

TRAINING MANUAL

QUALITY PRACTICES IN BASIC BIOMEDICAL RESEARCH (QPBR)

TRAINER

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Design: Lisa Schwarb

Layout: Sabine de Jonckheere

QUALITY PRACTICES
IN BASIC BIOMEDICAL RESEARCH (QPBR)
TRAINING MANUAL

FOR THE TRAINER

A tool for training and promoting
Quality Practices in Basic Biomedical Research (QPBR)
concepts in disease endemic countries



**World Health
Organization**



**For research on
diseases of poverty**
UNICEF • UNDP • World Bank • WHO

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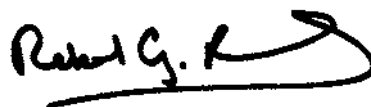
FOREWORD

A key aim of the Special Programme for Research and Training in Tropical Diseases (TDR) is to empower disease endemic countries (DECs) to develop and lead high quality research activities to internationally recognized standards of quality, and so contribute to TDR's primary mission of *"fostering an effective global research effort on infectious diseases of poverty in which disease endemic countries play a pivotal role"*.

One way we have approached this is to produce guidelines and training manuals that will help institutions and researchers attain the highest international quality standards in their research. In 2006 we published a handbook on Quality Practices in Basic Biomedical Research (QPBR) which received worldwide acceptance and acclaim, from both industry and academia. It also created a demand for training, especially in DECs.

This manual (for *trainers*), and the accompanying manual (for *trainees*) will help meet this demand, and will assist institutions in implementing good quality practices. The two manuals, together with the QPBR handbook, now form a sister series to the highly popular series on Good Laboratory Practice (GLP), which has had an impact on the way that laboratory research is carried out in many institutions and countries.

We anticipate that this manual will be useful to all those who aspire to undertaking biomedical research to the best international standards. We believe it will be particularly useful when used with the trainees' manual in workshops and courses on good quality practices. Used together, the QPBR series will help institutions and researchers ensure that research work is produced, recorded, reported and archived appropriately and in a cost-effective and efficient manner.



Dr Robert Ridley, Director TDR,
Special Programme for Research and Training in Tropical Diseases
Executed by WHO and co-sponsored by UNICEF, UNDP, the World Bank and WHO

ABOUT THIS TRAINING MANUAL

Quality practices in basic biomedical research are of paramount importance when resources are limited and when the results of research are to be used to advance science, shape policies or aid decision making. This applies particularly to disease endemic countries (DECs), although quality practices in research are just as essential for other parts of the world.

Establishing good quality practices in research can only improve the quality of research and the veracity of data derived from it. Guidelines on quality of research also steer researchers towards approaching their work in a similar way, no matter where they are working. This is a critical element in research, allowing experiments to be reproduced more easily and the body of evidence on a particular research issue to grow.

In the absence of national or international guidelines on Quality Practices in Basic Medical Research, in 2006 TDR published at WHO a *Handbook on Quality Practices in Basic Biomedical Research (QBPR)* to help researchers throughout the world produce high-quality biomedical research. The handbook highlighted non-regulatory practices that can be easily institutionalized at very little extra expense.

The QPBR handbook was so well received and the demand for training so high (especially in DECs) that the decision was made to develop this brand new manual for trainers of QPBR and an accompanying manual for trainees.

The two QPBR training manuals are based on the QPBR handbook and are designed around a course/workshop on QPBR. They therefore outline the goals of the course/workshop and the topics that should be covered. The manuals include a set of power point slides, questions and case histories on QPBR. The QPBR handbook explains why QPBR is essential and also provides help (through illustrative examples and templates) on how QPBR can be implemented.

The training manuals can be used to conduct standardized and validated training; they provide institutions and researchers with the necessary tools for implementing and monitoring quality practices in their research. Training of trainers will lead to propagation of the number of individuals who can train others about QPBR.

The QPBR series supports TDR's long-term mission of helping DEC's develop their own research activities. Training efforts throughout the world, especially in Asia, Latin America and Africa, will lead to the formation of a global culture of quality practice in research. This in turn should help institutions in their quest for partnerships with both the public and the private sector. Overall, the adoption of QPBR – facilitated by these training manuals – will have the effect of promoting cost-effective, accelerated research with a long-term positive effect on the development of products for the improvement of human health.

ACKNOWLEDGEMENTS

This manual for trainers is part of a suite of three documents produced by WHO/TDR:

1. *Quality Practices in Basic Biomedical Research Handbook* (orange)
2. *Quality Practices in Basic Biomedical Research Training Manual – for the Trainee* (turquoise)
3. *Quality Practices in Basic Biomedical Research Training Manual – for the Trainer* (brown)

Production of the two training manuals was made possible by the enthusiastic support of and contributions from WHO/TDR and the participants in scientific working groups set up under the auspices of WHO/TDR and collaborators.

Our thanks are also extended to those who helped in the production of the *Quality Practices in Basic Biomedical Research Handbook*, on which the training manuals are based. Sincere thanks go to Nadya Gawadi and David Long for their role in drafting this manual.

Comments and suggestions on all aspects of these QPBR training manuals are welcome for consideration in future revisions. Please contact:

Dr Deborah Kioy
TDR
World Health Organization
Avenue Appia 20
Geneva 27 – Switzerland

Tel: + 41 22 791 3524
Fax: + 41 22 791 4854
E-mail: kioyd@who.int

INTRODUCTION

The quality practices in basic biomedical research (QPBR) training manual is an accompaniment to a two-day training course on the subject. The course is divided into six sessions – sessions 1, 2 and 3 are structured for the first day and sessions 4, 5 and 6 for the second. The manual material has been put together to fit the six sessions (see contents page above).

How to use the WHO/TDR material

Course material:

WHO/TDR handbook on QPBR

Trainee manual, including:

- set of PowerPoint presentation slides
- list of goals for each section
- set of questions for discussion for each section
- workshop suggestions for each section
- case studies for discussion at the end of the training course.

Goals

Each section has a set list of ambitious pedagogical goals – at the end of the course you should be able to formulate the requirements of QBPR in order to transmit and implement them (in dialogue with your respective research institutions). The more lively the discussions and exchanges between you and the other participants during this course, the more you will learn; so contribute actively to all the workshop sessions and ask questions of the trainer.

The goals are set in a hierarchy from simple to complex cognitive skills: this is because you will be expected to complete an exceedingly complicated exercise (implementation of QBPR) when you return to your research institution. Simple knowledge of QBPR will not be sufficient for this task.

Bloom's taxonomy of learning domains* is used in the description of goals for each section. This system is not new but can be used relatively simply to categorize the level of abstraction of tasks that occur in educational settings.

*From Bloom, Benjamin S. *Taxonomy of educational objectives*. Boston, MA: Allyn and Bacon. Copyright (c) Pearson Education 1984. Adapted by permission of the publisher. Table copied from University of Victoria web site (<http://www.coun.uvic.ca/learning/exams/blooms-taxonomy.html>).

Competence	Skills Demonstrated
Knowledge	<ul style="list-style-type: none">• observation and recall of information• knowledge of dates, events, places• knowledge of major ideas• mastery of subject matter <p><i>Question Cues:</i> list, define, tell, describe, identify, show, label, collect, examine, tabulate, quote, name, who, when, where, etc.</p>
Comprehension	<ul style="list-style-type: none">• understanding information• grasp meaning• translate knowledge into new context• interpret facts, compare, contrast• order, group, infer causes• predict consequences <p><i>Question Cues:</i> summarize, describe, interpret, contrast, predict, associate, distinguish, estimate, differentiate, discuss, extend</p>
Application	<ul style="list-style-type: none">• use information• use methods, concepts, theories in new situations• solve problems using required skills or knowledge <p><i>Questions Cues:</i> apply, demonstrate, calculate, complete, illustrate, show, solve, examine, modify, relate, change, classify, experiment, discover</p>

Analysis	<ul style="list-style-type: none">• seeing patterns• organization of parts• recognition of hidden meanings• identification of components <p><i>Question Cues:</i> analyse, separate, order, explain, connect, classify, arrange, divide, compare, select, explain, infer</p>
Synthesis	<ul style="list-style-type: none">• use old ideas to create new ones• generalize from given facts• relate knowledge from several areas• predict, draw conclusions <p><i>Question Cues:</i> combine, integrate, modify, rearrange, substitute, plan, create, design, invent, what if? compose, formulate, prepare, generalize, rewrite</p>
Evaluation	<ul style="list-style-type: none">• compare and discriminate between ideas• assess value of theories, presentations• make choices based on reasoned argument• verify value of evidence• recognize subjectivity <p><i>Question Cues:</i> assess, decide, rank, grade, test, measure, recommend, convince, select, judge, explain, discriminate, support, conclude, compare, summarize</p>

SESSION 1

1.1 QUALITY PRACTICES IN BASIC BIOMEDICAL RESEARCH

Goalssta

At the end of the session, you should be able to :

- define basic biomedical research and place it in context with later stage research ;
- describe changes in the social and natural environment that are accelerating health problems today ;
- present the case for QPBR guidelines as an aid to selection of new projects and for the acceptance of new products/principles ;
- describe and exemplify the difference between the scientific content and the practical performance of research studies ;
- recognize the stages of biomedical research and give examples from everyday practice or examples that do not fit the model (include drug products, other products and/or principles for new therapies or strategies).



QPBR – What is basic biomedical research?

What is basic biomedical research?

Session 1:1:1

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QPBR – What is basic biomedical research?

Basic biomedical research refers to activities to find means of detecting, preventing or treating human disease

- Such research covers:
 - discovery and exploratory studies that precede the regulatory phases of drug development*
- or
- studies that precede programmes to develop other methods of disease control

* see (or skip) next 3 slides



Session 1:1:2



QPBR – What is basic biomedical research?

Drug development has four regulated stages:

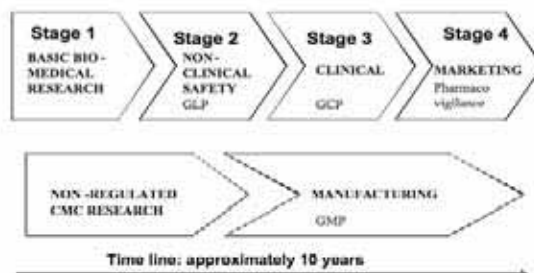
1. Non-clinical stage: to establish drug safety (Good Laboratory Practice – GLP)
2. Clinical stage: to establish safety and efficacy in man (Good Clinical Practice – GCP)
3. Post-approval stage: drug monitored for safety (Good Pharmacovigilance Practice – GPvP)
4. Manufacturing during clinical development and post approval (Good Manufacturing Practice – GMP)

Session 1:1:3



QPBR – What is basic biomedical research?

Seen in context, the regulated quality systems complement or succeed one another as shown



Session 1:1:4



QPBR – What is basic biomedical research?

GXP^{*} quality practices are supplemented by other guidelines

- WHO initiatives: standards for clinical chemical laboratories, chemical analytical laboratories and pathology laboratories (consult WHO web site)
- WHO quality assurance of pharmaceuticals (GMP) 2004
- ISO 25 guide, ISO 9000 and related documents

^{*} GCP, GLP or GMP regulated quality practices taken as one, irrespective of specific type

Session 1:1:5

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QPBR – What is basic biomedical research?

Basic biomedical research: drug development model

Basic biomedical research comprises three stages:

- 1a – discovery per se
- 1b – transitional research^{*}
- 1c – non-regulated, non-clinical research

^{*} sometimes called translational research



Session 1:1:6



QPBR – What is basic biomedical research?

Basic biomedical research: drug development model

Stage 1a – discovery per se:

- researcher notices signs that a compound may have therapeutic potential
- finds ways to establish whether this is a fruitful lead
- observation, literature, knowledge of traditional practices, screening



Session 1:1:7



QPBR – What is basic biomedical research?

Basic biomedical research: drug development model

Stage 1b – transitional research, researcher:

- tries to characterize active pharmaceutical ingredient (API)
- investigates how to produce and analyse API
- continues focused biological experimentation to investigate actions in cells, tissues or organisms



Session 1:1:8



QPBR – What is basic biomedical research?

Basic biomedical research: drug development model

Stage 1c – non-regulated, non-clinical research:

- biological tests on subcellular systems, tissues, whole animals provide evidence of efficacy – i.e. proof of principle (POP)*
- rigorously controlled studies with biological models
- demonstrates biological activity and potential for use in man
- requires sufficient supply of API



* not to be confused with field trials to demonstrate safety or clinical trials to demonstrate efficacy

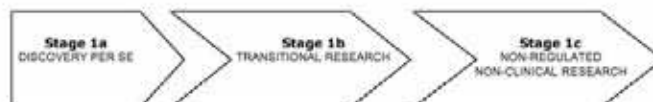
Session 1:1:9

13



QPBR – What is basic biomedical research?

- Basic biomedical research: drug development model



Session 1:1:10



QPBR – What is basic biomedical research?

Basic biomedical research: products other than drugs

- Also comprises three stages of research:

- 1a – discovery per se
- 1b – transitional research*
- 1c – practical proof of principle

* sometimes called translational research



Session 1:1:11



QPBR – What is basic biomedical research?

Basic biomedical research: products other than drugs

- Stage 1a – discovery per se:

- researcher's observations verify that there is a phenomenon worth pursuing



Session 1:1:12



QPBR – What is basic biomedical research?

Basic biomedical research: products other than drugs

- Stage 1b – transitional research
 - Researcher works out strategies for exploiting the observed phenomena
 - Makes prototype equipment or discovers how to modify/influence vectors, etc.
 - Performs preliminary experimentation

Session 1:1:13

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QPBR – What is basic biomedical research?

Basic biomedical research: products other than drugs

- Stage 1c – practical proof of principle (POP)*:
 - researcher uses an experimental model to demonstrate that the right relationships have been identified
 - may include studies to show potential applicability of these insights as practical methods for disease control
- * not to be confused with field trials to demonstrate safety or clinical trials to demonstrate efficacy

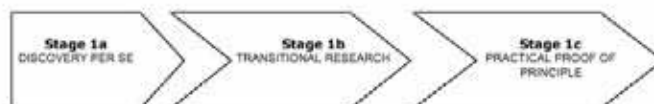


Session 1:1:14



QPBR – What is basic biomedical research?

Basic biomedical research: principles or products other than drugs



Session 1:1:15



QPBR – What is basic biomedical research?

Examples – handbook provides fictitious examples:

- potential drug candidates pp. 20-21
- other principles and products pp. 22-23
 - use these for discussion – give your own examples
- see next page for simpler products

Session 1:1:16

 **QPBR – What is basic biomedical research?**

Recent examples of principles and products other than drugs

- **Winners of INDEX – Design to Improve Life award in 2007:**
 - solar bottle – uses solar energy to purify polluted water
 - mobility for each one – US\$ 8 prosthetic foot for the victims of landmines
 - tongue sucker – prevents unconscious patients swallowing their own tongues
 - receptacle for used hypodermic needles – yellow plastic top mounted on recycled tin or jar

(see www.indexaward.dk)

Session 1:1:17

Questions

- What is basic biomedical research? Give an example from your own experience.
- What urgent health challenges is the world facing? Can you add more examples?
- Why is it difficult to match the needs for prevention and treatment with a supply of new products and/or principles to combat disease and other threats to health?
- Why are guidelines for basic research helpful in enabling the supply of new products and/or principles to combat disease and other threats to health?
- Describe the scope of the QPBR guidelines. Be specific about what is and what is not addressed.
- Why would guidelines facilitate the decision-making process for funding new projects?
- What is fraudulent research? Would the use of guidelines discourage fraud in basic biomedical research?
- What is meant by regulated research? Give examples of some of the regulations and what they cover.
- Where does QPBR fit into the stages of drug development research?
- What phases comprise basic biomedical research?

Workshops

1. Take an example of a research project from your everyday activity and place it in context as a stage in basic biomedical research. What activities preceded it and what will follow?

What is the aim of this project and what studies are involved? How will you consolidate the results for transition to the next stage? Are all the studies in the project at the same stage of basic research?

Present your discussion using the flip chart or board for diagrams, flow charts or any other presentation you prefer.

It is impossible to predict what topics the participants will choose. Bear in mind the descriptions in the QPBR handbook (pp. 17-23) and Appendix 2 (pp. 73-74) when listening to their feedback.

Points to cover in discussion

- *It is important that researchers are aware of the overall aims of the research project and their participation in it.*
- *It is important that researchers know where their particular studies are located in the overall research project, i.e. what comes before and what comes after.*
- *Research projects almost certainly proceed in logical steps with time points at which major decision(s) (GO/NO GO) are taken. It is important that researchers are aware of these milestone events and how their work contributes to the decisions.*
- *It is important that researchers know whether or not their work is covered by specific regulations.*
- *Even if no regulatory texts cover researchers' specific work, there is an evident need for good quality data and solid, credible results as this work will contribute to major decisions during the project.*

2. Use a flip chart to draw up a flow chart showing the different research and development stages for a new drug. Indicate the places at which QPBR and regulatory texts impact the development pathway.

For a basic diagram of the stages of drug development see QPBR Appendix 2, p. 74

1.2 WHAT IS QUALITY IN RESEARCH?

Goals

At the end of the session, you should be able to:

- define “quality” in general terms;
- explain the difference between the scientific content and the practical, organizational aspects of experimental science;
- define the purpose of QPBR in terms of data reliability and added value;
- list the quality attributes of basic biomedical research and outline their meanings;
- describe the sort of activity that the scientific community uses to validate studies and data;
- outline a set of variables affecting a study, possibly introducing bias;
- argue for the importance of careful planning and a written plan for each study;
- summarize the case for using standard procedures for routine activities;
- explain why a named individual needs to take high-level responsibility for the design and conduct of a study;
- explain the purpose of controls;
- assess critically how variables influence study results;
- describe the relationship between plan, study and data;
- describe a researcher’s needs for repetition of a study, e.g. in terms of data and documents.

TDR UNITED STATES OF AMERICA QPBR – What is quality?

What is quality?


Session 1:2:1

TDR UNITED STATES OF AMERICA QPBR – What is quality?

Quality in scientific research has two aspects:


1. fundamental scientific hypothesis
2. practical experimental aspect

Session 1:2:2

 QPBR – What is quality?

- If the underlying science is wrong even well-organized studies do not yield worthwhile results
- If studies are not conducted flawlessly – **high-quality experimentation** – the results obtained are suspect and will not advance knowledge

Session 1:2:3

 QPBR – What is quality?

	Sound science?	Quality practices?	Results acceptable?
Study 1	✗	✗	<i>NO</i>
Study 2	✗	✓	<i>NO</i>
Study 3	✓	✗	<i>NO</i>
Study 4	✓	✓	YES

Session 1:2:4



QPBR – What is quality?

