QUALITY MANUAL FOR THE

IMPLEMENTATION OF RESEARCH PROJECTS

VALL D'HEBRON INSTITUTE OF ONCOLOGY

LIABILITY COMPANIES

EDITORIAL			
Name	**Responsibility**	**Signature**	**Date**

REVIEW			
Name	**Responsibility**	**Signature**	**Date**

APPROVAL			
Name	**Responsibility**	**Signature**	**Date**

CHANGE HISTORY

Version	Date	Reason for change
1.0	June 2012	First Version of the Document
2.0	December 2012	Modifications derived from the December 2012 audit (Report IA_15189_FVHIO_34122012.pdf): - New quality policy - Include VHIO VAT number and company name - Structure of the documentation - No conflict of interest - Include responsibilities for key positions - Expansion item 3.6 - Servers and backups
3.0	April 2013	- Justification for the exclusion of design and development requirements is included (point 5.5). - The Quality Policy is modified to include the commitment to comply with all applicable legal and regulatory requirements (point 2.2.1). - An item for the analysis of process performance is included in the index of topics to be included in each year's Quality Report for review by Management (item 3.6.2). - Monitoring and measurement methods are included for the processes defined in this Quality Manual (point 6.2.3).
4.0	April 2016	Inclusion of UITM in the scope of the Quality Manual. Personnel selection criteria based on training and experience for key positions, and personnel documentation that is archived in VHIO's SSGG. The reference to the version of the ISO standards is eliminated and replaced by "in its current version". The previous EECC Royal Decree (223/2004) is replaced by the current one (1090/2015).
5.0	September 2022	Updating of personnel data, organization chart, groups and structures.

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1. INTRODUCTION AND MODEL OF MANAGEMENT

The purpose of this document is to describe the organization and the necessary processes carried out by the *Vall d'Hebrón Institute of Oncology* (hereinafter, VHIO) in the framework of the management and implementation of the biomedical research projects they carry out.

This Quality Manual summarizes the management system implemented at VHIO with the objective of providing support in:

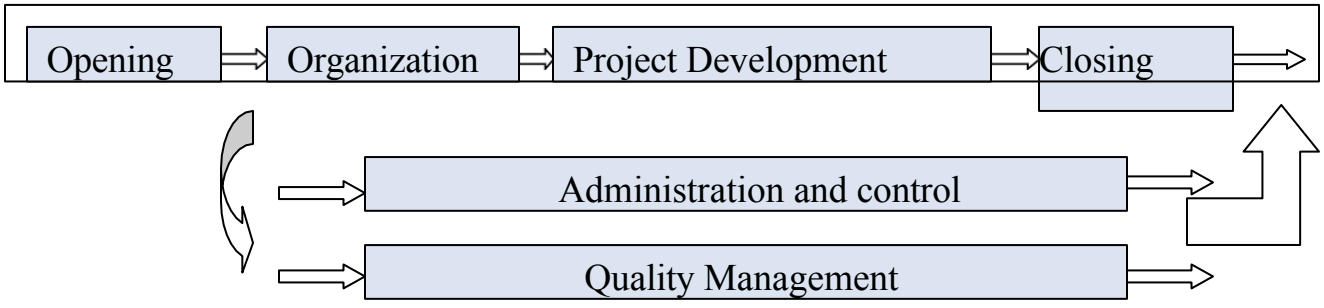
- Research activities
- To provide guidelines for the organization and effective management of research:
  - Analysis of the internal and external technological situation
  - Identification and assessment of threats and opportunities
  - Definition of objectives
  - Selection and management of an adequate project portfolio
- Ensure that no activities are lost that could generate results applicable to routine clinical practice that could lead to a breakthrough in patient health.
- Promoting research as a differential factor in competitiveness
- Help plan, organize and control the units that are part of VHIO Biomedical or

clinical research projects are characterized in:

- The continuous use of information, data and knowledge as well as its transformation and generation.
- The use of technology watch and the drive for creativity
- Risk management in the achievement of results
- Management of intellectual and industrial property, and its protection.
- Its multidisciplinary nature
- Its long-term duration and investment requirements

1.1. Purpose and scope of application

Every biomedical or clinical research project is subject to a life cycle as shown in the following diagram:



This Manual establishes the guidelines to be followed considering the management system as a set of effective and efficient processes in the activities of "Administration and Control" and "Quality Management".

1.2. Definitions and terminology

The definitions and fundamentals specified in the ISO 9001 and ISO 15189 standards in their current versions are used, as well as in the ICH E6 (Good Clinical Practices) and the Biomedical Research Law 14/2007.

In addition, it has been considered relevant to include certain definitions in this Manual:

Quality manual: Formal document approved by top management, which contains the organization's quality policy and system.

Quality policy: Quality policy is defined as the statement by VHIO of its intentions and principles in relation to its activities in research projects, providing a framework for its actions and for the establishment of its objectives and goals.

Quality system: The set of organization, responsibilities, methods and human and material resources to achieve quality.

Quality Plan: Document that establishes the specific practices, resources and sequence of activities all related to quality for a particular product, project or contracts.

Process Map: Schematic and/or graphic description of activities that serves to specify operationally the key and support processes of a Service.

Quality management: The way in which an organization is managed to achieve excellence. Aspect of the overall management function that determines and implements quality policy. Quality management includes: strategic planning, resource allocation and other systematic activities such as quality planning, operations and evaluations.

Improvement plan: Actions planned, prioritized, timed and directed to improve the degree and the evaluation process. They are a consequence of the value judgments and constitute a substantial and essential part of all the Reports.

Quality assessment: Systematic examination to determine whether the activities leading to quality are proceeding according to plan and whether the product or service is being delivered in an effective manner and is appropriate to achieve the intended objectives.

External client: refers to promoters, private entities, other departments or services of Vall d'Hebron and funding sources with which VHIO collaborates for the development of its activities.

Internal customer: refers in this case to VHIO departmental staff.
From the quality point of view, the internal customer becomes a particularly relevant customer, and a great deal of effort is devoted to collecting suggestions, measuring the level of satisfaction and initiating preventive and/or corrective measures to improve the satisfaction of this group.

1.3. Presentation

The Vall d'Hebron Institute of Oncology is a biomedical research center with scientists and physicians working together to associate basic science with clinical research. Its data are:

Holder: Fundació Privada Institut d'Investigació Oncològica de Vall d'Hebron
Head office:
CELLEX CENTER

C/ Natzaret, 115-117
08035 Barcelona

Registered data: Registered in the Registry of Foundations 2307
Tax Identification Code (C.I.F.): G-64384969

The Foundation's main purpose is to promote and develop excellence in research related to oncological diseases. VHIO also works to increase contributions to the development of new and improved therapies for the treatment of cancer.

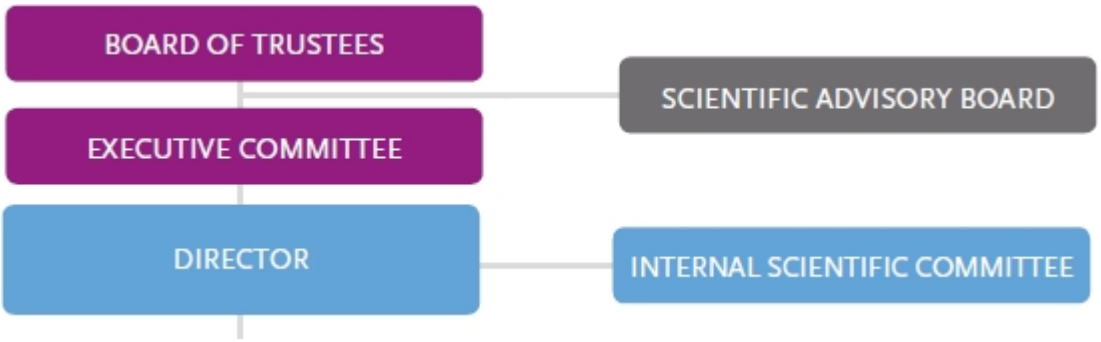
The pillars on which VHIO's raison d'être is based are:

- Scientific practice in the clinic for the benefit of oncology patients.
- Scientific research of excellence in the areas of basic, translational and clinical research.
- Scientific cooperation between national and international oncology research institutions.
- The promotion of all activities related to oncological research, thus contributing to improve the quality of life of the population.

