



ASNEMGE

COMPENDIUM

RESEARCH
and
PUBLICATION GUIDELINES

for Young Investigators in the field of Gastroenterology and Hepatology

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AIM OF THE COMPENDIUM

R. Stockbrügger

AIM OF THE COMPENDIUM

The idea to produce a compendium for Young Investigators in Gastroenterology and Hepatology was born during a Young Investigators' Market at the UEGW in Amsterdam 2001, when 83 Young Investigators from 23 countries in Europe exhibited posters and presentations about the research opportunities in their respective countries. In a discussion during this market, a general opinion was expressed by the participants that for initiating and performing own research, they needed advice and tutoring on the way to perform research maybe even more than funds. The idea was then born to frequently offer courses to Young Investigators in these matters and to make this educative effort one of the major services offered to their members by the ASNEMGE, and also by the OMGE, which are covering the various global organizations of Gastroenterology, including Europe and the Mediterranean area.

This manual is thought to serve the Young Investigators, but also their tutors and teachers, and ultimately the professional societies such as ASNEMGE and OMGE.

Aims for the Young Investigators

- To introduce basic rules of research, regarding:
 - motivation;
 - hypotheses and appropriate designs;
 - materials and methods;
 - evaluation of results;
 - publication strategies;
 - execution of publication;
 - initiating a research line and a research career.
- To help taking the first obstacles in initiating research in order to avoid early frustrations that might terminate a potential research career before it even has started.
- To facilitate publications from the beginning with minimum, international standards.

Aims for teachers and tutors

- To set a minimum standard for individual teaching and training in research matters in an international context, thereby also improving local and national standards.
- To provide references for further immersion into matters of research training.
- To minimize repetitive individual advice for every newly incoming potential Young Investigator and thereby gaining time for controlling and improving the results of the Young Investigators efforts.

Aims for ASNEMGE, OMGE et al.

- To respond to a frequently voiced demand by many Young Investigators.
- To create a course manual for regional, national and international training events
- To help to promote a uniform global standard of research in the field of Gastroenterology and Hepatology.

Finally, last but certainly not least:

- Help to promote a comparable standard of medical research and evidence-based health care for current and future patients, wherever they might live.

This manual will be continuously updated following suggestions by users, authors, and any others being interested in postgraduate teaching of Young Investigators in Gastroenterology and Hepatology. Ideas, contributions and remarks can be sent to the ASNEMGE (info@asnemge.org).

ASNEMGE has been the sole sponsor of this manual and is happy to provide it in an online downloadable version to everyone who needs it (www.asnemge.org).

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TARGET GROUP

R. Stockbrügger

TARGET GROUP

From the previous chapter it is evident that this manual is aiming at graduates who have plans for basic or clinical research in Gastroenterology or Hepatology, or who have already started with it and have encountered the first problems and need advice. It is mainly directed at training gastroenterologists, but also at non-medical post-graduate students concerned with research areas in, or close to Gastroenterology and Hepatology. If anyone else does not mind that most of the practical examples and problems are chosen from the Gastroenterology and Hepatology field, the manual might be useful also to this person. The manual might be helpful or interesting to anyone who is involved in some kind of bio-medical research.

The second target group exists of teachers and tutors of (post)graduate students. One might think that they would know all that is written in this manual. This might be, but still there are publications to be reviewed that show a nonchalance of some fundamental rules in setting up and publishing a study. Others may want to use the manual as a (minimum) basis for their methodological education individually or in groups, and yet others will leave the student to auto-educate and consider the manual as a start before the (PhD) student may ever touch a probe, a mouse or a human being for research purposes!

RESEARCH TYPES

D. Sorrentino



WHAT IS MEDICAL RESEARCH?

It is very difficult to define in a few words such a complex activity. Perhaps we could envision it as a human endeavour to prevent and cure human diseases, including aging. In a way, a battle for survival of the species. Seen from another perspective, research is what drives progress in Medicine - by using a scientific approach, not an empiric one. Medicine is far from being a precise science such as physics or mathematics. Yet, by applying a rigorous method of phenomenon observation, hypothesis formulation and hypothesis testing, medical scientists have been able to explain how the human body works and how to treat many ailments. Using a scientific approach, observed findings must be reproducible and should be disclosed to the academic community through peer-reviewed publications. In Medicine, research is traditionally divided into basic and clinical research. Such a distinction, however, is becoming more and more tenuous as new approaches such as genetic testing, cell targeted drugs and biological therapies, among the others, ideally bridge the lab bench with the bedside.

BASIC RESEARCH

Basic Research: Research conducted to increase the base knowledge and understanding of the physical, chemical, and functional mechanisms of life processes and disease. It is fundamental and not directed to solving any particular biomedical problem in humans or animals.

Basic research is often performed in experimental animals (from mice to apes, most often in rats) using various models such as the whole organism ("in vivo" studies) isolated tissues and organs (e.g. the liver) or single cells and organelles (e.g. freshly isolated hepatocytes, cultured cells, membrane vesicles: "in vitro" studies). On a smaller scale, studies can also be conducted on the very building blocks of cells: proteins, lipids, carbohydrates and nucleic acids.