QPBR covers:

- how to organize research work – good practices
- how to promote data reliability
- adding value to research by promoting data credibility

Session 1:2:5



QPBR – What is quality?

It should be possible for peers, scientific journals, development and funding partners or authorities to:

- verify authenticity of the experimental data
- check that the results reported are an accurate representation of the methods used and data obtained

This validates the data and makes them acceptable to the wider scientific community

Session 1:2:6



QPBR – What is quality?

The scientific community must be able to rely on the data and research reports or publications in order to:

- repeat studies
- confirm results/hypotheses
- build on the research to develop knowledge through further studies

Session 1:2:7

23



QPBR – What is quality?

- Quality is normally defined as:

the totality of characteristics of an entity ... that bear on its ability to satisfy stated and implied needs

- Here, the entity is research
- The stated and implied needs are for results solid enough to be used for the development of useful products or strategies for fighting disease

Session 1:2:8



QPBR – What is quality?

- To deliver these needs, scientific research must deliver results that are:
 - relevant
 - reliable
 - reproducible
 - ethical
 - auditable
 - in the public domain
- QPBR provides guidance on implementing practices that ensure that results have these characteristics

Session 1:2:9

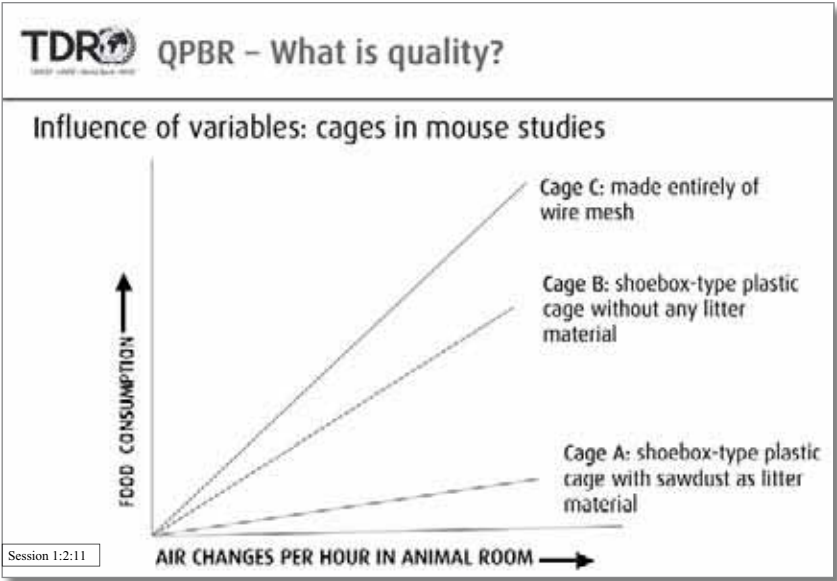


QPBR – What is quality?

Importance of variables

- Scientific activity must generate reliable data
- Meaningful scientific interpretation of results is possible only when founded upon reliable data
- Experimental variables must be kept under control in order to obtain reliable data
- Quality practices (like QPBR) are designed to help scientists to control the variables
- If variables are not controlled the research may yield false negative or false positive results

Session 1:2:10



TDR QPBR – What is quality?

Influence of variables: CPK in rat serum

Anaesthetic	Sampling point	CPK measured
Carbon dioxide	Retro-orbital sinus	100
	Heart	125
	Vena cava	86
Methoxyflurane	Retro-orbital sinus	184
	Heart	102
	Vena cava	69
Phenobarbital	Retro-orbital sinus	536
	Heart	423
	Vena cava	455
Ketamine	Retro-orbital sinus	224
	Heart	160
	Vena cava	169

Session 1:2:12



QPBR – What is quality?

Importance of variables

- Avoid all sources of bias in the experimental set-up
- Consider all influences and inputs to the study before activities begin
- Drawing up plans for the way the study is to be conducted and keeping to them during the experimental phases helps to keep the experiment under control

Session 1:2:13



QPBR – What is quality?

Need for tight control of variables requires researchers to:

- attach importance to careful planning in order to reduce unexpected events
- write detailed study plans
- use standardized techniques
- document all events

Session 1:2:14



QPBR – What is quality?

Importance of good planning

- one research project may contain many different studies
- write a study plan for each study
- ensure that a single scientist has overall responsibility for conduct of the study
- use standard operating procedures (SOPs) to detail each standardized technique

Session 1:2:15

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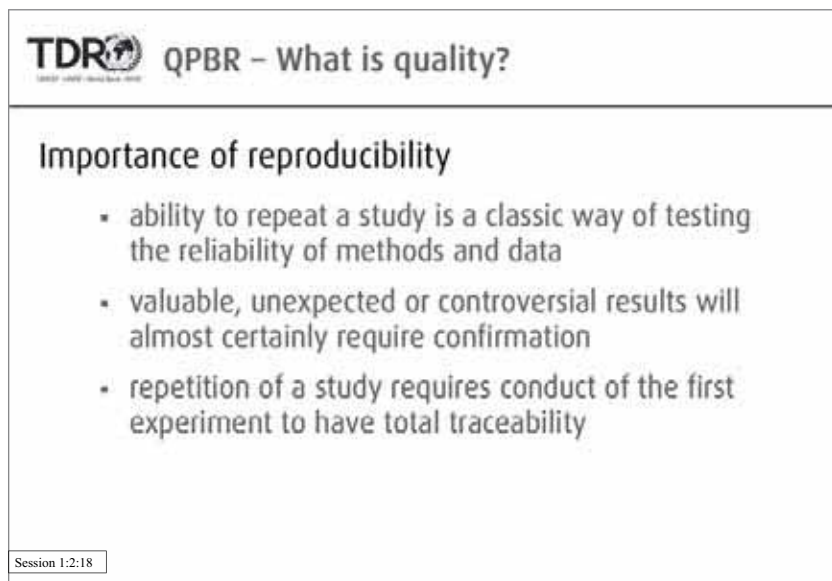
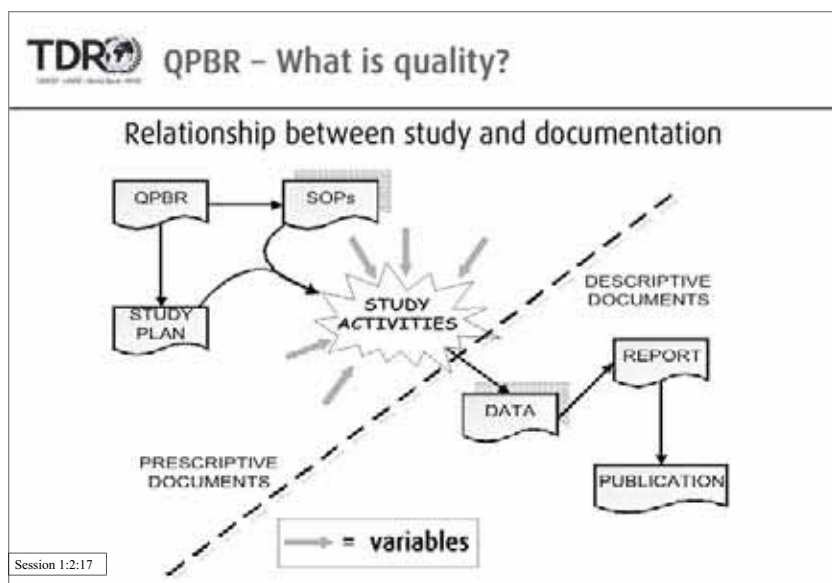


QPBR – What is quality?

Importance of controls

- use control groups of animals when performing in-vivo studies
- in other assays use controls, negative and positive, blanks and QC controls, which prove that the experimental set up is working
- consider intended statistical treatment of data before planning their collection

Session 1:2:16





QPBR – What is quality?

Experimental traceability relies on ability to reconstruct the way in which the study was:

- planned
- performed and monitored
- recorded and verified
- reported

Session 1:2:19

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QPBR – What is quality?

- QPBR is not concerned with the intrinsic value of the scientific hypothesis supporting the study
- QPBR will assist scientists to:
 - generate reliable data
 - reduce the risk of inconclusive results arising from uncertainty about controls, procedures or data
 - obtain data suitable for publication
 - produce credible studies and results

Session 1:2:20

Questions

- What are the two aspects of research quality? What does each aspect contribute to the total quality?
- What is the purpose of QPBR?
- Is there a practical advantage to making sure that your research work is well-organized?
- What value does well-organized research hold for other researchers?
- What is the definition of “quality” in QPBR? Do you agree? Are there other meanings?
- What are the quality characteristics of scientific research?
- Can you briefly define each one?
- What are experimental variables?
- What is the message of the two examples given?
- Why should you spend time on a written plan?
- What sort of information would you include to describe/control variables? Give two or three examples.
- How does the information in the study plan differ from the information in the data?
- Explain the intended scope of QPBR, including what is not covered.

Workshops

1. List the quality attributes of two or three everyday products or services (e.g. a drinking cup, cup of coffee, road, weather forecast, organizing a holiday). Could different examples of the same sort of product have different quality attributes? List your examples and their quality attributes on the flip chart.

DISCUSSION

“Quality is the totality of characteristics of an entity... that bear on its ability to satisfy stated and implied needs” (QPBR handbook, p.26). The aim is to demonstrate that if quality = product/service fit for need/use then formalized methods will produce a product that is fit for use every time. Note that the stated need/use drives the choice of attributes and that “high-quality” cannot be defined as a predetermined set of attributes. The structure of the argument is the same for all examples.

1. It is essential to define the product/service clearly, including its use.
2. List the criteria for success – the quality attributes.
3. Make a first sketch (possibly a mind map or fishbone diagram) of the practical steps to ensure that the right product of the right quality is obtained.

First example: a drinking cup

Product: a drinking cup

Definition: receptacle for:

- holding potable liquids and transporting them to your mouth
- use in your everyday household/at the village garden party/at the Queen's garden party/camping on K2/at the local primary school.

Attributes

- Common to all cups: rigid enough to hold liquid without spill; holds hot or cold liquid; does not burn your hand; rim must not become too hot; smooth rim.
- Further attributes depend on the ultimate required use of the cup: indestructible in a fall; microwaveable; disposable; translucent porcelain; gold enamel.
- Participants must understand that the paper cup and the translucent porcelain are both potentially high-quality products.

Having chosen ONE set of attributes in their discussions, participants should compose a mind map or fishbone diagram outlining the quality system required to achieve these. The quality system should cover: design, raw materials, production equipment, manufacturing processes, personnel, training, instructions etc.

Second example: a cup of coffee

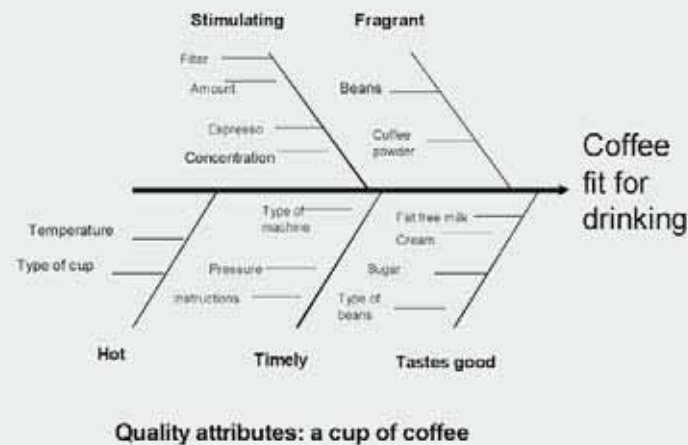
Product: a cup of potable coffee

Attributes

Common attributes: hot; fragrant; tastes good; stimulating; timely.

More specialized attributes influence the quality system for production: simple to make; decaffeinated or caffeinated; fruity or bitter taste; whitened; one cup or large amount for party; drink now or keep hot.

Having chosen ONE set of attributes, ask participants to compose a mind map or fishbone diagram with the headlines for production processes. N.B. HEAD LINES ONLY – there is another exercise on coffee in the workshop about SOPs.



Third example: a road

Product: a road

Definition: elongated piece of land that leads a person from place A to place B

Attributes

- **Common attributes:** start at A and end at B, person/goods still intact, in a roughly defined time.
- **More specialized attributes:** from city to city; for transporting goods; lead to bird sanctuaries; up and down mountains. Attributes: smooth surface; hard surface; drained; keep objective in view by use of signs or lack of confusing side-roads.
- **Specialized attributes:** coloured asphalt; barriers to fast traffic; grass in central reservation; noise barriers; wind protection; hairpin turns to accommodate gradient; military guards, etc. depending on proposed use.

Participants should construct headline mind map, as before. Again, different types of roads can be high-quality depending on the definition of the product.

Fourth example: a weather forecast

Product: a weather forecast

Definition: a prediction about the weather that allows a person to make an accurate plan for successful/suitable activities, appropriate clothing, transport

Attributes

- *Events are clearly described with regard to type, severity, time of onset, time to change, exact areas to be affected, any special danger warnings.*
- *Easily defined by bad quality, inaccurate account of events, omitted storm warnings, incorrect timing, inaccurate charting of regions.*

Participants should construct headline mind map, as before.

Final example: organizing a holiday

Product: holiday

Definition: a period of time intended to provide rest from a person's daily routines, returning intact and on time to resume normal duties

Attributes could be classified as follows:

- *sufficient time period to provide rest from duties*
- *sufficient interest to protect from boredom*
- *conflict minimized*
- *sufficient safety to return still-healthy person to duties*
- *timely return*

There will be different personal opinions on every attribute:

- *time: one weekend, one week, three weeks, three months;*
- *interest: defying death on K2; sunbathing in back garden; playing string quartets; visiting cultural sites; staying with Tibetan monks; sampling different cuisines etc;*
- *conflict: may arise from the interests of the group and/or the group/family structure;*
- *safety: prepared to risk being taken hostage, bombed, exposed to health hazards or self-inflicted harm (e.g. falling out of a hang glider);*
- *timely return: Is this critical? What is the tolerance? Why?*

Having decided on the exact attributes then the proper plan can begin, taking regard of:

- *time of year: season/temperature/school holidays;*
- *locality: country/language/traditions/cuisine;*
- *tourist attractions: sea & beach/mountains/countryside/monuments/art/folklore;*
- *composition of party;*
- *travel: duration/fare;*
- *hotel: price/quality/space/facilities.*

2. List the quality attributes for basic biomedical research. Is this an exhaustive list? Write down what each attribute means in practical, behavioural terms.

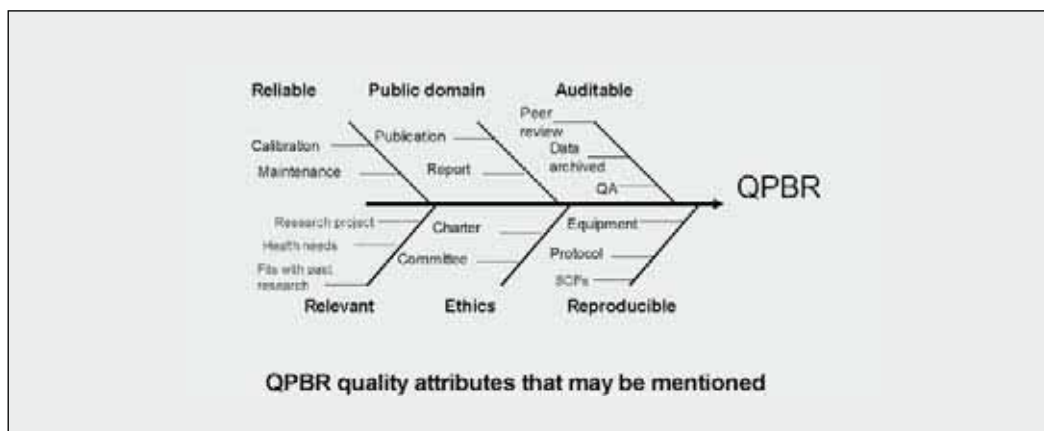
DISCUSSION

Product definition is “research results that are solid enough to enable development of useful products and principles for fighting disease” (QPBR manual p.26). Note the definition is rooted in practicality – the world needs help to fight disease. This definition ensures that people may confidently invest time and resources in activities based on the research results. It is then the researcher’s professional duty to obtain credible results.

Attributes:

- *relevant (focused on health sector, prevention, cure, root causes, principles);*
- *reliable and reproducible (could obtain similar results in similar setting);*
- *ethical (does not damage people, animals, environment);*
- *auditable (anyone could review records, data or reports and vouch for presence and authenticity of information therein);*
- *in the public domain (available for use, critical review/acclaim in published form).*

Some of the QPBR attributes are given as a fishbone diagram. This is not detailed and no doubt participants will develop other valid approaches.



3. Taking one or two studies from your everyday experience write a list of possible sources of bias and discuss measures you could take to minimize artefact to ensure the validity of your data. Present your discussion schematically on the flip chart/board.

DISCUSSION

- *Bias during experiments leads to unreliable or outright false data.*
- *In turn, these data lead the researcher to wrong conclusions. We often speak of false negative and false positive results.*
- *Bias can be introduced from many sources, including:*
 - *researcher – outcome of experiment is biased towards the result expected by the researcher;*
 - *samples selected – e.g. consigning all heavy animals to one study group or placing all non-smokers in group treated with placebo;*
 - *environmental factors during a study – e.g. collecting insects during periods of windy weather in one place and calm weather in another or placing caged animals on racks in group order so that groups on the lower level get less light;*
 - *result evaluation stage of a study – e.g. rejection of data on arbitrary grounds rather than previously agreed criteria;*
 - *reporting stage of a study – e.g. not reporting results that are “uninteresting” (usually negative) or against researcher’s expectations.*

- *It may be difficult to overcome bias. First, it is important to be as aware as possible of all the different types of bias that could affect the research. Before performing an experiment researchers should use a brainstorming session to identify possible ways that bias is introduced. The study protocol should pinpoint these difficulties and attempt to limit them. Variables and bias can be reduced by standardizing procedures (e.g. using SOPs) and ensuring that they are performing in the same way. Peer review helps to overcome the experimenter's own bias.*

4. Give an example of doubtful scientific results in your everyday activity or from the scientific literature. Was the failure due to scientific problems? Problems with experimental conduct/data? A mixture of both? Or something quite different? Use the flip chart to summarize your discussion as a table showing the type of failure and the actual circumstances.

You may wish to refer back to slides 11 and 12 of this section to show two examples of variables that introduce experimental bias and demonstrate the need for well-controlled studies with standardized procedures.

