

HANDBOOK

QUALITY PRACTICES  
IN BASIC BIOMEDICAL  
RESEARCH



World Health  
Organization

Special Programme for Research & Training  
in Tropical Diseases (TDR) sponsored by  
UNICEF/UNDP/World Bank/WHO





Special Programme for Research and Training in Tropical Diseases (TDR)  
sponsored by UNICEF, UNDP, World Bank and WHO

# HANDBOOK: QUALITY PRACTICES IN BASIC BIOMEDICAL RESEARCH

Prepared for TDR  
by the Scientific Working Group on Quality Practices  
in Basic Biomedical Research

# ACKNOWLEDGEMENT

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This handbook is designed to address the very important topic of quality in basic biomedical research. The quality practices outlined in this handbook provide the basis for a non-regulatory quality management system, which if applied properly, will enable institutions and individuals to produce credible research data. The quality management system is designed as an aid to research institutions and individual researchers wishing to improve the quality of their research data.

The existing draft Handbook on quality standards in basic biomedical research (2001). was reviewed by a specialist working group, convened by UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), consisting of scientists from around the world. An editorial group was mandated to write the current document based on comments from the working group. The revisions and additions suggested by the working group have been integrated into this current, expanded Handbook on quality practices in basic biomedical research (QPBR)..

The quality management system outlined in this Handbook will provide institutions and researchers with the necessary tools for the implementation and monitoring of quality practices in their research, thus promoting the credibility and acceptability of their work. The handbook highlights non-regulatory practices that can be easily institutionalised with very little extra expense.

TDR gratefully acknowledges the participation and support of all those involved in the production of this Handbook. Special thanks go to the editorial group, Nadya Gawadi, David Long and Jürg Seiler for their dedication and immense contribution.

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## FOREWORD

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This document is the revised version of the draft handbook *Quality standards in basic biomedical research* (TDR/PRD/QSBR/01.1), published in 2001. The draft handbook was based on the deliberations of a specialized scientific working group (SWG) convened by the UNDP/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases (TDR).<sup>1</sup> The SWG, composed of independent scientific experts, met in Geneva 4-6 September 2000 to discuss various aspects related to Good Laboratory Practice (GLP) and sound scientific working practices. They concluded there was a pressing global need for dissemination of information and guidance to cover basic biomedical research.

To this end, the draft document – a preparatory guide outlining the quality standards required in disease endemic countries for basic biomedical research – was produced. This preliminary publication was intended to serve as a working document, the first step towards developing an agreed set of guidelines on quality practices for basic biomedical research. It was circulated internationally to scientists and researchers involved in research on new strategies for preventing or fighting disease, including the development of new drugs. Comments and suggestions were canvassed with a view to incorporating feedback into a revised, final document.

To prepare this final document, an editorial group was put together to collate all the comments received in response to the draft document and to prepare a draft of the final document. The document was then discussed by a group of experts from a wide range of scientific disciplines at a review meeting in Geneva, 25-26 January 2005. The objectives of the review meeting were to:

- review the draft final document for content, scope and coverage of all important aspects
- review the appendices for suitability and applicability

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<sup>1</sup> Now the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases



- make recommendations for the publication of a final document, which was given a new title: *Quality practices in basic biomedical research*.

The quality practices for basic biomedical research described in this document do not address the scientific content of a research programme or proposal, but are concerned with the way the research work is managed.

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## SCOPE AND PRINCIPLES

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Basic biomedical research refers to the use of fundamental scientific principles in medical and biological research directed towards developing tools to detect, prevent or treat human disease. Basic biomedical research is commonly encountered in the discovery and exploratory stages of product/drug development. This type of research is not yet covered by any agreed national or international regulations and guidelines. Since production of credible research data can only be ensured by compliance with sound study management, the proposed ‘quality practices’ are concerned with the organizational, managerial and practical aspects of basic biomedical research. This handbook is a companion volume to the TDR handbook on quality practices for regulated safety research.<sup>1</sup>

This current handbook offers guidance and tools for the practical management of basic biomedical studies, ensuring that ideas are translated into action, and that ensuing information is accurately captured in order to enter the public domain.

The handbook:

- Defines basic biomedical research in the context of drug development and existing regulations and quality systems.
- Examines the organizational and practical framework for basic biomedical research studies irrespective of type (drug development or other fields of health research).
- Examines the role of prescriptive and descriptive documentation.
- Discusses how to record, report, review, archive and publish results in order to bring them into the public domain.
- Covers ethical concerns and biosafety.

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<sup>1</sup> TDR. *Handbook: Good Laboratory Practice. Quality practices for regulated non-clinical research and development*. Geneva, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), 2001 (TDR/PRD/GLP/01.2).

- Provides templates for standard operating procedures (SOPs), curricula vitae and training records, and some sample SOPs.

It is hoped that wide application of the quality practices proposed in this handbook will lead to cost-effective, accelerated discovery research and will ultimately benefit human health.

# 1. INTRODUCTION TO QUALITY PRACTICES IN BIOMEDICAL RESEARCH

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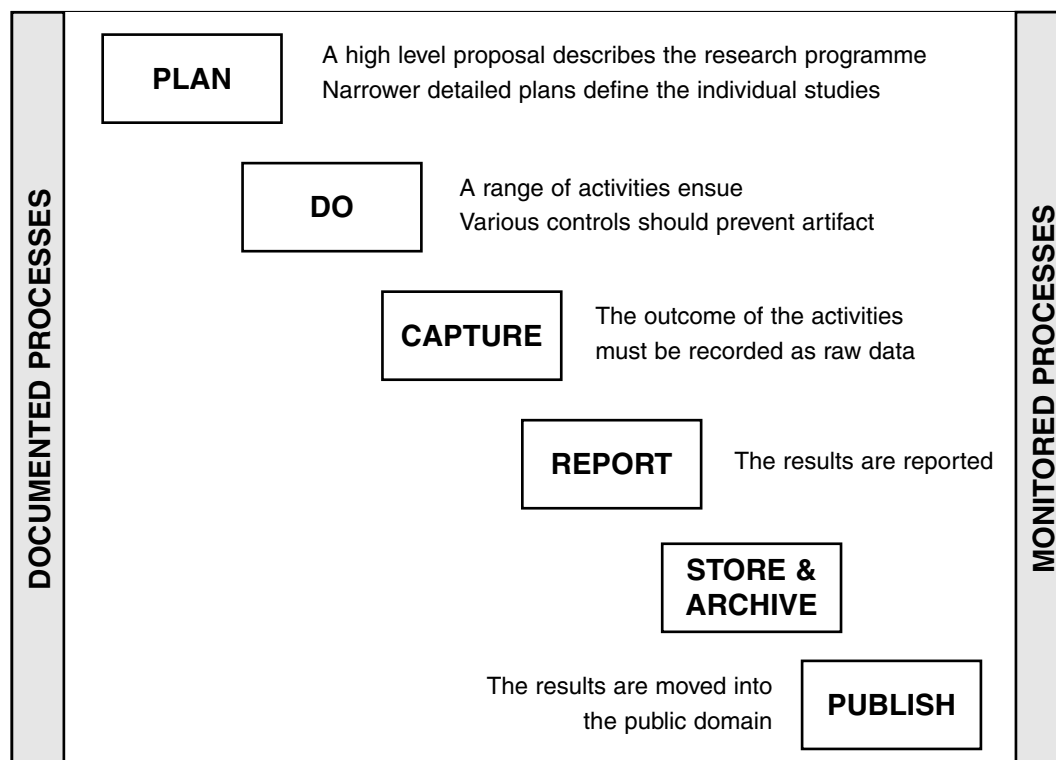
The world's population is facing serious health challenges in the form of newly emerging diseases or disease patterns e.g. avian influenza, severe acute respiratory syndrome (SARS), transmissible spongiform encephalopathies (bovine spongiform encephalopathy, Creutzfeldt-Jakob disease), human immunodeficiency virus (HIV), Ebola, and multidrug resistant diseases or organisms such as malaria. There are increasing difficulties in treating 'old' diseases such as trypanosomiasis, onchocerciasis, diabetes, hypertension and cancer. The problem is worsened by the changing age distribution in populations, greater population movements that promote transmission of diseases, new practices in land use, agriculture and forestry, and changing world climate, to name but a few. As a result, there is increased demand for new drugs and new principles for treatment, based on new knowledge about the causes and mechanisms of diseases, and for new methods of vector control. The search for these commodities and principles increases the need for scientific researchers and research programmes. With the continued restrictions in available funding, it is essential that basic scientific research as a whole, and especially in all fields connected with health issues, be conducted in a proper fashion using processes that minimize waste of resources and reduce the need for costly confirmation and repetition of work already performed.

Today, research facilities in many universities, hospitals, government institutions and industries are used for basic scientific studies relevant to the discovery and development of new strategies for fighting disease including products with potential usefulness in health care. Data from these activities need to be reliable to ensure a solid basis for deciding whether to invest in further development of a strategy or product. Since the activities fall outside regulatory scope, i.e. they are not covered by, for example, the Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (GLP), a need for guidance on quality practices in these areas has been recognized. This is why this handbook was commissioned.

It should not be surprising, therefore, to find that some controversies in the scientific literature could probably have been resolved earlier, more easily and better if the practical experimental conditions had been fully described, or if the supportive data had been properly collected.

It must be stressed here that the quality practices for biomedical research described in this document do not address the scientific content of a research programme or proposal, but are concerned with the way the research work is organized and planned, performed, recorded, reported, archived, monitored and published. Figure 1 sketches the main steps in this process.

Figure 1. Flow of research activities



Usually biomedical research is first outlined in a research proposal and then described more fully in individual study plans or protocols explaining why and how the experimental work will be undertaken. It is clear that if the basic underlying conditions of the experimental set-up are unclear or poorly documented, and if the raw data are incomplete, there may be fundamental doubts about the validity of the knowledge obtained and its contribution to science. The application and use of sound scientific principles in the conduct of basic exploratory and discovery studies, coupled with an attention to good quality practices, will optimize transparency in data and reporting. The availability of clear evidence will facilitate the choice of new strategies for pre-

venting or fighting disease, including the choice of new drug candidates for further development. Not only will investment in the wrong candidate waste resources and time, but it will also block capacity that could have been used for developing a more promising candidate.





## 2. WHAT IS BASIC BIOMEDICAL RESEARCH?

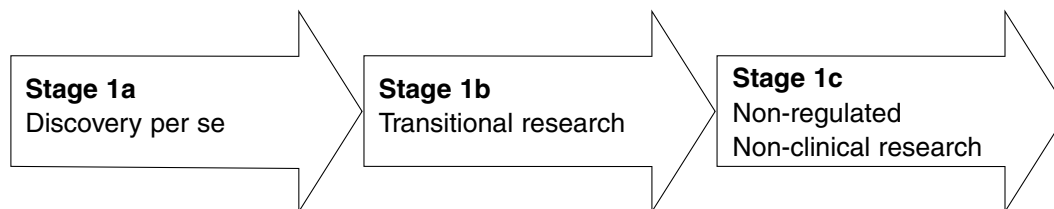
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Basic biomedical research refers to activities intended to find means of detecting, preventing or treating human disease. Such research covers the discovery and exploratory studies that precede the regulated phases<sup>1</sup> of drug development or programmes to develop other methods of disease control. These later stages of biomedical research are time consuming and require vast financial, human and technical resources; this is true whether new basic principles are being established or new drug candidates developed.

### 2.1 Basic biomedical research: drug development model

The candidates for further development come from the first R&D stage in basic biomedical research, often called 'discovery'. This discovery stage can be further subdivided into three: discovery per se, transitional research, and non-regulated non-clinical research (see figure 2). In table 1, the contents of each stage are illustrated by reference to three examples.

Figure 2. The three stages of basic biomedical research in drug discovery



<sup>1</sup> The regulated stages are:

- the non-clinical stage to establish drug safety
- the clinical stage to establish safety and efficacy in man
- the post-approval stage where the drug is monitored for safety, and its production carefully controlled.

For a brief account of basic biomedical research in the context of the regulated drug development process, and the quality practices appropriate to regulated stages, see Appendix 2.

### 2.1.1 Stage 1a: *discovery per se*

During this stage, the researcher identifies a possible new drug candidate. To begin with, the researcher notices signs that a compound may have therapeutic potential and finds ways to establish whether or not it is a fruitful lead to follow. The idea for the compound may come from direct observation, scientific literature, knowledge of traditional practices, or systematic screening. It is unlikely that the research progresses smoothly; the researcher will probably meet many dead ends and collect many inconclusive results. The researcher may not be able to formulate a testable hypothesis or make a firm plan (see table 1).

### 2.1.2 Stage 1b: *transitional research*

During this stage, the researcher tries to characterize the active pharmaceutical ingredient (API) and starts to investigate how to produce and analyse it, while continuing focused biological experimentation to investigate its actions in cells, tissues or the whole body (see table 1).

### 2.1.3 Stage 1c: *non-regulated, non-clinical research*

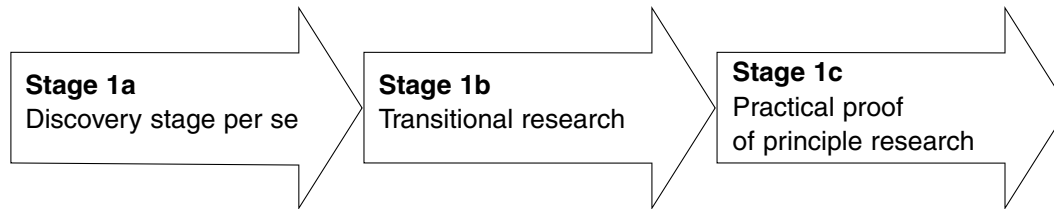
During this stage, biological tests on subcellular systems, tissues and/or whole animals provide evidence for efficacy – i.e. ‘proof of principle’(POP). These are rigorously controlled studies with biological models. They are needed to indicate whether the compound is biologically active, and whether it is likely to be efficacious in man, before time and resources are invested in the formal, expensive and regulated stages of drug development. A sufficient supply of well-characterized test compound has to be ensured (see table 1).

Thus this stage provides non-clinical proof of principle (not to be confused with non-clinical safety or clinical studies – see appendix 2).

## 2.2 Basic biomedical research other than drug development

Even if the research does not concern drug discovery and development, the stages are analogous, as illustrated in figure 3. In the discovery stage, ideas are formulated and tested by observation or experimentation. The contents of each stage of basic biomedical research for products other than drugs are illustrated by three examples in table 2.

**Figure 3. The three stages of basic biomedical research for products other than drugs**



### 2.2.1 *Stage 1a: discovery stage per se*

During this stage, observations verify that there is a phenomenon worth pursuing.

### 2.2.2 *Stage 1b: transitional research*

Having studied the available literature, the researcher attempts to formulate the causal relationships in his conceptual model of the situation in order to prepare the relevant experiments for stage 1c.

### 2.2.3 *Stage 1c: practical proof of principle (POP) stage*

Here the researcher demonstrates, in the experimental model, that the right relationships have indeed been identified. The researcher may also include the first studies to show the potential applicability of these insights as practical methods for disease control, prevention or cure. However, here the practical proof of principle stage does *not* include animal or field studies to demonstrate safety, nor any clinical studies that involve dosing or other interventions in man – these belong to the later stages (see appendix 2).

Table 2 provides examples of stages 1a, 1b and 1c.

**Table 1. Examples illustrating the three stages in basic biomedical research for drug candidates**

	Stage 1a
Example A	<p>A researcher suspects that one of the body's own macromolecules might be exploited to alleviate a progressive, crippling condition, common throughout the world. In the discovery stage the researcher makes efforts to establish whether this is a reasonable idea, and how the molecule might function. He/she finds out how to obtain a supply of the molecule for the next stages of research.</p>
Example B	<p>A researcher knows that a population traditionally uses a local herb to alleviate an affective disorder. But the herb contains dozens of interesting compounds, of which several might be the active principle. The researcher needs to establish whether only the herb is used, or whether other methods or drugs are used simultaneously. The herb is identified, and its habitat mapped. It is very difficult to establish at this stage whether the herb is effective or whether the population is enjoying a placebo effect. Although an observational study might be relevant at this stage, it is important to emphasize that this is not the right stage for a clinical study.</p>
Example C	<p>A large company with expertise in psychiatric disorders routinely screens many thousands of potential compounds from a 'drug library' shared with a neighbouring company which has expertise in another field. The screening programme is designed to detect molecules with a good 'fit' to the target receptors, and dozens are found each week. A database is used to list and profile the promising candidates, and further cheap screening tests are used to narrow the field further.</p>

Stage 1b	Stage 1c
<p>A universal problem arises: the body's own molecules quickly enter the body's own metabolism and do not remain at therapeutic levels long enough to be effective. The researcher might reason that if the molecule is modified by adding side chains, the extra bulkiness might slow its breakdown or elimination, extending the period of therapeutic activity. Activities at this transitional stage include finding the optimal number and type of side chains, and optimizing methods for production and analysis. The researcher experiments with possible formulations. There are also biological tests to establish binding properties and other characteristic.</p>	<p>Kinetic studies in intact animals provide evidence that the modified molecules stay longer in the body. Receptor binding studies might show that the molecule targets the right cells or tissues. An animal model may be used to test potential efficacy.</p>
<p>Having isolated the most promising active pharmaceutical compounds (API), the researcher further explores the biological activity in cell, tissue and/or animal models. He/she investigates whether to extract the compounds or whether to produce them chemically or by biotechnological methods. Further research includes optimizing methods for producing and analysing the compounds, as in the previous example.</p>	<p>Receptor binding studies and animal behavioural models are most useful for establishing potential for efficacy.</p>
<p>Having identified the most promising active pharmaceutical compounds (API) from the extended screening, the company explores the biological activity in cell, tissue and/or animal models. The company investigates how to produce the compound in quantities suitable for further testing. Further research includes optimizing methods to analyse the compounds, as in the previous example.</p>	<p>Receptor binding studies and animal behavioural models are most useful for establishing potential for efficacy.</p>

**Table 2. Examples illustrating the three stages  
in basic biomedical research for products other than drugs**

	Stage 1a
Example X	The researcher has noticed a relationship between the health of a population and their water supply, in comparison with a neighbouring population that enjoys better health. The researcher verifies, in an epidemiological study, that the health status really is different from that of the neighbouring group.
Example Y	A community needs to find the cause of an unusual pattern of neurological disease. <sup>2</sup> The prevalence of the neurological problem is mapped, verifying that the prevalence is higher than expected.
Example Z	A researcher suspects that the behaviour of an invertebrate vector is genetically controlled, and that it is possible to reduce the mating success of the vector by changing the genome. <sup>3</sup> The researcher attempts to map the genomes of the vector and a similar invertebrate with different behaviour.

