepared to directly store the derivatives in a reduced and optimized space within the conservation equipment classified by the type of container. In addition, derivatives are preferably stored separately in different equipment and preservation rooms as a safety measure.

So, long-term storage facilities may be located in one or more rooms or buildings and may even be assumed by several institutions when transportation of samples and temperature variations are minimized. In any case, sample handling and positions must be under control and restricted access. Both the preservation rooms and storage equipment are constantly controlled through a monitoring system that records critical parameters such as temperature, humidity, CO_2, and O_2 levels (where necessary) and the proper functioning of equipment (compressors, battery power, display) (**Figure 2**). The system triggers an alarm when any parameter is out of the established range, thus activating an emergency plan. Briefly, warnings are received by specifically dedicated staff available for 24 h who analyze and classify the failure to initiate the defined corrective actions. In case it could not be repaired, samples are evacuated to backup equipment.

If previous instructions are followed, samples could be preserved in good conditions for a long time. However, the specific period of time will depend on the type of sample but, most importantly, on the biomarker to be detected by a particular methodology, with a range from minutes to years [15]. In this sense, fitness-for-purpose procedures should be validated and established when a prospective workflow is designed, taking into consideration the general good practices that do allow the most use of samples [2, 12]. Independently, other approaches have been reviewed for the conservation of samples at room temperature by biobanks [25].

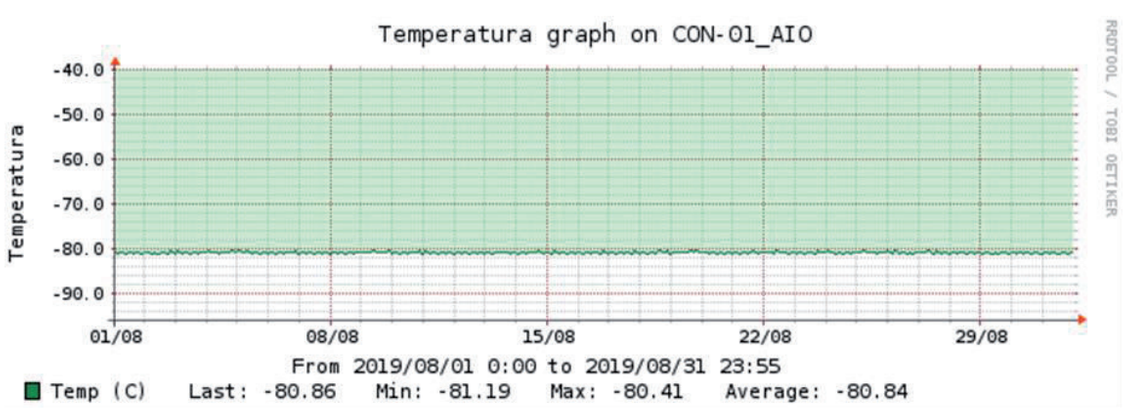

Figure 2.
Representative graph of a monitoring system showing a temperature of an ultra-freezer at −80°C.

Before sending of samples to analytical laboratories from the storage facilities, a checkpoint is introduced to guarantee that each aliquot is compliant with the corresponding study or with the necessary volume of sample to thus supplement with additional aliquots. Additional quality controls should be performed when incidents during the sample conservation occur or after a non-validated long-term storage. The remaining precious samples may be again received for long-term storage from the testing laboratories followed by a new quality control.

3. Traceability of biological samples

3.1 Electronic database

The electronic database used by biobanks allows the integral management of multicenter prospective projects with a maximum level of security through restricted access. Donors, biological samples, and associated information, as well as the ethical-legal documentation associated to the project, are recorded. In detail, the system allows an exhaustive control of collaborating centers and researchers, preparation of sample collection kits maintaining the traceability of all materials used, donor and clinical information, informed consent forms, ethical and scientific committees' approvals, agreements, sample handling by different sites (reception, processing, storage and shipments), quality incidents, and even the project monitoring by using any recorded information, for example, the recruitment rates from each clinical site. The electronic database may be also connected to external databases incorporating additional information such as temperature information from storage equipment. So, traceability is achieved from all the processes.