SESSION 2

2.1 ORGANIZATION

Goals

At the end of the session, you should be able to :

- explain why a formal organization is needed ;
- argue for the advantages of a clear allocation of responsibilities and activities ;
- describe management's roles and responsibilities ;
- summarize the checks and balances implicit in the use of peer review and quality assurance (QA) surveillance ;
- explain the practical purpose of the documents involved : quality policy, organizational chart, job description, curriculum vitae (CV) ;
- produce a model job description for three different roles.



QPBR – Organization

Organization & quality

Session 2:1:1



QPBR – Organization

Management's quality statement or policy is a central tool in the implementation of QPBR

- should be a short readable document
- delineates quality practices that all personnel should apply when conducting experimental work
- should be supported by written guidelines or SOPs at all levels
- management should be visibly supportive of these measures
- management should exercise control over these measures

Session 2:1:2



QPBR – Organization

Next slides aim to present the minimum number of roles necessary for implementing the TDR quality practices

- Actual jobs and positions (e.g. student, researcher, lecturer at different levels) would be mapped to these
- For example, principal scientist role could be taken by a professor or a PhD student
- It is necessary to delineate the roles even in small organizations in which one person may take several roles
- Principal scientist has the key operational role in ensuring study quality. A study cannot be performed without a principal scientist

Session 2:1:3

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QPBR – Organization/scientific activities

Director of organization

- policy, provision of resources, budget, supervision

Head of department

- use of resources, supervision, advice/support to junior staff, compliance with institutional policy and QPBR

Principal scientist

- conduct of study, scientific interpretation of results, veracity of data

Technician

- performance of procedures as required in study plan and SOPs

Session 2:1:4



QPBR – Organization/review

Other support staff

- fulfil duties according to instruction

Peer (scientist)

- scientific analysis and collegial criticism

QA personnel

- assist in implementation and maintenance of quality practices; help assure authenticity, traceability and consistency of data and compliance with TDR/WHO quality practices

Session 2:1:5



QPBR – Organization/ethics

Management

- implements peer review; establishes ethics committee and ethics manual

Peer reviewers

- provide scientific criticism for colleagues

All personnel

- compliance with ethics manual

Session 2:1:6



QPBR – Organization

- QA personnel are not employed routinely at research establishments
 - Role is becoming more widespread but not compulsory
 - QA personnel take an active role in implementing and maintaining quality measures
 - Through auditing activities QA keeps management informed of the level of compliance with quality requirements
 - Most effective to organize QA personnel independently of study activities



Session 2:1:7

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QPBR – Keynote

- Research institution should establish a written policy that describes its quality practices
- Responsibilities of each level of personnel should be defined and documented

Session 2:1:8



QPBR – Organization

Personnel and training

- Management should ensure that the responsibilities of staff at all levels are defined in written job descriptions
- Consider scientific field of activity and practical, supervisory and administrative duties
- Ensure that personnel take quality aspects seriously: tutors, PhD students and postdoctoral fellows in university settings. Also those employed in projects on a temporary basis

Session 2:1:9



QPBR – Organization

Personnel and training

- Qualifications and training should be adequate for the activities a person is required to undertake
- Management should verify the qualifications of new personnel at the time of recruitment
 - e.g. by phoning previous institutions and referees
- Further qualification obtained while in post should be documented in CVs
- Training should be offered at all levels and documented in separate training records
- Training should be complete before practical activities start

Session 2:1:10



QPBR – Organization

- Job description should contain:
 - job title
 - main responsibilities and main activities
 - line of reference
 - date and signature
- CV should contain:
 - list of previous appointments, dates, addresses
 - list of education and training, dates, addresses
 - other skills such as languages, IT

Session 2:1:11

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QPBR – Keynote

- 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

Session 2:1:12

Questions

- Who should issue a quality statement/policy? Why should they do this?
- What are the minimum roles needed for studies performed under QPBR?
- Why is the principal scientist a key position? Describe the responsibilities and activities of this person.
- Who is QA? What are QA's main responsibilities? Ideally, QA should be independent of the organization performing scientific study activities – why?
- What are the purposes of a job description?
- Why does an institution need to keep CVs for all staff?
- Why is training a core activity for achieving high quality in basic biomedical research?
- Why should training be documented?
- Why is it important to keep training records for personnel?

Workshops

1. Taking one of your own (or your department's) studies as an example, describe what roles are active and who (job title) occupies these roles. Tabulate responsibilities, roles and job titles. Identify any roles that are missing; situations in which two people appear responsible for the same activity; or responsibilities that are not covered.

DISCUSSION

- *Minimum roles required are: principal scientist, technician/assistant.*
- *Other roles could include a management representative, advisory colleague, statistician, specialized scientist contributing data, archivist, someone who performs peer review.*
- *Is there clear distinction between the job titles, roles and the different sets of responsibilities – or not?*
- *Clear allocation of responsibilities in a clear organizational structure is a prerequisite for good practice.*

2. In your discussion group, for each of your institutions, make a chart showing the incidence of the following: a quality policy, a QA group, routine use of peer review, use of job descriptions, use of training records. If any of these are missing, how would you propose to introduce them?

DISCUSSION

- *Some institutions will have a quality policy, QA, peer review, job descriptions and training records; some will not. Avoid any judgmental attitude.*
- *These tools are intended to strengthen the research process and therefore ensure data quality:*
 - *quality policy describes management's expectations of everyone at the institution;*
 - *QA supports the construction of a quality system (SOPs and other documentation), serves as a witness to the scientific activities and audits the data and research processes;*
 - *peer review makes it unthreatening to discuss activities and data with a knowledgeable colleague; the important role of reviewer will be accorded prestige and resources;*
 - *job descriptions clearly state the expectations for each individual and help prevent duplication or omission of tasks; training records show what training has been received.*

3. Write job descriptions for one or two persons in the group (bullet points rather than full text), using the points mentioned in slide 11 of the PowerPoint presentation on organization and quality.
4. Write a job description for the managers or assistants of one or two other persons in the group.

DISCUSSION

- *Some participants will be familiar with job descriptions. There may be some shyness because jobs often contain unstated expectations or duties.*
- *Especially in small start-up institutions where everyone is expected to lend a hand, a job description might be considered to limit flexibility or present potential conflict by dividing desirable and undesirable tasks between the available workforce.*
- *In reality, a job description:*
- *clarifies a person's responsibility and activities;*
 - *prevents encroachment from other people/roles and abrogation of responsibilities;*
 - *provides a good tool for assessment, along with the training record;*
 - *provides a firm platform for any discussion between employee and manager.*
- *Participants should write their manager's job description in order to appreciate any differences (or not) in their tasks.*
- *Participants should write their assistant's job description to see how that job fits into the whole spectrum of activity.*

2.2 PHYSICAL RESOURCES

Goals

At the end of the session, you should be able to:

- describe important factors to consider when building new facilities;
- argue for the importance of separating activities in research facilities;
- define different ways of separating activities;
- provide examples in which separation of research activities is fundamental to the integrity of research;
- differentiate between the scientist's responsibility for deciding what equipment to use and the need to ensure that all equipment functions correctly;
- argue for the need to implement calibration and maintenance procedures within a research organization;
- distinguish between preventive maintenance and repair;
- describe what documents are needed to ensure full traceability of calibration and maintenance;
- describe the content and use of a fault action report.



QPBR – Physical resources

Physical resources Buildings & equipment

Session 2:2:1



QPBR – Physical resources

- Physical resources are often divided into two categories:
 - research institute buildings
 - equipment used during research

Session 2:2:2



QPBR – Physical resources

Buildings

- Research management must provide facilities:
 - of suitable size, construction and location
- Obviously this depends on the type of research being conducted
- Following points are usually important:
 - suitability/adequacy for the study
 - maintenance
 - documentation, including site plans and tests performed

Session 2:2:3

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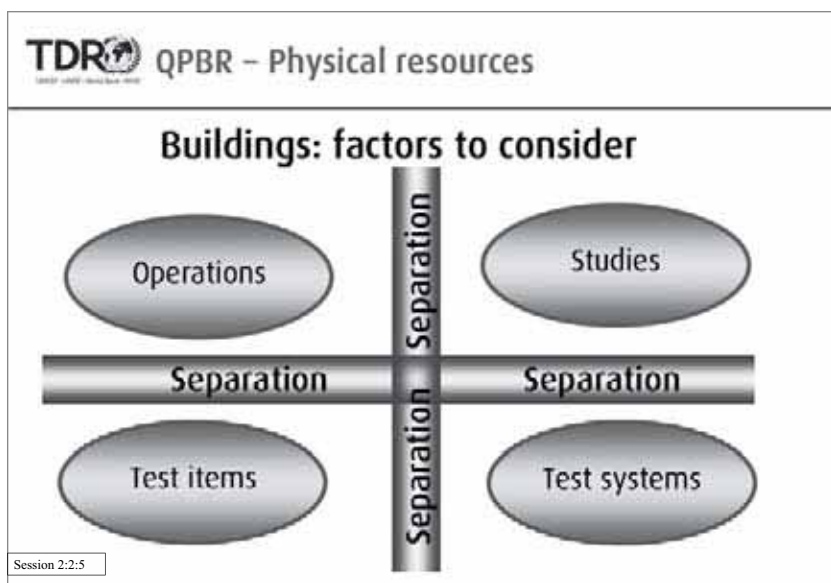


QPBR – Physical resources

Buildings: factors to consider

- Experimental
 - test systems
 - study types
 - number of studies
- Staff
 - safety and comfort
 - possible impact on study
- Operational
 - access/security
 - cleaning
 - storage
 - utilities and maintenance
 - waste disposal

Session 2:2:4



- TDR** QPBR – Physical resources
- Buildings: adequate separation**
- Physical separation
 - rooms
 - cabinets/isolators
 - air systems and filters
 - Separation by organization
 - defined work area
 - one-way systems
 - Different activities in same areas at different times
 - cleaning between activities
 - separate staff
- Session 2:2:6



QPBR – Physical resources

Buildings: adequate separation

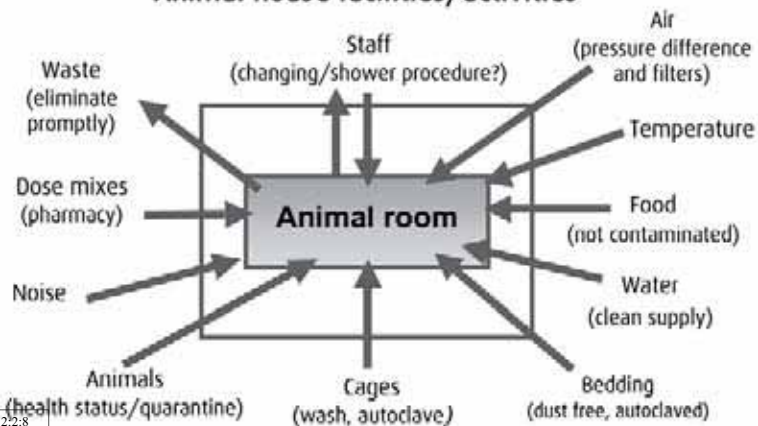
- Animal house facilities provide a good example of organizational constraints and separation
- There is a requirement to:
 - ensure adequate separation of animals and studies
 - prevent unintended movement of contaminants by personnel, air flow, waste products etc
 - provide adequate environmental conditions (temperature, humidity, light, air flow etc)
 - ensure correct husbandry (feed, water, care etc)

Session 2:2:7

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QPBR – Physical resources

Animal house facilities/activities

Session 2:2:8



QPBR – Physical resources

Equipment

- suitability
- calibration
- maintenance

Session 2:2:9



QPBR – Physical resources

Equipment: suitability

- Scientist's responsibility
- Sometimes require proof of suitability
- May need formal equipment qualification

Session 2:2:10



QPBR – Physical resources

Equipment: calibration

- Need proof of standard working conditions
- Calibration usually requires use of standards
- If feasible, link:
 - secondary working standards to -
 - primary standards to - national/international standards
- Fix frequency of calibration in SOP
- Respect calibration frequency

Session 2:2:11

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QPBR – Physical resources

Equipment: maintenance

- Preventive maintenance:
 - regular, frequent checks
 - regular replacement of some parts
- Curative maintenance:
 - fix it when it breaks
 - may need a pool of spare parts
 - may need back-up equipment and/or procedures
 - alarms can help


Session 2:2:12

 QPBR – Physical resources

Equipment: documentation

- Keep records of:
 - calibration checks
 - equipment service plan
 - fault action reports
- Ensure that there are SOPs for:
 - all maintenance actions
 - relations with outside contractors

Session 2:2:13

 QPBR – Physical resources

Equipment: fault action report

BUILDING N°/DEPARTMENT/ROOM	EQUIPMENT ID	
DESCRIPTION OF FAULT	Signature	Date
IMMEDIATE ACTION TAKEN	Signature	Date
ACTION BY ENGINEER	Signature	Date
INSTRUMENT OK FOR USE	Signature	Date

Session 2:2:14

TDR QPBR – Physical resources

Equipment: service label

INSTRUMENT N° _____

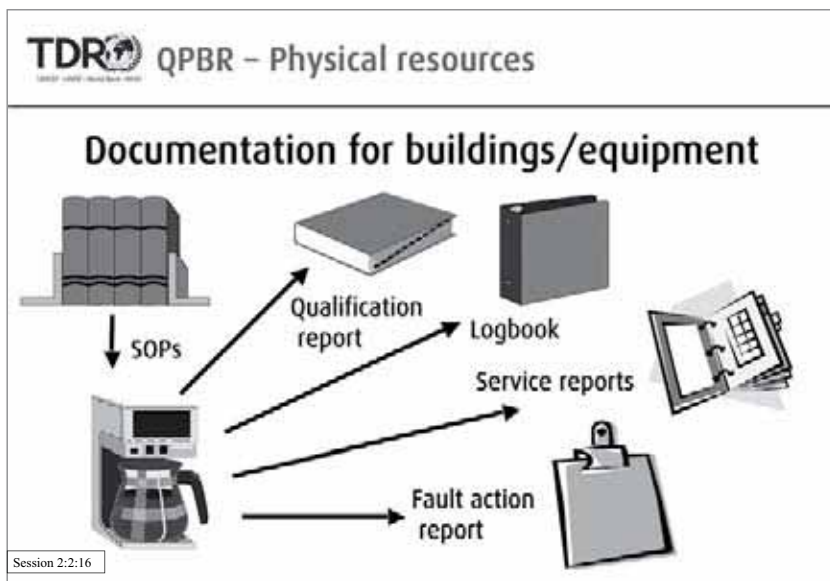
DATE OF LAST SERVICE _____

NEXT SERVICE DUE _____

NAME RESPONSIBLE METROLOGIST _____

Signature/date _____

Session 2:2:15



Questions

- What is separation of activities within a facility? Why is this concept important for the integrity of research?
- Give examples to show how a research project could be compromised by failure to separate research activities.
- Give examples of physical separations frequently found in a research environment.
- Does separation of activities always require physical separation? In what other ways could this separation be achieved?
- Why is the suitability of equipment said to be a scientific responsibility rather than an aspect of quality management?
- What is the difference between a primary and a secondary working standard?
- What SOPs do you think are required for equipment used in a laboratory?
- Give some examples of preventive maintenance performed in your own organization.
- What headings should be included in a fault action report? Who would write it? To whom should it be sent?
- What would a standard logbook contain?
- What would a standard apparatus file contain?

Workshops

1. Taking as examples two different pieces of equipment with which you are familiar, use a flip chart to describe:
 - a. how you would determine suitability for use
 - b. how you would recommend that calibration be performed
 - c. documents you would consider necessary to support the traceability of all actions involving the equipment.

DISCUSSION

- a. Determining suitability for use – the approach depends on the equipment but may include:*

- *simple statement that equipment has been used routinely and given satisfactory results in the range expected for the research intended;*
- *statement referring to the literature on use of the equipment under the same conditions;*
- *written comment that use follows “manufacturer’s recommendation” – is this sufficient?*
- *a suitability test associated with the equipment and the kind of work (e.g. analytical method) for which it is being used;*
- *formal qualification (installation qualification, operational qualification, process qualification).*

- b. Performing calibration – this decision also depends on the equipment but should consider the following:*

- *calibration demonstrates that equipment is running within acceptable limits, therefore the ranges of the equipment should be set by comparison with what is being measured;*
- *frequency of calibration should be fixed before each use (i.e. daily, weekly, monthly);*
- *in advance, establish what action should be taken in the case of calibration which is out of range – some equipment can be considered satisfactory provided it is within a fixed percentage of what is expected.*

- c. Documents required to support the traceability of all actions involving the equipment – it would be good practice to maintain a life-cycle file for the equipment. This would include:
- type and identity (inventory number) of equipment and locality;
 - date of receipt of equipment, testing documentation and commissioning details;
 - log of equipment use – facilitates troubleshooting when equipment malfunctions or breaks down;
 - records of all calibrations – to assure that equipment always functions within the required range;
 - any fault action reports when something goes wrong;
 - date when equipment is retired from use – can be placed in storage with the equipment (if this is not disposed of).

2. Consider a secondary standard used in your laboratory. Use a flip chart to map out the process by which it is linked to (a) a primary standard; and eventually (b) a national standard.

DISCUSSION

The link is assured by progressive calibration, using the process described below.

- *National standard authority provides the laboratory with a primary standard – certificate indicates that it has been checked against the national standard and gives its value. In the case of a check weight the certificate provides the exact weight of the primary standard, an identity number for the weight and a date of validity for the value. In the case of an analytical standard, the standard will be identified by its batch number; will have a use-by date associated with it and a detailed certificate of analysis.*
- *Upon receipt, the laboratory will verify the primary standard against its own secondary standard which will be used on a regular basis. In the case of a check weight the weight can be verified (say annually) to ensure that there*

is no significant change. Primary analytical standards may be used as they are (often after making separate aliquots to avoid possible contamination at each use) or tested against a purified batch of the same compound – the secondary standard (this is often the case in manufacturing companies).

3. List on a flip chart the information/documents that you would require from an outside contractor called in to service an identified piece of equipment that has broken down. What would you do with these documents?