By choosing a small (e.g. a cell organelle) rather than a large (e.g. the whole animal) experimental model one is able to precisely focus on a specific process and to dissect it from others. However, in doing so, the physiologic setting under which such a process takes place is inevitably lost. Thus, research conducted under carefully controlled, yet physiologically artificial conditions must always be corroborated by experiments conducted in more complex in-vivo models. Indeed, the ultimate test of a given medical hypothesis often has to be done in the human body itself.

What does it take to be successful in basic research? Basic research is often difficult, sometimes expensive and even time consuming. It requires a great deal of patience, careful planning and execution of experiments and capacity of analysis and synthesis in judging the results. Some people think that basic research should be conducted in centers with dedicated and properly suited laboratories, with (where needed) animal and radioactive facilities, and possibly with large, expensive machines and instruments (e.g. mass spectrometry, centrifuges, cold rooms, hoods etc) to be shared with colleagues. More important, basic research should be conducted in a competitive, stimulating environment where ideas, methods and knowledge are freely exchanged. Usually, basic medical research flourishes in institutions where other types of research - related or unrelated - also take successfully place (e.g. in other sciences, biology, chemistry etc).

In short, basic medical research requires a complex environment which should be supported by the local and national health/academic authorities. Such an ideal center should be the workplace for well-established investigators with expertise, know-how and prestige (that is, role models) capable of attracting funds and young trainees. Remember, every person (and every institution) has to begin somewhere and somehow! Ideally, the major long term objective of basic research should be one that aims at understanding and curing a human disease.

An excellent example of good basic research applied to clinical Medicine is the work of Oude-Elferink and colleagues. These authors first identified an animal (rat) model for the human Dubin-Johnson syndrome, which is characterized by impaired hepatobiliary transport of many compounds and chronic conjugated hyperbilirubinemia. They later demonstrated that these rats (called TR-) are defective in the canalicular multispecific organic anion transporter (cMOAT) which normally mediates hepatobiliary excretion of numerous compounds. They did so by showing that in these rats a single-nucleotide deletion in cMOAT gene resulted in a reduced messenger RNA level and absence of the protein. In further studies they isolated the human homologue of rat cMOAT, human cMOAT, and analyzed the corresponding cDNA from patients with Dubin-Johnson syndrome demonstrating that a mutation in this gene is the cause of the disease. Thus, the authors combined the use of basic science techniques and knowledge in molecular biology, biochemistry and physiology with the clinically relevant aim of elucidating the mechanisms of a human disease. Findings such these may also lead to new experimental therapies such as transgenic hepatocyte transplantation.

Are there ethical issues in basic research? Since basic research is not conducted in humans, ethical issues are far less limiting compared to clinical research. Thus, although a code of behaviour always applies when dealing with animals (see section 10, DEC), a given drug can be tested for its toxicity in e.g. rats. Likewise, the effectiveness of a new medicine can previously be tested in animals provided an experimental model of human disease does exist.

An exception to this rule is the research conducted with fetal and embryonal cells for the purpose of human cloning. This is a very important, still evolving ethical issue, which is currently debated in many different countries.

Who pays for basic research? As we mentioned before, basic research is very expensive. Aside from the research conducted in private industries (where money comes from sales of established products or it is provided by investors as in any enterprise), basic research is paid for by tax payer money through specific funds set apart by governments at different levels (regional, state, federal or even international such as in the E.U.). Ultimately, it is the politicians who decide how to spend public money (and how much) since funds are allocated to different sectors of medical research on the basis of priorities set up by special committees within e.g. the ministries of Health or Education. Such priorities are usually based on the perceived need to solve specific and important public health problems (e.g. AIDS, breast cancer, obesity) and may obviously change with time.

CLINICAL RESEARCH

Clinical Research: Research that takes place in a hospital or clinical setting and is focused on treating specific human and animal diseases and other ailments. Clinical research builds upon the knowledge learned through applied and basic research. Clinical research is conducted on human beings and takes shape in treatments and drugs that directly improve human healthcare.

Clinical research involves testing a new drug or a diagnostic method in appropriate trials with patients, but can also deal with pathogenetic mechanisms, quality of life assessment or other outcome measures. When such studies are planned and conducted within a certain period of time they are called *prospective* as opposed to *retrospective* studies, that is, those in which the effect of intervention (therapeutic or diagnostic) on the natural history of a given disease is evaluated “a posteriori” by consulting medical records or conducting interviews with the patients. For example, in a retrospective *case-control study* the effect of screening (e.g. sigmoidoscopy) on the incidence of a given disease (e.g. colon cancer) is investigated by first identifying the cases of colon cancer in a given population and then searching how many of those cases had been subject to sigmoidoscopy compared to a matched (for age, sex and all the known confounding factors) control population which did not develop cancer.

Prospective studies last much longer than retrospective ones, are more complex and require more resources. However, they represent the most important source of information in clinical research since the outcomes (the expected results) can be set out in advance and the quality and accuracy of the data collected is superior to that of retrospective studies. Ideally, to avoid biases linked to placebo effects, *intervention trials* should be conducted in a double blind fashion (investigator and patient unaware of the treatment given) and randomized. In addition, they should be long enough and include a large enough number of patients to minimize the likelihood of underobserving the expected event (e.g. the disease or the side effects of the drug under study).

What does it take to be successful in clinical research?