The VHIO Foundation is governed by the following bodies:

- Board of Trustees
- Executive Committee of the Board of Trustees
- Director
- Steering Committee
- Internal Scientific Committee
- It also has an advisory body, the SAB.

The governing bodies ensure that VHIO's mission is carried out effectively, so that the Foundation fulfills its goal of promoting and developing excellence in cancer research.

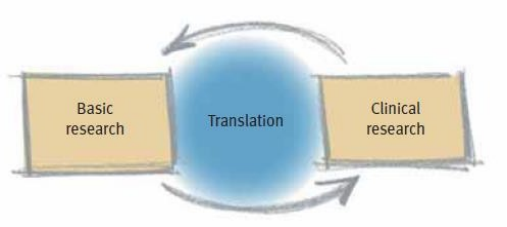


As a result of its spectacular growth and the increase in its scientific production of excellence, VHIO created a new scientific structure designed to meet this expansion phase and consolidate its translational research model.

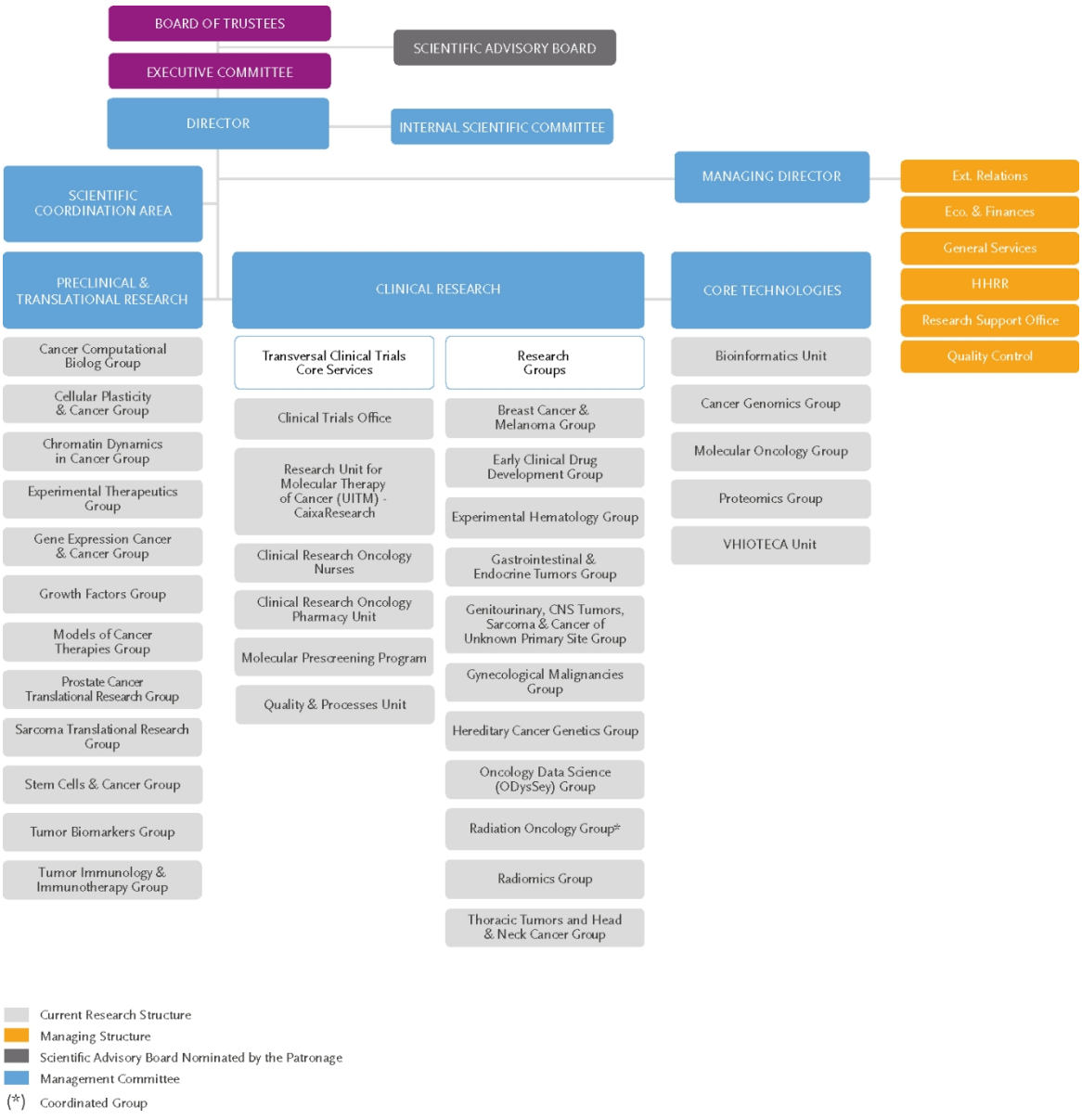
Previously, scientific activity was divided into two major areas, clinical research and basic research, which in turn incorporated several groups, each led by respective principal investigators (PIs).

At present, VHIO's scientific activity is structured into four major programs:

- Preclinical Research
- Translational Research
- Clinical Research
- Transversal Technologies.



The following figure shows the organizational structure of VHIO, as well as the groups that make up each of the programs mentioned.