<sup>2</sup> Sacks O. *The island of the colour blind*. Book II: *Cycad Island*. New York/Toronto, Alfred A. Knopf, 1997.

<sup>3</sup> Demir E, Dickson BJ. fruitless splicing specifies male courtship behavior in *Drosophila*. *Cell*, 2005, 121(5):785-794.

Stage 1b	Stage 1c
Is the problem really the water? The researcher decides what parameters to measure, and how to demonstrate causality. The researcher considers practical solutions to the problem.	The researcher demonstrates, using the experimental model, that the causal relationship has been identified, and perhaps includes the first studies to indicate the applicability of this insight as a practical method for disease prevention.
The researcher decides what to examine in the way of causal factors, e.g. diet, heredity, pollution. How will the assays be set up, and how will the suspected culprit be tested?	The researcher demonstrates, in an experimental model, that the right factor has been identified, and perhaps includes the first studies to show how to avoid or control the problem.
The researcher considers how to identify the relevant genes, and how to associate them with the mating behaviour.	The researcher demonstrates, in an experimental model, that the right genes have been identified, and perhaps includes the first studies to show that modified mating behaviour can be used as a practical method of disease control.





### 3. WHAT IS QUALITY IN RESEARCH ?

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There are two aspects of quality in research: a fundamental scientific aspect, and a practical experimental aspect. When the underlying science is wrong or the working hypothesis is ill conceived, the results obtained by even the best conducted experiments will not lead to a true advance of knowledge. On the other hand, even the best science, the most brilliantly reasoned working hypothesis, will not return results and answers that are acceptable to the scientific community if they are not supported by flawlessly conducted (i.e. high quality) experiments.

The matrix below explains how the quality of research and the quality of science are interrelated.

**Table 3. How sound scientific principles and good quality practices contribute to the credibility of results**

	Sound scientific principles	Good quality practices	Credibility of results
Scientific study 1	No	No	No
Scientific study 2	No	Yes	No
Scientific study 3	Yes	No	No
Scientific study 4	Yes	Yes	Yes

It is often claimed that science is self-policing in that research proposals and results are exposed to the scrutiny of peers, and are challenged by attempts to repeat and verify the experiments. However, the extent to which this process ensures the integrity of research and its results has been questioned. Broad and Wade<sup>1</sup> described many instances where spurious results were published and survived for some time. They traced the anomalies to organizational practices within the scientific endeavour itself. But also outright

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<sup>1</sup> Broad W, Wade N. *Betrayers of the truth. Fraud and deceit in science.* Oxford University Press, 1982.

fraudulent machinations and manipulation of data may not be ruled out, as recent experience and some highly publicized cases have shown. A group of scientists from the American Institute of Medicine<sup>2</sup> therefore recommended closer surveillance of scientific activities in order to assure reliability of new scientific results, and a Danish group<sup>3</sup> came to similar conclusions. Both groups called for clear organization of work, clear definition and allocation of responsibilities, close supervision of scientific work, good data recording practices, good facilities for data storage and retrieval, and proper training of scientists and other staff.

This handbook is intended to guide scientists in how to organize their research and add value to it by promoting the credibility of their data. It should be possible for peers, scientific journals, development partners, or authorities to audit studies to verify authenticity and reliable reporting of results, and this would help to validate the data and make the results acceptable to the scientific community at large, making it more likely there will be commensurate returns on the investment. The scientific community also needs to be able to repeat studies in order to confirm the knowledge and build further research on the results.

Normally quality is defined as “the totality of characteristics of an entity ... that bear on its ability to satisfy stated and implied needs”.<sup>4</sup> It is clear that there is a need to obtain research results that are solid enough to enable development of useful products and principles for fighting diseases. In order to fulfil these needs, scientific research must deliver results that are:

- Relevant
- Reliable and reproducible
- Ethical
- Auditable
- In the public domain.

These guidelines endeavour to put practices in place to ensure that results with these characteristics are achieved.

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<sup>2</sup> Institute of Medicine. *Report of a study. The responsible conduct of research in the health sciences*. Washington DC, National Academy Press, 1989.

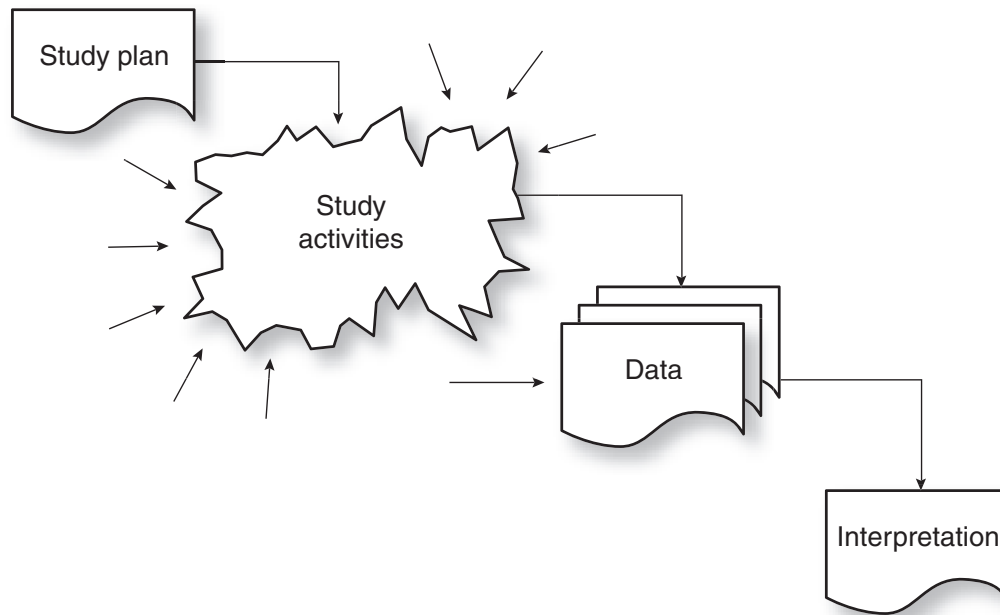
<sup>3</sup> Andersen D et al. *Scientific dishonesty and good scientific practice*. Danish Medical Research Council, 1992.

<sup>4</sup> ISO 8402: 1994: Quality management and quality assurance – vocabulary. *International Standard* 2<sup>nd</sup> edition, 1994.

### 3.1 Relationship between study and data

Scientific activity must generate reliable data. Figure 4 shows the relationship between plan, experiment, data and interpretation.

Figure 4. Study plan, study activities, data, interpretation (arrows denote variables likely to influence data integrity).



Meaningful scientific interpretation of study results is only possible when founded upon reliable data. Clearly, in order to obtain reliable data, the experimental variables that always affect studies must be kept under control. Quality practices are designed to help scientists control the variables. Such an approach is the only way to obtain reliable results and sound scientific interpretation, and to avoid being dogged by 'false positives' and 'false negatives'. This reasoning explains why best practices attach so much importance to precise planning (through the written study plan or protocol) and to use of standardized techniques (by following previously written standard operating procedures).

Where there is an experimental set-up, the scientist must put effort into planning and setting up controls or control groups. If the experiment involves exposing animals or in vitro systems to demonstrate pharmacological activity, a vehicle control must be

included as a minimum. The inclusion of a positive control is recommended as proof that the set-up is working. If the experiment includes analytical assays, the samples must include blanks and known quality control (QC) standards.

All sources of bias in the experimental or assay set-up should be explored and, if possible, brought under control. All influences and inputs to the study must be considered before the activities begin.

If the study is a purely observational study of events as they happen, without any intervention, information on the physical or social setting is vital for understanding the results. It is important to plan which parameters to study, to ensure a systematic and continuous record. Needed are: date, time, precise place, identity of the collector, the study ID, and the conditions which make each observation relevant and valid. For example, if you are comparing the behaviour of insects in different locations, you have to know whether you are comparing the same or different species before collecting the main body of data, and you need to define what constitutes the interesting differences in habitat. Or, if you wish to compare a group of people who visited a practitioner of traditional medicine with a group visiting a modern hospital, you have to check thoroughly the therapeutic practices at each location before starting observations.

In all cases, it is wise to obtain the advice of a statistician in order to collect enough data to be able to compare the results between groups and draw conclusions. The statistician will also advise on choice of appropriate statistical tests for the amount and type of data anticipated.

### **3.2 Data, records and report**

The account of the experimental surroundings, set-up and preparations is as vital to the understanding of results as are the results themselves. The study plan must include methods for limiting bias and sources of error. The records must contain descriptions of the whole experimental set-up, or the conditions for collecting specimens, or the conditions for the observational study. The data must be fully identified with respect to time, place, study identification and collector, and be followed and checked throughout processing and presentation. Finally, the report must contain descriptions of these aspects.

### 3.3 Reproducibility

Reproducibility is one way of testing the reliability of data. This means that if the investigator or someone else were to repeat the experiment in the same set-up, equivalent data would result. Or if specimens were collected in the field, another visit to the same or a similar habitat at the same time of day/year would yield a similar collection. Since especially significant, valuable or controversial findings often require confirmation by repeating a study, all studies should be designed, managed, controlled, recorded and reported sufficiently to ensure reproducibility of the findings.

### 3.4 The purpose of quality practices

The practices outlined below are intended to increase the likelihood that – provided the research has a scientific basis and the hypothesis is testable – research activities will generate reliable data suitable for publication and perhaps for further research aimed at detecting, preventing or treating disease. The use of quality practices should reduce the risk of obtaining inconclusive results on account of uncertainty about controls or because of unclear procedures. The use of quality practices should also change attitudes to certain aspects of research management that are not widespread today: routine supervision, review and audit, as used to confirm authenticity and veracity of results.



## 4. THE QUALITY PRACTICES IN BASIC BIOMEDICAL RESEARCH

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### 4.1 Organization

#### *4.1.1 Quality policy and staff responsibility*

It is essential for each research institution to have a written policy statement describing the quality practices to be applied by all personnel in the conduct of experimental work, irrespective of its nature. This statement need not be lengthy – it could for example just refer to this document. The policy statement would be supported by written guidelines outlining responsibilities at the different organizational levels. The administration (director) of the organization should be visibly and fully supportive of these measures, and should implement mechanisms for their application, exercising at least some level of control over them.

Responsibilities should include at least those in table 4.



Table 4. Matrix of responsibilities, roles and activities in basic biomedical research

	Organizational role <sup>1</sup>	Responsibility
Responsibility for scientific activities	Director of organization	Policy, provision of resources of all types, budget, supervision of activities.
	Head of department	Use of resources, supervision, advice and support for junior staff, compliance with institutional policy and WHO practices.
	Principal scientist (sometimes called principal investigator (see appendix 1))	Conduct of study, scientific interpretation of study results, veracity of study data.
	Technician	Performance of procedures as required in study plan and SOPs, or other instruction.
	Other support staff	Fulfil duties according to instruction.
	Peer	Scientific analysis and collegial criticism.
Responsibility for review of scientific activities	Quality assurance (QA) personnel <sup>2</sup> (if relevant)	Assist in implementation and maintenance of quality practices. Help to assure the authenticity, traceability, and consistency of data, and compliance with WHO/TDR quality practices.
	Management	Ethics committee. Ethics manual for the institution.
Ethics	All personnel	Compliance with the ethics manual.

<sup>1</sup> The intention is to present the minimum roles necessary for implementing the TDR quality practices. Actual jobs and positions, e.g. student, researcher and lecturer at different levels, would be mapped into these roles for the purpose of allocating responsibilities. For example, it would be possible for someone with the rank of professor, or with the rank of PhD student, to take the role of principal scientist. The principal scientist may in reality also be the head of department. In a very small team, one person may be filling the roles of head of institute, departmental leader, principal scientist and technician. The principal scientist plays the key role in ensuring study quality, in the sense that a study cannot be performed without a principal scientist.

<sup>2</sup> This role is becoming more widespread at research institutions, but is by no means universal or compulsory. Quality assurance personnel take an active role in implementing and maintaining quality measures, and, through their auditing activities, keep management informed of the level of compliance to quality requirements.

This model can be adapted to suit the needs of a small team or an individual researcher – see appendix 10.

**KEYNOTE****Quality policy and staff responsibility**

- The research institution should establish a written policy describing its quality practices.
- The responsibilities of each level of personnel should be defined and documented.

#### 4.1.2 Personnel and training

The organization's administration should ensure that the responsibilities of staff at *all* levels are defined and documented in job descriptions. Aspects to be considered are: scientific field of activity, practical duties, supervisory duties/delegation, administrative and financial responsibilities, communication, and keeping knowledge and skills up to date. There must be sufficient financial support for education and training activities.

While it is important to ensure that all staff are knowledgeable and well versed in the relevant quality aspects of experimental work, including planning, recording and reporting, this is especially relevant for tutors, PhD students and postdoctoral fellows in university settings. These staff members should be responsible for full application of the quality practices required by the institution and should not deviate from these. This requirement also holds for any institution where new staff are employed on a temporary, project-related basis.

Qualifications and training should be adequate for the activities that each person is to carry out. At the time of recruitment, management should verify the authenticity of the qualifications documented in the curriculum vitae (CV) by, for example, contacting named referees or checking on publications. While at the institution, staff may become further qualified through a structured course of study and may be awarded a diploma or degree from a recognized academic institution. These qualifications must be suitable for the type of research envisaged and should be documented in the person's CV, be verifiable and kept up to date.

Training is necessary for all staff (at all levels) to prepare them for using specialized or new techniques. Such training should be offered routinely; it will help to keep the

general level of expertise at the research institution up to date. Remember that training should be completed before practical activities start. This training should also be documented in separate training records held by the institution.

#### KEYNOTE

##### Personnel and training

- All personnel should have written job descriptions.
- All study staff must keep their CVs up to date.
- Training records of all staff members should be kept up to date.

## 4.2 Physical resources

The research institution's administration is responsible for providing facilities of suitable size, construction and location, and for providing suitable equipment to meet the requirements of the research programme and its individual studies. Fulfilling the requirements of the study does not necessarily mean that state-of-the-art constructions or equipment have to be provided. Instead, the institution's administration, in cooperation with the leader of the research group or the principal scientist, must carefully consider the objectives of the research programme, including its individual component studies, and decide how to achieve these with the facilities and equipment available in the local environment. Special attention should be paid to any risks for study integrity that could originate from the close proximity of different activities and studies; care should be taken to minimize any potential interference with the validity of the study, especially regarding the risk of confusion and mix-ups (of studies, test systems, test items, data) or cross contamination (for example, between chemical compounds or strains of micro-organisms). The purpose of such requirements is to ensure that the individual study is not compromised because of inadequate facilities or equipment.

All equipment should be suitable for its intended use both in the laboratory and the field. The actual choice of equipment will be based upon the scientific requirements for accuracy, precision, robustness and measurement interval. This choice is a scientific task and will be made by the institution's scientific management. It is good practice to draw up user requirement documents or specifications for equipment before purchase.

Once acquired, equipment must be properly calibrated and maintained, if necessary by a qualified and certified agent, to ensure accurate and consistent performance and to ensure that measurements are comparable to those from other laboratories. Calibration of balances is a good place to start (because one can follow up by calibrating volumetric equipment). Typically, the institution has a set of standard weights with which to calibrate the balances – at least once a year (secondary calibration). If there is an accredited standardization organization in the country, representatives check the institution's standard weights once every three years (primary calibration). In addition, daily checks with one standard weight will ensure validity of the weighing. Other equipment is calibrated in a similar way. It should be noted that equipment, adequately calibrated in laboratory conditions, may no longer be calibrated when transported into field conditions, and will routinely need rechecking before use.