DISCUSSION

- *Information on the company – name/function.*
- *Information on the specific technician – name and company position.*
- *Technician's written diagnosis of the problem.*
- *Details of work performed to correct the breakdown.*
- *Details of tests performed (qualification, calibration) to verify that the equipment is functioning normally after repair.*
- *Records/documents should be signed and dated.*
- *Signed and dated documents should be retained in the life-cycle file.*

4. Design a standard fault action report for your facility.

DISCUSSION

Fault action reports should trace a fault from discovery through to complete resolution:

- *fault description, including date and identity of person first finding the fault (signature);*
- *description of diagnostic tests, date and identity of person performing these (signature);*

- *description and date of work to repair fault (signature);*
- *details and dates of tests/calibration conducted to demonstrate that the fault is repaired (signature);*
- *technician's dated attestation that equipment is again working within specifications (signature).*

5. You have been asked to design and equip a laboratory which will be used for analytical work, including general analysis (potentiometry, high performance liquid chromatography [HPLC] etc.), microbiology and stability studies. List the points that you consider essential for drawing up a requirements document that will form the basis for requests for tenders from architects.

DISCUSSION

The essential point is that the design of the laboratory should allow for SEPARATION of different activities so that none is compromised by mix-ups, contamination or pollution.

- *Physical separation may be achieved by:*
 - *walls*
 - *cabinets*
 - *isolators*
 - *air locks*
 - *heating, ventilating and air conditioning*
 - *filters*
- *Separation of activities may also be achieved by organization:*
 - *defined work areas*
 - *one-way systems*
 - *different activities at different times in the same area*
 - *cleaning between activities*
 - *separate staff for different jobs*
- *With separation in mind, the following design features may be applicable to an analytical laboratory:*

- *area for receipt and storage of test items, reference compounds etc.*
- *storage area for solvents and reagents, small equipment and spare parts*
- *area for dispensing chemicals*
- *area for weighing materials – hoods and cabinets*
- *separate rooms for potentiometric, HPLC and microbiological activities*
- *controlled air flow systems for microbiological laboratories*
- *air locks and laminar flow systems*
- *air conditioning for rooms with sensitive equipment*
- *changing area for staff, if needed*
- *office space, rest rooms*
- *Materials used in construction should allow for easy and regular cleaning – smooth floors, surfaces, water resistant finishing paint.*

SESSION 3

3.1 DOCUMENTATION – OVERVIEW

Goals

At the end of the session, you should be able to :

- explain why full documentation is central to the value of a study ;
- define prescriptive and descriptive documents and give examples of each type ;
- provide in schematic form the relationship between prescriptive and descriptive documents and their relationship to the practical study activities ;
- explain why full records are necessary for study reconstruction ;
- describe the relationship between study data and the study plan and explain what a study file is ;
- describe the relationship between a study report and a publication ;
- argue for formalized storage of study documentation.



Documentation overview

Session 3:1:1

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- It is essential to maintain a full record of all information related to a study:
 - to allow correct scientific interpretation
 - to enable complete study reconstruction
- Documentation is the only way of demonstrating what went on at the time of the experiment
- *“Without documentation the process is meaningless; essentially there has been no study”*
(QPBR p.35)

Session 3:1:2



QPBR – Documentation

- Study records contain:
 - all the data generated
 - documents that prove that the required procedures were carried out at the right time
- Without complete records the study is invalid
- Missing data suggest that the procedure was never performed

Session 3:1:3



QPBR – Documentation

“If it ain’t written down...
it’s a rumour”^{*}

^{*} Aphorism used frequently by inspectors –
who could improve their grammar!

Session 3:1:4

TDR QPBR – Documentation

- Documentation may be divided into two broad categories:

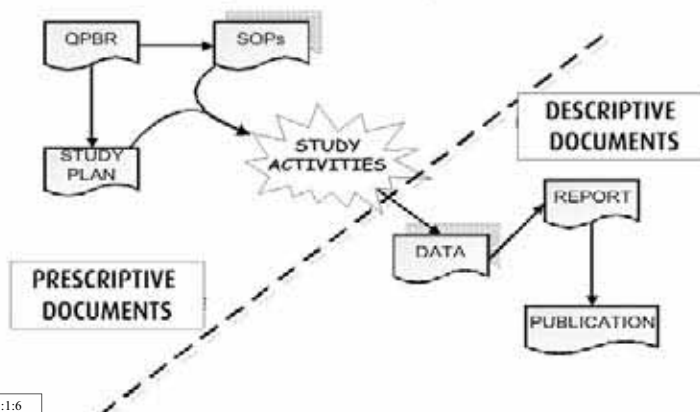
1. Prescriptive documents – give instructions on what is to happen during the study
2. Descriptive documents – describe what actually happened during the study

Session 3:1:5

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TDR QPBR – Documentation

Relationship between study and documents



Session 3:1:6



QPBR – 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 allow complete study reconstruction

Session 3:1:7



QPBR – Computerized systems

Computerized systems and archiving electronic data

Session 3:1:8



QPBR – Computerized systems

- Computerized systems are now used frequently for the collection of data and the transformation of these source data
- Before use, test the system to demonstrate that:
 - data are collected accurately, with correct date and time
 - no loss or corruption occurs when data are collected, transferred or backed up
 - there is password security that functions correctly
 - the person recording the data is identified properly

Session 3:1:9

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QPBR – Computerized systems

- Data should have the same attributes whether recorded via a machine or manually, i.e.
 - must be recorded promptly, accurately, legibly and indelibly (see previous slides)
 - a systematic way of identifying and saving files must be employed, noting the electronic address in the hard copy records
 - should be saved as read only if it is intended that colleagues will have access

Session 3:1:10



QPBR – Computerized systems

- **Any changes to data must be transparent**
 - This is easy in a notebook or worksheet (see above)
 - In computerized systems this is called the audit trail function
 - Not all computerized systems have the capacity to provide an audit trail in which the original data point is preserved; the change identified, time and date stamped; and a reason for the modification noted. If this capacity does not exist alternative means should be used, e.g. changes noted on a paper printout
- **It is essential to ensure that the systems used are updated correctly and that all people working on the same study within the same institution use the same version of a system**
 - Keep track of the software programmes/versions installed on each workstation
 - Employ a procedure in which new versions are installed only after they have been tested

Session 3:1:11



QPBR – Archiving electronic data

- **Electronic data must be archived carefully**
 - Decide on best medium to use (CD, internet store, tape, separate drive on backed-up computer etc)
 - Verify that transfer to this medium does not result in data loss or damage and that data can be recovered without problems
 - Store archived media appropriately, e.g. special cabinet for CDs or an off-site facility
 - Consider archiving data in two separate places so that they can be recovered after a natural disaster (fire, flood, earthquake etc.)
 - Restrict access and record who accesses the data
- **Appoint someone to be responsible for archiving electronic records and for the management of data access**

Session 3:1:12

Questions

Why is full study documentation essential to the validity of a study?

- Can you give examples of studies in which the scientific interpretation was doubtful because records were incomplete?
- What are the essential characteristics of prescriptive and descriptive documents?
- Give examples of prescriptive and descriptive documents that are used in your laboratory.
- What is the function of each document in slide 6 of the lecture on documentation?
- Where does your institution ask you to keep study records?

Workshops

1. Use a flip chart to draw up a flow chart that shows the relationships between a research proposal, study plan, study data, study report and publication(s) concerning the research programme.

DISCUSSION

Important relationships between the documents:

- *distinguish between levels e.g. a research proposal is a higher level document than a study plan;*
- *chart one-to-many relationships e.g. several study plans can belong under one research proposal.*

2. List some of the materials you would expect to have generated by the end of a study (the study file). How soon after the end of the study should the material be archived? For how long should each type of material be stored?

DISCUSSION

- *By the end of a study, at a minimum, there should be a study plan, study report and the raw data.*
- *Other likely materials:*

- study plan amendments;
- raw data such as printout from machines, e.g. weighing, blood parameters, chromatograms and more, depending on study design;
- electronic raw data;
- data derived from processed raw data, showing how the data were collated and worked out, perhaps subject to statistical treatment;
- specimens or samples;
- report sections contributed by colleagues;
- correspondence, reviewer's comments etc.
- Do not discuss general (non study-specific) data such as equipment logs, cleaning records and training records. These are relevant but will complicate this discussion and there is enough other material.
- The file should be organized clearly in boxes or binders and stored safely from the moment the study plan is signed, not left in a heap on a table or shelf.
- Participants may object that "I can always find any item in my chaos." This argument often reflects:
 - a confused mind
 - lack of time
 - items that are put aside because they do not fit into the expected categories.
- Ordering and archiving require energy, attention and time as they are integrated parts of the overall research effort.
- Study file material should be archived promptly – after the report is signed, at the latest. Participants may say that they do not have a safe storage place or that they are too busy to send it to archives.
- If data cannot be found subsequently, there is no study i.e. the easiest way to demonstrate that a study has been performed is to archive the study file.
- Papers should be stored indefinitely as should any specimens that will be useful indefinitely. Warn that some machine printout fades with time and so should be photocopied afresh and signed. The copy should be retained and the original discarded when it becomes impossible to read.
- Discard specimens or samples when they cease to yield any useful information.
- Participants should encourage their management to set a storage period and to decide whether materials belong to individual researchers or the institution.

3. In practical terms, how would management ensure the safe keeping of study documentation? Use the flip chart to draw up a to-do list for management.

DISCUSSION

- *At a minimum, management should provide physical tools for storage during and after the study:*
 - *binders or boxes*
 - *shelving or cabinets*
 - *a closed room (i.e. not a corridor or an area with open access) or fire-proof cabinets.*
- *Provide an SOP for organizing the study file to ensure that everyone follows the same procedure and everyone starts at the point the protocol is signed.*
- *Nominate a person responsible for custody of the study file.*
- *Archive should be a specially allocated area, protected from:*
 - *unauthorized access*
 - *potential damage (fire, water, pests, mould etc.)*
- *There should be an index to show what materials are in the archive and, ideally, a log of movements in and out (materials, persons).*

3.2 PRESCRIPTIVE DOCUMENTATION

Goals

At the end of the session, you should be able to:

- define prescriptive documentation and its relationship to the practical activities of studies;
- name the different layers of prescriptive documentation and describe their relationship to one another;
- describe the purposes of these types of documents and outline the approval process for each;
- define template, layout, format and content;
- give an outline of the types of information typically found in research proposals and in study plans and define the relationship (using a diagram) between these two documents;
- define the responsibilities necessary for the approval and issue of a study plan;
- distinguish between study plan amendments and study deviations;
- describe situations in which study plans and SOPs should be used;
- give examples of SOPs;
- describe the attributes of an SOP management system;
- understand how SOPs contribute to the basic research process;
- argue for the freedom and integrity of the creative research process, despite the use of SOPs.

Prescriptive documents

Session 3:2:1

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Descriptive documents come in various types:

- QPBR – sets out how studies should be organized
- research proposals and bids for work – set out the overall research intentions
- study plans – provide the design and timelines for specific studies
- SOPs – give detailed instructions on how to perform certain tasks

Session 3:2:2



QPBR – Prescriptive documents

Research proposal

- Includes information on:
 - scientific context of the research
 - overall objectives of the research
 - scope (or thrust) of the research
- Indicates the research scientists who will be responsible for sections or studies detailed in the proposal
- Indicates the stages of the research programme

Session 3:2:3



QPBR – Prescriptive documents

Research proposal

- Contains overall time frame and its component stages
- Usually approved by a review board and the management of the institution in which the programme will be conducted – involves allocating human and material resources to the research
- Funding organizations also may have to grant approval

Session 3:2:4



QPBR – Prescriptive documents

Study plan (protocol)

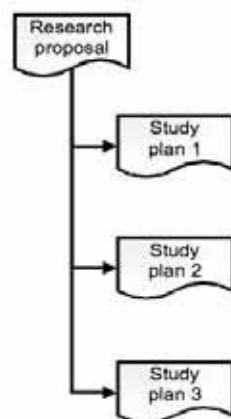
- Provides design and timelines for an individual study that forms part of the research proposal package
- Key document for communicating study intentions to all contributing staff and sponsors – content and layout should be clear
- Every study must have a study plan that is in line with the objectives of the research proposal

Session 3:2:5

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QPBR – Prescriptive documents



Relationship between research proposals and study plans

- A single research proposal may comprise several studies, each requiring a separate study plan
- Each study plan may be under the responsibility of a different scientist – possibly working in separate institutions

Session 3:2:6



QPBR – Prescriptive documents

Study plan gives detail on:

- study purpose and design
- intended methods
- names of scientists responsible for conduct of the study and interpretation of the results, with one person taking overall responsibility
- proposed dates for key events

Session 3:2:7



QPBR – Prescriptive documents

Study plan should allow the study to be repeated, providing sufficient detail on:

- Typical study plan contents**
- test item(s) and conditions for handling and storage
 - type of test system and how it will be handled
 - types and qualities of reagents
 - observations to be made
 - methods for data collection, verification and statistics (if appropriate)

Session 3:2:8



QPBR – Prescriptive documents

Study plan should allow the study to be repeated, providing sufficient detail on:

- methods for reporting and archiving
- ethical considerations
- reference to any previous preliminary work – to ensure traceability
- references to published work and the link to the particular study

Typical study plan contents

Session 3:2:9


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QPBR – Prescriptive documents

- Study plan should be detailed enough to allow the study to be repeated, BUT...
 - routine laboratory procedures covered by SOPs do not need to be described in full; a reference to the SOPs is sufficient
- Principal scientist may require approval from the study sponsor or his/her own management before proceeding with the study
- All those who will be using the study plan (and there may be many) will need their own copy


Session 3:2:10

 QPBR – Prescriptive documents

Use a distribution check-list to ensure that all staff receive the study plan

Study plan distribution list	Date received	Signature
Principal scientist Sponsor Technician in charge Analytical laboratory Clinical pathology Necropsy Statistician Quality assurance ***** *****		

Session 3:2:11

 QPBR – Prescriptive documents

Study plan should be approved by the principal scientist

- Signature of the study plan signifies that the study will be performed in strict compliance with the plan and with QPBR
- Principal scientist assures that all staff are aware of the plan and associated SOPs

Session 3:2:12



QPBR – Prescriptive documents

Changes to the study plan

- Subsequent major, intended modifications to the study plan:
 - require study plan amendment – authorized and signed by the principal scientist
- Minor, unintended deviations are recorded either in the laboratory notebook or on deviation sheets drawn up for the purpose

Session 3:2:13

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Keynote

Research proposal and study plan

- Research institution should:
 - define the difference between the research proposal and the study plan
 - have guidelines for the production, review and approval of research proposals
 - have guidelines for the production, review and approval of study plans
 - 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 to QPBR
 - should provide a format and a list of minimum contents for a study plan in accordance with QPBR recommendations
- Each individual study should be the subject of a single detailed study plan (one study = one study plan)

Session 3:2:14



QPBR – Prescriptive documents

SOPs:

- provide very detailed instructions for repetitive work – routine
- help to ensure that standard procedures are always performed in the same way, thus removing experimental bias and helping to reduce false negatives and false positives
- all research institutions already have SOPs in various forms – recipes for preparation of solutions, directions for operating equipment, step-by-step instructions for technical troubleshooting etc.

Session 3:2:15



QPBR – Prescriptive documents

One-off or non-standard techniques do not require SOPs BUT must be documented

“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”

Quotation generally attributed to Dr Joseph M Juran, based on an idea of Dr W Edwards Deming (two quality gurus)

Session 3:2:16



QPBR – Prescriptive documents

Management of SOPs:

Follow a defined, managed life-cycle:

- writing
- approval
- distribution
- update
- withdrawal

Session 3:2:17

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QPBR – Prescriptive documents

Centralizing SOPs:

- integrate all the procedures into a single, coherent centralized system – do not allow separate SOP systems to coexist in an institution as this will cause conflict and traceability problems
- use a standard SOP layout
- standardize formatting, numbering, approval, issuance, revisions, withdrawal and archiving
- implement a review system for SOPs so that sound techniques are used within the institution
- retain all versions of SOPs (even for techniques no longer used) to provide a complete historical record of the facility's processes
- a long SOP can be avoided by citing the relevant manual in a short SOP – this should pass through the management and review process like any other SOP

Session 3:2:18



QPBR – Prescriptive documents

- SOP systems provide the greatest benefit 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 policies and procedures (format, safety and hygiene, security, personnel management etc.)
- Ideally, the person most familiar with a technique should write the associated SOP – even if a senior person signs off the final approval
- Impose a minimum period for SOP review to avoid clogging up the system with waiting documents

Session 3:2:19



QPBR – Prescriptive documents

Use of SOPs:

- SOPs must be available immediately to staff when they need them
- Staff must fully understand the SOPs they use – this may involve specific training for any that are new or complex
- Staff must rigorously follow the SOPs they employ
- During study conduct, any deviation from the SOP must be documented – this may be the only way of explaining an unexpected result
- When documenting a deviation ensure that it is fully described, explained, signed and dated – the only way to preserve credibility

Session 3:2:20



QPBR – Prescriptive documents

Organizing SOPs:

- To help traceability and facilitate use, often SOPs are organized in a two-tier system:
 - for general policies and procedures
 - for technical methods
- Compile SOPs in an indexed manual for ease of consultation
- Avoid handwritten alterations to SOPs
- Ensure that any changes undergo a formal change control procedure and are reviewed properly before approval

Session 3:2:21

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QPBR – Prescriptive documents

Properly designed SOPs offer many benefits:

- standardized, consistent procedures – minimize person to person and test to test variability
- opportunities to optimize processes
- possibility of capturing technical and administrative improvements
- demonstrate management commitment to quality as part of the SOP process
- ease of documenting complicated techniques in study plans and reports (often a reference is enough)
- preserve continuity when there is personnel turnover
- readily available training manual
- means of study reconstruction after the event, even after a long lapse of time
- means of communication in the event of an audit, visit or technology transfer

Session 3:2:22



QPBR – Prescriptive documents

Successful implementation of SOPs requires:

- sustained support at all levels of management
- commitment to establishing SOPs as essential part of institution's culture
- SOP-based education and training so that all personnel perform the procedure in the same way
- effective SOP management system to ensure that SOPs are available in the right place

Session 3:2:23



Keynote

SOPs:

- Each research institution must establish appropriate SOPs covering the activities of the research institution and the study
- Content of SOPs should follow a standard format set by the research institution
- Institution must implement a system for the management of SOPs – to cover writing, signature, issuance, modification, withdrawal and archiving
- Institution provides and records SOP-based training

Session 3:2:24

Questions

- Why do you need to document your research activities?
- How would you know that time points had been kept / missed or that data are complete / missing?
- What is a template? What is the difference between a standard research proposal (an official form) and the content of a standard research proposal?
- What does a study plan contain? Contrast with a research proposal.
- Who takes overall scientific and organizational responsibility for the study plan and the conduct of the study?
- How do you deal with changes to the study plan?
- Give an example of what could constitute a study plan amendment and what would be classified as a study deviation. How would each of these be documented?
- How could you present instructions for detailed, repeated processes?
- Why is it important to have SOPs?
- Who should write standard operating procedures?
- What are the characteristics of a well-managed SOP management system?
- Can you give some examples of practical SOPs and administrative SOPs?
- Who approves the content and use of SOPs – and why?
- How do you deal with changes to SOPs?
- What is the difference between an SOP and an instruction left for a colleague?
- Would it be reasonable to write an SOP for a procedure that is a one-off in your laboratory? If not, how would you document this?
- Can a manual be used to guide (e.g. use of apparatus)? How would this knowledge be accessed some years after the event?