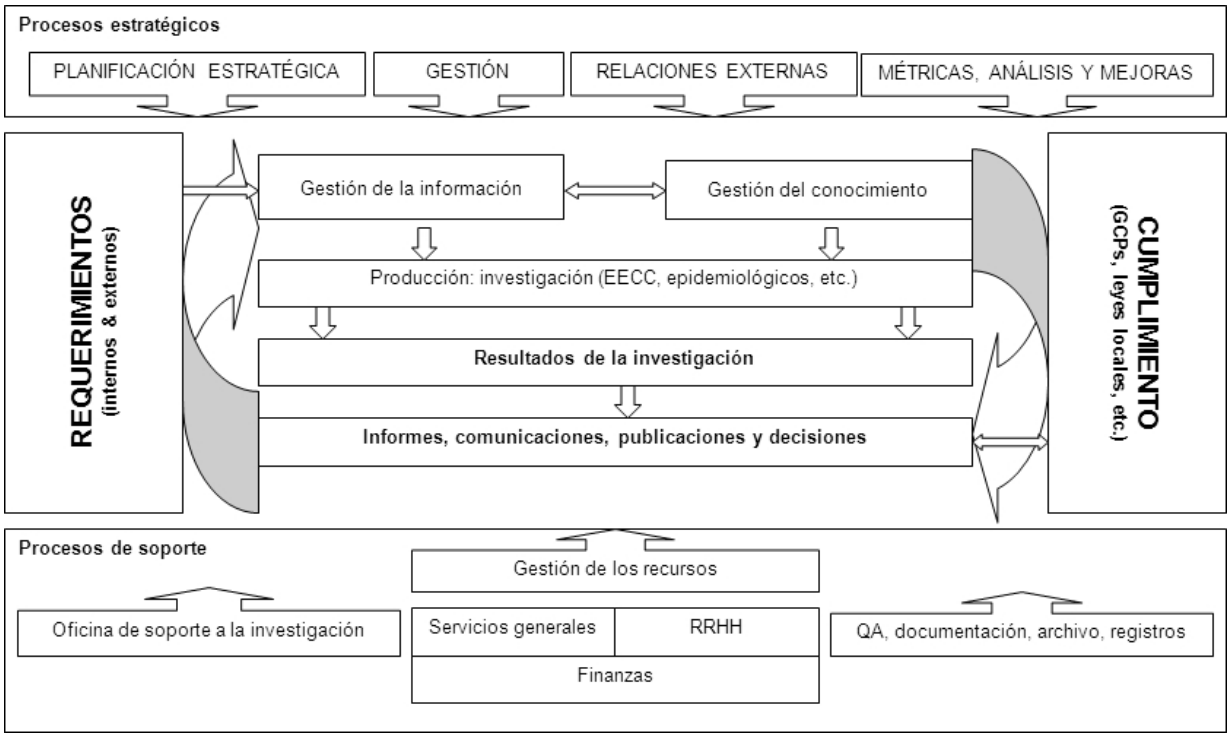

BOARD OF TRUSTEES
SCIENTIFIC ADVISORY BOARD
EXECUTIVE COMMITTEE
DIRECTOR
INTERNAL SCIENTIFIC COMMITTEE
MANAGING DIRECTOR
Ext. Relations
Eco. & Finances
General Services
HHRR
Research Support Office
Quality Control
SCIENTIFIC COORDINATION AREA
PRECLINICAL & TRANSLATIONAL RESEARCH
CLINICAL RESEARCH
CORE TECHNOLOGIES
Cancer Computational Biolog Group
Cellular Plasticity & Cancer Group
Chromatin Dynamics in Cancer Group
Experimental Therapeutics Group
Gene Expression Cancer & Cancer Group
Growth Factors Group
Models of Cancer Therapies Group
Prostate Cancer Translational Research Group
Sarcoma Translational Research Group
Stem Cells & Cancer Group
Tumor Biomarkers Group
Tumor Immunology & Immunotherapy Group
Transversal Clinical Trials Core Services
Clinical Trials Office
Research Unit for Molecular Therapy of Cancer (UITM) - CaixaResearch
Clinical Research Oncology Nurses
Clinical Research Oncology Pharmacy Unit
Molecular Prescreening Program
Quality & Processes Unit
Research Groups
Breast Cancer & Melanoma Group
Early Clinical Drug Development Group
Experimental Hematology Group
Gastrointestinal & Endocrine Tumors Group
Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site Group
Gynecological Malignancies Group
Hereditary Cancer Genetics Group
Oncology Data Science (ODysSey) Group
Radiation Oncology Group*
Radiomics Group
Thoracic Tumors and Head & Neck Cancer Group
Bioinformatics Unit
Cancer Genomics Group
Molecular Oncology Group
Proteomics Group
VHIOTECA Unit
Current Research Structure
Managing Structure
Scientific Advisory Board Nominated by the Patronage
Management Committee
(*) Coordinated Group

The VHIO was created in 2006 as a result of the need to bring together basic, clinical and translational oncology research activities at the Vall d'Hebron University Hospital campus and:

- Promoting clinical research at Vall d'Hebron Hospital.
- Develop and support biomedical research projects.
- Disseminate research and scientific heritage
- Editing publications and preparing studies
- Entering into agreements and collaborations
- Promote the training of healthcare personnel

1.4. Map of processes

Taking as a model the scheme of any Quality System, in which the key activities and processes must be considered to be fed back by the requirements of the "clients" (i.e., researchers, funding entities, patients, etc.) and the regulatory and legal requirements that apply, the general process map of VHIO is divided into three major groups.



These process groups are as follows:

- **Strategic:** these correspond to those that set the guidelines and operation of the VHIO and are carried out by the management bodies. Among them are:
    - Elaboration and monitoring of Strategic Planning
    - Preparation of the Annual Quality Management Plan and review of the Quality System.
    - Enhancement and follow-up of External Relations.

- Measurement, analysis and improvement.

- **Key:** are those that really provide the raison d'être of VHIO, providing added value to research projects, and include the processes directly related to the services of the Organization. Among them we find:

  - Research projects

    - Clinical research
      - Breast Cancer and Melanoma Group
      - Early Clinical Drug Development Group
      - Experimental Hematology Group
      - Gastrointestinal and Endocrine Tumors Group
      - Genitourinary, CNS and Sarcoma Tumor Program Group
      - Gynecological Neoplasms Group
      - Hereditary Cancer Genetics Group
      - Oncology Data Science Group (ODysSey)
      - Radiation Oncology Group
      - Radiomics Group
      - Thoracic Tumors and Head and Neck Cancer Group
    - Preclinical and translational research
      - Computational Biology of Cancer Group
      - Cellular Plasticity Group
      - Non-Colorectal Gastrointestinal Cancer Translational Research Group
      - Experimental Therapeutics Group
      - Gene Expression and Cancer Group
      - Growth Factors Group
      - Modeling Group for Antitumor Therapies
      - Translational Research Group in Prostate Cancer
      - Sarcoma Translational Research Group
      - Stem Cells and Cancer Group
      - Tumor Biomarker Group
      - Tumor Immunotherapy and Immunology Group
    - CORE TECHNOLEGIES
      - Cancer Genomics Group
      - Molecular Oncology Group
      - Proteomics Group

- **Support:** this section includes all those processes necessary for the control and improvement of the system, such as:

  - Human Resources
  - Research Support Office
  - General services and facilities
  - Finance
  - Communication
  - VHIOAcademy
  - QA, documentation, archiving, registration...

  As well as all the direct processes necessary to conduct research, especially in the clinical setting:

  - Clinical Trials Office
  - Clinical Trial Pharmacy
  - Clinical Trials Nursing

- VHIOTECA

2. QUALITY MANAGEMENT SYSTEM

The present document is the VHIO Quality Manual. As such, it specifies the Quality management system, affecting all the activities of the organization with an impact on the quality of research.

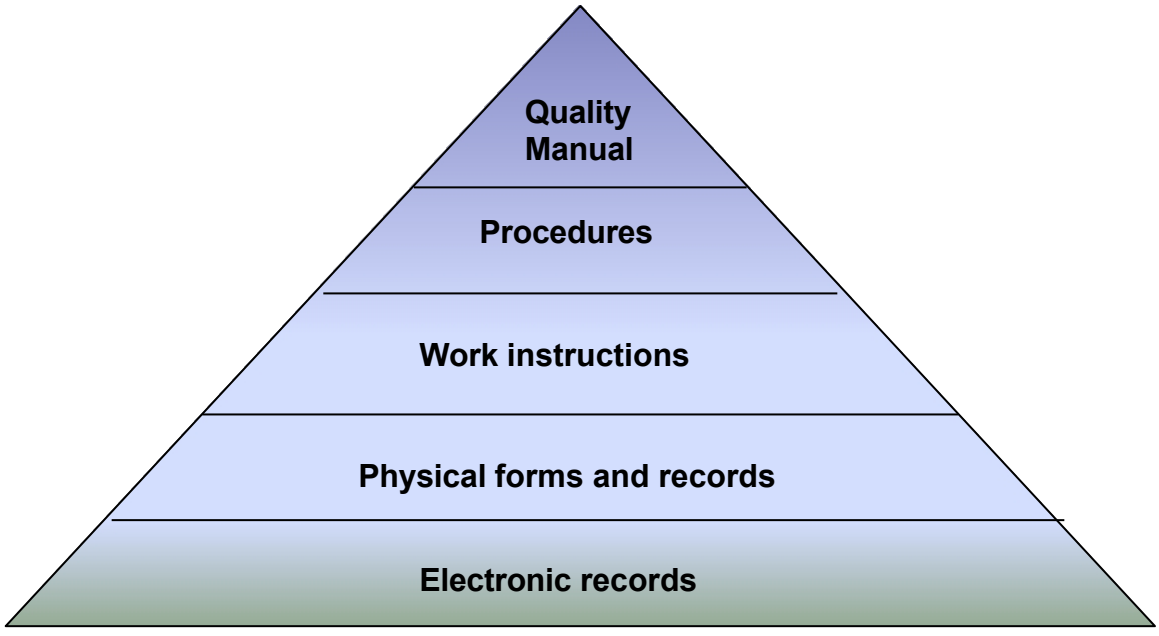
2.1. General requirements

The VHIO establishes and identifies the research activities included under the umbrella of its management system, as detailed in the process map. To do so, it must:

- Determining the sequence and interactions of these activities
- Determine the methods and criteria necessary to ensure effectiveness
- Ensure the availability of resources and information necessary to carry them out.
- Perform monitoring, measurement and analysis
- Implement the necessary actions to achieve the planned objectives.
- Establish and document the mechanisms for protection and exploitation of results.

2.2. Requirements of the documentation

The documentation of the Quality system and research projects includes documentation categorized according to the following pyramid:



Quality Manual: This document and the specific manuals.