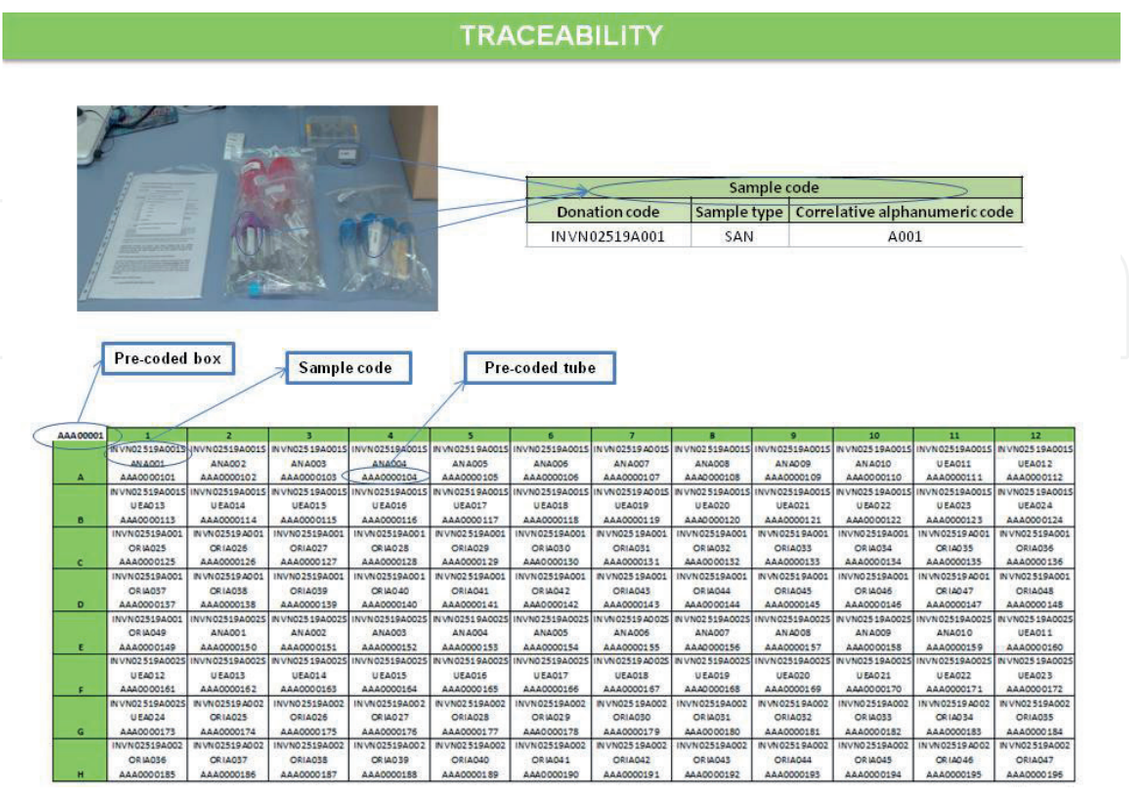

Figure 3.
Identification of samples and materials with structured codes and representative box map with pre-coded tubes.

3.2 Identification of materials and samples

Unique standardized codes are generated by the electronic database to identify each donation, sample, and material included in its corresponding collection kit, thanks to label printing (**Figure 3**). Therefore, samples (and associated information) are de-identified in compliance with applicable laws. Records included in the kit are also identified in relation with donations.

Commercially available pre-coded tubes are selected to prepare derivative aliquots so that specific pre-coded tubes are pre-assigned to each type of sample for a donation during the kit preparation by using the electronic database, supporting the traceability of samples (**Figure 3**). Similarly, racks for the pre-coded tubes included in the kits are identified as well. The process of generation of a new donation code to the positions of aliquots within the storage equipment is recorded in the electronic database. Code generation and identification also accompany manual or automated sample processing to identify the samples by using code readers.

4. Quality management system

A variety of quality standards can be implemented by laboratories, being requirements from ISO 9001 for the quality management system (QMS) the most widely used [26]. Briefly, ISO 9001 is characterized by a process-based approach following the plan-do-check-act cycle, not only focused on the quality of a product or service or the satisfaction of its users but on the way to obtain them. This QMS involves the definition and systematic management of the processes and the interactions between them in order to meet the legal, regulatory, and users' requirements and to achieve the expected results by continuously improving efficiency. Specifically for biobank activities, the ISO 20387:2018 Biotechnology-Biobanking-General Requirements for Biobanking has been launched under which other more specific standards will be additionally developed [27]. Next, quality assurance tools related with the harmonization and traceability of samples in multicenter prospective studies are shown.