What are the most desirable qualities in a clinical study? Certainly the number of patients and the length of follow-up are very important – mainly to minimize statistical uncertainties. Thus, to accumulate a large body of data in a relatively short time, prospective studies are often conducted as *multicenter trials* under the guidance of a coordinator or a study group. Therefore, the capability and stature to be a good organizer and motivator is fundamental to be successful in clinical research. Such a coordinator usually benefits greatly from the help of a good statistician and, at least in Gastroenterology and Hepatology, must collaborate closely with a pathologist. A good clinical investigator should also have a clear grasp of the basic mechanisms of the disease under investigation, be a good clinician and obviously be a good scientific writer.



For example, Barry Marshall almost 20 years ago had the great intuition that a bacterium could be the cause of peptic ulcer disease (long thought to be the result of many factors including diet, personality, environment etc). To prove his hypothesis he first isolated the bacterium (later called *Helicobacter pylori*) from the stomach of a patient with the disease. Then he ingested it and proved that the bacterium could be found in his own stomach and actually caused disease (an endoscopy performed before the experiment had not shown any disease or bacteria).

More recently El-Omar and colleagues and Figueredo et al have provided attractive explanations on why some patients with H.pylori infection may develop cancer while the majority doesn't. These authors have shown that infected patients with gastric cancer are much more likely to harbor a strain containing the pathogenicity island *cagA* and to have genetic mutations that allow for high expression levels of the cytokines IL-1 and TNF- α . The H.Pylori *cag+* strains promote production of intermediate cytokines which amplify the inflammatory process and cause the release of, among the others, IL-1 and TNF- α . These cytokines, in turn, are potent inhibitors of gastric acid secretion and thus cause atrophic gastritis, a premalignant condition. Deciding which genetic polymorphism (among thousands) had to be investigated in cancer patients was the difficult part of the studies and was based on a thorough understanding of gastric physiology and molecular pathogenesis of gastritis.

Ethical Issues. Clinical studies are always connected with ethical questions: does an intervention cause more harm than benefit? Is the patient properly informed about all risks and consequences? The Helsinki declaration and other regulations represent admirable efforts to curb abuse. However, there are no easy ways to solve ethical dilemmas. New issues emerge and will keep evolving with new opportunities (e.g. egg implantation, surrogate motherhood, gene therapies etc).

In general, clinical trials should be preceded by extensive preliminary studies in vitro or in animals:

- they should bear no harm to the patients
- they should be scientifically sound (e.g. must aim to answer an important clinical question with appropriate methods) and
- they should always be approved by properly informed patients and ethical committees.

Who pays for clinical research? Large drug trials are often commissioned and paid for by the company that makes the drug to be tested. For this reason, there is always the potential of a conflict of interest for both the company as the investigators conducting the study. It has become recent policy of major scientific societies and journals to specifically request and to disclose it to the public any of such potential conflicts before publication or meeting presentation of clinical data. Another potential byproduct of cooperation with pharmaceutical companies is the uncertain fate of negative results (that is, the lack of efficacy of a given drug) which often are not published at all. Smaller trials (not necessarily involving a new drug) may be conducted by individual investigators usually in academic hospitals: they often don't require major resources and the salary of participating doctors is paid for by the institution as part of their duties. As in basic research, funds may also come from private sources (foundations, patients' associations, scientific societies etc) and institutional (e.g. government) money. However, this is usually a minor portion of support and often it is restricted to specific subjects (for example, vaccine trials). Perhaps, the greatest difference, in monetary terms, with basic research is that the salary of clinical investigators is not dependent on grant funding but relies, instead, on their main clinical duties.

EPIDEMIOLOGIC RESEARCH

Epidemiology measures the occurrence of disease in human populations and the factors that influence their occurrence, severity, and outcome. Epidemiologic studies are particularly useful at the early stages of an investigation when the

A different type of clinical research is the *epidemiological research*. In these studies a given variable is investigated, without any intervention, in one or more given populations over time (for example, the incidence of gastric cancer in a population exposed to a diet rich in salt). These prospective studies are also called *observational*. Epidemiological studies can also be retrospective, for example in populations known to differ for at least one important risk factor for developing a given disease. Research in epidemiology may only require consultation of archives or interviews with patients. It is usually done outside the hospitals, in selected centers, and often provides essential clues to the causes of disease leading to further, interventional types of studies (for example, changing the diet in the population at risk). A potential drawback of the research in epidemiology is the need for accurate registries of disease. For example, while a registry of cancer does exist in most countries, an inflammatory bowel disease registry only exists in a few places in the world. In addition, it is very difficult to acquire reliable data related to diet, exposure to carcinogens, lifestyle etc and to discriminate between the effect of environment and that of the genetic set-up of a given population. That is why epidemiological studies are useful especially when done in homogenous populations.

Improvement of technology for diagnoses and research

In Gastroenterology and Endoscopy (as well as in a few other disciplines), an important branch of research is the development of technology to improve diagnosis and therapy of GI diseases. Recent examples are the development of the wireless endoscopic capsule, of instruments and techniques for the endoscopic treatment of obesity and gastrointestinal reflux, of high-frequency endoscopic ultrasound, of magnification in chromoendoscopy etc. The impact of these developments often goes well beyond that of new drugs and often changes completely the practice of the discipline. As past examples think about endoscopy for diagnosis and therapy of GI tract diseases, percutaneous liver biopsy for liver diseases, ERCP and more recently MRCP for biliary tract diseases. Ingenuity, problem solving capabilities and basic technical knowledge represent the best qualities to succeed in this field. This type of research is usually done solely in medical companies. However, it is often an original idea of the individual investigator, which is further developed and brought to the market by close collaboration with a commercial enterprise. The ever growing (and appreciated) importance of this field may change the emphasis of funding in Gastroenterology and Hepatology of major agencies worldwide in the near future.