Workshops

1. Taking two or three everyday processes as examples (e.g. making coffee, cleaning a bathroom, preparing a dinner party) make an outline for an SOP. Who would use these? Present the outline on the flip chart.

DISCUSSION

Everyday examples help to avoid discussions about best scientific techniques and enable participants to practice some generic SOP design skills. Start with a brainstorm for each process.

- *Define the product –it may be easy to define the product of the coffee making but there may be differing opinions on what constitutes the product of the bathroom cleaning; certainly, the product of the dinner party will be quite complex. Participants' decisions are not important; the aim is to provide experience of disagreement and negotiating specifications.*
- *Keep the work moving at headline level; prevent niggling into endless levels of fine detail and thereby getting stuck. Headlines should cover:*
 - *statement of purpose*
 - *expected area of action*
 - *date for coming into force*
 - *list of individual responsibilities*
 - *list of starting materials*
 - *list of activities (in order)*
 - *statement concerning how you know you have finished (the product)*
 - *documentation*
 - *references*

2. You are an expert in a technique which is a standard practice in your research institute. You are asked to write an SOP that will become the standard used by all the technical personnel who perform this technique.

Choose your domain of expertise and write an SOP (in summary form) for one particular standard procedure for the technique in question. You are not expected to

write the SOP in detail but should provide an outline of the sections you would include and the contents of each section. An annotated table, organized set of bullet points or a detailed flow chart would be effective responses.

You may wish to look at the SOP template in QPBR for guidance on the format.

DISCUSSION

- *As before, the purpose of this exercise is to gain practice in the technique of designing an SOP – taking the essential elements in a chosen process and committing them to a written form. It is not the intention to discuss best scientific technique in a given situation.*
- *Refer to the QPBR template in order to facilitate progress. Participants need to classify their knowledge into the separate components of the procedure, as explained above, rather than produce very detailed descriptions.*
- *Use tables, flow charts or bullets to free participants from the written narrative form*

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3. A non-controlled photocopy of an SOP was found pinned to the wall near the machine for which the SOP had been written. What are the possible unfortunate consequences?

DISCUSSION

- *At a minimum – operators may be using the machine incorrectly. The finding shows some additional types of failure:*
 - *if it is not clear when this photocopy was posted it will not be clear how long the data from this machine have been unreliable;*
 - *failed communication about how to distribute and use SOPs;*
 - *failure in training about the distribution and use of SOPs;*
 - *lack of respect for use of the current SOP or compliance with training instruction.*

- *If the photocopy was found by a due diligence reviewer it could foster general mistrust about the authority of the institution's quality system.*
- *If QA made the finding there is a chance that the issue can be discussed and rectified.*

4. Sometimes it is claimed that the use of a study plan or the use of SOPs limits the creative imagination and weakens the research process. Do you agree? What are the arguments for or against this view?

DISCUSSION

- *If some support this view, try to elicit exactly what is meant by creativity in this sense – get as much input as possible:*
 - *time spent writing a protocol (or SOPs) seems burdensome – it would be more exciting just to get on with the practical work;*
 - *it may be that the planned or unplanned activities of the day produce some unexpected observations that the researcher would like to pursue without further delay or red tape.*
- *Protocols offer several advantages:*
 - *communicate proposed actions to researcher and assistants (and management);*
 - *same activities can be repeated on another occasion but still enable recognition of deviations;*
 - *plan formulates expectations of results and (perhaps) the rules of play for statistical differences and P-values;*
 - *“failures” will lead to systematic changes in successive study plans.*
- *Use of SOPs means that routine procedures are written down:*
 - *in the long run, time is saved if procedures are not reinvented every day;*
 - *reproducibility is optimized.*
- *It is always possible to document an unexpected finding and its exploration or resolution by means of a study plan amendment or a note to file explaining the deviation and what was done. Use any well-known example of an unexpected finding that illustrates someone's creativity and place into QPBR context.*

For example, Alexander Fleming's discovery of the antibacterial properties of bread mould; Louis Pasteur's discovery of cholera vaccination after inoculating chickens with "old" cholera cultures (they recovered instead of dying); or the "side effects" of Viagra.

5. For very short assays or tests it may be difficult to decide whether to use SOPs or study plans. Give examples and outline solutions. Discuss how to manage a one-off instruction.

DISCUSSION

- *Ask participants to suggest short assays where confusion between SOPs and study plans may arise – assays involving bacteria, cells or isolated organs are typical.*
- *Emphasize difference between:*
 - *SOP – describes routine procedures irrespective of time;*
 - *study plan – specific with regard to time, date, place, people involved, test item or batch of test item, test system and its specification. Also requires a signature from the principal scientist.*
- *A one-off procedure within a study could be handled by a note to file or a protocol amendment.*
- *For a small study, a short protocol would be appropriate. This would contain time, date, place, people involved, test item or batch of test item, test system and its specification and a signature from the principal scientist. Rather than detailing exact procedures it would reference the SOP or enclose it as an annex. For routine, frequently performed assays, it might be appropriate to design standard, generic protocols and add only specific details (test substance, principal scientists and dates) to the generic protocol.*

6. Go through the SOP template and discuss the sections (including header and footer). Use the flip chart to tabulate the sections and the purpose of each. If you were to implement SOPs at your workplace would you add more sections, leave out sections or do something else entirely? For example, some organizations like to sign each page, some use electronic signatures, some keep to one page and some include a section on safety. Argue for your choice.

DISCUSSION

- *Familiarize participants with the generic contents of an SOP:*
 - *“administrative” information is essential for managing and understanding the SOP;*
 - *the most exquisitely worked-out procedure is of little use without its context – for whom it is intended, which part of the laboratory activities it supports, who wrote and who approved it and time when it comes into force;*
 - *grid for responsibility ensures that activities are assigned to specific roles;*
 - *documentation from the procedure is as important as the procedure itself.*
- *Be open to suggestions and arguments for producing and administering SOPs differently.*

3.3 DESCRIPTIVE DOCUMENTATION – RAW DATA AND RECORDS

Goals


At the end of the session, you should be able to:

- define descriptive documentation and its relationship to the practical activities;
- name the different layers of descriptive documentation and describe their interrelationships;
- describe what is meant by raw data and provide examples of raw data and derived data in a study from your everyday experience;
- explain what is meant by authenticity;
- assess the advantages and disadvantages of any given data collection method;
- outline the advantages and disadvantages of using computers to collect data;
- discuss how to organize contributions from several scientists;
- describe the contents of study records and their interrelationships.

 **QPBR – Documentation**

Descriptive documents

Session 3:3:1

 **QPBR – Descriptive documents**

Descriptive documents:

- describe what actually happened
- should produce records in strict compliance with the rules of the institution
- must identify who performed the procedure and when – signing (or initialling) and dating the data at the time of collection

Once collected, original data are called raw data

- SOPs define which data are to be regarded as raw data

Session 3:3:2



QPBR – Descriptive documents

Raw data are defined as:

- original recordings made during the course of a study

Raw data are necessary for understanding how a study progressed and for subsequent reconstruction

Session 3:3:3

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QPBR – Descriptive documents

From the raw data it should be possible to determine:

- what
- how
- when
- who

Session 3:3:4



QPBR – Descriptive documents

From the raw data it should be possible to determine:

- what was done – demonstrating compliance with the study plan

Session 3:3:5



QPBR – Descriptive documents

From the raw data it should be possible to determine:

- how it was done – demonstrating practical compliance with instructions in the study plan and detailed SOPs

Session 3:3:6



QPBR – Descriptive documents

From the raw data it should be possible to determine:

- when the work was performed – demonstrating existence of the events and their sequence in time

Session 3:3:7

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QPBR – Descriptive documents

From the raw data it should be possible to determine:

- who did the work – demonstrating conformity with the responsibilities that management delegated to suitably qualified personnel

Session 3:3:8



QPBR – Descriptive documents

Characteristics of the collection of good raw data

- **Attributability** – data can be traced to their source e.g. by study number, sample number, parameter etc:
 - unique identification of data relating to an individual study helps to prevent mix ups
- **Originality** – raw data constitute the first record of the observation:
 - data should not be collected on scraps of paper and then transcribed in their final form
 - when a computer is used to collect data it is necessary to define whether the signed printout or the electronic recording is the raw data
 - if electronic data are designated as raw data, the computer must be protected by password and backed-up regularly

Session 3:3:9



QPBR – Descriptive documents

Attributability and originality are assured by recording data:

- **promptly** – record immediately the observation is made, not some time after finishing, as memory is notoriously defective
- **accurately** – raw data must be a true record of the observation; this is central to the integrity of the study
- **legibly** – data that cannot be read are useless; records that are difficult to decipher raise doubts about their credibility
- **indelibly** – do not use media that can be altered without leaving trace (pencil)
 - any changes should be made in a way that does not obscure the original
 - all changes should be explained; person responsible for making the change should sign and date it

Session 3:3:10



QPBR – Descriptive documents

Compilation of data

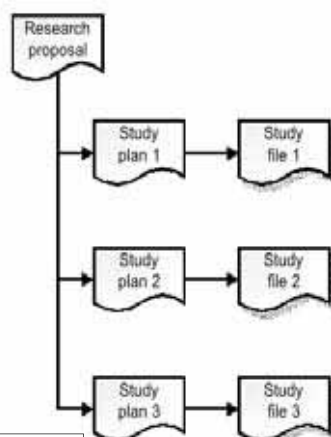
- Data should be recorded and organized to facilitate subsequent processes:
 - data processing and statistical analysis
 - interpretation
 - reporting
 - auditing
 - archiving
- Raw data for the study include:
 - handwritten observations
 - electronic data and printouts
 - analytical traces
- Total study records include:
 - raw data
 - data analyses and statistics
 - notes made during the study

Session 3:3:11

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QPBR – Documentation



- All the study records, the study plan and amendments and (later) the study report should be compiled in the STUDY FILE
- Study file, complete with all relevant documents, is archived as the study progresses (for long-term trials) or at the end of the study

Session 3:3:12

 **QPBR – Keynote****Good record keeping**

- Each research institution must implement rules for 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 raw data, the raw data must be clearly defined

Session 3:3:13

 **QPBR – Descriptive documents****Notebooks**

- Some organizations require notebooks to be used during studies, particularly during the very early stages of discovery
- Notebooks are usually numbered sequentially – sometimes by the laboratory's own organization, sometimes by an outside authority
- Notebooks can offer advantages for research that is a continuous process (small daily additions):
 - everything is in the same place, nothing gets lost
 - notebook is always at hand and is practical in the field
 - each person is responsible for his/her own notebook
 - consecutive numbering of notebooks is easy
 - in some countries patent laws require the use of paginated notebooks

Session 3:3:14



QPBR – Descriptive documents

Notebooks

- Disadvantages
 - Planning (prescriptive) and records (descriptive) are intermingled and it is difficult to see any amendments to a study plan
 - Sometimes one notebook contains data from different studies or technicians use their own notebooks when working on the same study. This complicates data compilation at the end of a study and makes it very difficult to be certain that all the study data have been reported
 - Notebooks do not contain everything. Data are also captured on other media (e.g. assay printouts, gels, slides) but this may not be clear from the notebook
 - When different notebooks are also used to record the status of laboratory equipment, it is difficult to follow the life-cycle of each apparatus

Session 3:3:15

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QPBR – Descriptive documents

Use notebooks with caution:

- ideally use a separate notebook for each study
- number all notebooks and pages consecutively before they are circulated
- keep first page clear for compiling an index when the book is full
- ensure that plans (prescriptive parts) are easily distinguished from records (descriptive parts)
- make clear when the line of enquiry is finished and you are ready to report
- reference any related activity and locations of data and specimens
- sign and date each day's work and make corrections following the rules of the institution – never tear out pages
- principal scientist should review and countersign the work promptly
- store notebooks safely when not in use
- notebooks and pages accessed must be referenced exactly in the report

Session 3:3:16

TDR QPBR – Keynote

Notebooks

- 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
- 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

Session 3:3:17

Questions

- Why do you need to document your research activities?
- What aspects of the research process do the data support?
- What is meant by raw data?
- Are there other types of data?
- What are the minimum identifiers of authentic raw data?
- Why is it important to collect data promptly? What else characterizes good raw data capture?
- What are the advantages /disadvantages of using loose, pre-printed data sheets?
- What are the advantages /disadvantages of using notebooks?
- What would you do if you realized that the raw data were incorrect?
- What is meant by study file? What is the minimum content of a study file?
- How do study reports relate to raw data?
- Do you use computers to capture data?
- Do you store raw data on the computer? Are there any special precautions to observe, given that a study loses validity if data are lost?
- What other raw data might be necessary (other than raw data pertaining to the study?)

Workshops

1. Taking one of your own studies as an example, make a list of the raw data parameters you collected and the format in which they were collected (i.e. data sheet, notebook, computer, machine output). Use a flow chart to follow the route of each parameter to the report (i.e. conversions, computer processing, statistics).

DISCUSSION

- *This exercise builds awareness of the complexity of data collection and data processing.*
- *Ask participants to identify places in the route where mistakes may occur and where checking procedures could usefully be employed.*

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2. Design a raw data form for the collection of blood samples that are to be sent to a bioanalytical laboratory for analysis.

DISCUSSION

Participants should discuss the purpose of the form

- *Firstly, has to be absolutely traceable back to the study for which the samples are needed.*
- *Secondly, has to function as a work order, at a minimum should carry:*
 - *study number*
 - *type of animal*
 - *date and timing (relative to dose)*
 - *requests for number of samples*
 - *exact type of sample (matrix, handling)*
 - *exact animal ID.*

3. Do you perform the experiments with other people? If so, how is data collection organized? How can the scientists understand each other's contribution and how is data checking performed? In your discussion group compare your ways of organizing this process. Present verbally.

DISCUSSION

- *Exercise teaches participants how to communicate their arrangements to collaborators.*
- *Look for clarity in their accounts and evidence of firm agreements between the collaborators concerning data collection and checking.*
- *Some participants may have been reluctant to make firm agreements with collaborators in case this was interpreted as lack of respect or trust.*
- *Discuss how data collection and data checking could be arranged to the benefit of all collaborators and as an integrated part of the research process. It is advisable to note these agreements within the initial study plan or any contract.*

4. How does your organization check the authenticity of data? How does it check accuracy? Make a list of activities on the flip chart.

DISCUSSION

- *There is great variation between approaches:*
 - *no checks*
 - *informal checking*
 - *other types of checking, including supervision by senior staff members, peer review, collaboration, QA audits, data checking of tables etc.*
- *Encourage participants to discuss whether these methods are effective and efficient.*

5. What would you do if you realized the data were incorrect – at the moment of collection? A day later? One month later? After the report is issued? After publication? Use the flip chart to tabulate these time points and the sort of action you consider appropriate.

DISCUSSION

- *Day of collection – go back; if there is a valid data value correct data clearly by hand but leave original value visible. Justify the change, add date and initial.*
- *Day later – method noted above may be in order if the valid data value still exists.*
- *Month later – it will be difficult to find a valid data value to replace the original:*
 - *could mark the values as unreliable (signing and dating the raw data) and then perform the data analysis with and without the unreliable values to produce two sets of results;*
 - *may be possible to repeat the study or part of it (N.B. a study plan amendment will be necessary).*
- *After report is issued, action depends on how flawed the data were:*
 - *withdraw report and replace with amended version; or*
 - *withdraw and repeat study.*
- *The case for unreliable data has to be very convincing to avoid any suspicion that the withdrawal and repeat could be based on dissatisfaction with the result of the study.*

6. Taking one of your own studies as an example, list the contents of the study records (= study file) and present on the flip chart. Divide the documents into prescriptive and descriptive.

DISCUSSION

- *Classify documents in two columns – prescriptive and descriptive.*
- *Look for, at least:*
 - *study plan*
 - *amendments, deviations*
 - *all study data*
 - *records of samples and specimens*
 - *intermediate documents showing various data collations and transformations*
 - *data analysis and statistics*
 - *final report*
 - *correspondence, minutes of meetings.*

3.4 DOCUMENTATION – REPORTS AND STORAGE

Goals

At the end of the session, you should be able to:

- explain why it is important to protect study documentation during the whole course of the study and after the report is complete;
- categorize reports into prescriptive and descriptive documents;
- explain the relationship between individual study reports, articles in the literature and the global account of an entire research project;
- describe in general terms what comprises a study report;
- specify the individual responsibilities of those who author, review, edit and approve a study report;
- explain management's role in generation and issue of reports;
- argue for the necessity of allocating human and physical resources to archiving activities;
- distinguish between archiving and storage in a locked/ fireproof cabinet;
- explain management's role in ensuring the integrity of study documentation.

Reporting results

Storage of results

Session 3:4:1

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- Each study (defined by its study plan) must have a report
- Report contains:
 - account of the study
 - description of any deviations from the plan
 - tabulated results
 - presentation of significant results
 - critical discussion
 - conclusion
 - list of references, notebooks, literature etc.