Records of repairs, routine maintenance and any non-routine work should be retained. This is to ensure the reliability of data generated and to prevent loss or corruption of data as a result of inaccurate, inadequate or faulty equipment.

#### KEYNOTE

##### Physical resources

- Facilities must provide adequate protection in order to avoid putting the studies at risk through mix-ups, confusion, or cross contamination.
- Equipment must be suitable for use in the study; suitability should be supported by documentation.
- A calibration and maintenance programme for equipment must be established, documented and maintained.

### 4.3 Documentation

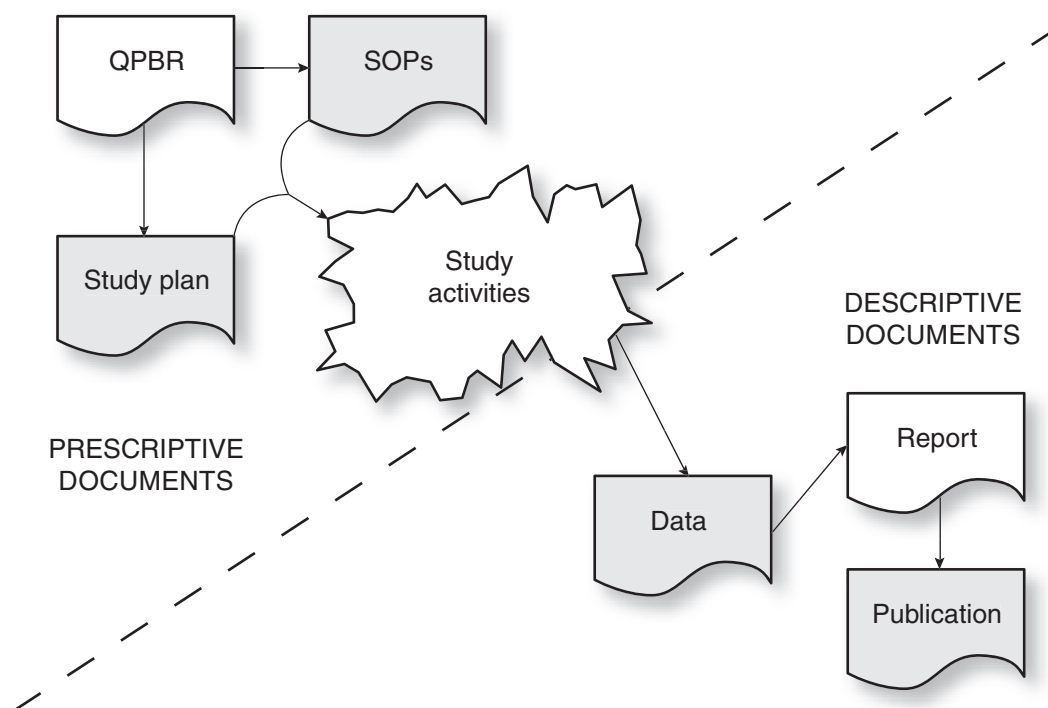
Making a full record of all information is essential not only to permit appropriate scientific interpretation of the results but also to enable complete reconstruction of the study, should this be necessary. Documentation is the only way of demonstrating what actually went on at the time of the experiment. *Without documentation the process is meaningless; essentially there has been no study.* As well as containing the data generated,

the study records must prove that all the required procedures were correctly carried out at the stipulated time. If complete records are not made, the study validity is compromised. Missing data suggest that either the procedure concerned was never performed or that the data have been lost. In either case the study is seriously compromised and may have to be repeated from scratch. Documentation may be divided into two broad classes:

- *Prescriptive documents* that give instructions as to what is to happen during the course of a study.
- *Descriptive records* that describe what actually happened during the course of the study.

Figure 5 illustrates the relationship of prescriptive and descriptive documents to one another and to the study activities.

**Figure 5. Prescriptive documents, study activities and descriptive documents**



Prescriptive documents include research proposals, study plans and standard operating procedures, and are a preparation for practical activities. Descriptive documents include raw data, any derived data, study reports and publications. For example, the

dosing instructions in a study plan are prescriptive – they do not constitute proof that the animals were dosed. One has to make specific records to show that this was the case – these are descriptive.

Appendix 9 shows another way of presenting the hierarchy of prescriptive and descriptive documents, setting them in context with training as the means of translating written instruction into managed activity.

#### KEYNOTE

##### General documentation

- Research institutions should maintain both ‘prescriptive’ and ‘descriptive’ documents.
- Research institutions should ensure that there are full records of all study activities, sufficient to provide complete study reconstruction.

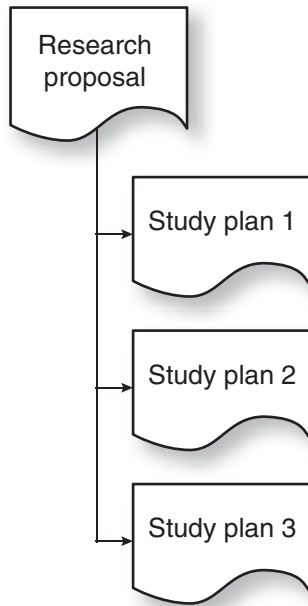
#### 4.3.1 *Prescriptive documents: research proposals and study plans*

In basic research, a study, or a set of studies, is usually outlined as part of a research proposal. A research proposal is a document outlining 1) the scientific context, 2) the overall objectives, and 3) the scope (or thrust) of a research programme. Although the proponent, usually a research scientist(s), is responsible for the scientific content of the proposal, all research scientist(s) responsible for running the programme must be indicated in the proposal. The proposal should also outline the main stages in the research or, in the case of a large programme, describe the individual component studies and indicate the general timeframe of each study in the overall programme. Normally a review board or the management within the institution approves the document, since human and financial resources have to be found to support the work. It is essential that each research institution has a policy or guidelines describing the generation, review and approval of research proposals. Most grant-giving organizations provide an application form to guide the contents and layout of the proposal.

The study plan (or study protocol) is a document describing in detail the proposed conduct of an individual study. Because it is the key document for communicating the intentions of the study to all contributing staff and sponsors, its contents and layout should be clear. Every study must therefore have a plan which is in line with the overall objectives of the research proposal.

For clarity, the research institution should define in writing the relationship between the research proposal and the study plan(s), and the responsibilities attached to each (see Fig. 6).

Figure 6. Relationship between research proposal and study plans



The study plan should describe the study design in detail, including the purpose, intended methods, and names of persons who will carry out the study and interpret the experimental data. Proposed dates for key events should also be stated.

The information in the study plan should be sufficiently detailed to enable the study to be repeated exactly, if necessary. The study plan is, therefore, likely to contain details of the:

- test material and conditions for its handling and storage
- type and quality of reagents and equipment
- type of test system and how it is to be handled
- observations to be made
- methods for data collection, evaluation, verification and (if appropriate) statistical analysis
- methods for reporting and archiving results

- ethical implications of the experiment, where appropriate (for example, in research involving animals), and discussion on this topic.

As noted above, procedures considered routine in the laboratory may be described in standard documents of the institution, such as SOPs. Therefore the study plan need not explain such procedures in full detail but could instead reference the relevant SOPs. It is good practice for the research institution to standardize the sections needed in all study plans.

If an experiment is based on previous preliminary work, this work would normally be referenced in the plan to ensure traceability to the early data, justifying certain parameters investigated in the main experiment. References cited in the study plan should either come from published peer reviewed sources or from internal research reports where data or documentation are available. Both published sources and internal reports must be verifiable. The link between the proposed activities and the published material must be explicit.

The principal scientist has the authority for final approval of the study plan. He/she signs to show his/her full responsibility for performing the study according to the plan and in compliance with quality practices in biomedical research (QPBR). The principal scientist should ensure that the technicians responsible for day-to-day conduct of the experimental stages are familiar with the study plan and its associated procedures. Such instruction should be documented in the study notes.

Subsequent major, intended, changes to the study plan will need authorization – in a document called the ‘study plan amendment’ – from the principal scientist since any change may entail significant modification to the scientific purpose of the study. However, minor deviations from the plan may simply be recorded in the laboratory notebook or recorded on specifically designed data sheets which are then filed with the rest of the data.



**KEYNOTE**

**Research proposal and study plan**

- The research institution should define the difference between the research proposal and the study plan.
- The research institution should have guidelines for the production, review and approval of research proposals.
- The research institution should have guidelines for the production, review and approval of study plans.
- Each individual study should be the subject of a single detailed study plan (one study = one study plan).
- The research institution should provide a format and a list of minimum contents for a study plan in accordance with QPBR recommendations.
- The research institution must make it clear that the principal scientist's signature on a study plan indicates that he/she takes full responsibility for the conduct of the study according to the plan and according to QPBR.

### 4.3.2 Standard operating procedures

Standard operating procedures (SOPs) are documents that provide instructions for activities of a repetitive, routine nature in a very detailed manner. Such standardized, approved, written working procedures are required by classical quality assurance techniques, indeed by good management.

Remember the quotation generally attributed to Dr Joseph M Juran:

*“Use standards [i.e. SOPs] as the liberator that relegates the solved problems to the field of routine, leaving the creative faculties free for the problems that are still unsolved”.*<sup>3</sup>

SOPs follow a defined life cycle: writing, approval, distribution, update, and withdrawal.

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<sup>3</sup> <http://specializedqualitypublications.com/B.htm>.

Every institution, or laboratory or facility within an institution, will certainly already have a collection of standard procedures under various headings and in differing forms, e.g. recipes for the preparation of buffer solutions or tissue culture media, directions for the operation and maintenance of apparatus and instruments, or step-by-step instructions for commonly performed activities (appendices 4-6 provide examples). These should become integrated into a fully coherent system with a standard layout, which should be predefined by management. This should lead to centralized organization of formatting, numbering, issuance, modification, withdrawal and archiving, which will help avoid duplication of effort, incoherence, delays, lack of traceability and incomplete distribution. The system should thus encompass all standard activities and there should not be separate, conflicting systems for conveying directives to personnel, such as memos.

The greatest benefits of such a system of standardized procedures can be expected if there is comprehensive coverage of:

- Standard scientific techniques
- Equipment, disposables, and reagents
- All critical stages of study design, management, conduct and reporting
- ‘Scientific’ administrative policy and procedures (e.g. format, safety and hygiene, security, personnel management).

Ideally, the individuals most familiar with the activity to be described in an SOP should also write the document. Furthermore, there should be somebody responsible for each SOP (author or other person responsible) to handle queries and keep each procedure updated. It is a good idea to impose a minimum time requirement for periodic review.

It is perfectly acceptable to use a manual if this is more appropriate than an SOP for the purpose. In this case, the SOP would reference the manual by name, edition, and physical placement. The SOP would be reviewed like any other SOP, taking special account of the continued relevance of the manual in relation to the current equipment. Once the equipment is retired, the SOP and manual must be withdrawn and archived.

SOPs should be immediately available to all individuals performing the respective tasks. Staff must fully understand the SOP and follow it rigorously. Deviations from the standard way of performing these activities should be handled like deviations from study plans, i.e. they have to be described, justified, signed and dated, in order to preserve the credibility of the system.

For reasons of traceability and ease of use, a two-tier system of SOPs is often the preferred approach. In such an approach, one tier may reflect general policies and pro-

cedures (e.g. protocol writing, review, approval, distribution and modification, SOPs, general rules for equipment use and maintenance, archives). The second tier may represent technical methods (e.g. histological staining methods, analytical methods, specific procedures for use and maintenance of equipment). It is advisable to present the SOPs (SOP manuals) as a binder with an up-to-date table of contents, logical chapter divisions and selective distribution, to avoid a mushrooming pile of dust-gathering paper that often gets misplaced. All alterations to SOPs must be made through formal revisions; notes and changes in the form of handwritten comments in the margin are not admissible.

All withdrawn SOPs, whether no longer used or superseded by a revised version, should be archived carefully in order to make a complete historical record of the test facility's procedures.

Properly designed SOPs will bring the following benefits to the laboratory:

- Standardized, consistent procedures (person-to-person and test-to-test variability minimized)
- An opportunity to optimize processes
- Capture of technical and administrative improvements
- Demonstration of management commitment to quality as part of the SOP approval process
- Ease of documenting complicated techniques in study protocols and reports (a simple reference to the procedure is often sufficient)
- Continuity in the event of personnel turnover
- Availability of a training manual
- A means of study reconstruction after the event, even after a lapse of years
- A means of communication in the event of audit, visits, technology transfer.

The successful implementation of SOPs requires:

- Sustained support from all levels of management with commitment to establishing SOPs as an essential element in the organization and culture of the laboratory.
- SOP-based education and training of personnel so that all personnel perform the procedures in the same way.
- An effective sound SOP management system to ensure that current SOPs are available in the right place.

**KEYNOTE****Standard operating procedures (SOPs)**

- Each research institution must establish appropriate SOPs covering the activities of the research institution and the studies performed.
- The contents of SOPs should follow a standard format set by the research institution.
- The institution must implement a system for the management of SOPs. This will cover the writing, signature, issuance, modification, withdrawal and archiving of SOPs.
- The institution provides and records SOP-based training.

**4.3.3 Descriptive documents: good record keeping**

Data should be collected in strict compliance with the rules of the institution. It is important to identify who collected the data from a given procedure and when. This is why it is necessary to sign and date all data at the time of recording.

*Raw data* are defined as all original recordings made during the course of a study. The data should indicate:

- *What was done* – demonstrating compliance with the study plan.
- *How it was done* – demonstrating compliance with practical, experimental instructions (in the study plan and relevant SOPs).
- *When the work was performed* – demonstrating the existence of the events and their sequence in time.
- *Who did the work* – demonstrating conformity with the responsibilities delegated by management to suitably qualified personnel.

Characteristics of the collection of good raw data are:

- *Attributability* – data can be traced to their source, e.g. by study number, sample number, parameter. Unique identification of data pertaining to an individual study helps to prevent mix-up of data.
- *Originality* – raw data constitute the first recording of the observation. Raw data should not be recorded on scraps of paper for transcription into a final form. If you use a computer to record or capture the data, you need to define whether the signed

printout or the electronic records constitute raw data. If you decide to define the electronic record as raw data, the computer must be protected by password, and be backed up frequently.

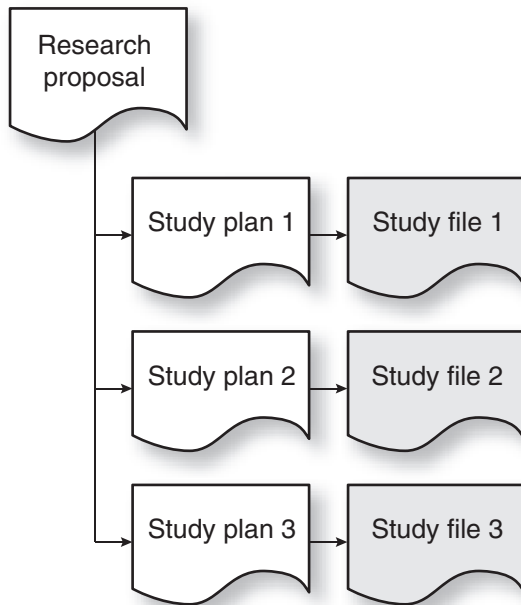
To ensure these characteristics, data must be recorded:

- *Promptly* – data have to be recorded immediately the operation is completed. It is not acceptable to make the record some time after the job has been finished, since memory may fail or become inaccurate, which may lead to data loss or faulty records.
- *Accurately* – the raw data have to be a true representation of the observation, and accuracy is thus absolutely central to the integrity of the study.
- *Legibly* – data that cannot be read are useless, and records that are difficult to decipher raise doubts in the minds of the reader as to their credibility. Therefore, write legibly.
- *Indelibly* – one of the common problems in research is that data are often recorded in pencil and are subject to subsequent changes without this being evident, which in turn may lead to suspicions of deliberate tampering. Use of indelible and waterproof ink eliminates this problem. Any changes to raw data should be made so as not to obscure the previous entry. The person responsible for the change (or the person approving it) should then sign and date the change, and the reason for the change should be indicated, if necessary. It is furthermore necessary to check the robustness of the print-out from instruments: some fade quickly at room temperature or when stored in plastic folders. In such cases, an authorized (signed and dated) photocopy should be prepared for storage.

Data should be recorded and organized in a way that supports and facilitates both recording and all subsequent processes (e.g. data entry, reporting, audit, archiving).

The total collection of records, including raw data, analyses, printouts, and any other documents relevant to the study, constitute the study file. This study file also contains the study plan and amendments, and the study report. The study file, together with all documents relating to the study, are stored in the archives (see also section 4.3.6.). Figure 7 shows how the study file is related to the research proposal and study plans.

Figure 7. Relationship between research proposal, study plans and study files

**KEYNOTE****Good record keeping**

- Each research institution must implement rules regarding the recording of raw data.
- Raw data and other records should be sufficiently detailed and complete to ensure study traceability and reconstruction.
- If computers are used to acquire, modify, manipulate or archive data, the raw data must be clearly defined.