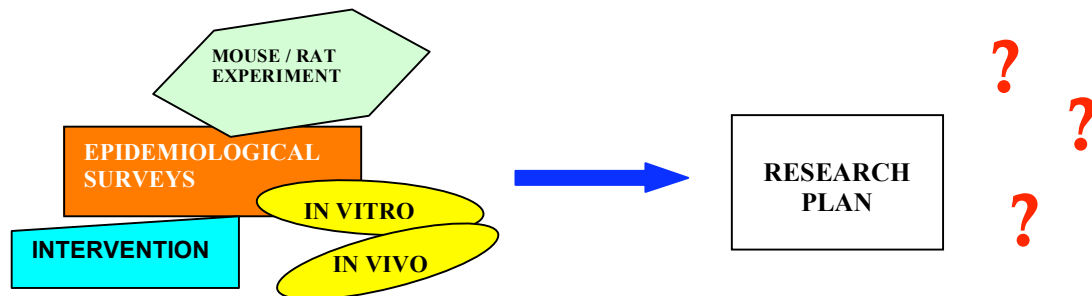
Basic or clinical?

Choosing a field of research is often linked to several factors. An impression, an idea, a dream are often more important than a rational choice. Likely, the young investigator may not be able to fully comprehend the future implications of his/her choice. As our knowledge and medical technology evolve, basic and clinical research intermix and merge more and more often. Ideally, a good basic medical scientist should conduct research that will eventually help understand and cure a disease. Likewise, a good clinical investigator should always conduct studies based on the known basic pathophysiology of a given disease. A good tutor, a good academic center and much passion are essential ingredients in any circumstance. Above all, the would-be investigator should keep in mind that, with all its practical limitations, research is and will remain the very foundation of human knowledge and progress in Medicine.

BACKGROUND OF A RESEARCH PLAN

D. Jonkers & K. Scheele

BACKGROUND OF A RESEARCH PLAN



Why doing research?

Before starting research you have to ask yourself: why doing research? Are you interested in doing research yourself or do you have to do research, for example because it is required to find a job or is it a part of your (clinical) training.

It is also good to keep in mind whether you are planning to do just one study or are aiming to obtain your PhD-degree and whether you wish to continue doing research in future. These aspects may play a role in choosing your research topic. Be aware that the research topic you will handle may affect your future career and may have consequences for the topic(s) you will be working on in future.

How to choose your research topic?

Mostly a certain research plan will be developed because there is specific interest in a topic. This can be:

- *Following an existing research line of a department or institute*
Several institutions or departments have certain research lines they are working on and future research has to fit in these research lines. This can be a general theme such as 'Inflammatory bowel disease', 'Colorectal cancer' or 'Inflammation' but sometimes these themes have been defined more specifically such as 'The role of the immune system in inflammatory bowel disease' or 'The role of diet in colorectal cancer'.
- *Research that follows the outcomes of a earlier study*
It can be very effective to start with the outcomes of a recent study from other researchers and to do follow-up research or to broaden the subject, or even to look more in-depth to (a certain aspect of) the subject.
- *Research based on clinical experience of problem(s)*
Daily practice, both in the clinic or on the laboratory, can face you with specific problems or specific gaps in knowledge, which require further study.
- *Interest of teacher*
Your teacher can be very much interested in a certain topic and asks you to address this topic.
- *Personal interest*
You are very much interested in a certain topic or disease yourself. If possible, try to find a tutor (and grants) to explore your idea and interest. However, possibly you are not always 'free to choose your research topic'.
- *Question of industry to perform a study.*
Sometimes the pharmaceutical or food industry contacts a department or clinician/ researcher to perform a study. Frequently these questions are about clinical trials but can also be connected for example to the pathophysiological or epidemiological aspects of certain diseases.

➤ *Participation in a multi-centre study*

Especially if limited numbers of patients are available or if very large epidemiological studies have to be performed, other investigators may approach you to participate in a multi-centre study. Generally, a research plan will be then made by the co-ordinating centre, but mostly your input and thinking along with them is required or appreciated.

Generally it is wise to discuss the general topic of your research plan with your local teacher or supervisor (before you go into detail and do a lot of work) to see whether the topic of interest fits within the existing research lines (if required) or to check whether other possible obstacles can be expected (conflict of interest, competition, finances, facilities, duplication of research etc).



After the interest comes . . .

Once the interest in a research topic is defined by you (and your supervisor), you first need to collect all the available information on the topic to be able to make a research plan. Where can you find this information?

➤ Literature

- Depending on your background, you first may have to collect *general information* or to update your knowledge on the topic. For this aspect you can use general books on Gastroenterology, Immunology, Microbiology, etc., as well as websites such as www.gastrohep.com.
- Subsequently you have to search for more *specific information* on your topic. Very specific as well as very recent knowledge is mostly not available in books but can be obtained from articles using literature search programs and internet. Frequently used literature search programs are Medline (Webspirs, Ovid technologies, webspirs@ovid.com) and Pubmed (www.ncbi.nlm.nih.gov/entrez).
- Most libraries in universities and hospitals can introduce you into the literature search programs. Define keywords on your topic to start with searching. Generally, searching with one keyword (such as colorectal cancer) results in to many hits and you have to limit your search with a combination of words (colorectal cancer and diet) or use synonyms.
- Use both the most recent literature as well as check what has been done in earlier years. This may even be a start for your introduction!
- When reading the literature, be always alert whether the studies described have been performed and analysed correctly and whether valid conclusions have been drawn from the data (see also Chapter 7-14).