4.1 Protocols, records, and other documents

The definition of processes (strategic, key, and support) involves identifying every factor involved (staff, equipment, method) with the objective of describing them through procedures and keeping them well controlled. Strict adherence to procedures by each stakeholder involved in the multicenter projects is mandatory to avoid pre-analytical deviations. A scheme summarizing the project workflow may be useful to clearly represent the responsibilities of all the stakeholders (**Figure 4**).

Clear and schematic protocols are developed for each type of collection device included in the kits in order to make easier the procedure interpretation (**Figure 5**). This action is especially critical when kits are targeted to donors for collection at home. The protocols include associated records to be filled with pre-analytical information of donations or samples, to report any incident that occurred during collection and preservation, even rack maps as guide for derivatives aliquoting into the specific tubes.

After centralized derivatives are obtained, a technical report specifying the sample processing features is accompanied in the shipments to analytical laboratories. Once all the samples for a study are sent from storage facilities to analytical laboratories, a final report is prepared with the missing samples, because of insufficient quantity of aliquots or any incident reported, and with the remaining

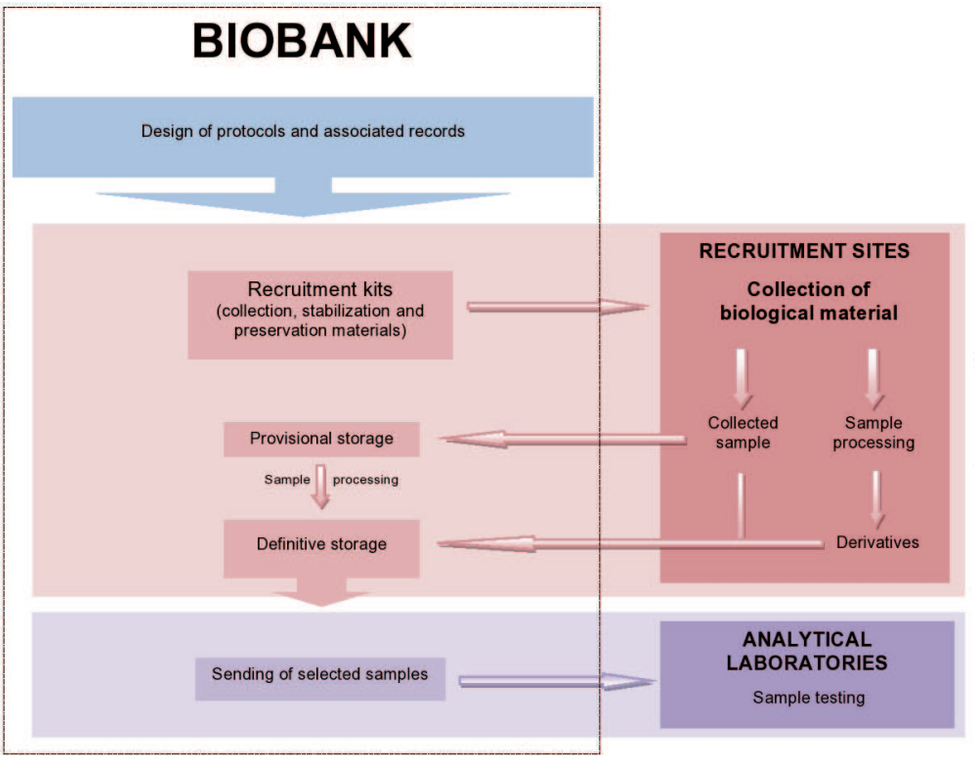

Figure 4.
Biobank-supported workflow for sample handling.