**4.3.4 Use of notebooks**

During the early discovery stage, some organizations require researchers to use notebooks to record all activities in the laboratory or the field. Usually these notebooks are numbered consecutively, sometimes by the laboratory administration, sometimes by the

scientist. Where research is done as a continuous process, where there are daily small modifications to a plan, and daily experiments in pursuit of a principle or method (for example, if you are manipulating the physical properties of a molecule in order to optimize its biological half-life), the notebook is the obvious tool for recording progress. There are advantages to this approach:

- Everything is in the notebook, nothing gets lost.
- The notebook is always to hand, practical to carry around in the laboratory and the field.
- Each person can be responsible for his/her own book.
- It is easy to archive consecutively numbered books.
- Patent laws in some countries require the use of notebooks.

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However, there are pitfalls to this seemingly obvious approach:

- Planning and records are mixed in the same pages. It is then difficult to see the amendments to a plan, or to ascertain whether data comply with the plan, or whether deviations are intended or unintended. It would be difficult to decide which are the valid data for inclusion in the report. It would be difficult if not impossible to audit the report.
- Some laboratories allow staff to record data from different studies in the same notebook, so it is difficult to trace the continuity of one study. Or the converse: some laboratories allow staff to use two or more notebooks (perhaps each dedicated to one technician) in which they can record data from the same study. This makes it difficult to ascertain that a report includes *all* the data.
- The notebooks do not contain everything. Often data are placed in other media: printouts, assays from other laboratories, gels, histological specimens, which can be mislaid.
- If different notebooks also record the status of laboratory equipment, it is not possible to follow the life cycle of a particular piece of equipment.

So – use laboratory notebooks with caution. If you choose to use them, observe at least the following:

- Ideally use a separate notebook(s) for each study. Avoid mixing many studies in one book.
- Consecutively number both notebooks and all pages before the notebook goes into use.
- Keep the first pages clear. When you have finished with the notebook, make a good

index on the front pages, showing the contents of the rest of the book.

- Make sure plans are easily distinguished from records. Make sure amendments to plans refer back to the original plan, with page and date, and number the amendments consecutively.
- Make it clear when the line of enquiry finishes and you are ready to report.
- Reference any related activity and its data – for example, samples for assay, and the assay results. Reference any data or specimens held in another place: a separate binder, or data in another laboratory. Reference any computer files.
- Sign and date each day's work. Make corrections as soon as errors become evident, and correct them so that the original entry is visible and the new data are legible. Write the justification for the correction, sign and date the correction. *Never tear pages out.*
- The principal scientist should promptly review and countersign the work of technicians, paying attention to any corrections.
- Keep the notebooks safely when not in use, and archive them promptly when full.
- In the report, reference exactly the notebooks and the pages accessed.

#### KEYNOTE

##### Notebooks

- The research institute must define when the use of notebooks is mandatory and when the use of loose leaf files is preferable for the recording of raw data.
- The research institute must have guidelines for filling out notebooks and data collection sheets, and for handling all the different types of raw data, samples and specimens.

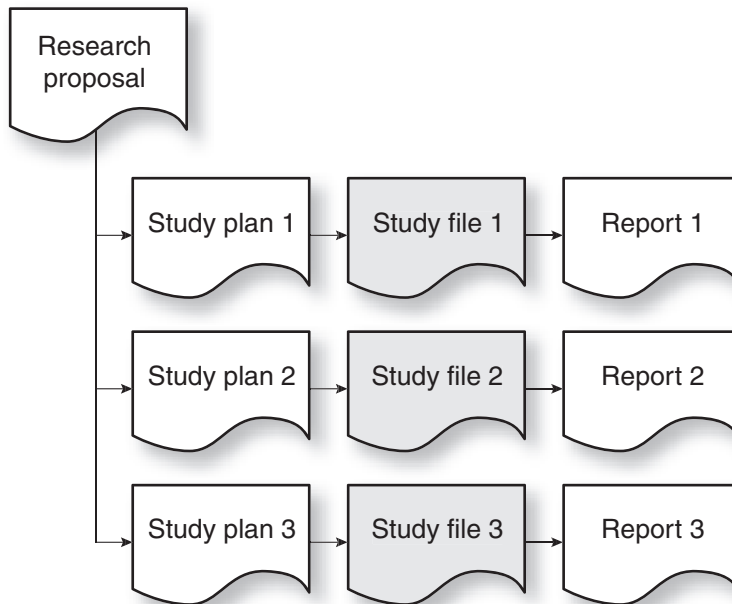
#### 4.3.5 Reporting results

Each study (defined by its study plan) requires a report. The report contains an account of the practical conduct of the study, any deviations from the intended course of action, tabulated results, a presentation of the significant results, a critical discussion, and a conclusion. There will be a list of references, including references to both literature and laboratory notebooks. If a colleague contributes a section of the report, the colleague retains responsibility for the scientific veracity and quality of his/her contribution. However the principal scientist still takes responsibility for the overall scientific con-



tent of the report and scientific interpretation of the results as a whole. Figure 8 shows the relationship of the study reports to the previous documents.

**Figure 8. Relationship between research proposal, study plans, study files and study reports**



The writing must be done immediately the practical work and data collation are completed, while the study is still fresh in the mind. If you need to check findings with the technician, the probability is that the technician is still working with the organization and will be available to help clarify obscurities in the records. It is essential to consider, describe, evaluate and report all the study results, taken in context with the original study plan. Leaving out results that do not fit is called selective reporting and is not acceptable practice. Results that do not fit may be precisely those that lead to an improved hypothesis for further testing.

**KEYNOTE****Reporting results**

- Each study should be the subject of a study report (one study = one report).
- The report must contain a true and accurate representation of *all* raw data.
- The report should contain a scientific discussion of the results and a conclusion.
- Any deviations from the study plan should be explained in the study report.
- Although other specialist scientists may contribute sections to the report and sign the interpretation of their results, the principal scientist has overall responsibility for the report's content and its scientific interpretation.

**4.3.6 Storage and archiving of records**

During the study, the principal scientist must ensure safe storage of data and other study file documents under his/her own responsibility. This may entail finding a dedicated shelf area or a cabinet in the laboratory where all files can be kept safely until reporting is complete. At the end of every study, all raw data pertaining to the study should be collected together with the study plan and final report or summary of the results, and combined into a single package of information – the study file. The study file will also contain any other relevant material pertaining to the study, for example exchanges of letters between the principal scientist and experts he/she may have contacted, the institution's ethics committee approval, order forms for animals, details of animal health status and water analysis. The idea is that there should be sufficient material for reconstruction of the trial, for checking and for verification.

This study file should then be formally archived in order to guarantee integrity of the data and of the study. When single data sets from a finalized study are needed for another study, there should be formalized procedures for the retrieval of studies or study parts from the archives.

The records retained are a great deal more than a just a compilation of papers or a set of figures. The collected data represent the value (in time, resources and economic potential) of the research performed. Therefore the administration and physical placement of the archive facilities must be of a quality that matches the assets laid down in the data.

Access to the archive facility should be limited to authorized personnel, and the facility must protect records from physical damage, interference and loss. Stored material should be logically and practically arranged to facilitate rapid retrieval. It is furthermore advisable to allocate a person to be responsible for the archive.

The institution should retain all records for at least the period of time it takes to develop the product; it is recommended either to follow the national guidance or to stipulate a period of 10-20 years after publication. In some countries there are national archives for research data; if such facilities exist, they should take priority over institutional storage facilities.

#### KEYNOTE

##### Storage and archiving of records

- Systems for identifying and indexing documents (in notebooks, on data collection sheets, as printouts or as electronic data) must be established before the study starts, to ensure complete traceability of the study and rapid retrieval of documents from the archives.
- Study documents should be archived together at the end of the study.
- Access to and retrieval of documents should be limited to authorized personnel only.

## 4.4 Supervision/quality assurance

### 4.4.1 *Reviewing staff qualifications*

The institution's administration must implement a procedure for regularly checking that staff qualifications and training are sufficient for their assigned responsibilities. Additional training and updated CVs and training records will be the result of this check. The verification should commence when new staff join the institution (see also section 4.1)

**KEYNOTE****Reviewing staff qualifications**

- The research institution should verify staff qualifications as part of the recruitment process.
- The research institution should, as a routine procedure, periodically review qualifications of staff in relation to their responsibilities.

**4.4.2 Verification of results**

In the first instance, the principal scientist has primary responsibility for the quality and reliability of his/her data. The administration of the research institution, however, also plays a critical role in ensuring the quality and reliability of the data collected at the institution. Production of reliable quality data requires careful supervision. This supervision is often at two levels: 1) supervision related to the scientific content, often requiring scientific experience and insight into the relevant specialist area, and some level of confidentiality, and 2) supervision to assure the systems and procedures used to generate data are sound and are followed.

The validity of scientific research depends on how well design, conduct and documentation will withstand scrutiny. The scientists responsible for conduct of the study must therefore ensure that there are verification procedures in place that will confirm the quality and reliability of the data. The signature of a responsible scientific member of staff should attest that sufficient reviews at all levels have been made to verify the data.

Verification activities may also need to be performed by someone from outside the study staff or organization, in which case the verification is called an 'audit'. An audit means the systematic scrutiny of raw data in a study and the verification of their correct representation in the final report or publication. While it is unusual to implement systematic independent auditing in research institutions, it is only through care at the level of data acquisition and data recording that the study can be validated at all by audit. A successful audit relies on the traceability and transparency of all events contributing to the study.

It is also possible to organize external third party audits by professionals who look at the systems, studies or specific data. This approach is particularly relevant since national regulatory monitoring authorities do not inspect research that falls outside the

regulatory scope of Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP).

It is important to ensure that auditors understand their obligations with regard to confidentiality of data. A contract outlining what the auditor is at liberty to reveal, and to whom, should be generated before the audit.

#### *4.4.3 Evaluation and review of final report*

The research institution should have a policy or guidelines for scientific evaluation and reporting of results. There are many ways to do this. The institution could choose to authorize a superior or peer to review a portion of the raw data, and to evaluate the technical and scientific content of the report. This person would assure management that the report is a fair and complete account of the activities as documented in the raw data. After this, the report would be circulated to the rest of the scientific staff for discussion and comment before the final report is sent out of house. Internal reports used as the basis for further work would need equally rigorous treatment.

It is also possible to arrange an external review of the work. Academic institutions are familiar with the practice of an external examiner who assesses PhD theses; the external review of research work would work in a very similar manner.

#### **KEYNOTE**

##### **Verification of results and reports**

- The principal scientist has primary responsibility for the quality, integrity and reliability of the study results.
- Senior management has responsibility for ensuring the timely and routine review of study data.
- The research institution should arrange for verification of study activities and results by persons independent of the study.
- It must be possible to audit the report and to trace all results back to the raw data of the study.

## 4.5 Publishing practices

It is good practice to publish<sup>4</sup> scientific results in a timely way. The advantages are:

- Scientific results are moved into the public domain. This is an intrinsic part of the scientific process. The public, having funded much scientific work, has a legitimate interest in knowing the outcome.
- The researcher is exposed to peer review or to informed discussion and challenge.
- The scientific community becomes aware of the research. Therefore other researchers are able to build on the results, or can avoid duplicating efforts.
- The scientist becomes a known figure in his/her field, strengthening the chances for obtaining further funding and continuing his/her scientific investigations.

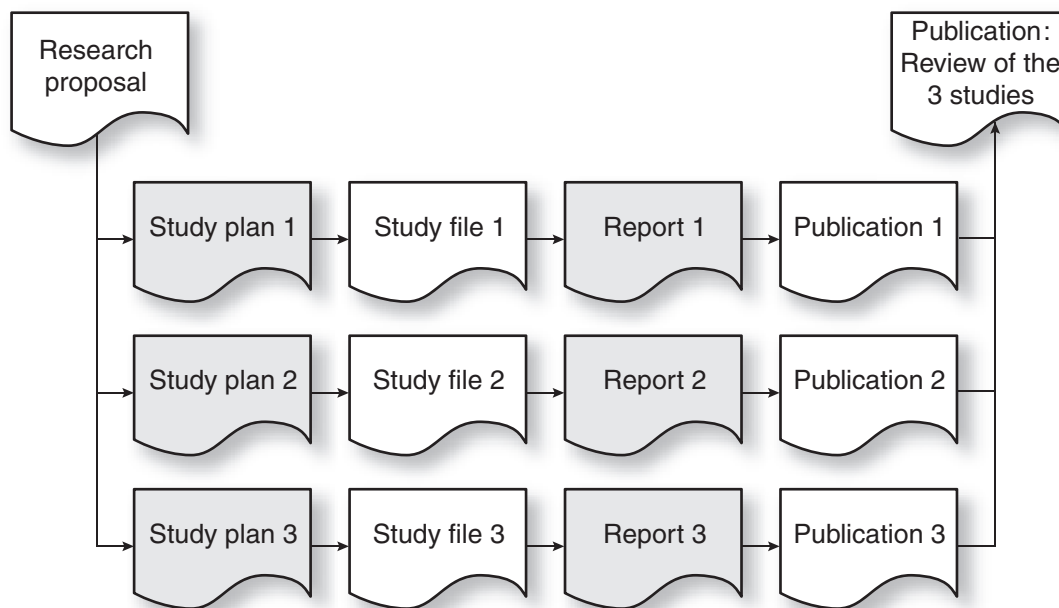
Since publishing is such an essential process for moving ideas into the public domain, research organizations should have a policy for publishing results. The policy should cover issues such as:

- At what point in a project it is necessary or advisable to publish
- Where and how to publish
- The institute's procedures for review
- The conventions for co-authoring papers
- The necessity for including significant data fairly and accurately in publications
- Whether the research data are the intellectual property of the researcher, the institute or the grant giving body
- Ownership of patent rights.

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<sup>4</sup> A broader term is to 'disseminate' – a term which could include monographs, reports to authorities for inclusion in public policy, pamphlets, and chapters in books. This handbook examines the pros and cons of publication in scientific journals as a way of securing a reasonably widespread, permanent and retrievable record in the public domain.

Figure 9. Relationship between research proposal, study documentation and derived publications



#### 4.5.1 Reporting the results in smaller, separate publications

This practice allows full and detailed exploration, especially if there have been follow-on plans and activities to elucidate unexpected observations or unclear findings. But it is not acceptable to break down or rehash the study simply to obtain more published papers out of the same material. Review papers presenting an overview of all studies, and of similar studies showing the same or contrasting results, will help colleagues needing to orient themselves quickly. But again, the habit of writing repeated reviews about the same material, in different journals, to build a list of publications, is unhelpful unless a materially new interpretation is presented. Figure 9 shows the individual publications and the review article.

#### 4.5.2 Publishing negative results

If the study was well controlled and well executed, and the data were fully and promptly recorded, then negative results are valid and should be available to the scientific community. This practice will save spending resources on other attempts to follow the same path. There has been criticism of the reluctance of researchers, both commercial and

academic, to submit negative results, and of the reluctance of journals to publish them. But it seems that the scientific community is beginning to understand the importance of also knowing what did not return expected results.

#### *4.5.3 Assigning credit to contributors*

The author should give credit to others who contribute work, ideas, or results. If the paper borrows extensive material from other published sources, the material must be cited loyally, and the authors and full bibliographical references must be identified. If the work draws on the unpublished work of colleagues, it is necessary to obtain permission and give acknowledgment. If the contribution is large, it may also be appropriate to include the person in the list of authors. One must also be aware that colleagues may not be ready to publish their ideas, and that you may infringe their patent rights.

#### *4.5.4 List of authors*

If the paper is the result of collaboration between several persons, the list of authors, and the choice of principal author, can become issues. Different institutions have different conventions, but in general it is best that the person who generated the idea and contributed the majority of the work (probably the principal scientist) should be the principal author. Sometimes people are surprised to find that they have become a co-author after they performed only a modest part of the laboratory work according to instruction, or because they discussed the content with the author; there must be consensus amongst all the authors as to who should appear on the list and what responsibility they will accept. The automatic inclusion of the leader of the group or the professor or head of an institute on all author lists of papers from his/her institute serves no scientific purpose. It does not signify that he/she was active or that he/she takes full personal responsibility for the veracity of the paper. Neither is it a desirable habit to present lists of over a dozen authors, because responsibility for the reliability of data, reports and publications becomes too diffuse for accountability.

#### *4.5.5 Choice of publishing forum*

Publishing carries most weight if the study can be submitted to a well reputed, specialist, peer-reviewed journal. Journals provide instructions on format, style, content and length, including the position of the principal author's name in the list of contributors. While the approval process may take some time, especially as reviewers usually



make comments and suggestions for improvement, the advantage is that publication in a peer-reviewed journal is considered reliable and earns respect for the authors.

It is also possible to publish by presenting posters or lectures at conferences. Here, formal peer review is not always practised since conference sponsors/organizers often make calls for papers and accept all contributions. After the conference, the papers appear in the proceedings of the meeting. Sometimes commercial sponsors hold conferences with dual purposes: education, and as a vehicle for marketing activity. The sponsor may be advocating a viewpoint that is not necessarily in line with the conclusions of the presentations, so researchers must be prepared to stand by their own conclusions.

It is not recommended practice to publish through press conferences, newspapers, interviews, TV coverage or web-page releases until the formal publication is available. Only rarely does a journalist properly understand the content of a study or the significance of its contribution, so the message will not be accurate in these types of media.