➤ Internet

Nowadays a lot of information can be found on internet using for example Google, Yahoo, AltaVista, etc. Always be critical on the quality of the information and the websites you find as they will not always be of an academic level.

➤ Recent congresses



(Recent) findings presented as oral or poster presentations at congresses will not always be available (yet) as full papers in journals. It is advisable to check for new data published as abstracts at (recent) congresses. In the field of Gastroenterology, two important congresses are the Digestive Disease Week (www.ddw.org, abstracts are published in 'Gastroenterology') and the United European Gastroenterology Week (www.uegf.org, abstracts are published in 'Gut'). Also national meetings and congresses or symposia on more specific topics can be checked such as: liver/pancreas, gastrointestinal malignancies, mucosal immunology, nutrition, IBD, etc.

➤ Asking experts

Visit experts and talk to them, mail them and ask questions. Don't do this in the first week of your search for knowledge, but once you have acquired a lot of knowledge and questions are popping up in your head, most experts are very likely to answer your questions and share their interests.

Now you have knowledge . . .

If you have come to a complete update of your research topic, you will have increased your knowledge on the topic which will contribute to the contents of the research plan, because:

- you know what exact topics people in the field are working on;
- you know the gaps in knowledge and areas where further research is required;
- you know the names of experts in the field.

With this information you can further define your research plan. Hereby it is important to keep in mind if your research is worthwhile:

- Is the topic relevant from social, economic and/or scientific point of view?
- Are there any ethical considerations?
- Will the research result in new data (no one is interested in or willing to pay for duplicated studies)?
- Can the research be financed? Can you apply for grants on this topic or contact the industry?
- Does the topic fit within the research line of your department or institute (if required)?
- Is it feasible to perform a study? Do you have the knowledge, patients, facilities, time and/or personnel to perform this study?

If you have defined the outline of your research plan, try to get as much input (further suggestions, critical remarks, etc.) as you can before writing the definite research plan by discussing it with your supervisor, with your department and colleagues (especially if you need their co-operation), with connected disciplines and again, don't hesitate to contact experts in the field!!

And then . . .

When you are sure about the research topic to be studied, you have to check being able to perform the study and to be supervised adequately (see also chapter 5, 10-12). Then, writing the final research plan starts with a good hypothesis or set of hypotheses (see also chapter 7).

FIND A TEACHER,
A LABORATORY AND
AN INSTITUTE

R. Stockbrügger

FIND A TEACHER, A LABORATORY AND AN INSTITUTE

You have now decided to start with research, either on its own or in connection with clinical or other professional activities. You have to accept that research is not anymore an individual ego-trip. It is nearly always teamwork, either in one place, or in collaboration with other centres nationally or internationally. This means for you that you have to find or to organize your research environment, which consists mainly of an Institute, Laboratory and Teacher(s).



Let us start with the most important part, the teacher(s). If you look back at your primary and secondary school, teachers were given facts: no choice at all. During graduate schools this improved: many times you could choose between alternatives. In research, the choice is really up to you, but unfortunately the risk is also. If you do not ascertain the quality and the appropriateness of your teacher for your individual research intention, for your own way of planning, working, and behaving, you might get disappointed, lost and losing a unique intellectual and career chance. Starting research is many times like growing up in a family, only this time you have to choose your parents and your siblings!

How to find a teacher?

The easiest way of finding a teacher is to become inspired by someone you have heard personally or whose scientific productions you have read: “love at first sight”. You start following that person; you deepen your impression and finally you make an appointment to declare your wish to perform research together with her/him.

The same may happen the other way around: a teacher sees a potential brain with hands and asks whether this person would like to join her/his team. Be a bit careful here: if you say “yes”, you might have diplomatic difficulties to retract your decision if you subsequently find out that the teacher in question would not have been your first choice. Therefore, rather show yourself honoured by the offer, create yourself time for further inquisitions and decide later.

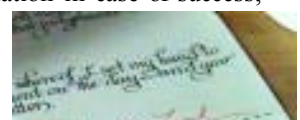
One of the better ways to join a teacher or a group is by recommendation of some trusted friends, colleagues, or other young investigators, already successfully engaged.

The other entrance is through the search of the subject: if you want to study the behaviour of mast cells in IBS your (national) choice may be quite limited. Do not hesitate to be selective, but be prepared to renounce to your original research topic if you cannot find the good teacher and research surroundings! The table below will help you to select your teacher: if you score 5 items or more: you found him!

Criteria for a good teacher:

- Age: will he be around at the end of your thesis?
- Knowledge: has he enough and recent knowledge on the subject?
- Time: does the teacher find enough time for you?
- Money: is the teacher good in raising funds?
- Previous promovendi: did someone succeed his thesis with this teacher? What are his or her experiences?
- Name: does the teacher have a good name in the working field, among colleagues, among students?
- Understanding: did the teacher listen to you – hear anything of what you told him?