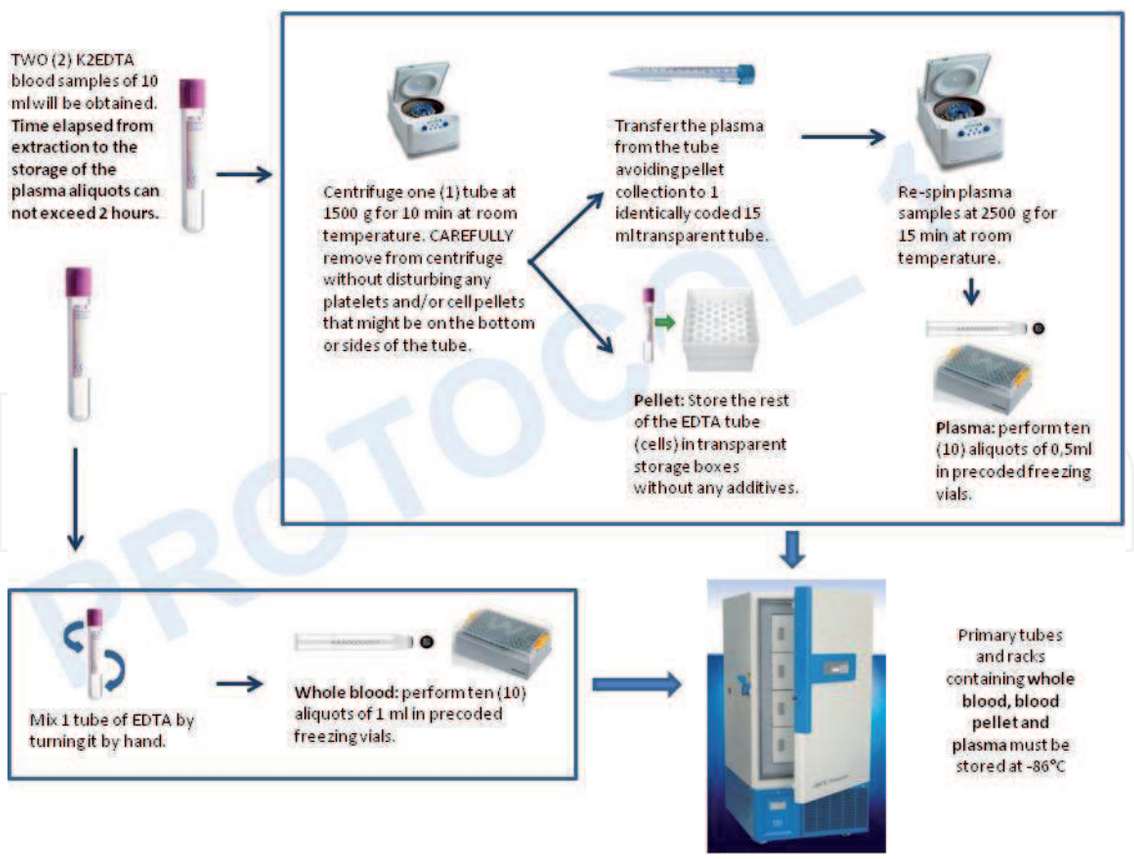

Figure 5.
Representative schematic protocol for derivative stabilization and preservation.

material for the study. Transaction forms specifying the samples included are necessary to declare the derivative shipment to the next facility involved in the project workflow.

4.2 Risk management tool

As part of the quality assurance tools, the processes of prospective sample collection, stabilization and processing, conservation, and distribution in multicenter research studies are managed under a global approach based on risk analysis, aimed at preventing undesired results. Since incidents are treated in the format of corrective and preventative action (CAPA) and root cause analysis (RCA) documentation, these records are used as reference.

So, the implementation by the biobanks of a comprehensive quality control for sample collection kits before shipment to recruitment sites is a result from this risk analysis. The potential consequences (inadequate preservation of samples due to inappropriate devices, containers, or additives, lower amount of derivatives for analysis, or loss of traceability) and costs of this process (new shipment of replacement kits and time of technician dedicated to kit checking), in addition to the number of nonconforming kits detected, have been evaluated. Quality control of kits is performed with a checklist, and follow-up of kit preparation and shipments is made with a specific record. Similarly, a checklist for the recruitment sites is included to track the reception of kits.

In addition, a training activity for the staff from the recruitment sites is organized before initializing the donors' recruitment to present the procedures for sample handling and the kit composition and usage. On the other hand, a pilot in a recruitment site is necessary to validate the model designed and to propose improvement measures.

5. Conclusions

The biobank-supported workflow, specifically designed and implemented for each research study, allows obtaining prospective, harmonized, and quality samples avoiding pre-analytical bias and contributing to the validity of the analytical results. Through biobanking processes and continuous and overlapped checkpoints, quality derivatives are obtained based on common and evidence-based standard operating procedures and supervised materials, with associated traceability information in relation with their collection, processing, conservation, and distribution. The effective workflow established is valid for large and complex multicenter projects.

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Conflict of interest

The authors have declared no conflict of interest.

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