Procedures: Documents that describe a process, detailing the activities that comprise it and those responsible for it. It also indicates the records derived from its execution.

Instructions: Mandatory document detailing the operation to carry out an activity. These are parts of a procedure that, operationally, it is decided to create as a separate document for greater agility in updating and implementation.

Guidelines: Document of recommendations about a certain activity or process. They are not mandatory.

Records:Documentary evidence of the performance of an activity.

2.2.1. General

Therefore, the system includes documented statements of a quality policy and management of the research carried out by VHIO, the procedures required according to ISO 9001 and ISO 15189 standards in their current versions for laboratories, the GCP (Good Clinical Practices), and all those additional documents (work instructions and guidelines) deemed necessary to ensure efficiency in planning, operation and control activities.

The following is the VHIO Quality Policy defined and approved by the Management. The signed original of this policy is located at the VHIO Management facilities.

VHIO Quality Policy

*The VHIO conceives **Quality as a** broad concept that extends to all areas of activity of the organization, that goes beyond its purely formal aspects and that is developed under criteria of **pragmatism, efficiency and flexibility**. The VHIO **Quality Policy** is an instrument that reinforces **corporate cohesion** and **identity**, and provides a frame of reference for us to carry out our activity in a responsible and sustainable manner.*

*Quality is key to ensure **competitiveness**. VHIO's Management assumes the objective of achieving **optimal** levels of Quality for the services of biomedical research projects in Oncology, translated into the satisfaction of the needs of customers, whether internal or external to Vall d'Hebron. As well as demonstrating the **administrative capacity** and **technical competence** of VHIO **laboratories** to perform the relevant clinical analyses in the biomedical research carried out. And all this backed by ensuring the **allocation of resources that allow its development** and implementation through adequate infrastructure, means and the necessary, competent and qualified personnel.*

*The **degree of satisfaction** corresponds to the level of compliance with both explicitly communicated requirements and those identified through our initiative. It is evaluated through active verification of such compliance.*

*The contribution of VHIO staff is a key element for the achievement of the Quality objectives. The Management will ensure **compliance with the legal and regulatory requirements** to which the activity carried out by VHIO is subject, and will ensure that the objectives and the Quality Policy are published and known by VHIO staff at all times, and that the staff has the appropriate training and means to make them a reality.*

Finally, the Management is committed to continuous improvement in its processes and activities, establishing specific improvement objectives and how to measure our progress. The conclusions of the improvement activities may be reflected in changes in both the Quality System and the management system, and - if applicable - in the Quality Policy itself.

Dr. Josep Tabernero Caturla VHIO
Director

April 2013

2.2.2. Manual of the quality

The Quality System is the tool created to implement this quality policy, and involves all staff working in, collaborating with, or supplying VHIO. This Quality System is appropriate to the activity of the Institute, and is independent of the systems implemented in the Hospital or other centers attached to it.

VHIO's Quality system is based on:

- The identification of basic processes that make up the organization's activity.
- The assignment of responsibilities in the performance of these processes, defined in this manual or in the respective procedures.
- Identification of the resources and infrastructure necessary to carry out the activities.
- The implementation of documented procedures in those processes where it is advisable.
- The establishment of adequate communication channels, in this manual and in the respective procedures.
- The establishment of continuous improvement mechanisms, based on the objective measurement of process performance, the analysis of the data thus collected, and the implementation of preventive and corrective actions based on this analysis.
- The establishment of specific objectives, and the periodic and systematic review by management of both the system and the degree of compliance with the objectives.
- The establishment of a procurement process in accordance with the development, requirements and characteristics of the research projects.

2.2.3. Control of the documents

Documents and records under VHIO documentation control are archived in protected directories and accessible by staff through the VHIO intranet by entering a user name and password. Except for certain documents and records of the laboratories that are archived in their directories and under their custody, as detailed in the Quality Manuals of the laboratories or in the relevant procedures.

The aforementioned website is structured in folders in order to facilitate access to the documents, among which are:

- **Quality Docs List**: Excel sheet (read-only) with the updated list of the documentation included in the web.
- **Quality documentation**: current and obsolete versions of manuals and procedures in pdf format, current versions of manuals and procedures in non-modifiable Word format.
- Applicable **regulations and legislation** that must be kept under control.
- Molecular Pathology and Genomics laboratories **performance catalogs.**
- **Bibliography,** which due to its importance in the opinion of those responsible, it is essential to keep under control.

The documents required by the VHIO management system are controlled and governed by procedure PR_GENER_0001 "Documentation control and management procedure", unless contractual clauses or project specifications indicate otherwise.

The objective of this process is to ensure that the information generated in, or necessary for, the Institute's activities is available and up to date at all times. This information, contained in documents, includes records as a particular case.

The procedure includes a detailed record of the activities carried out and the results generated by them.

To achieve this objective, the process includes:

- Identification of the need for a new document or modification of an existing one.
- The allocation of resources for the preparation, review and authorization of new documents, or changes to existing documents, and the management of these activities.
- The filing, registration, and distribution of new documents, and the disposition of cancelled or obsolete documents.

2.2.4. Control of the records

Records are a special type of document, as they are the source of evidence that activities are carried out in accordance with VHIO requirements and procedures.

Procedure PR_GENER_0001 "Documentation control and management procedure" includes the special treatment for this type of documents (records), defining the necessary controls for their identification, storage, protection, recovery, conservation time and disposal.

3. RESPONSIBILITY OF THE ADDRESS

3.1. Commitment of the Management

VHIO's Management is responsible for coordinating and managing the activities of the quality management system. These are delegated to Management. From this point on, any reference to Management should be understood as Management, unless otherwise specified.

To this end, it has the following attributions, among others:

a) Establish Quality objectives.

b) Approve the Quality Manual and its modifications.

c) Receive, and record system nonconformities and improvement proposals (see PR_GENER_0007) "Nonconformity procedure"). This activity can be delegated.

d) Ensure that identification, management and reporting of corrective and preventive actions are carried out (see PR_GENER_0002 "Corrective and preventive actions procedure").

e) Ensure that qualified internal auditors are available or, if not, outsource them (see PR_GENER_0003 "Internal audit procedure").

f) Ensure the maintenance of records relating to the System, as detailed in this Manual.

g) Ensure the availability of material resources

h) Establish the policy for the protection and exploitation of the results obtained in the research carried out, ensuring compliance with the requirements of the promoters of the same, if applicable.

i) Prepare the review of the Quality System and the establishment of the objectives for the subsequent period. For this purpose, prepare a report based on the analysis of data on:

- the results of the audits carried out during the period,
- the degree of customer satisfaction,
- non-conformities produced in VHIO processes,
- the status of ongoing corrective and preventive actions, including proposals for improvement, and follow-up of actions defined in previous reviews,
- possible changes affecting the quality system, taking into account the foreseen activities and actions in progress.

The communication channels established in this Manual, the collection of indicators and the different procedures ensure the availability of this information. The Management may delegate the execution of the activities derived from its attributions to VHIO's own personnel, or may choose to subcontract certain quality activities.

3.2. Stakeholders and approach to customer

VHIO's mission is to encourage, promote, coordinate and ensure the execution of quality biomedical research. Therefore, the activities are aimed at excellence, efficient resource management, continuous improvement of processes and the search / capture of opportunities to carry out research projects that contribute to achieving research excellence and become a benchmark for it.

Therefore, the process map (see section 1.4) considers as key processes those that have a positive impact on meeting the demand of researchers, on the motivation and involvement of the human team, on ensuring legal and regulatory compliance, and on paying special attention and care to the innovations resulting from the research carried out.

As mentioned in the previous section, VHIO's activities have their raison d'être in the requirements demanded by our "clients", meaning any organization or person related to the Institute in the definition of requirements that aim to increase knowledge for the improvement of health or the quality of life of our society.

These external actors and their requirements include the initiatives of the researchers, the requirements of the funding entities of such initiatives or of private promoters (pharmaceutical industry) or other types of calls for proposals.

3.3. quality policy

VHIO management ensures that, at all times, the policy is appropriate to the purpose and priority areas of research.