When you have found your teacher, contracting starts. Contracting about the terms of your engagement regarding period, financing, outcome in type and number of publications, possibilities of continuation in case of success,



but also escape routes in case of failure. The contracting period is a phase of testing between teacher and research fellow: be careful to accept a teacher who is not disposed to perform this brainstorm phase in a responsible way. Such teacher may have even less time to support you later on.

If possible, end your “contracting phase” with a written document: the most appropriate would be that you yourself gather the result of the above discussions in a letter submitted to your potential teacher and kindly ask for a written confirmation of the agreements described. Then, you have a guideline in your hand which is much more secure than a “let’s just start and then we will see how it works”.

How to find a laboratory?

The place where and with whom you will be doing your research will most of the time be laboratories, offices, libraries and other information providing facilities including their staff. Try to get a glimpse at them! If you are supposed to continue with a method or a study where someone else has to leave over, try to learn to know that person to become introduced to the method and the persons involved.

Looking for the right teacher, you nearly automatically will learn about the institution you might become working at. Not only you have to be backed by a good teacher, also your teacher needs to be supported by a good institution: a spirit of collaboration and discussion, joint conferences, social occasions and interchangeability of methods and means are good signs. Power competition, fire walls between departments, “they and we” are bad signs. When coming to see your potential teacher, try to have a look to the laboratory where you are supposed to work, have a coffee or a beer with some of your future fellows and test the situation. Most of the time, walking in and out of offices, speaking to secretaries and laboratory staff, you will find reflexes of the general atmosphere.

Criteria to choose the institute or laboratory

- Are the employees happy? Both during working hours as after?
- What kind of equipment is being used? (none – old fashioned - high tech)
- Is there any working space for you? (computer, table)
- Working hours (expected): do they work from 7 till 11 p.m.?
- Is the institute well known? For what reason? (*good drinking lads, or quality of work*)
- How many other workers are in the laboratory? (*none-> the last one died three years ago*)
- Politics between the institute / laboratory / teacher / other institutes in the field
- Are there other overhead facilities (*coffee machine, copier, etc*)

Why all this?

You have decided on a big step and a huge effort, which might cost you years of your life. Certainly, it may give you a lot of pleasure; success and it might possibly be the most decisive step in your career. However, if you are not successful because of wrong assumptions, superficial observations, or just because of innocent optimism and blind trust in others, you might lose every good will and positivism, and you might never want to return to research. More than that, you might have lost some of the most exiting and beautiful years of your life. Therefore, try to be trustful and daring at the same time as you are attentive and critical: you will need this combination of characteristics in many situations to come.

WHAT IS A HYPOTHESIS?

C. Hawkey

WHAT IS TRUTH?

For a long time, science was seen as inductive. All you had to do was to observe nature long enough, make the right references and you were a great scientist. Unfortunately this approach did not take into account bias and errors and did not make scientists test whether their view of the world was right or wrong.

What is a hypothesis?



Karl Popper and others promoted the modern view that all scientific accounts should be based upon a hypothesis – a testable reductionist view of what underlies observed phenomena. By derivation hypothesis means beneath a thesis – but this is rather unhelpful because the definition of a thesis is quite close to that of a hypothesis.

The important thing about a hypothesis is that it is a tentative as yet unproven proposition which is subject to verification through subsequent investigation. As Peter Medawer put it, it is an imaginative preconception of what might be true which is then subject to critical scrutiny. The critical difference from just describing observations or making inferences is that hypotheses avoid bias by requiring the scientist to state in advance what he is testing. Otherwise it is always possible to make retrospective sense of a pattern of events that actually occurred by chance. Without a hypothesis, all statistical analyses (see below) is invalid.

So how do I start?

Most people want to start in research by sticking with the familiar and finding evidence that supports it. Then they can feel they have joined the world of science. This is usually a big mistake. True science is always testing the robustness of existing hypotheses (often wrongly described as facts) and trying to find a better explanation of observations. Once you are into science, this is very easy because research throws up unexpected findings. When you are starting, it can be difficult but you need to try to identify questions that are unanswered or where existing answers are unsatisfactory. At the start, you may need some help from an existing scientist who will always have an excess of things to investigate. However, make sure your mentor is truly hypothesis driven rather than churning out data that are supportive of a preconceived position (that his or her reputation may well depend upon).

The role of unexpected or change findings

These can be a rich source of new hypotheses once you have started research. Yet most people assume that unexpected findings must be wrong and subconsciously or explicitly suppress them. Yet it is the observations that challenge the current view of the world – the finding of bacteria in people with peptic ulcer, the observations that moulds inhibited growth of staphylococcal colonies or the converse observation that cultures of brucella abortis contaminated by a mould grew faster.

Should all hypothesis challenge existing wisdom?

There is an argument that, because the purpose of hypothesis driven science is to progress through ever better explanations, that most such research should question existing notions (whether someone else's or your own). However this is far from absolute. One thing your critics will want to know when you do a piece of research is whether your methods are reliable. One way to do this (see below) is to confirm data that someone else has produced and that you do not wish to challenge whilst pursuing your new hypothesis in an area where you do wish to challenge existing data. In this way you give increased authority to the novel work by showing you are sufficiently competent to confirm previous data. This is important when you start out. Unfortunately, most young and many older researchers are contented simply to generate data that are supportive of a particular idea (usually this year's fashion). This approach is largely a waste of time. You can legitimately conduct a new trial to support an old hypothesis if there is doubt or uncertainty about it – for instance if previous results are mixed or if previous studies were small leaving doubt about the size of an effect.