#### 4.5.6 *Patents and scientific publishing*

In some ways, the need to publish conflicts with the need to file patents. A patent is desirable if the results of the study promise novelty, inventiveness and utility sufficient for a new product or principle. Without a valid patent, business partners are not willing to invest in developing an idea into a viable product. To be patentable, an idea has to display 'novelty', which means that *it must not have been published previously in any way*, including by the same person filing the patent. In other words, premature publication can spoil the chances of obtaining a patent. Publication in terms of patent law covers not only formal peer-reviewed publication but also the more informal types discussed above, and even public discussions where there are no written records.

For more guidance on publications, and to understand the expectations of scientific journals, please consult *Good publication practice for pharmaceutical companies*,<sup>5</sup> which concerns publication of clinical trials results. This publication represents the editors' point of view, since editors have to be certain of the veracity of the materials they publish.

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<sup>5</sup> Wager et al. Good publication practice for pharmaceutical companies *Current Medical Research & Opinion* 2003, 19 (3):149-154 (<http://www.cmrojournal.com>).

**KEYNOTE****Publishing practices**

The research institution should have a written policy for publications. This policy should contain specifications for:

- Authorship
- Peer review
- Patenting
- Data integrity – including publication of negative results
- Situations where multiple publications are permitted
- Preferred forum (i.e. journal, conference, poster session, etc.).

## 4.6 Ethical considerations

Even in the earliest stages, the principal scientist has ethical responsibilities towards the people, including any bystanders, involved in the study, as well as towards the experimental animals and environment. It is essential to carry out a risk analysis before starting the study; this should also form part of the application for funding. The risk analysis should assess the potential likelihood of a mishap, and the impact of a mishap, and weigh these against the potential benefits of the study.

In the laboratory, the principal scientist must train personnel to exercise safe working practices<sup>6</sup> with regard to apparatus and chemicals. Laboratory personnel must also be able to avoid the risk of accidental infection from test agents or experimental animals (see section 4.6.1).

For all studies involving human subjects, even in the early stages (whether discovery or development), Good Clinical Practices are the correct quality and ethical standards. In turn, Good Clinical Practice requires compliance with Good Manufacturing Practice (GMP) for manufacturing and formulation of investigational medical product (IMP).

<sup>6</sup> World Health Organization. *Laboratory biosafety manual*. Geneva, World Health Organization, 2004.

The TDR ethical guidelines<sup>7</sup> and the TDR SOPs<sup>8</sup> offer guidance in interpreting and implementing good clinical practices in both observational and interventional studies involving human subjects.

The principal scientist must ensure that laboratory animals are kept according to the current guidelines for animal welfare, and that the study does not entail unnecessary suffering on the part of the animals.<sup>9</sup> An unnecessarily large number of animals should not be exposed to experimentation, while the involvement of too few animals will weaken the strength of a study such that these animals are used to no purpose. Animals should be available on time. If they are ordered too early, they may be too old for inclusion in the study and will be sacrificed in vain. The guidelines also contain instructions for training of personnel in the humane and safe handling of animals.

Ethical dilemmas may arise from ancillary data. For example, if a tissue or blood sample (donated for the purpose of testing quite another principle) reveals that a person is suffering from a serious illness, has the principal scientist any obligation to inform that person, or the authorities?

Field trials can entail a risk of unintentional human exposure to chemicals or pathogens. If such a risk is identified, either an ethical committee must be consulted or permission must be sought from a person who represents the group at risk.

Field trials can also affect the environment. For example, water supplies, the food chain, or the ecological balance between competing species can be affected. There are guidelines for the control of genetically modified organisms (GMOs)<sup>10</sup> used in laboratory or field trials.

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<sup>7</sup> TDR guidelines for ethical clearance. <http://www.who.int/tdr/grants/grants/ethical2.htm>.

<sup>8</sup> Karbwang J, Pattou C. *Standard operating procedures for clinical investigators*. Geneva, TDR (TDR/TDP/SOP/99.1) <http://www.who.int/tdr/grants/grants/files/sop.pdf>.

<sup>9</sup> Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes [http://europa.eu.int/comm/food/fs/aw/aw\\_legislation/scientific/86-609-eec\\_en.pdf](http://europa.eu.int/comm/food/fs/aw/aw_legislation/scientific/86-609-eec_en.pdf).

<sup>10</sup> The Edmonds Institute. *A manual for assessing ecological and human health effects of genetically engineered organisms*. <http://www.edmonds-institute.org>.

**KEYNOTE****Ethical considerations**

- The research institution should set high ethical standards and have a written ethical charter which must apply to all personnel. This charter must address people, animals and the environment.
- In particular, the charter must describe the need to respect human rights.
- The charter must address the welfare of animals and protection of the environment.
- The research institution should establish an ethics committee to consider the ethical implications of its research programmes and approve standard procedures and individual studies.

If the researcher is working in an institution where there is an ethics committee, this committee should have an opportunity to see and discuss not only each study plan, but also the practices and procedures of the institution as a whole (see section 4.1).

**4.6.1 Biosafety**

In recent years, the number of research programmes involving new technologies that employ subcellular systems (e.g. genetic manipulation, development of monoclonal antibodies, gene therapy, use of viruses as vectors, investigations of prions) has increased considerably. These new technologies have developed our awareness of the importance of biosafety guidelines, which can help prevent novel organisms and microorganisms accidentally reaching the environment or infecting man, both of which are potentially catastrophic. Institutions that pursue research in these fields must be aware of the dangers. Laboratory risks reside principally in the handling and disposal of biohazardous materials; the containment of such materials at different levels, depending on the potential risk, is the principal approach used worldwide. Facilities are classified at four danger levels, with different sets of precautions necessary at each level. If there is no national biosafety legislation, the institution must comply with the provi-

sions set out in the WHO *Laboratory biosafety manual*<sup>11</sup>. Risks in the field must also be considered, since genetically modified organisms may not behave as expected once released into the environment.<sup>12, 13</sup>

#### KEYNOTE

##### Biosafety

- The research institution must establish written safety practices for working with hazardous materials, including biological and chemical materials.

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<sup>11</sup> World Health Organization. *Laboratory biosafety manual*. Geneva, World Health Organization, 2004.

<sup>12</sup> Iowa State University. *Regulation of genetically engineered organisms and products*. Biotechnology Information Series, Iowa State University, 1995 ([www.extension.iastate.edu/Publications/NCR557.pdf](http://www.extension.iastate.edu/Publications/NCR557.pdf)).

<sup>13</sup> Young OP et al. Regulation of transgenic arthropods and other invertebrates in the United States. In: Handler, AM, James AA, eds. *Insect transgenesis: methods and applications*. Boca Raton, CRC Press, 2000:369-371.

## 5. CONCLUSIONS

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The need for quality practices in basic biomedical research, whether pertinent to drug discovery or to the early stages of research in other health fields, has been articulated through several meetings held under the auspices of TDR/WHO. It is indisputable that the selection of drug candidates for further development or the selection of new strategies for preventing or fighting disease must be based on reliable research data. Such reliable data can only be derived from studies that are both scientifically valid and properly managed. Sound study management promotes international acceptance because the responsible scientist is able to demonstrate unequivocally that the data are complete and reliable.

This handbook offers quality practices – guidance and tools – for the practical management of research studies. It does not address issues of scientific content of studies.

Well managed studies are not the result of decisions taken as the activities unfold. They are studies performed in compliance with pre-established processes within agreed organizational structures. Appropriate management involves:

- careful planning
- exemplary performance according to the plans
- full and unambiguous recording of the raw data generated
- reporting with narrative and data accurately reflecting the actual events and raw data of the study
- storage/archiving of all study records and documents prior to possible publication.

In this way, studies can withstand scrutiny from scientific peers.

The management of a research organization should first set up the organizational and physical framework, including ethical guidelines, for the type of work envisaged. This should ensure that, prior to embarking on research activities, a researcher plans the proposed work, detailing, referencing and documenting in the study plan the intended processes and procedures. This documentation of study activities prescriptively, prior to

embarking on the work, will force the responsible scientist and management to evaluate the study goals and design with respect to resources, timing, study records and training. Such planning will assist in the conduct of the study and help avoid unexpected events that might otherwise negate a good study, as well as allow consideration of ethical and biosafety issues.

Well planned studies lead to activities which are formally recorded. As the study progresses, orderly descriptive documentation of the results and observations following an already well thought out structure will assist the proper reporting and verification of the study outcome. The records should be sufficiently detailed to allow reconstruction of the study, permitting the work to be reproduced if required. The records should form the backbone of scientific interpretation by the responsible scientist, and become the basis for any subsequent publication. Proper storage and archiving of the results for later retrieval, verification, publication or commercial exploitation is an integral part of the data management process.

The fact that responsible scientists define the processes in advance adds credibility to the whole of the study and greater acceptability to the results. In no way does this structured approach restrict the innovation or technical freedom of the scientist, nor does it prevent a scientist from modifying the plans as the study progresses. On the contrary, the structured approach helps the scientist to eliminate, control or understand the variables that inevitably impact on studies, enabling a valid and confident interpretation of the study data. In this way, sound study management contributes to the credibility of results and their scientific meaning.

This handbook highlights the fundamental importance of careful documentation at each stage of the study process, as well as the need to monitor the various stages. Without considering these two aspects of the study process, there can be neither study transparency nor study reconstruction, both of which are essential for study recognition by peers and, where appropriate, acceptance by official bodies such as the World Health Organization, registration authorities or health ministries.

The wide application of the practices proposed in this handbook will promote high quality, well managed studies and reliable data. This will lead to international recognition of the study results, which in turn will promote more cost-effective, accelerated discovery research with a long-term positive impact on human health.

## 6. APPENDICES

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- 6.1 Appendix 1: Glossary and definitions
- 6.2 Appendix 2: Applicable quality practices for drug or therapeutic product development
- 6.3 Appendix 3: Standard operating procedure: template and instructions
- 6.4 Appendix 4: Example of a standard operating procedure: pH meter
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- 6.11 Appendix 11: 'Must do' – a short list of activities necessary for implementation





# APPENDIX 1

## GLOSSARY AND DEFINITIONS

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Term	Definition
1. API	Active pharmaceutical ingredient: any substance or mixture of substances intended for use in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes the active ingredient of the drug product. <sup>1,2</sup>
2. Archive	A collection of records and documentation generated as a result of research activities. Characteristics of such an archive are: <ul style="list-style-type: none"> <li>• There is an allocated area for this collection.</li> <li>• The area is protected from fire, water, pests.</li> <li>• The contents are protected from loss or theft.</li> <li>• The contents are indexed to ensure rapid and accurate retrieval.</li> <li>• Often there is an individual responsible for administration of the archive.</li> </ul> See also 'storage'.
3. Attribute: attributable	To regard as the work of a specified agent, place, or time. <sup>3</sup>
4. Audit	See 'quality audit'.
5. BBR	Basic biomedical research.
6. Calibrate: calibration	To check, adjust, or determine by comparison with a standard (the graduations of a quantitative measuring instrument). <sup>3</sup>

<sup>1</sup> International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q7A. *Good Manufacturing Practice guide for active pharmaceutical ingredients*. November 2000 ([http://www.ich.org/MediaServer.jserv?@\\_ID=433&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_ID=433&@_MODE=GLB)).

<sup>2</sup> Eudralex 2005. The rules governing Medical Products in the European Union. Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. *Part II, Basic Requirements for Active Substances used as Starting Materials* ([http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005\\_10\\_03\\_gmp-partII-activesubstance.pdf](http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005_10_03_gmp-partII-activesubstance.pdf)).

<sup>3</sup> *The American Heritage ® Dictionary of the English Language*. Fourth Edition, 2000 (<http://www.yourdictionary.com>).

Term	Definition
7. CMC	Chemical, manufacturing and controls: research pertaining to the characterization of a chemical entity, whether intended for use as a drug or as an environmental chemical. This research uncovers the chemical structure and characteristics of the substance, defines processes for manufacture, and describes and validates methods for analysis and control.
8. Control	To verify or regulate (a scientific experiment) by conducting a parallel experiment or by comparing with another standard. <sup>3</sup>
9. Credibility	The quality, capability, or power to elicit belief. <sup>3</sup>
10. Curriculum vitae (CV)	A summary of one's education, professional history, and job qualifications, as for a prospective employer. <sup>3</sup>
11. Database, data bank	A collection of data arranged for ease and speed of search and retrieval. <sup>3</sup>
12. DEC	Disease endemic country: a country where a specified disease(s) is endemic, posing a constant threat to the health and productivity of the community.
13. Descriptive	Involving or characterized by description; serving to describe. <sup>3</sup>
14. Discovery stage	The stage of research where new principles are discovered and confirmed.
15. Experimental study	A study where the scientist makes a physical intervention, for example dosing, or setting new organisms out in a habitat, or removing vectors' food plants.
16. False positive False negative	Meaning that the experimental results apparently confirmed the hypothesis, even though it was wrong. Meaning that experimental results apparently disproved the underlying hypothesis when it was, in fact, correct.
17. GCP	Good clinical practices: a set of quality practices for managing clinical trials in an ethical way, in order to generate valid data and ensure reliable reporting. Covers <i>all</i> trials in human subjects. <sup>4,5</sup>

<sup>4</sup> World Health Organization. Guidelines for good clinical practice (GCP) for trials for pharmaceutical products. In: *The use of essential drugs. Sixth report of the WHO Expert Committee*. Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850).

<sup>5</sup> International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Topic E6: *Good Clinical Practice: consolidated guideline*. 1996 ([http://www.ich.org/MediaServer.jserv?@\\_ID=482&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_ID=482&@_MODE=GLB)).

Term	Definition
18. GLP	Good Laboratory Practice: a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. <sup>6</sup> GLP studies usually use animals, plants or subsystems as the test systems – they do not involve human subjects.
19. GMO	Genetically modified organism.
20. GMP	Good Manufacturing Practices: a set of quality practices for managing the manufacture, controls and release of medical products for human (or veterinary) consumption. Note that there are separate guidelines for the production of active pharmaceutical ingredient (API) in bulk and for finished drug product (formulated and packed). <sup>7</sup>
21. GXP	A term coined for the use of GCP, GLP and GMP, as defined above, without specifying which. This is allowable because the GXPs are based on the same main philosophy but differ in detail.
22. IMP	Investigational Medicinal Product: a pharmaceutical form of an active substance or placebo being tested in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form. <sup>8</sup>
23. Indelible	Impossible to remove, erase, or wash away; permanent. <sup>3</sup>
24. Integrity (in research)	The reported results are honest and accurate and are in keeping with generally accepted research practices. <sup>9</sup>

<sup>6</sup> Organisation for Economic Co-operation and Development. *OECD Principles on Good Laboratory Practice* (revised 1997). Paris, 1998 (ENV/MC/CHEM[98]17).

<sup>7</sup> Eudralex. Volume 4: *Medicinal products for human and veterinary use: Good Manufacturing Practice* (<http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm>).

<sup>8</sup> Eudralex. Volume 4: *Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice Manufacture of Investigational Medicinal Products*.

<sup>9</sup> Institute of Medicine. *Report of a study. The responsible conduct of research in the health sciences*. Washington DC, National Academy Press, 1989.

Term	Definition
25. Non-regulated basic biomedical research	The stages of biomedical research starting with discovery and including some development stages but not those regulated by GLP, GCP, GMP or any other regulatory requirement.
26. Observational study	A study where there is no intervention on the part of the scientist. See ‘experimental study’ above.
27. Originality	The first and genuine form of something, from which others are derived. <sup>10</sup>
28. Prescriptive	Making or giving injunctions, directions, laws, or rules. <sup>3</sup>
29. Principal investigator	<p>In WHO: a term used to denote the person who applies for a grant and is responsible for carrying out and reporting scientific studies.</p> <p>In GLP: a term used to denote an individual who, for a multi-site study, acts on behalf of the study director and has defined responsibility for delegated phases of the study (OECD GLP).</p> <p>In GCP: a term used to denote the physician who is responsible for carrying out a clinical trial according to a clinical test protocol and according to international ethical standards, and who is responsible for the welfare of his patients.</p>
30. Principal scientist	In this monograph: a term used to denote the individual who is responsible for the scientific design, planning, performance, and reporting of a scientific study. This person is responsible for the scientific value of the study, the quality of the data, and the interpretation of the results.
31. Promptly	Carried out or performed without delay. <sup>3</sup>
32. Proof of principle (POP)	<p>In drug discovery: a pharmacological study that examines the efficacy of a drug candidate in an experimental model that mimics human disease.<sup>11</sup></p> <p>In disease prevention: a study that provides proof that the idea will work in a practical set-up.</p>

<sup>10</sup> McLeod WT. *The new Collins Dictionary and Thesaurus*. London, Collins, 1987.