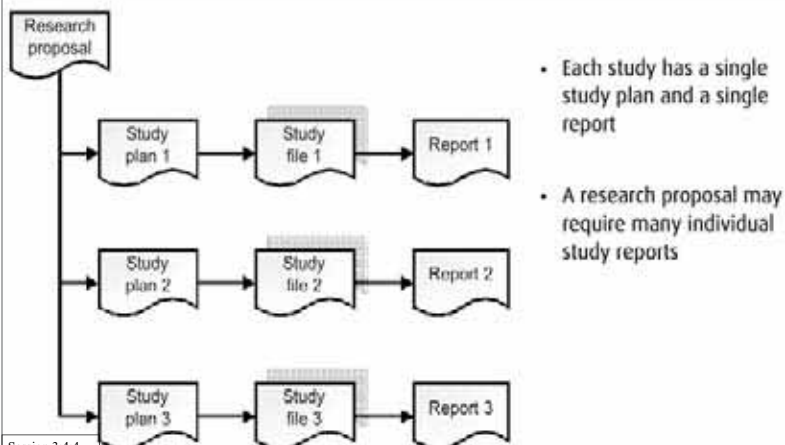
Session 3:4:2

TDR QPBR – Reporting results

- When there are contributions from several colleagues:
 - each of the scientists retains responsibility for the veracity and quality of their own contribution
 - principal scientist takes responsibility for the overall scientific content of the report and interpretation of the results as a whole
- Writing the report:
 - do so as soon as the practical work is complete – while the study is fresh in the mind
 - evaluate all the results
 - do not omit results without providing an argued justification in the report

Session 3:4:3

TDR QPBR – Documentation



Session 3:4:4



QPBR – 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 contents and its scientific interpretation

Session 3:4:5

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QPBR – Documentation

Storage and archiving of records

Session 3:4:6



QPBR – Storage & archiving

- During the study. Principal scientist has direct responsibility for ensuring safe storage of data and other study file documents
- End of the study. All the raw data, the study plan and final report are combined into a single package of information – the study file:
 - also contains material such as letters between scientists about the study, approval from the institution's ethics committee, results of water analyses, etc.
 - should contain all the information needed for perfect reconstruction of the planning and conduct of the study
 - will be subject to verification and checking


Session 3:4:7



QPBR – Storage & archiving


- Study file should be formally archived in order to protect the data from loss and damage
 - Requires a procedure to cover archiving – when principal scientist passes responsibility for the study file to the archivist
 - Also requires formal procedures covering retrieval of the study file (or parts of it) from the archives

Session 3:4:8

**TDR** QPBR – Storage & archiving

- The records are much more than just a collection of documents, they represent the value (in time, resources and economic potential) of the research
- To protect the assets laid down in the institution’s work the archive facility should be sufficiently large and well-built to:
 - limit access to the archives to authorized personnel only
 - protect archive materials from physical damage (e.g. flood, fire, pests)
 - retain the records for at least the time it takes to develop the product through all its stages to market approval or use in the community

Session 3:4:9


**TDR** QPBR – Storage & archiving

Archive submission form

DEPT./GROUP: PROJECT: STUDY N°:	Holding number :
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QUANTITY	DESCRIPTION	COMMENTS
Date	Signature of submitter	Signature of archivist


Session 3:4:10

 **QPBR – Storage & archiving**

Archive: history/events form

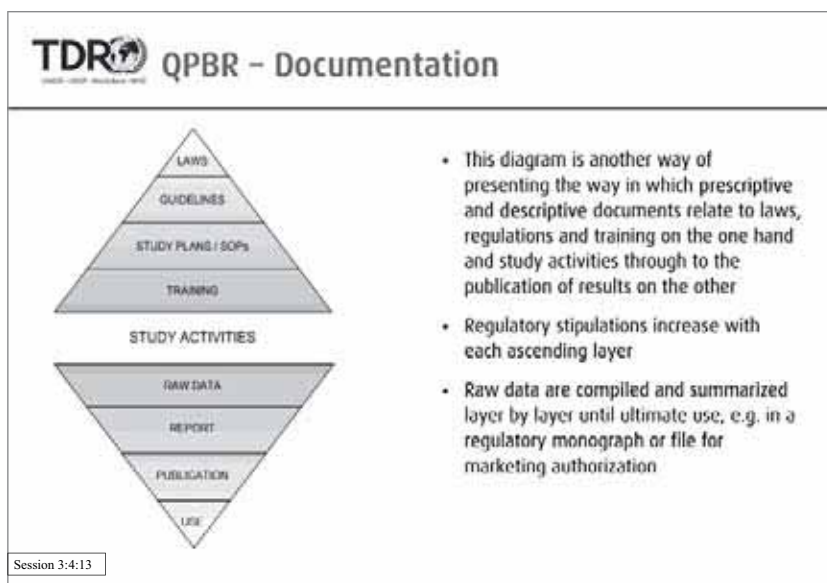
Date	Events	Authorization

Session 3:4:11

 **QPBR – 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 the 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
 - Electronic data and documents should be stored in read only format

Session 3:4:12



Questions

- Why is it necessary to have a procedure for protecting study documentation?
- Where should study materials (data, samples, specimens etc.) be stored during the practical activities; during writing /editing of the report; after the report has been issued?
- What is management's role in the generation and management of study documentation?
- How soon after completion of the practical activities should the report be written?
- How do study reports relate to the protocol?
- How do study reports relate to raw data?
- What are the main sections of the study report?
- Who should review the report before approval and issue?
- What does the reviewer's activity actually mean in terms of what they have reviewed or checked? What does their signature signify?
- Who is responsible for the completeness of the study file?
- What are the characteristics of a well-managed archive system? How are these different from the characteristics of the fireproof cabinet?

- What sort of documentation should an archivist keep to show that the archive is properly managed?
- Besides study documentation, what other documentation might an archive contain?
- How does your facility approach the need for archiving electronic data?
- For how long should study documentation be kept? What about specimens, samples, test item(s)?
- Should it be possible to remove materials from the archive?

Workshops

1. Describe the ideal writing, review, editing and approval process for scientific reports produced in an imaginary research facility. Use the flip chart to tabulate authors and reviewers according to job title, activity, responsibility, meaning of signature.

DISCUSSION

- *Often, writing up is perceived as one step rather than an articulated process. Ask participants to identify the steps in writing – their order, content and purpose.*
- *Suggest constructing a flow diagram to clarify the process before tabulating the information as required:*
 - *author holds ultimate responsibility for quality and content;*
 - *reviewer can offer a great deal of help in presentation, clarity, scientific context, scientific logic – and should give the author a hard time!*
 - *assistant staff might perform a close quality control check of tables, numbers and conversions;*
 - *QA looks for consistency, readability, compliance with any company standards and authenticity but does not question the scientific content and value as this is the remit of the peer review;*
 - *management may also review, in this case raises questions such as – does this work reflect the standard of my institute? Management will assure the world that the study was financed by and performed in their institute.*
- *Contributions differ according to role.*

2. Design a form for transferring materials to the archive.

DISCUSSION

- *Principal scientist, not the archivist, should prepare material for handover to the archive.*
- *Such preparation requires the compilation of a full inventory of the materials listed in workshop 6.*
- *Materials require sufficient identification to enable the archivist to recognize them. Look for:*
 - *study number;*
 - *study title;*
 - *name of principal scientist;*
 - *name of person who compiled the list*
 - *inventory page for each section of study file, with space to list the individual documents;*
 - *number of documents in each section and (possibly) number of pages.*

Form may contain space for further deliveries – when related to an interim report or if analytical data are expected later.

3. Draw up a flow chart to describe the handover of documentation and material from the laboratory to the archive, showing when (during / after the study) this would be done.

DISCUSSION

- *Ideally study materials should be classified before the start of any practical work so that data can be filed in the correct binder or box from the outset.*
- *A formidable sorting and inventory task awaits any principal scientist who waits until the end of practical activities before writing up, and certainly before delivery to the archive.*

- *Look for:*
 - *classification*
 - *(practical work)*
 - *collection of data*
 - *organized storage*
 - *(writing up)*
 - *check inventory and fill out form*
 - *deliver to archive*
 - *obtain receipt, keep receipt in own records.*
- *Note that it is not acceptable to request an archivist to receive unsorted material.*

4. List the SOPs necessary to ensure effective management of the archive.

DISCUSSION

- *SOPs must contain sufficient managerial authority to require the inventory and handover steps detailed in workshops 2 and 3.*
- *Principal scientist must produce the inventory and drive the handover. Archivist should not be required to draw up the inventory, fetch data from the laboratory or chase up material from studies that ended some time ago.*
- *Archivist must have the authority to limit access to the archive.*
- *Beyond this, the SOPs should cover at least:*
 - *compilation of the study file inventory;*
 - *checking the study file inventory;*
 - *maintaining the archive inventory (all studies listed by ID, title and time of delivery to archive);*
 - *procedure for handovers;*
 - *access, lending out material;*
 - *physical maintenance and cleaning.*

5. List the records required to document that the archive is kept under control during the whole lifetime of the stored documents.

DISCUSSION

- *Encourage participants to take the archivist's point of view – needing to know what is in her/his custody at all times.*
- *Nothing must enter, be moved within or removed from the archive without the archivist's knowledge.*
- *Documentation will contain at least:*
 - *copy of receipt of study file;*
 - *inventory of all studies in the archive (ideally searchable spreadsheet or database);*
 - *logbook of visitors;*
 - *records of temperature and humidity etc. (if used);*
 - *records of lending and receipt of data;*
 - *records of cleaning and pest control;*
 - *records from repairs or service to equipment, building, emergency activities etc.*

6. How is it possible to prevent the archive from becoming a repository for unwanted materials? Discuss how to keep the archive functional and how to remove obsolete materials. Tabulate the persons who would give permission for removal/destruction of material in the archive.

DISCUSSION

- *Laboratories always require more space so archivists are under continual pressure to accept boxes of unsorted goods – e.g. notes and reference articles of someone on sabbatical or on maternity leave; old equipment or objects from the laboratories that might come in useful.*
- *Archivists must have the authority to refuse inappropriate material (noted in SOPs and job descriptions).*
- *Ask participants to define what might make materials obsolete.*
- *Quality policy or SOP for the archive should define obsolete materials and describe the procedure for removing or destroying material – such activities should involve at least:*
 - *principal scientist*
 - *QA*
 - *management*
 - *archivist.*

SESSION 4

4.1 SUPERVISION AND QUALITY ASSURANCE

Goals

At the end of the session, you should be able to:

- argue for the contribution that different supervisory and review roles bring to the quality of the research activities and results;
- explain the necessity for formalizing both scientific and process (QA) review;
- explain the relationship between the documentation in section 3 (CVs, training records) and supervision/QA;
- make a plan for a model review;
- suggest improvements in supervision at your own institution (if necessary);
- read the scientific literature and analyse the reports of scientific studies in terms of science and process.




QPBR – Supervision and quality assurance

An earlier slide listed the quality attributes of scientific data:


- relevant
- reliable
- reproducible
- ethical
- auditable
- in the public domain



This means that:

- the scientific content fits the research proposal and the design and conduct are likely to produce a result that can be believed and built on
- independent staff can verify the generation and existence of the results

Session 4:1:2


QPBR – Supervision and quality assurance

It is already common practice for scientists to review one another's work before publication

- A supervisor usually helps a researcher to formulate the study hypothesis and practical plan of action. But here there is a difference of rank. It is not clear who would routinely review a senior researcher's hypothesis and plan of action
- A researcher may ask a colleague to review a report or paper for publication. This might function well. However, the colleague may not have the time to do this thoroughly; may not be rewarded for it; may not know how to do it; or may be too polite to make a stringent review
- It is certainly very unusual to challenge the results of a study by checking back to raw data or (for example) apparatus logs

Session 4:1:3



QPBR – Supervision and quality assurance

In order to bring supervision into the realm of routine activity, management's quality policy must include provision for:

- review of staff qualifications
- institution's procedures for scientific review
- organization and procedures for technical review
- technical (QA) review

Session 4:1:4

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QPBR – Supervision and quality assurance

- It is important that policy and provisions for review are formulated to make it clear that this is a routine and non-threatening activity
- It must be clear that all the scientific staff contributes to review activities
- And that all scientific activities are subject to review
- Scientific review is so important that the peer reviewer should sign for his/her activity

Session 4:1:5

 **QPBR – Supervision and quality assurance**

- Clearly, staff must be qualified to do their job well in order to take primary responsibility for the quality and reliability of their own data
- Staff must be qualified enough to contribute to the review activities
- The CV and the training record provide documentary evidence of the suitability of staff qualifications
- Management must implement a procedure for checking staff qualifications and training

Session 4:1:6

 **QPBR – Supervision and quality assurance**

At the moment of recruitment, management need not be afraid of verifying CV information by:

- verifying the existence of previous workplaces or educational institutions
- checking publications
- contacting referees

Session 4:1:7

 QPBR – Keynote**Reviewing staff qualifications**



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

Session 4:1:8

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 QPBR – Supervision and quality assurance

A previous presentation indicated that quality in science has two aspects:

-  fundamental scientific aspect
-  practical experimental aspect

Session 4:1:9

TDR QPBR – Supervision and quality assurance

- When the underlying science is wrong even well-organized studies do not yield worthwhile results
- If studies are not conducted flawlessly (high-quality experimentation) the results obtained are suspect and will not lead to an advance in knowledge

Session 4:1:10


TDR QPBR – Supervision and quality assurance

- The flawless conduct of the studies (the experimental work) can be subject to QA review
 - Undertaken by QA staff or an external auditor, this review would cover:
 - comparison of study plan and raw data from the study
 - comparison between ongoing activities and the study plan and SOPs
 - presentation of raw data in the final report
 - procedures for generating, capturing, processing, storing and retrieving data
 - physical framework for the study



Session 4:1:11

TDR QPBR – Supervision and quality assurance



- During review, both the scientific and the technical reviewers are aware of the layered nature of the documents they deal with
- Much review compares information in different layers of both prescriptive and descriptive documentation
- This assures management that:
 - study activities are on course
 - raw data are compiled and summarized layer by layer until ultimate use (e.g. in a regulatory monograph or file for marketing authorization)

Session 4:1:12

TDR QPBR – Supervision and quality assurance

Does the scientific review overlap the QA review?

- Not in principle
- In practice, scientific and QA reviewers sometimes examine the same aspects of a study... and disagree
- In such cases the findings may be discussed constructively

Session 4:1:13

QPBR – Supervision and quality assurance

Ideally, both scientific and QA reviewers should be independent of the study activities

- Principal scientist is primarily responsible for the quality of the study and performing his/her own checks
- Principal scientist's staff are responsible for the quality of their contribution and do their own checking
- Scientific reviewer should have no direct interest in the performance of the study
- QA reviewer should be independent of all study activities
- Allows reviewers to take a dispassionate view

Session 4:1:14

QPBR – Supervision and quality assurance

Confidentiality and the external auditor

- External auditors must understand their obligations concerning confidentiality of data
- It is good practice to write a confidentiality agreement outlining what the auditor may see and what he/she is at liberty to reveal. This should be signed by the institution and the auditor before the audit

Session 4:1:15

 **QPBR – Supervision and quality assurance****Evaluation and review of the final report**

- Institution should have a policy or guidelines for evaluation of the final report
- Reviewer (superior or peer) should read the report carefully and also compare it with the raw data
- Reviewer should be able to assure management that the report is a fair and complete account of the scientific activities
- Circulation of the report to other scientific staff for discussion and comment helps to ensure that the report is of an acceptable standard

Session 4:1:16

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 **QPBR – Keynote****Verification of results and reports**

- 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
- 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 to the raw data of the study

Session 4:1:17

Questions

- What is understood by scientific quality? What aspects are emphasized in this presentation?
- It is claimed that quality means that an entity complies with its specifications (attributes). What are the quality attributes of scientific data? Can you add any more?
- What provisions does the scientific community already make (more or less formally) to ensure reliable scientific results? Is this a successful strategy?
- Why should management propose both scientific and process (QA) supervision?
- Why should management verify staff qualifications at recruitment? Why should management insist that staff and human resources update CVs and training records during subsequent work at the institution?
- What is the difference between scientific and process supervision?
- What do peer reviewers look for?
- What do QA reviewers look for?
- Ideally, both the peer reviewer and the QA reviewer should be independent of study activities – why?
- Can you describe the process for reviewing a final report?
- Why would an institution call in an external auditor?

Workshops

1. Make a plan for the review of a final report (or for an experimental process e.g. dosing or weighing). What tools would the peer reviewer and the QA reviewer use for the review? What would they look for? Write a to-do list for each role or present the plan as a tabulation or diagram on the flip chart.

DISCUSSION

Participants must define the process they will review and then split it into process steps.

- **Report:**
 - *QA reviewer looks for the study plan and checks consistency with this. Then looks for consistency, readability, conformance with company standard, completeness. May check aspects of the raw data.*

- *Peer reviewer looks for scientific context, logic, methodology, correct interpretations, presentation and clarity.*
- *Practical activity (define and split into steps):*
 - *QA reviewer looks for conformance with study plan and SOP and prompt documentation.*
 - *Scientific peer reviewer considers whether the activity is scientifically sound or whether it engenders some form of bias or unreliability.*

2. Do you expect the scientific review and the QA review to overlap? Give reasons for your answer. If yes, give examples from your own practice. If they overlap, what can be done to resolve differences between the parties?

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DISCUSSION

- *In theory, reviews do not overlap; in practice they often do.*
- *Wait for participants to provide examples.*
- *If participants provide no examples, try the first or both examples given below.*
 - *Principal scientist claimed that two animals found dead in cage had died of convulsions during the night. Peer reviewer thought this reasonable (given the mode of action of the drug) but QA reviewer disagreed since there were no observational data about convulsions.*
 - *QA reviewer detected a discrepancy between the numbers in a table and the same numbers in the text. Peer reviewer had checked these numbers but said that the discrepancy, though an error, was not scientifically significant. QA reviewer said that the deviation showed that the data collation/writing process was unreliable. Principal scientist said that correction would cost too much time, for no added accuracy. QA reviewer said that the report could not be completed without correction.*
- *If parties cannot resolve their issues, they must seek arbitration from management.*
- *Occasional overlap is acceptable but wastes time if both review the same aspect.*

3. In your discussion group, make a frequency chart covering the presence of the following in the institutions represented: requirement to use peer review, description of this review, signature of peer reviewer, requirement for QA review, description of process review, provision for resolving differences.

- *Ask participants to construct the chart and discuss the different models.*

4. How do the underlying science and the flawless experimental process contribute to the quality attributes? How does one know what comprises the underlying science? How does one know anything about the execution of the experiment? From your own everyday activities, or from the literature, give some examples of instances where either the science or the process seems to have failed. Use the flip chart to note: approximate date and place of the study; focus of the study; the result; and what seemed to be wrong.

DISCUSSION

- *First, ask participants for an example of an experiment in which the results could not be repeated, casting doubt on the validity of the study and the result.*
- *Obtain enough information to be able to analyse the events in terms of either science or practical execution.*
 - *Use participants' example if possible.*
 - *One famous example with health implications was the reported detection of the molecular memory of water. It is still not clear whether the results stand and whether they show that molecules imprint an electromagnetic "signature" in the water molecules in which they are dissolved, nor whether therapeutic potential is realized through the electromagnetic interactions or the conventional "lock and key" fit between molecule and receptor.*

4.2 PUBLISHING PRACTICES

Goals

At the end of the session, you should be able to:

- argue for the necessity of moving scientific results into the public domain;
- explain the necessity of a formal policy and procedure for this process and the issues that management would address in these documents;
- explain the relationship between studies and publications and the advantages and disadvantages of multiple publications of the same work;
- argue for the necessity of allocating defined responsibility to authors;
- appraise current publishing practice and (if necessary) suggest improvements;
- choose critically the most advantageous forum for any given publication;
- protect the potential for patenting (where relevant).