From observation to hypothesis

Once you know what you want to investigate, the art is to construct a useful hypothesis. A useful hypothesis is one that is:

- plausible
- specific
- easily testable.

As stressed below, the important thing for hypothesis to be useful rather than right (there is probably no such thing). It is the question, and the way that it is framed and then tested that matters, never the answer (see below).

The development of penicillin was based upon the hypothesis that moulds produced a substance that inhibited the growth of bacteria. This hypothesis leads to the specific of penicillin. For the opposite effects on brucella those stimulatory substance could be found. However, when it was discovered that brucella grew better in the presence of carbon dioxide the hypothesis that moulds facilitated its growth by CO₂ production could be tested. For Helicobacter pylori and ulcers the initial hypothesis was fundamentally simple although once it was proven, a further hypothesis linking Helicobacter pylori with acid hyper secretion that characterized duodenal ulcer patients had to be formulated.

Whilst writing the above, it occurs to me that Helicobacter pylori grows better in the presence of CO₂ ... I wonder if investigating a relationship between fungi, CO₂ production and Helicobacter pylori would be worthwhile. This illustrates a further good source of hypotheses, mainly idleness and random thinking (but see plausibility and robustness below).

So why do I need a hypothesis?

There are at least three good reasons to make your research hypothesis-based.

1. They make you focus your ideas
2. Nearly every piece of research has an implicit hypothesis behind it. If you haven't constructed a hypothesis you probably don't understand well enough the area you want to research on.
3. Grant giving bodies love to see them

What makes a good hypothesis?



A good hypothesis is one that is clear and specific, amenable to precise testing and which can be easily disproved if it is wrong. I personally like very precise stated hypotheses because they produce the clearest focus in thinking and if disproved allow you to move unequivocally on. Once you have expressed your hypothesis you need to develop a

research plan with aims and methods. In practice (as illustrated below) this often involves the development of sub-hypotheses which themselves determine your experimental approach.

Hypothesis testing

Hypothesis testing is done by conducting experiments that will ideally yield one set of results for the hypothesis to be true or not. Most hypotheses require several sets of experiments for evaluation. This often means establishing some valid measurements, and correlating them with a condition to which they might be linked. Unfortunately most people stop there, but most hypotheses require an active intervention and a prediction of what this will do to be tested robustly. At the same time there is an opportunity to investigate biologically plausible mechanisms (this will strengthen the hypothesis) and obtain additional supporting data.

For example, the hypothesis that ulcers might be caused by a bacteria was initially tested by an intervention, namely ingesting the bacteria. This particular experiment was however not pivotal – an ulcer did not result but the fact that an inflammatory state (active gastritis) that is associated with ulcers resulted did support the hypothesis (and also yielded mechanistic supporting data). A stronger piece of evidence supporting a specific link with ulcer disease came from experiments in which eradication of *Helicobacter pylori* with antibiotics largely prevented ulcer recurrence. Even this was not 100% conclusive – some of the antibiotics persisted in the mucosa where ‘cyto-protective’ effects could possibly have explained the data.

Two conclusions:

1. Doing a single experiment that totally supports or disproves a hypothesis is extremely difficult.
2. Several experiments are needed and often an intervention should be positive (in the example above, testing

Are there drawbacks to hypotheses?

The phrase ‘Young Turk’ refers to young people who were members of a revolutionary party in the Ottoman Empire, eager for radical change of the established order, who carried out the revolution of 1908 and deposed the Sultan Abdul Hammed II. When successful investigators start they are ‘Young Turks’ because they recognize the purpose of research is to question and replace enfeebled truisms which are the remains of previously radical new ideas. Unfortunately, successful researchers end up as members of the establishment defending progressively enfeebled versions of the ideas that initially made them famous.

What happens under these circumstances is, that people forget that research is about questions and that hypotheses are unproven and/or only partial propositions that at any time represent a best explanation of observed phenomena. Those who end up defending a particular view make the related mistakes of thinking the so called answer they established is more important than continuing to ask questions and of fitting observations to a particular point of view.

So how do you avoid bias in research?

This is where the prospective nature of a hypothesis and the construction of a proper statistical plan come in. As outlined below, most experiments should have only one primary endpoint (unless appropriate statistical adjustments are made). Even so, it is amazing how, once the results are in, researchers convince themselves that they have actually asked a slightly different question. In clinical trials there is improving protection against this as many journals now require submission of the original trial protocol with the original primary hypothesis stated so that they can check whether the paper is written valid. For other types of research, particularly that is conducted in the laboratory; similar levels of discipline are seldom practiced. It becomes quite easy to discard some results as ‘outliers’ and for the original hypothesis to ‘evolve’ as the work progresses. In extreme cases this can amount to fraud but in the vast majority it is merely a matter of being vigilant in continuing to test exactly the original hypothesis and not to let this change subtly as you go on so you end up testing wishful thinking.