To this end, it has administrative and technical personnel. The first group is responsible for general administration, personnel management and economic management. The second group is responsible for scientific management and project execution, including clinical trials and research projects, the preparation and implementation of training plans and technological and/or scientific surveillance. The quality policy is reviewed periodically and this review is reflected in the Management Review Report.

3.4. Planning

On an annual basis, the Management will establish the objectives for the following period, as well as the amount of investments to be allocated for their achievement.

3.4.1. Objectives of the quality

Special mention should be made of the quality objectives as a particular case of the objectives set by the aforementioned policy.

Based on the results of the indicators collected during the year, quality objectives will be established in accordance with the policy, and must always be measurable and consistent with it.

3.5. Responsibility, authority and communication

3.5.1. Responsibility and authority

The VHIO has personnel to cover the functions and responsibilities in all the activities of the research projects it carries out. These functions include all the activities necessary for:

- Identification and analysis of problems and opportunities
- Planning, monitoring and control of project portfolios
- Monitoring, control and documentation of results
- Protection and exploitation of results
- Measurement, analysis and continuous improvement

3.5.2. Structure, organization and responsibilities (organization chart)

The VHIO is organized according to areas, which may be carried out by internal personnel or outsourced to third parties:

- Research Support Office (EECC and research projects)
- Legal (subcontracted)
- Human Resources, which includes Training
- Administration and finance
- General Services

See organizational chart included in section 1.3 of this document.

The structure of the VHIO follows the organizational model of the Foundations for Biomedical Research. In our case, this is:

- Management Committee
    - Director: Josep Tabernero, MD
    - Scientific Director: Alejandro Piris, PhD
    - Manager: Carles Constante
    - Deputy Manager: Sergi Cuadrado
    - Communications Director: Bianca Pont

- Internal Scientific Committee:
    - Elena Garralda, MD
    - Francesc Bosch, MD

- Joan Seoane, MD
- Enriqueta Felip, MD
- Josep Tabernero, MD
- Laura Soucek, PhD
- Paolo Nuciforo, PhD
- Alejandro Piris, PhD
- Carles Constante

In general terms, the Directorate is responsible for all structural or scientific matters of general interest, and for implementing the recommendations of other bodies.

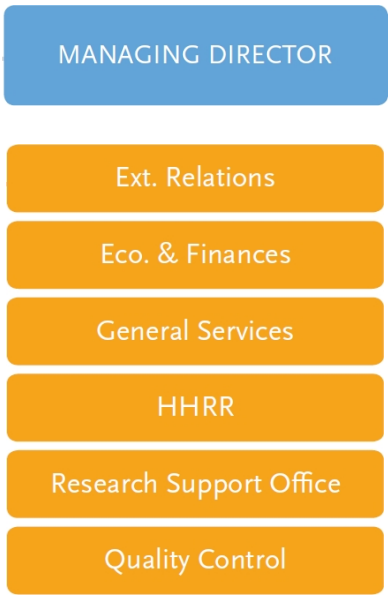
Main functions:

- Coordination and strategic planning of the Institute's research and knowledge transfer.
- Coordination of research programs
- Follow-up and coordination of the execution of the scientific activity, the center's strategic plan and the annual activity plan
- Promotion and development of the scientific community and its constituent members.
- Discussion and preparation of proposals to be approved by other governing bodies

Responsibility for the overall Quality System of VHIO lies with the Deputy Management, which is delegated to the different areas that make up VHIO for technical aspects that require expert knowledge. For this reason, there are specific Quality Managers in the laboratories and other areas (such as the Clinical Trials Office). This is a key position in the Organization, whose responsibilities in case of absence are assumed directly by VHIO Management. The functions and responsibilities of the Quality Manager are:

- Ensure knowledge of and compliance with the VHIO Quality System.
- Define and execute the Annual Quality Audit Plan.
- Review, together with Management, compliance with the Annual Quality Plan and define the quality objectives for the following period.
- Ensure training in the VHIO Quality Manual and Quality System procedures.
- Design, implementation, monitoring and improvement of internal processes.
- Definition of procedures, work instructions, models, ...
- Definition of indicators and their follow-up (scorecard).

The Institute also has research support services that are organized into specialized functional areas.



VHIO's structural areas are further divided into:

- Preclinical and translational research
  - Computational Biology of Cancer Group
  - Cell plasticity group
  - Non colorectal gastrointestinal cancer translational research group.
  - Experimental therapeutics group
  - Gene expression and cancer group
  - Group of growth factors
  - Antitumor therapies modeling group
  - Sarcoma Translational Research Group
  - Stem cells and cancer group
  - Tumor biomarkers group
  - Immunotherapy and Tumor Immunology Group

- Clinical research
  - Breast cancer and melanoma group
  - Early clinical drug development group
  - Experimental hematology group
  - Gastrointestinal and endocrine tumor group
  - Genitourinary, CNS and Sarcoma Tumor Program Group
  - Group of gynecological neoplasms
  - Oncology data science group (ODysSey)
  - Radiation oncology group
  - Group of thoracic tumors and head and neck cancer.
  - Hereditary cancer group

- Cross-cutting technologies
  - Molecular Pathology Group
  - Cancer Genomics Group
  - Proteomics Group
  - Bioinformatics Group

- VHIOTECA

- Clinical Research Support Services
  - Clinical Trials Office
  - Oncology Pharmaceutical Care Unit
  - Oncology Clinical Nursing Unit
  - Molecular prescreening program
  - Molecular Therapy Research Unit (UITM)
  - Quality and Processes Unit

In addition, the VHIO relies on external expert advice.

3.5.3. Representative of the Address

In the context of research projects, the VHIO Directorate designates the Research Support Office, as Representative to, independently of its other responsibilities, carry out the control of research activities, among which the following stand out:

- Maintain the research management system
- Keep management informed of the current status of the management system and improvement needs.
- Promote and encourage the knowledge of all research activities to the rest of the VHIO.

3.5.4. Communication internal

The VHIO has internal communication channels that ensure the flow of information among its own and external personnel.

The following tools are available for this purpose

- Website www.vhio.net
- E-mail list that constitutes the distribution list for the periodic dissemination of information of interest.
- Bulletin boards
- Personalized information
- Intranet

3.6. Review by Management

3.6.1. General

VHIO's Management will convene an annual meeting with the heads of each of the Institute's Areas or Departments it deems necessary, in order to review the Management System and assess the status of non-conformities and needs for improvement.

Minutes (record) shall be kept of such meetings.

3.6.2. Information for the revision

In order to conduct the aforementioned meeting, the following documentation must be obtained and/or distributed to all attendees prior to the meeting:

- Results of previous reviews
- Internal and external audit reports
- Reports and indicators of the Molecular Oncology and Genomics laboratories, including reference to the results of the intercomparison programs in which they have participated in the year under review.

- Evaluations by authorities or agencies
- Measurement and analysis of indicators
- Results of stakeholder assessments
- Process performance analysis
- Status of corrective and preventive actions, both general and specific to the laboratories considered.
- Recommendations for improvement
- Significant changes produced
- Supplier evaluation, if applicable

3.6.3. Results of the review

As a result of this review, and as will be recorded in the corresponding minutes, all decisions taken regarding the improvement of the System, and the needs and use of available resources for its implementation, will be included.

The agreed decisions will be reflected in the Annual Report to be prepared by the General Management.

The Report will be distributed to all attendees, and to the personnel considered appropriate by the General Management or Management. VHIO Management will ensure the follow-up of the objectives set and the activities established as a result of the review, within the estimated deadlines.

3.6.4. Other revisions

In addition to the annual management reviews, the VHIO Quality Manager holds periodic meetings to monitor the Quality System, both general and specific, from an operational and detailed point of view.

The topics discussed during these meetings are reflected in the minutes kept by the VHIO Quality Manager and distributed to all attendees.

4. MANAGEMENT OF RESOURCES

The objective of this process is twofold:

- to manage the existing resources, both human and material, in the different projects and general processes that make up VHIO's activity.
- ensure the availability of new resources.