<sup>11</sup> Source: John Hyttel, Dr. Scient. Zealand Pharma. Personal communication, 27 March 2005

Term	Definition
33. Quality assurance (QA)	In this document: used to denote a person or a department independent of study performance, whose activities assure management of the quality of research studies within the research institute. It is not universal practice to employ QA personnel in BR organizations, neither is it mandatory. QA personnel would typically assist in establishing working processes, audit procedures and audits, review documents, and assist with building up the archive.
34. Quality audit	Systematic and independent examination to determine whether quality activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable for achieving the objectives. <sup>12</sup>
35. Quality (in research)	The rigour with which experiments are designed and carried out, statistical analyses performed, and results recorded and reported. <sup>6</sup> Quality is also defined as ‘the totality of characteristics of an entity (which can be a product, an activity or a process) that bear on its ability to satisfy stated and implied needs’. <sup>9</sup> In recognition of the stated needs of the community for new methods to improve human health, in this document these characteristics are defined as: <ul style="list-style-type: none"> <li>• Relevant</li> <li>• Reliable and reproducible</li> <li>• Ethical</li> <li>• Auditable</li> <li>• In the public domain.</li> </ul>
36. Raw data	All original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study. <sup>6</sup>
37. Reliability	Able to be trusted, dependable. Data that one can act upon.
38. Repeatability	The circumstance that another research team can carry out a study and obtain results equivalent to the original.
39. Reproducibility	The circumstance that the same team can repeat a study and obtain the same result (within acceptable limits).
40. Research institute	In this document: used to mean any entity that engages in BR, irrespective of organization, funding, size, or specialist field of activity.

<sup>12</sup> ISO 8402: *Quality management and quality assurance – vocabulary*. International Standard, 2<sup>nd</sup> edition, 1994.

Term	Definition
41. Research proposal	A plan for a research programme containing one or more studies. The research proposal outlines the scientific purpose and medical relevance of the studies, and the relationships between the studies. The proposal also contains a budget and a timeline.
42. SOP	Standard operating procedure ; documented procedures which describe how to perform tests or activities normally not specified in detail in study plans or test guidelines. <sup>6</sup> Characteristically, SOPs are : <ul style="list-style-type: none"> <li>• Authorized</li> <li>• Managed</li> <li>• Current.</li> </ul>
43. Specimen	Any material derived from a test system for examination, analysis, or retention. <sup>6</sup>
44. Sponsor	An entity which commissions, supports and/or submits a non-clinical health and environmental safety study. <sup>6</sup>
45. Storage	The act of storing goods or the state of being stored. <sup>3</sup> (There are no particular conditions for responsibility, indexing, retrieval or protection.)
46. Study file	All the raw data, records, documents and specimens pertaining to a study. Includes study plan and study report.
47. Study plan	A document that defines the objectives and experimental design for the conduct of the study, and includes any amendments. <sup>6</sup>
48. TDR	UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.
49. Test system	Any biological, chemical or physical system, or a combination thereof, used in a study. <sup>6</sup> For example, test animals.
50. Test item	An article that is the subject of a study. <sup>6</sup> See also IMP
51. Traceability	The circumstance that any given statement in a scientific report or publication can be traced back to its source in the study data.
52. Training record	Records of any training undertaken within an institution, usually in practical routines as required by study plans and SOPs.

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<b>Term</b>	<b>Definition</b>
53. Transitional research	The stage of research following discovery per se, and preceding non-regulated, non-clinical research. In the transitional stage, causalities are thoroughly explored, and assays or prototypes are developed.
54. Transparency	Easy to see through, understand, or recognize; obvious. <sup>10</sup>
55. Veracity	Conformity to fact or truth; accuracy or precision. <sup>3</sup>
56. Verification	To check or investigate the truth of by investigation. <sup>3</sup>
57. WHO	World Health Organization.





## APPENDIX 2

# APPLICABLE QUALITY PRACTICES FOR DRUG OR THERAPEUTIC PRODUCT DEVELOPMENT

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1. Stage 1 comprises basic scientific discovery and exploration of substances with the potential for yielding new drugs or product candidates. This stage is not covered by any officially recognized quality standard. The ethical conduct of work in this area of basic or applied research depends entirely on the individual scientist's judgement. Consequently, mutual acceptance of data from different laboratories has been difficult. This research is the subject of this handbook and is described more fully in chapter 2.
2. Stage 2 covers the 'safety testing' of drug candidates in non-human models, usually animals. Such studies are termed 'non-clinical' as they are not performed in man. Safety tests include toxicology and safety pharmacology studies, with potential extension to pharmacokinetics and bioavailability. Typically, the conduct of these studies must comply with international standards such as the OECD Principles of Good Laboratory Practice<sup>1,2</sup> or equivalent national regulations.
3. Stage 3 encompasses clinical studies in man. Here, Good Clinical Practice<sup>3,4</sup> is the basis for quality standards, ethical research conduct and regulatory compliance. GCP must be instituted in all clinical trials from Phase I (to demonstrate tolerance of the test drug) through phase II (where the dose-effect relationship is confirmed) to phase III (full-scale, often multicentre, clinical trials in hundreds of patients to confirm therapeutic efficacy and safety).
4. In Stage 4, the post-approval stage, the drug has been registered and is available on the market. However, even after marketing, the safety of a drug in its 'normal' use is monitored through formalized pharmacovigilance procedures.<sup>5</sup> If there are any subsequent clinical trials (phase IV), they must also comply with GCP.

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<sup>1</sup> OECD. *OECD Principles on Good Laboratory Practice* (as revised in 1997). Paris, Organisation for Economic Co-operation and Development, Environmental Directorate, Chemicals Group and Management Committee, 1998 (ENV/MC/CHEM(98)17).

<sup>2</sup> TDR. *Handbook on Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development*. Geneva, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), 2001 (TDR/PRD/GLP/01.2).

<sup>3</sup> World Health Organization. Guidelines for good clinical practice (GCP) for trials for pharmaceutical products. In: *The use of essential drugs. Sixth report of the WHO Expert Committee*. Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850).

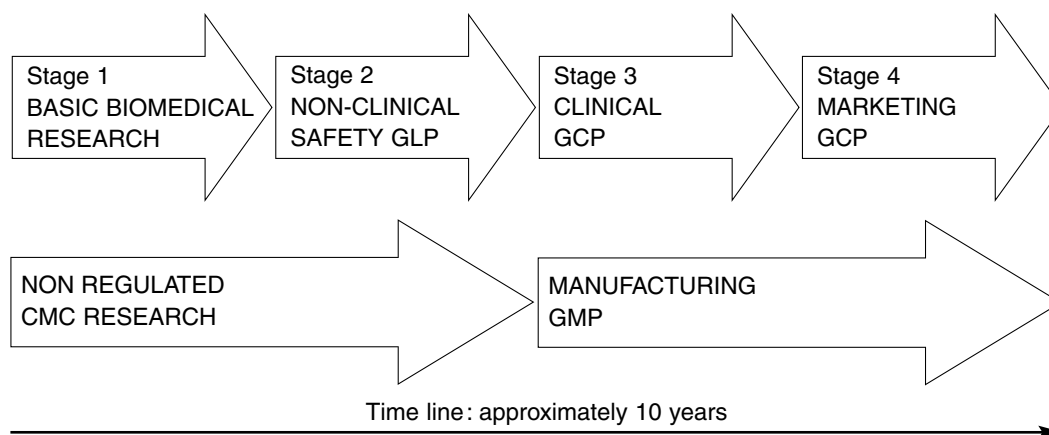
<sup>4</sup> International Conference on Harmonization. ICH Topic E6: *Guideline for Good Clinical Practice*. 1996 (CPMP/ICH/135/95) (<http://www.emea.eu.int/pdfs/human/ich/013595en.pdf>).

<sup>5</sup> WHO Programme for International Drug Monitoring, Uppsala, Sweden (<http://www.who-umc.org/whoprog.html>).

From the clinical stage onwards, throughout the rest of a drug's lifetime, Good Manufacturing Practice (GMP)<sup>6,7,8</sup> applies to all manufacturing and control of bulk and formulated product.

These different steps in classical drug development are summarized in figure 10 below:

**Figure 10. Drug development stages and their respective quality practices**



These GXP ‘quality practices’ are supplemented by other existing WHO quality initiatives governing the activities of laboratories that typically support the drug life cycle, such as clinical chemical laboratories, chemical analytical laboratories and pathology laboratories. In addition, International Organization for Standardization (ISO) guidelines such as ISO 25 guide, ISO 9000 and related documents, promote the development and use of standards for calibration and testing, again complementing the work of laboratories complying with the WHO good practices.

The research and development (R&D) of a new drug usually takes 10-12 years from discovery to registration and marketing. It is estimated that 5% of R&D costs is spent at stage 1, the discovery stage, 10% on stage 2, the non-clinical testing stage, and the remaining 85% on stage 3, the clinical and registration stage.

Clearly, it is essential to take extreme care in selecting, during the earlier and cheaper stages, the right drug candidates or the right principles for disease control for further development. The better the selection during stage 1, the more the development becomes cost effective overall as fewer molecules are abandoned ‘en route’ during stages 2 and 3 after further studies have been conducted at considerable expense.

<sup>6</sup> World Health Organization. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials volume 2 updated edition: good manufacturing practices and inspection*. Geneva, World Health Organization, 2004.

<sup>7</sup> Eudralex. Volume 4: *Medicinal Products for Human and Veterinary use: Good Manufacturing Practice* (<http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm>).

<sup>8</sup> Eudralex. Volume 4: *Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice Manufacture of Investigational Medicinal Products*.

APPENDIX 3

STANDARD OPERATING PROCEDURE:  
TEMPLATE AND INSTRUCTIONS

---

The intention of this template is to provide guidance as to the layout of a standard operating procedure, and indicate the intended content of each section.

**STANDARD OPERATING PROCEDURE**

LOGO

Title: **write descriptive title in bold**SOP no: **123**Business process: e.g.  
**pharmacology, CMC**

Project: XYZ

Edition no: **01**

Topic: for example, apparatus

Applies to: **the name of the unit expected to use the SOP**

Valid from: date (dd mm yy)

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**Signatures**

	<b>Name</b>	<b>Signature</b>	<b>Date</b>
Author	Type name	Write signature	Write date of signature
Peer review	Type name	Write signature	Write date of signature
QA review (if there is QA at the institution – otherwise omit)	Type name	Write signature	Write date of signature
Management approval	Type name	Write signature	Write date of signature

**Purpose**

Write the purpose(s) of the procedure. Start with bullet point, e.g.:

- To ensure correct and frequent maintenance of XYZ.
- To ensure humane sacrifice of experimental animals.
- To ensure uniform content and layout of experimental protocols.
- To describe computer back-up procedures for experimental data.

## STANDARD OPERATING PROCEDURE

# LOGO

<b>Title: write descriptive title in bold</b>		<b>SOP no: 123</b>
		<b>Edition no: 01</b>
Business process: <b>e.g. pharmacology, CMC</b>	Project: XYZ	Topic: for example, apparatus
Applies to: <b>the name of the unit expected to use the SOP</b>		Valid from: date (dd mm yy)

1. Introduction .....	2	5. Definitions and abbreviations .....	3
2. Responsibilities .....	2	6. References .....	3
3. Procedures .....	2	7. Change log .....	4
4. Records and archives .....	3	8. Appendices .....	4

### 1. Introduction

Write a short description of the principles involved and in what situation to use this procedure.

### 2. Responsibilities

Person or role	Activities
e.g. Principal scientist	Describe what activities the scientist is responsible for, e.g. designing the procedure, training, supervision, performing defined steps of the procedure.
e.g. Technician	Describe what activities the technician is responsible for, e.g. complying with this procedure, performing defined steps of the procedure, recording data.

### 3. Procedures

Put all the procedures here. Use Word styles – or similar – to manage titles at different levels, if possible.

Useful to start with materials and equipment. Be precise with regard to the name, grade and supplier of materials, the name, model and supplier of equipment.

**STANDARD OPERATING PROCEDURE**

LOGO

**Title: write descriptive title in bold**SOP no: **123**Business process: e.g.  
**pharmacology, CMC**

Project: XYZ

Edition no: **01**

Topic: for example, apparatus

Applies to: **the name of the unit expected to use the SOP**

Valid from: date (dd mm yy)

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Then proceed to a description of the procedures, step by step. Use a simple, active language e.g. ‘add 5 ml’ rather than ‘5 ml are added’.

Any statistical treatment of data is also a procedure, and if relevant, should appear in this section.

**4. Records and archives**

Write in this section the records you expect to make to document the procedure, and where these records will be stored and eventually archived.

**5. Definitions and abbreviations**

Abbreviation	Full expression and definition
e.g. ml	Millilitre
AOA	Any other abbreviation encountered in the text

**6. References**

Number	Title	Reference or link
Number of reference in the order it appeared in the text	Full title of the reference, and the authors’ names. If there are very many authors, write ‘Author, A.N. et al.’	Write the bibliographic reference or give a link to a relevant website
Ref. 2	Full title, author	Reference or link

**STANDARD OPERATING PROCEDURE**

LOGO

<b>Title: write descriptive title in bold</b>		<b>SOP no: 123</b>
Business process: e.g. <b>pharmacology, CMC</b>		<b>Edition no: 01</b>
Project: XYZ	Topic: for example, apparatus	
Applies to: <b>the name of the unit expected to use the SOP</b>		Valid from: date (dd mm yy)

**7. Change log**

<b>Edition no</b>	<b>Replaces</b>	<b>Change since last edition</b>
Write current version	Write number of previous version	Write changes since last version. If many changes, write 'extensive changes to the whole text' (or similar)
For version 01	Write 'N/A'	New document

**8. Appendices**

<b>Number</b>	<b>Title</b>
01	Title of appendix 1
Or write 'N/A' if there are none	Write 'N/A' if there is no appendix





APPENDIX 4

EXAMPLE OF A STANDARD OPERATING  
PROCEDURE: pH METER

---

It is recognized that there are many ways of using and calibrating a pH meter, normally based on the manufacturer's instructions. The purpose of this appendix is to show how to format the instructions for using a pH meter in the template for a standard operating procedure.

## STANDARD OPERATING PROCEDURE

# LOGO

**Title: pH meter operation and maintenance**

**SOP no: 001**

**Edition no: 01**

Business process: **Pharmacology**

Project: all

Topic: Apparatus

Applies to: **Therapeutic drug monitoring and pharmacology laboratory**

Valid from: 15 May 2005

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### Signatures

	<b>Name</b>	<b>Signature</b>	<b>Date</b>
<b>Author</b>	A. Walubo	<i>Andrew Walubo</i>	<i>1 May 2005</i>
Peer review	D. Long	<i>David Long</i>	<i>2 May 2005</i>
QA review	N. Gawadi	<i>Nadya Gawadi</i>	<i>10 May 2005</i>
Management approval	D. Kioy	<i>Deborah Kioy</i>	<i>10 May 05</i>

### Purpose

- To ensure uniform operation of the pH meter.
- To describe maintenance of the pH meter.

**STANDARD OPERATING PROCEDURE**



<b>Title: pH meter operation and maintenance</b>		<b>SOP no: 001</b>
		<b>Edition no: 01</b>
Business process: <b>Pharmacology</b>	Project: all	Topic: Apparatus
Applies to: <b>Therapeutic drug monitoring and pharmacology laboratory</b>		Valid from: 15 May 2005

1. Introduction .....	3
2. Responsibilities .....	3
3. Procedures .....	3
3.1 Materials .....	3
3.1.1 <i>Equipment</i> .....	3
3.1.2 <i>Reagents</i> .....	4
3.1.3 <i>Disposables</i> .....	4
3.2 Preparation of reagents .....	4
3.3 pH-meter operation and maintenance .....	4
3.3.1 <i>Operation</i> .....	4
3.3.1.1 <i>Making a measurement with the M90</i> .....	4
3.3.1.2 <i>Operating Hints</i> .....	5
3.3.2 <i>Calibrating the M90</i> .....	5
3.3.3 <i>pH sensor information</i> .....	6
3.3.4 <i>Precautions and limitations:</i> .....	6
3.3.5 <i>Maintenance and troubleshooting:</i> .....	6
3.3.6 <i>Display codes and problem-solving:</i> .....	7
4. Records and archives .....	7
5. Definitions and abbreviations .....	8
6. References .....	8
7. Change Log .....	8
8. Appendices .....	8

## STANDARD OPERATING PROCEDURE

# LOGO

**Title: pH meter operation and maintenance**

**SOP no: 001**

**Edition no: 01**

**Business process: Pharmacology**

**Project: all**

**Topic: Apparatus**

**Applies to: Therapeutic drug monitoring and pharmacology laboratory**

**Valid from: 15 May 2005**

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### 1. Introduction

This procedure applies to the operation, maintenance and calibration of the Mettler Toledo PM90 pH meter used in the pharmacology laboratory.

The M90 is a portable microprocessor-based, pH, conductivity and dissolved oxygen meter.

### 2. Responsibilities

Person or role	Activities
Principal scientist	Definition of the procedure, training, monitoring procedure for adequacy.
Technician	Compliance with this SOP. Reports any problems to principal scientist.

### 3. Procedures

#### 3.1 Materials

##### 3.1.1 Equipment

Mettler Toledo PM90 pH-meter with:

- pH sensor
- pH electrode fill solution
- Battery.