QPBR – Publishing practices

Bringing scientific results into the public domain

Session 4:2:1



QPBR – Publishing practices

- An earlier slide listed the quality attributes of scientific data:

- relevant
- reliable
- reproducible
- ethical
- auditable
- in the public domain



- This means that the results must be moved from the laboratory setting to the wider community
- Without publication, the scientific research might just as well have never been done

Session 4:2:2

 **QPBR – Publishing practices**

It is good practice to publish results in a timely way

Advantages:

- results are moved into the public domain while the activities are relevant and state of the art
- timely publication is part of the scientific process – the public (directly or indirectly) funded the activity and have a legitimate interest in the outcome
- researcher becomes exposed to peer review and scientific challenge
- other researchers can build on the results and avoid repetition of the same study
- scientists become known in their field and increase the chances of funding and further research

Session 4:2:3

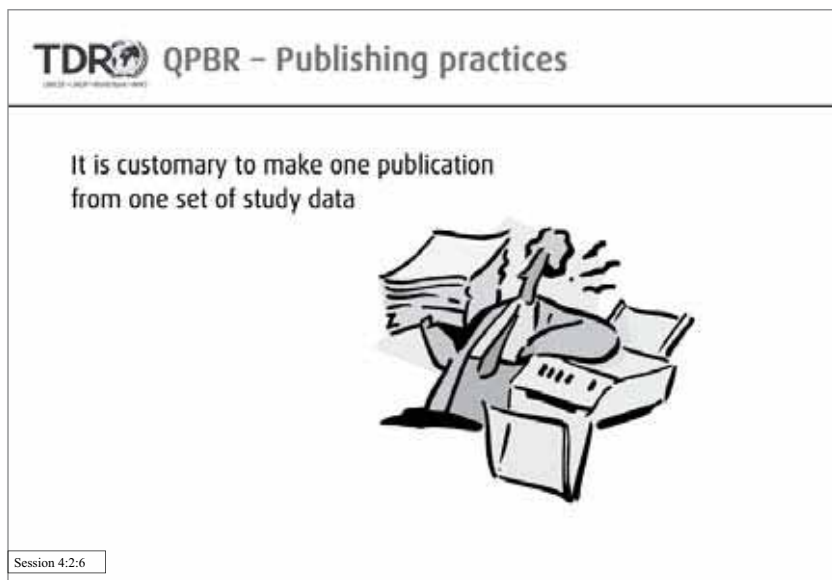
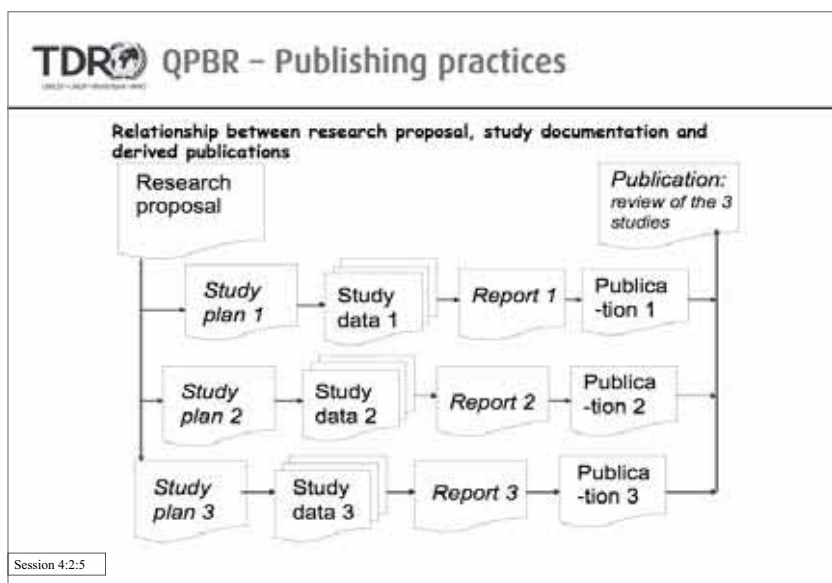
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 **QPBR – Publishing practices**

Since publication is the essential process for moving ideas into the public domain, the institution should have a policy covering issues such as:

- at what point in a project it is advisable to publish
- institution's procedures for review
- conventions for coauthoring papers
- necessity of including significant data fairly and accurately in publications
- whether research data are the intellectual property of the research institute (or the grant giver)
- ownership of patent rights

Session 4:2:4



 **QPBR – Publishing practices**

- **But it is possible to produce more than one publication**
 - **Advantages:**
 - allows elucidation of unexpected observations or follow-up studies
 - allows full and detailed exploration that may be too long for a single publication
 - **Disadvantages:**
 - lengthens author's publication list BUT adds to the volume of scientific publications without adding new knowledge or insight
- **It is not acceptable to publish the same material in slightly different ways in different journals**

Session 4:2:7

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 **QPBR – Publishing practices**

- **Advantages of publishing review articles:**
 - present overview of similar studies, sometimes with conflicting results
 - help colleagues to orient themselves quickly
 - may present materially new interpretation of known data
- **Disadvantages of multiple reviews:**
 - same as previous slide – unless materially new insight is presented

Session 4:2:8



QPBR – Publishing practices

- **It is rather unusual to publish negative (inconclusive) results**
 - If the study was well-controlled and well-executed, the negative results are valid and interesting
 - Publication prevents resources being wasted trying to replicate the same study
 - Researchers have been reluctant to publish
 - Journals have also been reluctant to publish
- **But the scientific community is beginning to understand the importance of knowing what did not return expected results**

Session 4:2:9



QPBR – Publishing practices

Assigning credit to contributors

- Always give credit to others who contribute work, ideas or results
- Published sources: quote loyally and give names and full bibliographic reference
- Unpublished sources: obtain permission from author and give acknowledgment. Show consideration for his/her own publication strategy
- Consider including the author of the unpublished source in the list of authors – if the contribution is significant

Session 4:2:10

 **QPBR – Publishing practices**

List of authors

- If the paper is the result of a collaboration, follow institution's policy or agree in advance who will be an author and who will be principal author
- Principal author: person who generated idea and undertook most of the work
- Do not include people who made only a modest contribution or contributed activities as part of a routine job
- A very long list of authors dilutes individual responsibility for the integrity of the results
- There is no particular reason for automatic inclusion of the head of the laboratory

Session 4:2:11

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 **QPBR – Publishing practices**

Choice of publishing forum – scientific journals carry most weight

- There is considerable competition to have results accepted
- Journals provide instructions on format, style, content, length, position of principal author – follow these instructions carefully
- Takes time for review – revisions may be requested and take more time
- Final result is considered reliable and earns respect for the author

Session 4:2:12



QPBR – Publishing practices

Choice of publishing forum – posters and conferences

- Posters and lectures are fun to make and stimulate discussion; attendance may be subsidized
- Posters and lectures are not usually peer-reviewed since the sponsors of conferences often call for material and take what comes
- Posters and lectures appear in the proceedings of meetings
- A conference may promote a certain viewpoint – you may have to defend your own conclusions if they are not in line

Session 4:2:13



QPBR – Publishing practices

Choice of publishing forum – we do not recommend using the press as a single channel

- Can use the press as soon as the formal publication is available
- Even then, press conferences, newspapers, TV coverage or web-page releases will give rise to inaccuracies
- Journalists rarely fully understand the content of a study or its significance

Session 4:2:14

 **QPBR – Publishing practices****Patents and scientific publishing – beware!**

- A patent is required if the results of the study promise novelty, inventiveness and utility sufficient for a new product/principle that could earn some revenue
- Often, a partner will not invest without a patent
- To be patented, an idea must display novelty
 - i.e. not published previously in any way, even if the publication is by you
- Be aware that informal publication such as press, posters etc (including public discussion) also count as publication.

Session 4:2:15

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 **QPBR – Keynote**

Research institution should have a written policy for its publications. This policy should contain specifications for:

- authorship
- peer review
- patenting
- data integrity
- situations in which multiple publications are permitted
- preferred forum (i.e. journal, conference, poster session etc)

Session 4:2:16

Questions

- What is understood by public domain?
- Why is “in the public domain” one of the quality attributes of basic scientific data?
- What is the purpose of moving results into the public domain?
- What sort of issues would be addressed in an institute’s publishing policy?
- One study: one publication – is this idea tenable?
- Why should anyone publish negative results? Give an example if you can.
- What are the different methods of publishing? Give examples.
- Why does the need to move results into the public domain sometimes conflict with the need to patent a finding?
- Where can you find authoritative advice on the presentation and format of publications?

Workshops

1. QPBR claims that moving results into the public domain is an integral part of the basic research process. Why does QPBR make this claim? Whose interests are involved? Why should management have a formal policy and procedure in place to cover this part of the process?

DISCUSSION

- *The answers are not obvious. Ask participants whether the community has a right to know and benefit from scientific results – if not, why not?*
- *Does the community directly or indirectly finance the activities?*
- *Results brought into the public domain are exposed to public scrutiny and some may not survive (most scientific journals use some sort of review process to weed out improbable or ill-founded results).*
- *It is in the authors’ interest to publish – to advance their careers.*
- *Institutions certainly have an interest in generating good publications in order to obtain grants for more research. For this reason, management should have a publication policy covering:*
 - *at what stage in a research project to publish and the mechanism for review within the institute;*
 - *the type of publication to pursue: e.g. peer-reviewed journal, symposium funded by a drug company or interview in the local paper.*

2. In your discussion group, for each of the institutions represented, indicate the number and the level of staff normally represented in the author list of a publication in a scientific journal. Tabulate your information on the flip chart. Indicate the level of staff represented in the acknowledgements list. Is a holder of a specific rank automatically listed as an author? Is anyone automatically thanked? What are the pros and cons of your present practice? For each institution indicate the presence or absence of a publication policy. If you wanted to implement a publication policy, where would you seek support?

DISCUSSION

- *There are different practices for publications and for awarding credit for publication.*
- *When participants have tabulated their information, encourage discussion of their findings. Look for:*
 - *number of authors in lists*
 - *job titles of authors in list*
 - *leader of institution – automatically included or always first/last?*
 - *unwritten rules.*
- *If participants feel that a publication policy would be advantageous – what would be their argument? Whom should they approach to bring such a policy into effect? Listen for:*
 - *peer group*
 - *management group.*

3. Taking an anonymous or fictitious study suggested by your everyday experience, draw a diagram on the flip chart showing the plan, study, the report, proposed publication and the review publication or posters you have planned (do not ruin your chances of patenting with this activity!).

DISCUSSION

The purpose is to repeat the exercise of classifying prescriptive and descriptive documentation and the relationship between different levels of reporting using an example well-known to each participant.

4. List the advantages and disadvantages of the different publishing fora identified in the questions above or in the manual. Give examples from your own experience.

DISCUSSION

- *Ask participants to name different fora (look for scientific journals, posters, lectures at symposia, newspapers, television interviews, chapters in scientific books, web sites).*
- *Each forum has pros and cons:*
 - *scientific journal may take time for review and revision but carries most prestige;*
 - *symposium funded by a private company may have narrow interest and an uncritical attitude to scientific value;*
 - *as with television, publishing in the daily press is exciting but often inaccurate, carries no prestige and may harm chances for subsequent publication or subsequent patent;*
 - *if work has already been published in a scientific journal, subsequent media coverage is acceptable as long as this is not pursuing sensational news for its own sake or misrepresenting the findings.*
- *Participants should understand that there may be a price to pay for taking a short cut around the scientific journals by going directly to the media.*

4.3 ETHICAL CONSIDERATIONS

Goals

At the end of the session, you should be able to:

- define “ethical” in the context of basic biomedical research;
- summarize the case for a formal policy and procedure for ethics (including ethics committee);
- perform a simple risk analysis;
- outline a draft charter for an ethics committee and its line of reference in the organization;
- list the relevant guidelines for Good Clinical Practice (GCP), animal welfare, safety, biosafety and environmental protection in order to facilitate access and enable consultation;
- explain why human experimentation is governed by, and requires, special standards (GCP, data and personal privacy);
- anticipate controversy and participate in discussions on ethical issues.



QPBR – Ethical considerations

Honouring ethical responsibilities

Session 4:3:1



QPBR – Ethical considerations

- An earlier slide listed the quality attributes of scientific data:
 - relevant
 - reliable
 - reproducible
 - ethical
 - auditable
 - in the public domain
- This means that it must be ensured that experimentation is performed in a “morally correct” way
- Of course, this might mean different things to different people but ...

Session 4:3:2



QPBR – Ethical considerations

... in the context of early stage science we mean that the scientist has a responsibility not to cause unnecessary suffering or harm to:

- people involved as subjects or bystanders
- experimental animals
- the environment

Session 4:3:3

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QPBR – Ethical considerations

- We recommend that a risk analysis is carried out before starting a project/study
 - Risk = likelihood x impact of possible mishap
- Weigh the risk against the potential benefit to society
 - Look at all the possible ways that things can go wrong, causing suffering or damage
 - Anticipate any dilemmas the results may entail
 - Include the risk analysis in the funding application

Session 4:3:4

TDR QPBR – Ethical considerations

- Working in the laboratory entails a fair amount of risk for personnel
- Consider risks from:
 - apparatus, chemicals, allergens
 - accidental infection from microorganisms or test animals
 - accidents while working alone
- DO ensure that there is/are:
 - SOPs
 - contingency plan
 - training



Session 4:3:5

TDR QPBR – Ethical considerations

- For studies involving human subjects, GCP is the proper ethical and procedural standard
 - GCP studies involve the use of investigational medicinal products produced according to GMP
 - Supportive data from laboratories should be GLP standard or similar
- Consult:
 - TDR ethical guidelines
 - TDR SOPs for clinical studies
 - ICH guidelines for GCP

Session 4:3:6



QPBR – Ethical considerations

- A non-invasive, observational study may not need GCP but it will still be necessary to consult the local ethical committee if:
 - study may invade personal privacy
 - study may influence the behaviour of subjects or of the health instances involved (practising physicians, clinics, practitioners of traditional medicine etc.)

Session 4:3:7

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QPBR – Ethical considerations

- Use of laboratory animals
 - Study itself must not entail unnecessary suffering
 - Do not include too many animals – but sufficient to give meaningful power in the results
 - Timing – animals must not arrive too soon and die needlessly
 - Train personnel in handling and caring for animals
- Read and follow available guidelines for animal welfare



Session 4:3:8



QPBR – Ethical considerations

- Ancillary data may involve a dilemma
- For example, your in vitro study needed only human blood or tissue but you have noticed a pathological state in some donor blood/tissue
 - Will you inform the donor? Or were the samples blinded?
 - Have you written into the institutional ethics charter that no medical opinion would be given in this situation?

Session 4:3:9



QPBR – Ethical considerations

Field trials may unintentionally involve bystanders:

- compounds or methods to control insect or other vectors may affect surrounding population
- by affecting water or food supplies



Session 4:3:10



QPBR – Ethical considerations

Unexpected effects on the environment

- Knock-on effects of controlling the identified vector
- Escape of microorganisms/organisms into the environment (follow WHO or national guidelines)
- Escape of chemicals or metabolites into the environment
- Changes in water supplies, food chains, ecological balance



Session 4:3:11

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QPBR – Ethical considerations

Some aspects of the results may have an extreme and unforeseen impact on society:

- use as weapons
- effects on future generations, individuals or populations



Session 4:3:12



QPBR – Ethical considerations

Institution should establish an ethics committee that:

- must have management support (right to veto)
- represents all levels of personnel – not just scientific
- takes time for deliberation and records minutes
- may seek support from local community ethics committee



Session 4:3:13



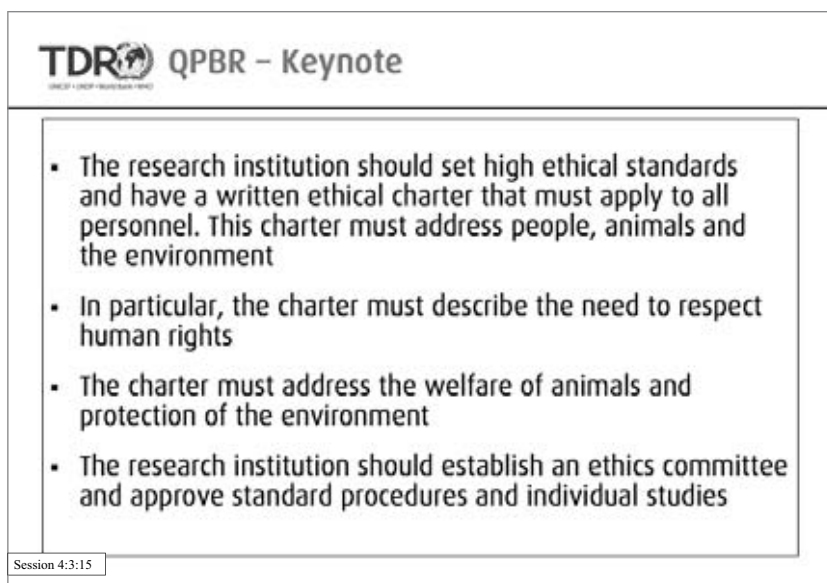
QPBR – Ethical considerations

Ethics committee – activities:

- writes the charter for adoption by management, taking regard of human rights, animal welfare and environmental protection
- reviews actual practices and ensures that these are documented (SOPs)
- reviews individual study plans
- discusses ad hoc issues that may arise



Session 4:3:14



TDR QPBR – Keynote

- The research institution should set high ethical standards and have a written ethical charter that 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 and approve standard procedures and individual studies

Session 4:3:15

Questions

- Why is “ethical” part of the QPBR quality attributes of basic biomedical research?
- What does “ethical” mean in this context? What types of issues are involved?
- What is a risk analysis?
- What sorts of risks are entailed in laboratory work? For whom?
- Is your institution governed by national or international guidelines/regulations for safety at work, animal welfare, environmental protection, GCP? Where can you access these? Is an individual at your institution responsible for finding such guidelines and advising management on compliance?
- What is the special standard for studies involving humans? Is it always relevant?
- Why is Good Laboratory Practice the standard for laboratory work supporting clinical studies? Is this always the case?
- How could you prevent unnecessary suffering for laboratory animals in your studies? Does this cover all types of animal?

- Do incidental observations (e.g. tissue samples taken for another purpose) engender any ethical problems?
- What is an ethics committee?
- What sort of work do they do?
- Are any of their activities controversial? Give examples.