To achieve this objective, this process includes the following activities:

- Identification of resource requirements in the different projects and general processes.
- Planning, coordination and control of the distribution of resources among the different projects.
- Evaluation of options for the acquisition of resources.
- Identification of material resources whose use is shared and must be controlled (equipment, laboratory and/or clean room space, tools, etc.).
- Preparation of VHIO's annual budget in accordance with the objectives set.

4.1. Provision of resources

Responsibility for the management of VHIO's own resources lies with Management, and is reflected and formalized in the organization's annual budget.

In the case of the management of resources associated with projects, the responsibilities for their management are listed below, and are detailed in the corresponding procedures:

- The initiation of a selection process and/or authorization of a contract is the responsibility of the Manager and must follow VHIO's internal contracting rules.
- The selection process is the responsibility of the project manager, as well as the Principal Investigator of the project.
- The assignment of VHIO personnel to projects is the responsibility of the person in charge of the area under which the project is managed (depending on whether it is a clinical trial or a research project).
- The evaluation of the degree of satisfaction of the interested parties is the responsibility of the Area Manager, who may delegate this responsibility to whomever he/she deems appropriate.
- The selection and establishment of collaboration with external entities that provide services/products necessary for the development of the project is the responsibility of the Principal Investigator, who may request the support of VHIO Administration.

This general process has as input the updated project plans provided by the project leaders and principal investigator, as well as the identified needs of the general process leaders. The output of this process is the allocation of resources.

4.2. Resources human

4.2.1. General

VHIO personnel involved in biomedical research activities have the necessary qualification levels and are motivated to perform their work. The absence of conflicts of interest of VHIO personnel in relation to their work is also carefully evaluated. To this end, Management periodically ensures that there are no incentives linked to specific results, nor that the staff has relationships with funding sources of a nature that would not ensure the independence of the work performed.

For this reason, the VHIO has documentary evidence of the level of qualification of its personnel.

The key human resources management process is the one by which an updated record is kept of all the people associated with the VHIO, whether they are its own personnel or not.

A record of the following documents will be kept for each person associated with the VHIO:

- Updated job *descriptions* (*job description*)
- Updated CV
- Training record
- Results of the performance evaluation or satisfaction assessment

4.2.2. Competence, awareness and training

VHIO's Human Resources Department is responsible for preparing the Training Plan, with the collaboration of personnel from other Areas or Groups. The General Management will ensure that this Plan is in line with the objectives and strategies set.

The Heads of each of the Areas or Groups that make up the VHIO are responsible for promoting cooperation between research groups and networks.

4.3. Infrastructure

The VHIO has a defined working space located in the Cellex Building, C/ Natzaret, 115- 117, 08035 Barcelona. In these facilities, the VHIO carries out its research activities, basic research in the laboratories of the buildings destined for such research, and clinical research in the hospital units adapted for such activity.

The VHIO has servers where all the information generated by general services is stored, as well as that of the laboratories and other areas. The servers are physically located in different physical points depending on the communications ring and the equipment is backed up. Specific directories with exclusive access to certain areas of the VHIO, and others with shared access among them, are defined.

4.4. work environment

The General Management ensures the maintenance of an adequate working environment to achieve the objectives set. To this end, there are periodic performance evaluations and evaluations of the satisfaction of the research personnel. The results are evaluated periodically in order to adopt the necessary corrective or preventive measures.

5. SERVICE PROVIDED: RESEARCH PROJECT ACTIVITIES

5.1. Identification of processes and activities

The VHIO will ensure at all times, through the development of its activities, that the research (whether clinical trials or not) is in accordance with:

1. Research projects must respect the fundamental principles established in the Declaration of Helsinki, in the Council of Europe Convention on Human Rights and Biomedicine, in the UNESCO Universal Declaration on the Human Genome and Human Rights, as well as comply with the requirements established in Spanish legislation in the field of medical research, personal data protection and bioethics, with Law 14/2007, of July, on Biomedical Research and the other requirements established in Spanish legislation in this regard.

2. The projects shall comply with the legal and regulatory provisions in force and those that modify or develop them, and specifically:

   a) Projects involving research on humans or the use of biological samples of human origin must comply with the provisions of Law 14/2007, of July 3, 2007, on Biomedical Research and other relevant legislation in force.

   b) Projects involving animal experimentation must comply with the provisions of current legislation and, in particular, with Royal Decree 1201/2005, of October 10, on the protection of animals used for experimental and other scientific purposes, and Law 32/2007, of November 7, on the care of animals during their exploitation, transport, experimentation and slaughter.

   c) Projects involving the use of genetically modified organisms must comply with the provisions of Law 9/2003, of April 25, 2003, on the Confined Use, Voluntary Release and Commercialization of Genetically Modified Organisms, and its implementing regulations.

   d) Projects involving the use of biological agents must comply with the provisions of Law 31/1995, of November 8, 1995, on the Prevention of Occupational Risks, and the Royal Decrees that develop it in terms of risks related to exposure to biological agents.

   e) Projects involving clinical trials must comply with the provisions of Royal Decree 1090/2015 of December 4.

   f) Research projects involving the use of human embryonic stem cells or cell lines derived from them, as well as research projects involving the use of cells and tissues of human origin in the field of regenerative medicine must comply with the provisions of Law 14/2007, of July 3, on Biomedical Research and Royal Decree 2132/2004, of October 29, establishing the requirements and procedures for requesting the development of research projects with stem cells obtained from supernumerary pre-embryos, as well as the rest of the legal regulations in force.

5.1.1. Management of calls for proposals for research projects

This call management process includes all activities related to the identification, selection, dissemination, distribution, presentation, awarding and follow-up of project opportunities by VHIO researchers and/or research groups.

This includes both external calls, whether public or private, as well as those promoted by VHIO itself and whose cost is derived from the Institute's own budgets.

The Foundation assigns professionals from the Research Support Office to follow up and track whether any call for grants for biomedical research projects has been published in any of the sources or dissemination platforms.

In the case of detection of a call of interest, it is distributed internally to all VHIO researchers, so that they can apply if they believe that their research may be eligible for such support.

Any researcher interested in participating in the call for proposals must communicate it in writing. The investigator's proposal is reviewed and evaluated. In the case of a favorable opinion, the VHIO is responsible for preparing the application to apply for the call for proposals by making the corresponding registration at the institution or submitting it according to the Law of the Legal Regime of Public Administrations and Common Administrative Procedure, or in accordance with the terms and conditions of the call for proposals.

If the resolution is favorable, the new project is registered and the Principal Investigator is notified in writing.

When the call comes from a private entity, it is not an official resolution but a service contract between that entity and the Foundation or Principal Investigator.

5.1.2. Trials clinical trials

According to Royal Decree 1090/2015 of December 4, 2015, which regulates clinical trials with medicinal products, a clinical trial is defined as any research conducted in humans to determine or confirm the clinical, pharmacological and/or other pharmacodynamic effects, and/or detect adverse reactions, and/or study the absorption, distribution, metabolism and excretion of one or more investigational medicinal products in order to determine their safety and/or efficacy.

Depending on the objectives and characteristics, clinical trials are divided into four phases.

The VHIO is responsible for the management, supervision and control of clinical trials conducted by the Oncology Service of the Vall d'Hebron Hospital and promoted by the pharmaceutical industry.

5.1.3. research projects

In the case of biomedical research projects (not clinical trials), they are divided into:

- Publicly funded projects. This category includes all projects financed by the European Commission, the Ministry of Science and Innovation (ISCIII), Education, Industry, Health, etc. Or, projects financed by the Autonomous Community.
- Privately funded projects. Any research project in which the source of funding is a private company.

Biomedical research projects (and this is also applicable to some clinical trials) have a special characteristic, and that is that the results obtained may differ substantially from the initial objectives, but are nonetheless valuable.

Project management includes the planning, organization, monitoring and control of all aspects of the project in a continuous process to achieve its objectives. An effective way to carry out such management is by dividing the project into phases that allow, on an ongoing basis, to assess the degree of compliance with the objectives set and to evaluate the associated risks.

Project results are the achievements at the end of the project. They may be a faithful reflection of the objectives foreseen at the beginning, or exceed them, or fail to achieve them, although in the latter case it does not necessarily imply that the project has not achieved significant accomplishments.