**STANDARD OPERATING PROCEDURE****LOGO****Title: pH meter operation and maintenance****SOP no: 001****Edition no: 01**Business process: **Pharmacology**

Project: all

Topic: Apparatus

Applies to: **Therapeutic drug monitoring and pharmacology laboratory**

Valid from: 15 May 2005

**3.1.2 Reagents**

- pH 7 buffer solution
- pH 4 buffer solution
- Distilled water
- Saturated KCl solution.

**3.1.3 Disposables**

- Glass beaker
- Lint-free tissue paper.

**3.2 Preparation of reagents**

- The supplier manufactures all the buffers, and the pharmacology laboratory orders them on a regular basis.
- Prepare KCl solution by dissolving an excessive amount in approximately 30 ml distilled water.

**3.3 pH-meter operation and maintenance****3.3.1 Operation****3.3.1.1 Making a measurement with the M90**

1. Remove the sensor wetting cap and slide the vent sleeve to expose the fill hole.
2. Press 'mode', 'read', 'cal' or 'M' to turn meter on and start measurement.
3. Place sensor into solution.
4. Automatic endpoint detection freezes the display when plateau is reached; to manually endpoint, press 'read'. Press 'read' again to start new measurement.
5. Continuous measurement may be selected by pressing and holding 'read' for 4 seconds. Return to auto endpoint by pressing and holding 'read' for 4 seconds.
6. After use, close the fill hole and replace the wetting cap.

## STANDARD OPERATING PROCEDURE

# LOGO

**Title: pH meter operation and maintenance**

**SOP no: 001**

**Edition no: 01**

**Business process: Pharmacology**

**Project: all**

**Topic: Apparatus**

**Applies to: Therapeutic drug monitoring and pharmacology laboratory**

**Valid from: 15 May 2005**

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### 3.3.1.2 *Operating hints*

1. Use distilled water when transferring from one solution to another.
2. Response time is a function of the sensor and the solution. If the solution is at a different temperature, allow more time for the sensor to respond.
3. Avoid handling the sensor tip.
4. Make sure no large air bubbles are trapped under the sensor when making measurements.
5. Do not use calibration standards after the expiration date.
6. The wetting cap should contain pH 7 buffer.
7. For greatest accuracy, calibrators and samples should be at the same temperature.
8. Keep the electrode filled with the appropriate fill solution to prevent reading drift.

### 3.3.2 *Calibrating the M90*

For greatest accuracy, calibrate the meter regularly.

*For accuracy to one decimal point:*

1. Place the sensor in the pH 7 buffer-calibrating medium.
2. Press 'cal': cal 1 is displayed. After endpointing, the display automatically updates itself to the calibrated value shown or to the temperature compensated value.
3. If 'read' is pressed after Cal 1 update, the meter assumes that one point calibration only is required. Samples can now be measured.

*For accuracy to two decimal points:*

1. Place the sensor in the pH 4 buffer-calibrating medium.
2. Press 'cal': cal 2 is displayed. After endpointing, the display automatically updates itself to the calibrated value shown or to the temperature compensated value.

**STANDARD OPERATING PROCEDURE**

LOGO

**Title: pH meter operation and maintenance****SOP no: 001****Edition no: 01**Business process: **Pharmacology**

Project: all

Topic: Apparatus

Applies to: **Therapeutic drug monitoring and pharmacology laboratory**

Valid from: 15 May 2005

**3.3.3 pH sensor information***For optimum performance:*

1. Before use, remove wetting cap from tip of sensor and slide the vent sleeve to expose the fill hole.
2. Make sure that the fill solution is not more than 25 mm below the fill hole. Add KCl solution if necessary.
3. Gently tap the sensor to remove any air bubbles at the ceramic junction.
4. Condition the new sensor by soaking in pH 7 buffer for 2 hours. Prolonged soaking is not recommended.
5. After use, check the level of fill solution, reposition the vent sleeve to cover the fill hole, and replace the wetting cap containing pH 7 buffer (if the sensor will not be used again for more than 2 days, it is recommended to use saturated KCl in the wetting cap).

**3.3.4 Precautions and limitations**

1. Do not wipe the sensor tip; instead blot dry with a lint-free tissue.
2. Do not leave the sensor in organic solvents, strong basic solutions, concentrated fluoride solutions, or hydrofluoric acid for extended periods. Measurements made in these solutions should be taken quickly and the sensor rinsed immediately with distilled water.
3. After rinsing, soak in pH 7 buffer for 2 hours.
4. Do not measure solutions outside a temperature range of 0 – 100°C.

**3.3.5 Maintenance and troubleshooting**

Prolonged use and ageing may lead to reduced performance, i.e. to slow response, low slope values, continuous drift or erratic readings. This may be caused by:

1. *Air in junction* – remove air bubbles by gently tapping.
2. *Excess KCl crystals* – KCl crystals may build up and settle on the sensor tip, or the KCl may become discoloured. Remove the old fill solution and use warm distilled water to dissolve the crystals. Remove water and refill using fresh KCl solution.



## STANDARD OPERATING PROCEDURE

# LOGO

**Title: pH meter operation and maintenance**

**SOP no: 001**

**Edition no: 01**

**Business process: Pharmacology**

**Project: all**

**Topic: Apparatus**

**Applies to: Therapeutic drug monitoring and pharmacology laboratory**

**Valid from: 15 May 2005**

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3. *Blocked junction* – KCl crystals can block the junction. To test for this, blot the tip dry and air dry for one hour. If no crystals appear at the tip of the sensor, the junction is blocked. Remove the ceramic junction using tweezers and inset new junction. Tap gently to remove any air bubbles.
4. *Contaminated pH bulb* – i.e. protein/oil contamination.  
If protein: soak the sensor in 10% pepsin solution adjusted to pH 2 with HCl for 30 minutes. Rinse with distilled water and soak in pH 7 buffer for 2 hours.  
If oil: wash sensor tip with 50% water-acetone solution. Do not soak the sensor in acetone solution as this may cause the seals to deteriorate. Rinse with distilled water and soak in pH 7 buffer for 2 hours.

### 3.3.6 *Display codes and problem-solving*

Please see operating manual.

## 4. **Records and archives**

Record in your laboratory notebook that you have calibrated the pH meter according to this SOP.

Record the readings with date, project, and your signature, immediately.

Note any malfunction of the pH meter in your notebook, and report the malfunction to the principal scientist.

Note maintenance activities in the equipment log for the pH meter.

Store the notebook in the fireproof cabinet when not in use, and in the archives after the end of the study.

The principal scientist archives the logbook when it is filled out.

**STANDARD OPERATING PROCEDURE****LOGO****Title: pH meter operation and maintenance****SOP no: 001****Edition no: 01**Business process: **Pharmacology**

Project: all

Topic: Apparatus

Applies to: **Therapeutic drug monitoring and pharmacology laboratory**

Valid from: 15 May 2005

**5. Definitions and abbreviations**

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Abbreviation	Full expression and definition
KCl	Potassium chloride

**6. References**

Number	Title	Reference or link
N/A	N/A	N/A

**7. Change log**

Edition no	Replaces	Changes since last edition
01	N/A	New document

**8. Appendices**

Number	Title
N/A	No appendices for this SOP



APPENDIX 5

EXAMPLE OF STANDARD OPERATING PROCEDURE:  
USE OF OHAUS BALANCE

---

As was the case for the previous example, there are different ways of using and calibrating a balance, normally based on the manufacturer's instructions. The purpose of this appendix is to show how to format the instructions for using a balance in the template for a standard operating procedure.

## STANDARD OPERATING PROCEDURE

# LOGO

**Title: Operating the OHAUS balance**

**SOP no: 002**

**Edition no: 04**

Business process: **CMC**

Project: all

Topic: Apparatus

Applies to: **Chemistry unit**

Valid from: 21 Dec 04

### Signatures

	Name	Signature	Date
<b>Author</b>	Myriam Arevalo Herrera	Myriam Arevalo Herrera	2 Dec 2004
Peer review	David Long	<i>David Long</i>	<i>2 Dec 2004</i>
QA review	Nadya Gawadi	<i>Nadya Gawadi</i>	<i>2 Dec 2004</i>
Management approval	Deborah Kioy	<i>Deborah Kioy</i>	<i>20 Dec 04</i>

### Purpose

- To describe the calibration and operation of the OHAUS balance.

**STANDARD OPERATING PROCEDURE**



<b>Title: Operating the OHAUS balance</b>		<b>SOP no: 002</b>
		<b>Edition no: 04</b>
Business process: <b>CMC</b>	Project: all	Topic: Apparatus
Applies to: <b>Chemistry unit</b>		Valid from: 21 Dec 04

1. Introduction .....	2
2. Responsibilities .....	2
3. Procedures .....	3
3.1 Calibration .....	3
3.2 Daily Maintenance .....	3
4. Records and archives .....	4
5. Definitions and abbreviations .....	4
6. References .....	4
7. Change log .....	5
8. Appendices .....	5

**1. Introduction**

**2. Responsibilities**

Person or role	Activities
Coordinator of the chemistry unit	Design of procedure. Training of research assistant
Research assistant	Reviews SOP. Complies with SOP when carrying out procedure.

## STANDARD OPERATING PROCEDURE

# LOGO

**Title: Operating the OHAUS balance**

**SOP no: 002**

**Edition no: 04**

Business process: **CMC**

Project: all

Topic: Apparatus

Applies to: **Chemistry unit**

Valid from: 21 Dec 04

### 3. Procedures

#### 3.1 Calibration

This procedure is to be performed as a routine once a month, and ad hoc if the balance needs re-calibration:

1. Verify that the balance is levelled by checking the spirit level at the rear of the balance.
2. Turn on the balance by pushing the button 'on'.
3. Verify that the weight unit required is correct (g).
4. Place the receptacle that will contain the sample on the balance plate.
5. To tare the balance, push the buttons 'on/off'; the screen must show '0.000g'.
6. Position the control sample until the required amount is obtained.
7. Remove the receptacle and the sample.
8. Sign the user log sheet every time you use the balance.

#### 3.2 Daily maintenance

1. Make a control weighing with an agreed weight (same one each time) and record the result. Recalibrate the balance if the control weighing shows a different value.
2. Protect the balance plate with a sheet of paper before weighing.
3. Do not weigh hygroscopic substances.
4. Remove any material left inside the balance using the brush.
5. Make sure the spatula is clean before use.
6. Do not weigh more than 100g.
7. Sign the user log sheet every time you use the balance.

**STANDARD OPERATING PROCEDURE****LOGO****Title: Operating the OHAUS balance****SOP no: 002****Edition no: 04****Business process: CMC****Project: all****Topic: Apparatus****Applies to: Chemistry unit****Valid from: 21 Dec 04****4. Records and archives**

Register all use and maintenance on the user sheet QM-02-FMT-017.

These sheets are archived, as they are filled up, in the central archive.

Individual values are to be recorded in study file forms, and signed. Study file to be archived in the central archive at the end of the study.

**5. Definitions and abbreviations**

<b>Abbreviation</b>	<b>Full expression and definition</b>
g	gram

**6. References**

<b>Number</b>	<b>Title</b>	<b>Reference or link</b>
N/A	N/A	N/A



## STANDARD OPERATING PROCEDURE

# LOGO

**Title: Operating the OHAUS balance**

**SOP no: 002**

**Edition no: 04**

Business process: **CMC**

Project: all

Topic: Apparatus

Applies to: **Chemistry unit**

Valid from: 21 Dec 04

### 7. Change log

Edition no	Replaces	Changes since last edition
02	01	Added instruction about filling out the user sheet
03	02	Added precaution about hygroscopic substances
04	03	Added details on records and archives

### 8. Appendices

Number	Title
N/A	N/A

APPENDIX 6

**EXAMPLE OF STANDARD OPERATING PROCEDURE :  
CULTIVATION OF THE T2 CELL STRAIN**

---

The example is intended to show how to accommodate disparate and complex instructions into the template. Beyond the standard sections on: purpose, introduction, responsibilities, data and archive, abbreviations, references, history, and appendices, the SOP also contains sections on: safety, materials, reagents, storage and QC, the culture procedure itself, and calculations.

## STANDARD OPERATING PROCEDURE

# LOGO

Title: **Cultivation of the T2 cell strain**

SOP no: **003**

Edition no: **02**

Business process: **Discovery**

Project: all

Topic: Assays

Applies to: **Biology**

Valid from: 21 June 05

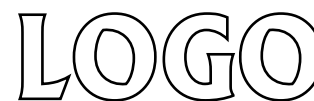
### Signatures

	Name	Signature	Date
<b>Author</b>	Myriam Arevalo Herrera	Myriam Arevalo Herrera	5 May 2005
Coordinator of cell biology unit	David Long	<i>David Long</i>	<i>5 May 2005</i>
QA	Nadya Gawadi	<i>Nadya Gawadi</i>	<i>5 May 2005</i>
Scientific director	Deborah Kioy	<i>Deborah Kioy</i>	<i>15 May 05</i>

### Purpose

- To describe how to cultivate and thaw T2 cells for new studies.

**STANDARD OPERATING PROCEDURE**



<b>Title: Cultivation of the T2 cell strain</b>		<b>SOP no: 003</b>
		<b>Edition no: 02</b>
Business process: <b>Discovery</b>	Project: all	Topic: Assays
Applies to: <b>Biology</b>		Valid from: 21 June 05

1. Introduction.....	3
2. Responsibilities.....	3
3. Procedures.....	3
3.1 Safety.....	3
3.2 Materials.....	3
3.2.1 Cells.....	3
3.2.2 Disposable Equipment.....	4
3.2.3 Apparatus.....	4
3.3 Reagents and solutions.....	4
3.3.1 RPMI for washing.....	5
3.3.2 RPMI with serum.....	5
3.4 Storage.....	5
3.4.1 QC of procedure.....	5
3.5 Culture procedure.....	5
3.6 Results and calculations.....	6
4. Records and archives.....	6
5. Definitions and abbreviations.....	6
6. References.....	7
7. Change log.....	7
8. Appendices.....	7

## STANDARD OPERATING PROCEDURE

# LOGO

Title: **Cultivation of the T2 cell strain**

SOP no: **003**

Edition no: **02**

Business process: **Discovery**

Project: all

Topic: Assays

Applies to: **Biology**

Valid from: 21 June 05

### 1. Introduction

This procedure is valid for all personnel within the cell biology unit of the Institute of Immunology, Valley University. It is part of a series of standard operating procedures for using T2 lymphocyte response.

### 2. Responsibilities

Person or role	Activities
Coordinator of the cell biology unit	Design of procedure. Training of research assistant.
Research assistant	Reviews SOP. Complies with SOP when carrying out procedure.

### 3. Procedures

#### 3.1 Safety

Treat all materials as biohazardous. Wear gloves and lab coat as protection. Materials must be washed in bleach (5% hypochlorite) before they are removed from the laboratory.

#### 3.2 Materials

##### 3.2.1 Cells

T2 cells frozen in liquid nitrogen (vials containing  $6 \times 10^6$  cells in 1 ml of RPMI + FCS and DMSO 20%).

**STANDARD OPERATING PROCEDURE**

LOGO

**Title: Cultivation of the T2 cell strain****SOP no: 003****Edition no: 02**Business process: **Discovery**

Project: all

Topic: Assays

Applies to: **Biology**

Valid from: 21 June 05

**3.2.2 Disposable equipment**

Glass flask, conical	250 cc [catalogue no.]	[supplier]
Micropipettes	20 and 2000 microlitres [catalogue no.]	[supplier]
Tips for micropipettes	New, sterile [catalogue no.]	[supplier]
Serological pipettes	5 and 10 microlitres [catalogue no.]	[supplier]
Pasteur pipettes	Sterile [catalogue no.]	[supplier]
Falcon tubes	15 ml [catalogue no.]	[supplier]

**3.2.3 Apparatus**

Laminar flow cabinet	Code number	Room number
Incubator	37° C, 5% CO <sub>2</sub> [model]	[supplier]
Inverted microscope	[model]	[supplier]
Refrigerated centrifuge	Microfuge [model]	[supplier]
Camera	[model]	[supplier]
Automatic pipettes	[model]	[supplier]

**3.3 Reagents and solutions**

RPMI	[catalogue no.]	[supplier]
Trypan blue	[catalogue no.]	[supplier]
Fetal calf serum (FCS)	[catalogue no.]	[supplier]
HEPES	[catalogue no.]	[supplier]
Penicillin	[catalogue no.]	[supplier]
NaHCO <sub>3</sub>	[grade] [catalogue no.]	[supplier]
NaOH 1M	[grade] [catalogue no.]	[supplier]
HCl 1M	[grade] [catalogue no.]	[supplier]
Distilled water	sterile	Laboratory's own production.

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### 3.3.1 *RPMI for washing*

Weigh out:

- 10.4 g RPMI
- 5.95 g HEPES
- 2 g NaHCO<sub>3</sub>
- 1 ml penicillin.

Put these into an Erlenmeyer flask. Adjust to 1 litre with sterile distilled water, shake until the solutes are dissolved and adjust the pH with 1M NaOH or 1M HCl if necessary. Pass through a 0.22 micrometer filter and store in culture bottles at 4°C for up to 15 days.

### 3.3.2 *RPMI with serum*

1. To 900 ml of the above solution, add 100 ml of FCS.
2. Mix and store in sterile bottles at 4° C for up to 15 days.

### 3.4 **Storage**

RPMI	Sterile bottles 500 ml and 1000 ml	Refrigerator 2-8° C for up to 15 days
FCS	Sterile tubes 500 ml	Freezer -70° C until use.