Workshops

1. Your institution needs to set up an ethics committee. How many members are required? Who (which groups) should be represented? Use the flip chart to list the essential components of a draft charter for an ethics committee.

DISCUSSION

- *Ethics committees should be broadly based with regard to gender, background, profession and affiliation to the institution in order to ensure a wide range of opinions.*
- *Discussion should aim to discover how to achieve this composition. Listen for :*
 - *one member with specialist scientific insight*
 - *veterinarian (if institution works with laboratory animals)*
 - *zoologist or botanist (if field studies are envisaged)*
 - *physician (if people are to be involved either as part of studies or as bystanders).*
- *It is equally important to include people from other backgrounds in order to provide the layperson's view, for example :*
 - *homemaker*
 - *musician*
 - *builder*
 - *farmer*
 - *technician*
 - *cleaner*
- *Select an odd number – enough for a good discussion but not so many that it is impossible to arrange meetings.*
- *At a minimum the charter should cover :*
 - *institutional policy*

- *scope*
- *activities of the ethics committee, including:*
 - *oversight of each individual protocol*
 - *treatment of ad hoc events*
 - *review of SOPs involving animals or people*
- *Charter should give some administrative detail on the composition of the committee, including the number required for a quorum.*

2. For one or more studies from your experience, brainstorm the risks involved for people, animals and the environment. Tabulate on the flip chart. Assess risk by indicating the impact and likelihood of each.

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DISCUSSION

- *Ask participants to select a study and consider the potential for doing damage.*
- *In the first round, confine this to a list of factors. Do not let participants jump to solutions, preventive actions or dismissal (“but it will not happen because...”).*
- *In the second round consider the likelihood of occurrence for each item on the list. Assign arbitrary numerical scores (1, 2, 3) to reflect increasing likelihood.*
- *Use an arbitrary numerical scale (1, 3, 10) to assess each item’s impact on the environment or on people.*
- *Multiply likelihood by impact to indicate what really might be problematic. This indicates where preventive action should be focussed or where a contingency plan should be put in place.*

3. For one or more human studies from your experience or from your reading, discuss the relevance of using the special guidelines (on GCP, ethics, privacy) for human studies. Why should this be necessary?

DISCUSSION

- *Need for balance between reasons for performing a study and the expected benefit. Listen for:*
 - *motivation of physician*
 - *enthusiasm*
 - *scientific curiosity*
 - *need to advance drug development or validation of other treatment.*
- versus:*
 - *right to give informed consent*
 - *right to withdraw*
 - *right to conventional treatment*
 - *right to reparation if things go wrong.*
- *Listen also for protection of physicians (if they have followed a correctly approved protocol in good faith).*
- *Also essential – community’s right to know what is in the protocol.*
- *Time permitting, suggest a discussion of the pros and cons of trials in vulnerable groups, such as:*
 - *people with incurable or life-threatening conditions*
 - *people with mental illness*
 - *children.*

4. For a study from your experience, list the factors that impact negatively on the welfare of the animals involved. What could you do to prevent or minimize these effects?

DISCUSSION

- *Listen for:*
 - *discomfort and pain*
 - *side effects*
 - *length of time on study*
 - *temperature extremes in the laboratory*
 - *water ran out*

- *food ran out*
- *bitten by cage mates*
- *inhumane procedures*
- *incomplete anaesthesia*
- *rough handling*
- *noise*
- *light on all the time*
- *cages too small*
- *smell of urine*
- *dropped on floor*
- *animals became obese, etc.*
- *What was done? Was it easy to make changes? Listen for:*
 - *yes, it was easy*
 - *it was not easy but I argued my case*
 - *resistance from managers or staff*
 - *expense*
 - *indifference, inertia or ridicule.*
- *What about the treatment of invertebrates kept in captivity? Also fish, amphibians and other unusual test systems to which we do not usually extend our ethical judgement.*
- *For prevention, listen for:*
 - *reassessment of study requirements*
 - *retraining of assistants*
 - *increased frequency of routine checks on animals*
 - *refurbishment of animal house, its equipment and utilities*
 - *consider other test systems to replace vertebrates.*

SESSION 5

5.1 CASE STUDIES

This session consists entirely of discussions around case studies. These are based on actual events but have been modified slightly. Discuss what happened, identify the real issues and suggest solutions to the problems.

You may be asked to present a case of your own.

5.1.1 *Test item in animal model*

You are the responsible research scientist running a study to determine the efficacy of a test item in an animal model, using treated groups and an untreated control group. When the bioanalytical results are reported it is shown that some blood samples from control group animals contain traces of the test item.

What are the likely causes of this situation?

What should you do?

What can you do to ensure that this is unlikely to happen in the future?

DISCUSSION

Likely causes

- *Control animals have been exposed to the test item (e.g. airborne contamination, misdosing) at some time.*
- *Mislabelling or mix up of the samples sent for bioanalytical analysis.*
- *Contamination of samples at some time during the bioanalytical process.*

Possible actions

- *Use different means to check possibility that control group has been exposed*

to test item. For example, verify that dosing records are complete and SOP states clearly how the dosing should be conducted (e.g. use of new, clean catheters when changing dose groups). Verify whether or not test item is volatile as this could explain exposure. During this investigation check that the operators have been properly trained and follow relevant SOPs.

- As far as possible verify that the analytical laboratory has performed the work under conditions that preclude mix ups or contamination (e.g. clear labelling at all times during the analytical process, clean glassware, no data recorded in wrong columns).*
- Decide whether the traces of test item are likely to impact on the validity of the study you are performing. Remember these are traces. The impact analysis is a scientific problem and, of course, the conclusion depends upon the purpose of the scientific research.*

How to prevent this happening again?

Obviously this depends on why it happened, but the following could be considered:

- change dosing method;*
- rewrite SOPs with greater clarity to reduce likelihood of contamination during dosing, misdosing or exposure due to volatile material;*
- retrain technicians so that SOPs are followed scrupulously;*
- ensure that levels of cleanliness and routine cleaning procedures are sufficient to preclude contamination problems in the bioanalytical laboratory.*

5.1.2 Results not to be reported

You are a researcher running a study which is part of a larger project. Your results run contrary to results from other scientists performing other studies for the project. When you report your results the project leader informs you that he would like you to repeat certain parts of the study and, should you obtain results more “favourable” to the project, report only the second set of results.

How would you deal with this situation?

DISCUSSION

- *There is no valid reason to repeat unless there is evidence that the differences in results are due to problems in the performance of parts of the study. Consequently, the researcher should ask the project leader to review his/her work in detail and identify the problem area (divergent results are not sufficient grounds for repeat).*
- *All cases of repeats should be documented carefully and the reasons for them noted in the study documentation. In such cases it may be worthwhile for the researcher to ask the project leader for a written, signed and dated document covering the reasons for requesting the repeats. This justification should be kept as part of the study files.*
- *If it is decided to repeat parts of the study, a formal modification to the research study plan should be drawn up, signed and dated before the repeat work is performed.*
- *Reporting only those results that are “favourable” to the research project constitutes fraud by omission. This is unethical and the researcher should refuse to do this.*
- *The research report should including the reasons for performing the repeats and the scientific justifications. Include both sets of results, even if it is clear that one set is invalid. The report should state clearly which set is invalid and the reasons for this decision.*

5.1.3 Unreported values

When examining a report and the data from a study that one of your subordinates has been running you find several instances in which out of range values have not been cited in the report.

How should you react to this?

DISCUSSION

- *Out of range values cannot simply be ignored.*
- *Discuss with your subordinate why the values have been omitted. Is there a valid scientific reason?*
- *If you agree with the reasons given, ask your colleague to modify the report to include the values, explain that they have not been included in the calculations and give the reasons for their omission.*

5.1.4 Technology transfer

You are about to embark on a new type of study within your department. This involves analytical techniques of which your technicians have no experience. The techniques are well-mastered by a group in another department and the director of your institution has requested that you organize a technology transfer between the two laboratories.

How would you proceed? How would you document this? How would you ascertain whether the transfer has been successful?

DISCUSSION

- *Technology transfer should be organized between the two parties and be well-documented (as outlined below).*
- *It is good practice to write a technology transfer protocol that includes:*
 - *identity of the two laboratories, usually termed the owner laboratory and the receiving laboratory;*
 - *name of the person responsible for each of the laboratories, these two will be the signatories of the technology transfer protocol.*
 - *general description of the technique to be transferred; actual technique described in a detailed methods document or an SOP may be appended to the protocol.*
 - *description of the process of transfer – usually divided into steps such as:*
 - *receiving laboratory technicians trained by technicians from the owner laboratory, at either site;*

- *newly trained technicians trial the new technique on their own and at their own site;*
- *development of a testing plan – may comprise several analyses performed by staff in the owner site and staff in the receiving site and comparison of the two sets of results.*
- *description of acceptance criteria (e.g. statistical tests to be performed on the two sets of results to demonstrate comparability);*
- *dates of the various steps of transfer.*
- *Protocol is followed and the results of the various tests are collected.*
- *Technology transfer report is written. This includes the data generated, statistical calculations and the conclusion of the tests, stating whether or not the transfer has been successful. The report should be signed by the two persons who signed the protocol.*

5.1.5 Blood sample logistics and handling

Your study will entail repeated collection of blood samples (every month for nine months) from a population and subsequent transfer to a laboratory for analysis. Transfer will be carried out by a company said to be specialized in handling biological materials which claims that it can guarantee cold storage conditions throughout the transport period.

Design a raw data form covering the collection of blood samples and chain of custody to the analytical laboratory.

DISCUSSION

There are innumerable ways of designing such a form (or forms). However, the following points should be clear from the form layout and contents.

- *First part of form (or first of two forms) concerns the collection and delivery of samples:*
 - *signature of person who collects the blood*
 - *date and time samples collected*

- *specific study – study identity number etc.*
- *identity of individuals providing blood – probably coded if human blood*
- *amount of blood collected – e.g. minimum volume per tube, number of tubes*
- *conditions of collection – heparin tubes etc.*
- *actual method of blood withdrawal could be covered in an SOP*
- *storage conditions before transfer to analysis laboratory – e.g. time of storage, cold store*
- *date and time samples sent to laboratory*
- *transport conditions – cold storage, polystyrene packaging etc.*
- *dispatcher – name of company (if contract service used), signature of person who physically transported the samples.*
- *Second part of form (or second of two forms) concerns the receipt of samples at the analytical laboratory:*
 - *date and time of receipt;*
 - *signature of person receiving the samples;*
 - *result of QC check that all samples arrived (number received compared with number sent), breakages or unsatisfactory samples;*
 - *date and time of storage before use;*
 - *conditions of storage before analysis – frozen, cold store etc.*

5.1.6 Multisite multi-headaches

A funding organization has agreed to fund a study for which you will be the overall responsible scientist. This will be a multisite study involving the collection of similar data from different geographical areas. All the data generated by the sites will be sent to you for scientific interpretation and inclusion in a final report. The sites have adopted different methods for collecting data – notebooks, loose-leaf files or data collected directly on computers (electronic data).

How will you ensure that all the data from the various sources are sent to you without problems and that the data you receive are reliable?

How will you organize the data so that you can compile your report easily?

How will you deal with the archiving of raw data and other documents at the end of the study?

DISCUSSION

- *Ensuring that all data are sent to you and are reliable*
 - *Request that the data or certified copies (signed and dated photocopies) are sent directly to you.*
 - *Provide the same pro-forma sheets for collecting data or ask for the data to be transcribed from their usual media (notebook, loose-leaf file, computer). This option would require each site to perform a check that no transcription errors occurred during the transcription process. Insist that each site provides a signed statement that this QC verification has been conducted.*
 - *Provide the format for collecting data in a simple spreadsheet (e.g. Excel). This will help in the next step.*
- *Organizing the data*
 - *Transfer the data to prepared formatted summary sheets.*
 - *If original data are in different formats (or there are photocopies of data) it is vital to ensure that there have been no transcription errors. This verification should be performed by someone else, either by double entry of the same data with a check for errors or by independent data verification (QC). The use of spreadsheets for data collection on each site will save time at this stage.*
- *Data archiving*
 - *Ensure that all data will be available at any time in the future.*
 - *Check that each site has appropriate archiving facilities and will not dispose of any data without referring to you. This may not be easy as many sites lack adequate archiving facilities or archiving and retrieval procedures.*

5.1.7 Scientific peer review

As a well-known senior scientist in a specific field of research you have been contacted to review the work of a scientist working in a different research institution.

How would you go about reviewing this researcher's work?

DISCUSSION

- *Peer review of this sort is quite acceptable and this request implies no a priori suspicion of malpractice. Indeed, peer review would be routine in an ideal world.*
- *Reviewer should start by reading the reports generated by the research.*
- *Reviewer should compare at least the critical data presented in summary form in the report with the actual raw data of the study(ies) in order to ensure that the scientist concerned has not been over selective in the data presented.*
- *Researcher should review the research proposal and individual study plans to ascertain whether the proposed research has been conducted scientifically as planned. If there have been changes (this is likely) the researcher should reach an opinion as to whether or not the changes to the research method were valid.*
- *When satisfied with the manner in which the science has been performed, the reviewer should consider the discussion and conclusions in the research report and say to what extent he/she agrees or disagrees with these, and for what reasons.*
- *A reviewer who finds cases of incomplete or suspect data or unexplained deviations should consider recommending a full audit by a QA professional. This would require the approval of the research institute in which the work was conducted.*

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5.1.8 Preparing a policy document

The director of your institute has asked you to lead a group to write a policy document on the process for publishing the results of the institute's scientific research.

What points would you ensure are discussed during group meetings before preparation of the policy document?

DISCUSSION

- *Types of data that may be published and the types of data that should be considered confidential. Definitions and examples would be helpful.*
- *Relationship between the various partners in publication – researcher, institute, funding body etc.*
- *Rules for co-authoring papers.*
- *Publication approval process, including which are the preferred media and who gives final approval.*
- *Peer review for scientific content and how this should be organized.*
- *Audit or data review to guarantee the credibility of results and how this should be organized.*
- *Publication of “negative” results.*

5.1.9 Investigating the unexpected

You are running a study in which an analytical result is unexpectedly out of specification for a parameter that usually remains constant.

What investigations would you perform to elucidate whether or not the result is valid?

DISCUSSION

- *Stress the need to check that:*
 - *results have been recorded and calculated correctly;*
 - *instruments were all within calibration and maintenance limits and equipment was correctly calibrated or checked before use;*
 - *reagents had not passed their use-by dates;*
 - *analyst scrupulously followed the method/SOP, method/SOP has not been changed recently, SOP is completely up to date and method/SOP used is the current document;*
 - *analyst is not new to this procedure and is trained correctly for the technique (look at documentation for this);*
 - *test item was stored under the right conditions;*

- *sampling procedure and preparation of the aliquot were performed correctly.*
- *Then discuss –*
 - *What conclusion would you draw if the checks listed above reveal no apparent problems?*
 - *If sufficient test item aliquot is left over from the first analysis should this be used for supplementary analyses (to check the “odd” result) or should new samples be taken?*
 - *Who should perform these additional analyses? The same analyst or a different person?*
 - *What decisions can be made if the new analyses give different results (i.e. results conform to the expected)? Is a third set of analyses necessary to confirm the second?*

5.1.10 Implementation case study

You have been appointed chairman of a small team charged with implementation of QPBR at your research institution.

Where will you start? What will be the main steps to implementation? What pitfalls can you anticipate on the way to implementation?

On the flip chart, construct a plan that shows the main sections of your project (no more than ten steps). Before starting the exercise decide whether you prefer to discuss QPBR for a small team, a larger institution or the discovery departments of a larger company. If there is sufficient time, the task can be repeated for one of the other settings. Discuss any differences.

DISCUSSION

- *Ensure agreement within the implementation team: common understanding of goals, timeframe, benefits, keynote items, order of events.*
- *Management commitment: there may be implications for both financial and human resources (because agreed areas of responsibility and the requirements*

- for peer and QA review also require capacity) and temporary inconvenience if changes to facilities or equipment are needed.*
- *Management and team reach written agreement on scope and benefits of project, goals and end date.*
 - *Project structure, responsibilities, steering group, reporting to management.*
 - *Communicating project to the rest of the institution – initially, during project, at successful completion.*
 - *Management and staff should understand that the implementation process will require financial and time resources but there will be advantages for everyone.*
 - *Budget for the project.*
 - *Project plan.*
 - *What action will you take if you encounter problems? What problems might arise (practical, expertise, resource, time pressure, resistance, financial – any more?)*

Then discuss –

- *What can be done without immediate expenditure? e.g. organization, personnel, CVs, job descriptions, understanding of new routines. Are there any advantages in starting with these aspects? Identify areas of current expertise, areas where expertise is required, need for training, potential resistance of various kinds e.g. to job descriptions, review, need to archive.*
- *Identify physical areas involved – are improvements needed? Areas may be suitable but lack documentation (e.g. floor plans, preventive maintenance, SOPs).*
- *Identify equipment involved – again, are improvements or only documentation needed?*
- *Sourcing – animals, chemicals, laboratory disposables. Are the supplies suitable for purpose, specified, stable, documented?*
- *Data – does everyone understand meaning of raw data and how they become reported data? Is there a need for training in the generation and processing of valid data? Is there provision for safe keeping of data during the studies? Is there an archive? Will the institution need to establish physical facilities for storing data? Are the provisions for electronic data capture/processing/storage sufficient, understood and documented?*

- *Review and publication – is the need for review accepted? What would happen if the reviewer had no time available or a researcher claimed to be above review? Would management help you write a clear policy for publication? Will there be resources for dedicated QA activities?*
- *Possible ethical issues at the institution (see workshop 4 on that topic)? For example, setting up an organizational unit/expertise to deal with routine activities/problems.*
- *Policies, SOPs. Best area to start? There will be different ideas and many may be right – just ask for the reasoning. Time frame? Review?*
- *Training needs. Identify needs for different groups in the institution. When will this occur? How many sessions will be necessary – before, during or after the project?*
- *End of project – definition. Celebration.*

SESSION 6

6.1 WRAP-UP AND EVALUATION

This session concludes the workshop. Having discussed what you have liked or disliked about the entire workshop you will be asked to complete an evaluation form. This can be submitted anonymously.

6.2 ISSUING OF CERTIFICATE AND CLOSURE

Only those who attend the entire workshop receive a certificate of participation. This should be signed by the organizer and the TDR programme coordinator.

End of the workshop.

ISBN 978 92 4 159920 7



TDR/World Health Organization
20, Avenue Appia
1211 Geneva 27
Switzerland

Fax: (+41) 22 791-4854
tdr@who.int
www.who.int/tdr

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