The research project management process must meet the following requirements:

Responsibilities - there must be a responsible person assigned and details of all personnel involved and their roles in it.

Memory - the VHIO must ensure that the Principal Investigator has prepared the Memory of the project, and that this document is under documentation control and versioned. Its minimum contents should be about:

- The objectives pursued by the project and the methodology to be applied to achieve them.
- Innovation of the expected results and state of the art study.
- Protection of ownership of results
- Applicable legislation or regulations.

Planning - the project manager keeps the project schedule up to date, which is divided into phases, tasks and interactions between them. The manager ensures that the number of phases is appropriate to the complexity of the project. The planning also details the persons in charge assigned to each phase, the expected results and the foreseen execution dates/timelines. The person in charge periodically monitors compliance with the planned schedule. If deviations are detected, the causes and impact are documented and, if necessary, the plan is updated by generating a new version of the plan. The reasons for the change are recorded for inclusion in the final project report. The planning activities also include, as detailed in the procedure, the identification and evaluation of risks, establishing a contingency plan to remedy or avoid negative impacts on the development of the project.

Budget - The project budget follows the format established by the project's funding entity. This document includes all necessary cost estimates, specifying how and where resources are obtained, and how they are allocated to the project. The project manager maintains up-to-date information on the dedication of personnel assigned to the project. All costs must be documented and traceable to their origin.

Documentation - Unless otherwise required by the project, all project documentation shall be in accordance with procedure PR_GENER_0001.

Exploitation of results - Usually, the terms and conditions of research projects include the steps to be followed for the exploitation, protection and dissemination of the results expected from the project. This considers whether a new product or process has been identified, the potential market, the type of protection to be applied (patent, utility model, industrial secret), the economic exploitation, the exploitation account and the benefits of the project.

5.1.4. Management and analysis of samples

The laboratories within VHIO's Transversal Technologies area provide the sample analysis services required for clinical trials and research projects carried out by other areas of VHIO or the Hospital's Oncology Service.

In addition, as mentioned above, they can act as a central laboratory for multicenter clinical trials.

The services provided by the laboratories, organization and details are described in their specific Quality Manuals. See MA_GENOM_0001 as the specific Quality Manual for the Genomics Laboratory and MA_PATMO_0001 for the Molecular Pathology Laboratory.

5.1.5. Contract management, collaborations and alliances

The objective of establishing alliances or collaborations can be diverse, ranging from the need for expertise in a given area, to the use of a technology, to technology transfer agreements.

The process of identification, selection, contract negotiation and maintenance of this type of agreements between the VHIO and organizations external to the Institute is treated individually, and there is no standard process, but depends on the characteristics and purpose of the collaboration, the external agent, and other factors.

5.1.6. Resource management human resources

The VHIO has a personnel management area that is responsible for the following functions:

- Selection and recruitment planning and management
- Supervision of contracts and agreements
- Payroll system administration
- Maintenance of personnel records
- Procedures for updating, monitoring and expanding Human Resources procedures.
- Training and Development
- Management of Health and Safety procedures

5.2. Results of the management of the projects

The following is a list of the minimum documentation that every project managed and executed by the VHIO generates:

- Request
- Provisional resolution
- Final resolution
- Acceptance of assistance
- Proof of expenses and payments, such as invoices, delivery notes, purchase orders, etc.
- Economic and scientific justification, included in the annual and final reports.
- Audit reports.
- Investigator's file for clinical trials

The VHIO is responsible for the custody of all the documentation associated with the projects, being the retention period of the same the one marked by the regulations and/or conditions of the project.

5.3. Follow-up and control

5.3.1. Results of research projects

It is crucial for the VHIO to record and document, keeping this information up to date, the research activity carried out and the results derived from it. For this reason, the Institute keeps an updated record of the projects (from any source of funding), the percentage of annual income they represent according to their modality, and a record of the contracts or alliances it maintains in force.

On an annual basis, the ratio between the number of projects subsidized versus those requested, the annual volume of income from projects versus the number of researchers, and the annual volume of income from contracts/collaborations versus the number of researchers are evaluated. All these ratios are used to analyze efficiency and to detect dysfunctions that can be used to implement improvements that will help to obtain better results.

In addition, the VHIO also collects other indicators that allow it to periodically evaluate the following concepts:

- **Visibility.** The indicators considered are:
    - Impact index of publications in which VHIO researchers have been involved and number of them.
    - Awards or other awards or recognitions
    - Annual number of doctoral theses defended by VHIO researchers and the average time taken to complete them.
    - Other mentions.
- **Researcher's activity**. In this case, information will be collected about:
    - Evaluation of the productivity of each researcher in terms of income, theses supervised and publications.
    - Number of researchers who are members of editorial boards of peer-reviewed scientific journals.
    - Positions in scientific societies
    - Patents
- **Final reports**. This section on the results of biomedical research projects includes information about:
    - Number of submissions by the deadline for final project reports.
    - Categorization by type and number of deviations from expected results.
    - Analysis of the possible causes of the deviations
    - Documentary evidence of communication of these results to stakeholders.
- **Mobility of research personnel**. Data is collected on:
    - Number of stays in other national or international centers.
    - Ratio between the number of months of stay of VHIO research personnel in other centers compared to the total number of researchers.
    - Conversely, the ratio between the number of months of stay of non-VHIO research personnel compared to the total number of visiting researchers.
- **Degree of compliance with the strategic lines** established by the VHIO. It is important to evaluate the extent to which the research projects carried out by the VHIO have been aligned with the strategic lines set out in the Plan. For this purpose, the following indicators are used:
    - Continuity of the strategic line over time. It is measured according to whether two consecutive subsidized projects have been obtained in the line, or whether the company is immersed in a long-term project.
    - Relationship between investments in scientific equipment and revenues.
    - Impact of the results of research projects in routine clinical practice.
- **Continuity of research teams**. A research team is considered to have continuity if it maintains its activity for at least two consecutive projects at VHIO.

- To account for the training activity of new researchers.

- **Stakeholder satisfaction**. Data is collected on:

  - Results of the assessments of VHIO's contracting agents. See procedure PR_GENER_0006 for stakeholder satisfaction assessment.
  - Categorization and number of non-compliances of the projects
  - Results of audits or inspections.

5.3.2. Identification and traceability

Traceability is defined as the ability to follow the history, application or location of everything under consideration.

The objective of traceability assurance is to ensure that the level of traceability of the results of research projects is sufficient to adequately identify corrective and preventive actions, as well as to allow verification of compliance with requirements, if applicable, in a bidirectional manner.

Bidirectional is understood as the ability to follow the history of the project in both directions: from the final report to the initial requirements, and from the requirements to the final report.

The aforementioned procedure distinguishes between:

- Traceability of purchased products. Therefore, the PR_GENER_0004 purchasing procedure requires the initiator of the purchase to include in its request the requirements to be met by the purchased product or subcontracted service, as well as the verification of the product/service received.
- Traceability of project activities. The Principal Investigator is responsible for the preparation of the work instructions, specifying or including fields to perform the identification of materials and components, and sufficiently detailing the operations to be performed.

  The research team notes in the work instructions the data required by the instructions and any incidents or deviations from them.
  The project manager includes the identification of the elements up to the applicable level.
- Traceability of activities on the result. The project manager records any activity carried out with the results derived from it (publications, papers, protection or patent application,...).
- Requirements traceability. In order to carry out the requirements verification through the different phases of the life cycle of a research project, it may be convenient to prepare the traceability matrix of the project. This matrix shows the relationship between the requirements and the tests or activities of the project.

5.3.3. Protection and exploitation of results

The exploitation of research results derived from projects carried out by VHIO researchers are channeled through the Institute for analysis.

If such results are susceptible to protection, the Principal Investigator should communicate this fact to VHIO's Direction and/or Management as soon as possible, so that the corresponding procedures can be carried out if such results require protection.

The VHIO must, at all times, rely on compliance with Royal Decree 55/2002, of January 18, on the exploitation and transfer of inventions made in public research entities, in accordance with the provisions of Article 20 of Law 11/1986, of March 20, 1986, on Patents.