### 3.4.1 *QC of procedure*

Send culture media for sterility testing in the sterility laboratory.

### 3.5 **Culture procedure**

1. Prepare culture media and reagents according to the SOP on reagent preparation (ref. 1).
2. Make a cell count after thawing, according to the SOP on thawing cells (ref. 2), making a 1:10 dilution with trypan blue to check cell viability (should be >50%, or thaw another vial).
3. Suspend cells in a 250 ml flask in culture medium RPMI 1640 with 10% FCS.
4. Incubate at 37° C and 5% CO<sub>2</sub> for 24 hours.
5. From this stage on, the cell culture is processed depending on the experiment that is to be performed: follow the study plan.

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6. The remaining cells are frozen according to the SOP on freezing cells (ref. 3) and labelled with date, ID of cells, and cell count.
7. *Limitation of the procedure*: if there is a delay in using the cells, store the cell culture at 4°C for no more than 24 hours.

**3.6 Results and calculations**

Count the cells under the microscope (no. of cells x  $10^3$  x dilution x volume of cells in medium) to estimate the number of cells per ml.

**4. Records and archives**

Register all weighing and volumetric measurements in the laboratory books. Record the reagents, including batch numbers.

Record the ID of the cell vial, and all culture conditions.

**5. Definitions and abbreviations**

Abbreviation	Full expression and definition
FCS	Fetal calf serum
HEPES	4-(2 hydroxyethyl)-1-piperazine ethanesulfonic acid
RPMI	Roswell Park Medical Institute (culture medium)



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### 6. References

Number	Title	Reference or link
1	SOP preparing reagents and culture media	CL-01-SOP-002
2	SOP thawing cells	CL 01-SOP-004
3	SOP freezing cells	CL-01-SOP-003
4	Rose RR et al. <i>Manual of clinical laboratory immunology</i> . 3 <sup>rd</sup> edition	Washington DC, American Society for Microbiology, 1986.
5	Weir DM. Cellular immunology.	In: <i>Handbook of experimental immunology</i> , vol. 2. 3 <sup>rd</sup> edition. Oxford, 1978.

### 7. Change log

Edition no	Replaces	Changes since last edition
02	01	Changed source of FCS. Added details on records and archives

### 8. Appendices

Number	Title
1	Storage control for liquid nitrogen samples (CL01-FMT-002)

APPENDIX 7

TEMPLATE AND INSTRUCTIONS  
FOR CURRICULUM VITAE (CV)

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The purpose of this appendix is to give guidance on how to fill out curriculum vitae (CV) details in the template. It is recognized that there are other valid ways to present CV information. Whether you use this template or another layout, remember to provide sufficient detail for verification. The later sections on personal situation are entirely optional.

## CV for first name, surname

<b>First name and surname</b> (include middle names if you wish):	<b>Tel.:</b> 12 34 56 78
<b>Title</b> (if relevant) <b>or letters:</b>	<b>Mobile:</b> 91 01 11 21
<b>Full address</b> , including post code and country:	<b>e-mail:</b> namesurname@address.dk

### 1. Resumé

Write here a *very short* account of your activities to date.

Write here a *very short* account of your educational background.

(‘Very short’ means not more than 20 lines. This is just an appetizer!).

### 2. Career

<p><b>Position and main responsibilities</b> Write the most recent position first, and continue in reverse chronological order Date start, date stop (or continuing) Title of position Name of organization Address or website List of main responsibilities and tasks</p>	<p><b>Organizational reference</b> Name and position of your manager Add telephone number if this person will provide a reference for you (if needed)</p>
<p>Date start, date stop Date start, date stop (or continuing) Title of position Name of organization Address or website  List of main responsibilities and tasks ... and so on</p>	<p>Name and position of your manager Add telephone number if this person will provide a reference for you (if needed)</p>

## CV for first name, surname

### Education

Again, write in reverse chronological order, with the latest qualification listed first. It is up to you how far back you go – include the educational levels that you feel are relevant for the purpose.

Date start, date finish	Title of qualification, educational institution, town, country
Date start, date finish	Title of qualification, educational institution, town, country
Date start, date finish	...and so on

### Further education and training

Reverse chronological order. Include the name of the course or programme, the name of the institution and the country, and dates for start and finish. Both specialist scientific courses and other more general courses (for example, management courses, communication, language) are of interest.

- ABC
- XYZ

### 3. Membership of professional societies and positions of special responsibility

Date start, date finish or continuing	Name of society Your position within the society (member, secretary, treasurer – as appropriate)
Date start, date finish	...and so on

### 4. Publications

Date	Name of publication (full title), volume and number. Write the names of any co-authors
Date	...and so on

### 5. Languages

Name of language, write whether it is fluent and whether it is written or spoken or both. Also list languages which you can read or understand, even if you do not speak or write them well.

### 6. Information technology

List your IT skills, if any.

## CV for first name, surname

### 7. Personal data

Date of birth

Nationality

Civil status (optional), i.e. whether married, single, children.

Interests (optional) – for example, it might be of interest to include any involvement with your local community e.g. your children's school, or participation in e.g. sports or music, since this indicates something of your organizational skills, or your energy, persistence and enthusiasm.

Do *not* include religious or political affiliation, state of health, sexual orientation, or financial situation.

Signature: *First Name Surname*

*Date*

## APPENDIX 8

# TEMPLATE AND EXAMPLE FOR TRAINING RECORD

---

This template is intended to capture the main details about in-house training: the type and content of the training, and the signature and dates of trainee and trainer. Normally there is one trainer and several trainees.

If two colleagues have collaborated on a new standard operating procedure, it is necessary to document training in this SOP and to describe the contents. This can include the fact that a workshop is being held on the new SOP; in this case it does not really matter who takes the role of trainee and who the role of trainer.

### TRAINING RECORD

LOGO

[type first name] [type surname]

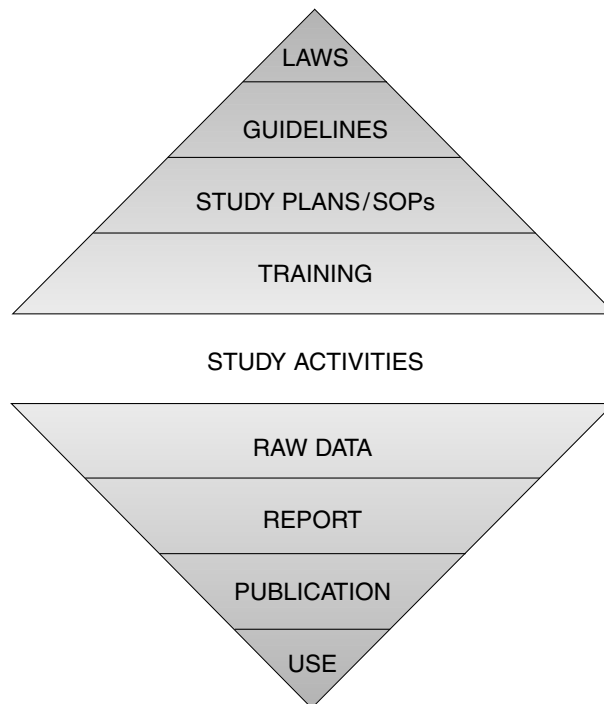
Training	Signature trainee/date	Signature trainer/date
Use of PH meter 01 May 05	<i>Nadya Gawadi 01 May 05</i>	Andrew Walubo 01 May 05
<i>Weighing with OHAUS Balance Balance 07-May 05</i>	<i>Nadya Gawadi 07 May 05</i>	<i>Myriam Herrera 07 May 05</i>
<i>Cultivating T2 cells 9-10 May 05</i>	<i>Nadya Gawadi 10 May 05</i>	<i>Myriam Herrera 10 May 05</i>

## APPENDIX 9

# DIAGRAM: PRESCRIPTIVE & DESCRIPTIVE DOCUMENTATION AND TRAINING

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The diagram shows another way of presenting the hierarchy of prescriptive and descriptive documents, setting them in context with training as the means of translating written instruction into managed activity. Note that legislative stipulations are amplified in detail for each layer. Conversely, details in raw data are concentrated and shortened for use in the report, then further summarized for use in the publication, and finally made even more concise for ultimate use (as in a compendium or governmental monograph).







## APPENDIX 10

# ADAPTING **QPBR** TO A SMALL TEAM OR AN INDIVIDUAL RESEARCHER

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The management tools presented in QPBR also apply to small teams or individual researchers, even though some adaptations need to be made.

	Small team	Individual
<b>Organization and personnel</b>	<p>Agree how the work is to be distributed, and write down and sign a list of responsibilities and activities. This list should cover:</p> <ul style="list-style-type: none"> <li>• How to change the scope and contents of the study.</li> <li>• The use and maintenance of equipment.</li> <li>• The use and care of animals (if any).</li> <li>• The structure of the study file, and how to record data.</li> <li>• Who is to write, and who is to review, the report.</li> <li>• How to archive data and specimens.</li> <li>• How, where and when to publish, and how to share authorship.</li> <li>• Ethics.</li> <li>• Biosafety and safety.</li> </ul> <p>Record the addresses and activities of any other research units who provide services. Update and file the CVs carefully.</p> <p>Keep a training record for all members of the team.</p>	<p>Write a ‘to do’ list of your own responsibilities and activities. Record the addresses and activities of any other research units who provide services.</p> <p>Update and file your own CV and the CVs of key personnel in all other units providing services.</p> <p>Keep a training record.</p>

	<b>Small team</b>	<b>Individual</b>
<b>Facilities, equipment</b>	<p>Check that facilities and equipment will be suitable for the study and will be available for the proposed length of time.</p> <p>Ensure that calibration and maintenance of equipment is carried out and documented.</p> <p>Write down the procedures for using equipment, and be sure that the whole team uses the same procedures.</p>	<p>Check that facilities and equipment will be suitable for the study and will be available for the proposed length of time.</p> <p>Ensure that calibration and maintenance of equipment is carried out and documented. Write down the procedures for using equipment, and follow them.</p>
<b>Documentation</b>	<p>Organize data collection sheets and distribute them to the team (or notebooks or computers as appropriate).</p>	<p>Plan structure of the study documentation before starting.</p>
<b>Prescriptive documentation</b>	<p>Write, date and sign a study plan. Write amendments to the plan as needed, and date and sign them.</p> <p>SOPs: decide which procedures to standardize and agree how to authorize and sign off; otherwise refer to main text of this handbook.</p> <p>These documents may be handwritten in notebooks.</p>	<p>Write, date and sign a study plan. Write amendments to the plan as needed, and date and sign them.</p> <p>SOP: make a careful written and dated description of the procedures you use, and follow them. Update the description as needed, keeping the previous versions.</p> <p>These documents may be handwritten in notebooks.</p>
<b>Descriptive documentation</b>	<p>Records: follow main text.</p> <p>Report: follow main text.</p> <p>Archive: follow main text.</p> <p>These documents may be handwritten in notebooks.</p>	<p>Records: follow main text.</p> <p>Report: find (if possible) colleagues willing to help with the review.</p> <p>Archive: sort your records, specimens and reports, index them, and store them carefully.</p> <p>These documents may be handwritten in notebooks.</p>

	<b>Small team</b>	<b>Individual</b>
<b>Study reports</b>	Even if you are part of a small group, it is possible to ask a colleague to review your report to confirm that in his/her view it reflects the raw data generated by your study.	Ask someone who is attached to another department or university to review your report to ensure it is an accurate account of the study and its results.
<b>Publishing</b>	Be careful not to compromise your own chances of patenting. Refer to the main document.	Be careful not to compromise your own chances of patenting. Refer to the main document.



## APPENDIX 11

# ‘MUST DO’ – A SHORT LIST OF ACTIVITIES NECESSARY FOR IMPLEMENTATION

---

The following table summarizes the most important points required for compliance with QPBR. The list has been compiled in order to facilitate implementation of QPBR; it is not intended to be exhaustive but it will enable research institutions to know whether they meet the fundamental QPBR requirements. The list will also help when preparing to train staff in QPBR requirements.

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### **Organization** (section 4.1)

#### **Summary of requirements in this section**

#### ***Quality policy and staff responsibility*** (section 4.1.1)

- The research institution should establish a written policy describing its quality practices.
  - The responsibilities for each level of personnel should be defined and documented.
- 

#### ***Personnel and training*** (section 4.1.2)

- All personnel should have written job descriptions.
  - All study staff must keep their CVs up to date.
  - Training records for all staff should be kept up to date.
- 

### **Physical resources** (section 4.2)

#### **Summary of requirements in this section**

#### ***Physical resources*** (section 4.2)

- Facilities must provide adequate protection in order to avoid putting studies at risk through mix-ups, confusion or cross contamination.
  - Equipment must be suitable for use in the study; suitability should be supported by documentation.
  - A calibration and maintenance programme for equipment must be established, documented and maintained.
-

**Documentation** (section 4.3)

**Summary of requirements in this section**

**General** (section 4.3)

- Research institutions should maintain both ‘prescriptive’ and ‘descriptive’ documents.
  - Research institutions should ensure that there are full records of all study activities, sufficient to provide complete study reconstruction.
- 

**Research proposal and study plan** (section 4.3.1)

- The research institution should define the difference between the research proposal and the study plan.
  - The research institution should have guidelines for the production, review and approval of research proposals.
  - The research institution should have guidelines for the production, review and approval of study plans.
  - Each individual study should be the subject of a single detailed study plan (one study = one study plan).
  - The research institution should provide the format and a list of minimum contents for a study plan in accordance with QPBR recommendations.
  - The research institution must make it clear that the principal scientist’s signature on a study plan indicates that he/she takes full responsibility for the conduct of the study according to the plan and according to QPBR.
- 

**Standard operating procedures (SOPs)** (section 4.3.2)

- Each research institution must establish appropriate SOPs covering the activities of the institution and the studies performed.
  - The contents of SOPs should follow a standard format set by the research institution.
  - The institution must implement a system for the management of SOPs; this will cover the writing, signature, issuance, modification, withdrawal and archiving of SOPs.
  - The institution provides and records SOP-based training.
- 

**Good record keeping** (section 4.3.3)

- Each research institution must implement rules regarding the recording of raw data.
  - Raw data and other records should be sufficiently detailed and complete to ensure study traceability and reconstruction.
  - If computers are used to acquire, modify, manipulate or archive data, the raw data must be clearly defined.
- 

**Notebooks** (section 4.3.4)

- The research institute must define when the use of notebooks is mandatory and when the use of loose leaf files is preferable for the recording of raw data.
  - The research institute must have guidelines for filling out notebooks and data collection sheets, and have guidelines for handling all types of raw data, samples and specimens.
-

---

**Reporting results** (section 4.3.5)

- Each study should be the subject of a study report (one study = one report).
  - The report must contain a true and accurate representation of *all* raw data.
  - The report should contain a scientific discussion of the results and a conclusion.
  - Any deviations from the study plan should be explained in the study report.
  - Although other specialist scientists may contribute sections to the report and sign the interpretation of their results, the principal scientist has overall responsibility for the report’s contents and scientific interpretation.
- 

**Storage and archiving of records** (section 4.3.6)

- Systems for identifying and indexing documents (in notebooks, on data collection sheets, as printouts or as electronic data) must be established before the study begins, to ensure complete traceability of the study and also rapid retrieval of documents from the archives.
- Study documents should be archived together at the end of the study.
- Access to and retrieval of documents and data should be limited to authorized personnel only.

---

**Supervision/quality assurance** (section 4.4)

**Summary of requirements in this section**

**Reviewing staff qualifications** (section 4.4.1)

- The research institution should verify staff qualifications as part of the recruitment process.
  - The research institution should, as a routine procedure, periodically review qualifications of staff in relation to their responsibilities.
- 

**Verification of results and reports** (sections 4.4.2 & 4.4.3)

- The principal scientist has primary responsibility for the quality, integrity and reliability of the study results.
  - Senior management has responsibility for the timely and routine review of study data.
  - The research institution should arrange for verification of study activities and results by persons independent of the study.
  - It must be possible to audit the report and to trace all results back to the raw data of the study.
-



**Publishing practices** (section 4.5)

**Summary of requirements in this section**

***Publishing practices*** (section 4.5)

- The research institution should have a written policy for publications. This policy should contain specifications for:
  - Authorship
  - Peer review
  - Patenting
  - Data integrity – including publication of negative results of the study
  - Situations where multiple publications are permitted
  - Preferred forum (e.g. journal, conference, poster session).

**Ethical considerations** (section 4.6)

**Summary of requirements in this section**

***Ethical considerations*** (section 4.6)

- The research institution should set high ethical standards and have a written ethical charter which must apply to all personnel. This charter must address people, animals and the environment.
- In particular, the charter must describe the need to respect human rights.
- The charter must address the welfare of animals and the protection of the environment.
- The research institution should establish an ethics committee to consider the ethical implications of its research programmes and approve standard procedures and individual studies.

---

***Biosafety*** (section 4.6.1)

- The research institution must establish written procedures for working with hazardous materials, including biological and chemical materials.
-



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