5.4. Shopping

5.4.1. Process of purchases

VHIO is the managing and executing body of the research projects (clinical trial or not) carried out by its Investigators. Therefore, purchases to be made in the framework of such projects must be subject to the procurement procedure PR_GENER_0004. This procedure establishes the guidelines and steps to follow for the acquisition of products and services, ensuring legal compliance in terms of publicity and public concurrence, and under the umbrella of the General Law of Subsidies 38/2003, of November 17.

This procedure differentiates between the purchase of materials and the contracting of services for the VHIO, from those purchases intended for the development of research projects, or for the activities of a research group.

Once the need for a purchase has been identified, the requirements must be established and the supplier selection and purchasing procedure PR_GENER_0004 must be followed.

5.4.2. Information from purchases

As mentioned in the previous section, the purchasing process begins when a need is identified. The request for such purchase reflects the information and characteristics of the product to be purchased or the work to be subcontracted. Procedure PR_GENER_0004 details how this information is collected.

It also includes information on the requirements that the product must meet in order to be accepted for purchase, and which will be verified upon receipt. In the case of subcontracting of personnel, the purchase information to be included will refer to the minimum qualification of the requested personnel.

5.4.3. Verification of purchased products

Once the purchased product is received, it will be visually inspected in order to verify the suitability of the product received. In the event that the product requires specific verifications, these must be stated in the purchase request information, as well as who must carry them out.

5.5. Design and development

Sections 5.1 to 5.4 of this document highlight the origin, characteristics, funding sources and legislation applicable to biomedical research projects carried out by the VHIO.

The PRODUCT developed by the VHIO is considered to be each of the research projects carried out. From the previous points it can be deduced that there are no PRODUCT design and development activities, but rather that the VHIO participates in calls for projects already designed, so its participation is the execution of these projects and the obtaining of results.

For this reason, the Design and Development requirements established in the current version of the ISO 9001 standard, section 4.2.2, are excluded from the scope.

6. MEASUREMENT, ANALYSIS AND IMPROVEMENT

The VHIO, through its Quality System, defines, communicates, implements and evaluates the effectiveness of the methods and tools used to measure, analyze and improve its activity in research projects.

6.1. General

As mentioned in previous sections, the VHIO prepares an annual plan. Monitoring activities should be directed towards two evaluations; on the one hand, monitoring compliance with the Plan, and on the other hand, monitoring compliance with the commitments acquired for the implementation of research projects.

6.2. Tracking and measurement

The following sections detail some of the measures adopted by VHIO to ensure the monitoring and measurement of research projects.

6.2.1. Customer satisfaction and researchers

Periodically, and following the procedure PR_GENER_0006 for the evaluation of the satisfaction of the interested parties, the opinion of the clients about the operation of the VHIO and its services is requested. The results of these surveys are analyzed in order to identify areas for improvement, or to open the detected non-conformities according to procedure PR_GENER_0007.

6.2.2. Audit internal

The purpose of VHIO's internal audit procedure PR_GENER_0003 is to specify how internal audits of its quality system are conducted, including planning, definition, data collection, and presentation of results.

The objective of internal audits is to provide a tool for continuous improvement of the quality system, through a systematic evaluation of its adequacy, effectiveness and degree of compliance, and the definition of corrective actions and improvements.

The VHIO's Management is responsible for planning the audits, defining dates, areas and/or processes to be audited, and auditors who will carry them out. It will present the conclusions and recommendations of the audits to the competent body. It will ensure that qualified personnel are available to carry out internal audits, or failing that, it will select external personnel to subcontract this activity.

Prior to the audit, the scope and criteria shall be established and the auditees shall be notified sufficiently in advance of the audit. Management authorizes the audit reports.

In the event that the internal audit is performed by VHIO personnel, the assigned auditor is responsible for preparing it in accordance with the scope set for the audit, preparing questionnaires, setting up interviews, and identifying what documentation will be required during the audit. He collects the data by studying the documentation and questionnaires, and interviews with the personnel affected by the audit. Finally, it evaluates the data obtained in accordance with the predefined criteria, drawing practical conclusions and recommendations, leaving these reflected in an audit report.

Any person involved with the audited processes or areas has the responsibility to collaborate with the auditor in the collection of data.

This procedure requires sufficient auditors with specific training, so that it is possible to audit all areas of the Foundation without anyone evaluating their own work.

The quality managers of areas or laboratories are required to plan their internal audits, which must be included in the annual plan.

6.2.3. Monitoring and measurement of projects

To monitor and measure projects, the VHIO has tools that allow it to analyze indicators and an alarm system for deviations from requirements or planning.

As indicated in section 5.1.1 of this Quality Manual, most of VHIO's research projects come from external calls for proposals, whether public or private.

The intrinsic characteristics of biomedical research projects make it clear that most of the commonly used project management standards do not apply.

In a biomedical research project, we cannot establish a priori time milestones since obtaining results is closely linked to experimental observation. Then, follow-up measures are established based on compliance with the presentation of the scientific and/or economic progress reports required by the call for proposals.

VHIO's Research Support Office ensures compliance with the schedule for the submission of reports, requiring the Principal Investigator of the project to provide the scientific information to be included.

The success of a biomedical research project cannot be measured by the results themselves, but by the impact they have on the improvement of people's health or their contribution to the advancement of science. In this sense, the following are considered:

- Publications derived from research results, taking their impact factor as an indicator.
- Filing applications and obtaining patents.

The case of clinical trials deserves a separate mention, since in this type of project there are detailed schedules and plans included in the *Investigator File* of the project and the responsibility for updating them usually falls on the study sponsor, not on the Principal Investigator of the study. Therefore, they are not considered in the scope of this section.

6.3. Control of deviations

The VHIO has a spreadsheet managed and maintained by the Institute's quality manager to manage deviations. See SOPs PR_GENER_0007 and PR_GENER_0002.

6.4. Analysis of data

The VHIO has data and information whose sources are the results of stakeholder satisfaction surveys, the assurance of the traceability of project requirements, and the results derived from them, which allow it to demonstrate the effectiveness of the system, or in the absence of such demonstration, allow it to identify points for improvement.

6.5. Improvement

VHIO's quality system has been implemented in a way that allows the identification of problems and the improvement of its effectiveness through the results derived from analysis tools (internal audits, satisfaction surveys, etc.).

6.5.1. Continuous improvement

Any VHIO staff member or associated researcher may identify a possible system nonconformity, or a request for improvement, in which case he/she communicates it to the Institute's Quality Manager.

If the request is rejected, the reason for the rejection must be recorded and reflected in the nonconformity or change request closure report, and communicated to the initiator.

Note: *This identification can occur at any time during the VHIO's activity. However, it is formalized when performing internal or external audits (through audit reports), or as a result of evaluation and follow-up activities.*

The identification of a nonconformity, regardless of the means of entry, involves the investigation of its cause to determine whether corrective action is required to remedy the deviation, or, if it cannot be remedied, improvements can be made by including preventive actions to avoid its repetition in the future.

The management and treatment of corrective and preventive actions are described in the following sections, and in detail in procedure PR_GENER_0002.

6.5.2. Corrective actions and preventive actions

The Management, or its delegate, evaluates in its reviews of the quality system, the possibility of opening corrective and/or preventive actions as a consequence of such nonconformities or improvement requests, as well as based on the quality objectives set. See SOP PR_GENER_0002 for details of the process.

Management should include in its reviews of the system an assessment of the effectiveness of the actions taken, based on the data provided by the system manager.

7. REFERENCES

	Document
[1]	ISO 9000, in its current version, Quality management systems: fundamentals and vocabulary.
[2]	ISO 9001, in its current version, Quality management systems: requirements
[3]	ISO 15189, in its current version, Clinical laboratories. Particular requirements for quality and competence
[4]	ICH E6 Good Clinical Practices
[5]	Document de treball Requisits EC phase I actualització 2014 Proposta 02-12-2014 versió Generalitat de Catalunya, Departament de Salut, Direcció General d'Ordenació i Regulació Sanitàries (Generalitat de Catalunya, Department of Health, Directorate General of Health Planning and Regulation)
[6]	RD 1090/2015 regulating clinical trials with medicinal products.