Endpoints

Another way of avoiding bias is by making sure you normally only have one endpoint. Statistical methods are based upon the idea that you are investigating how likely it is that the answer you obtain to one question arises by chance. If you ask many questions, the likelihood of getting a positive chance result increases. If you ask 20 questions and set your statistical probability at $p=0.05$ (testing that there are 19 out of 20 chances that any result

does occur by chance) and you do this 20 times, you will get a result by chance that has the magic $p=0.05$. You are then in danger of feeling you have succeeded and falling in love with the data because it was nice to you and gave you a positive p value. Unfortunately however, of course, you have actually been lured into make believe.

Can I really only test one endpoint?

You can test as many endpoints as you like as long as you know which one is the primary endpoint. Related (secondary) endpoints are generally only proven if a significant result in them is found once the primary hypothesis has been proven by showing a difference in the primary endpoint of the study. If you test the same endpoint but there is a 3-way comparison (a versus b, b versus c, a versus c), you normally have to adjust the p value: dividing 0.05 by 3 (with the number of comparisons) which gives you 0.017. You need to look at significant levels for this p value before you can say that any comparison is significant (at the 0.05 level ... I hope that is clear!).

What is a null hypothesis?

For the non statistician this is not a very helpful phrase. When you test a hypothesis, you are technically testing whether A is the same as B. If your statistics show there are 19 chances out of 20 that it is not, you have reached a p value of 0.05 to reject A being the same as B. But it seems to me this is the same to all intents and purposes as saying there are 19 chances out of 20 that A is different to B. So don't worry about the phrase!

What is a hypothesis generation?

As stressed above a hypothesis is an imaginative conception of what might be true that is prospectively tested. This goes into the primary endpoint of a study. Secondary endpoints generally concern supportive and or mechanistic data. In addition it is perfectly acceptable to look carefully at your data from a neutral point of view to see if it suggests any new ideas. You may (as Nan Sartz did) give sulfasalazine to an unselected group of patients with arthritis testing the hypothesis that this would relieve arthritic pain (which it didn't significantly). You may notice (as she did) that the colitic patients with arthritis happened to get better. Because this was not a pre-specified idea, the initially research did not prove it, but it was an observation that gave rise to a new hypothesis, that sulfasalazine would prevent relapse of ulcerative colitis for subsequent prospective hypothesis testing.

Thus examining your data in as biggest detail as possible from every possible angle is important, provided you do not make the mistake of thinking that relationships are found in this way prove anything. All they do is act as a source of new hypothesis for testing – but this process of hypotheses generation is the way in which most skilled researchers progress from one study to another.

FROM HYPOTHESIS TO A RESEARCH PLAN

C. Hawkey

FROM HYPOTHESIS TO RESEARCH PLAN

Once you have a hypothesis, it is important to operationalise it. That is to say, you have to devise clear cut actions to test whether your hypothesis is realistic. *It is important to note that you can never prove a hypothesis!* You can only see if it stands up to the most rigorous testing. Therefore, your approach needs to include attempts to disprove your hypothesis as well as gathering supporting evidence. Most weak research only does the latter.

| There are several steps to operationalising a hypothesis into a research plan.

1. Ask whether existing information already disprove your hypothesis or makes it implausible

First, you have to test the robustness of your own idea against the existing literature. This can be difficult. On the one hand, if you have a genuinely new idea, the literature will of course be full of concepts that do not support it. Are these simply the biased utterances of investigators less perspicacious than you? On the other hand, there is no point testing a hypothesis if there is convincing literature that already disproves it.

At this stage, you have got to be tough with yourself. Most ideas can be seen to be wrong before they are ever tested. If you find this is the case, you will be SAD and reluctant to discard your wonderful idea, but there is no point in researching it if failure can be predicted.

2. Critical appraisal

This is an important capacity, which you need to apply in assessing whether the literature undermines your hypothesis or whether it remains visible. Most people take headline research results at face value (uncritical absorption). With critical appraisal you decide whether the interpretation of the research is likely to be true. Hypercritical appraisal which involves unthinkingly dismissing research just because it has flaws is as bad as uncritical absorption – the question to be applied is always whether the results are on balance likely to be true.

3. Generating a new hypothesis

If this first step leaves your original idea in tatters, do not worry. It is very likely that the process described above will have led you to degenerate many more and stronger ideas that should then form the basis of your experimental work.

4. Strengthening your hypothesis

The initial statement of a hypothesis seldom survives in its original form critical appraisal of the literature. Even if the literature leaves your hypothesis unscathed, you can probably improve it. Improvement means making the hypothesis more precise and testable. Improving a hypothesis goes along with planning experiments to test it. This process of operationalisation of your research generally involves the following:

- Generating sub-hypotheses. These might be 2, 3 or 4 hypotheses that are components of your original hypothesis. This is important because these sub hypotheses are often the basis of the research plan.
- The research plan. This must consist of studies that will, as far as possible, unequivocally lead to support or rejection of your hypothesis or sub-hypothesis depending upon outcomes. Many pieces of research involve:
 - Confirming previous results that you think are correct.
 - Gathering non-critical data that are supportive of but not a robust test of your hypothesis. If you think that mediator x causes disease y, you will generally need to show that mediator x is elevated in disease y. You can see this as a necessary, but not sufficient, part of testing a hypothesis. Unfortunately, many people think this is all you need to do but this only shows an association that may just be an epiphenomenon. To show that x causes y you will normally need:
 - An intervention. You need to show that if you alter mediator x I has a predictable (hypothesis driven) effect on disease y or some surrogate of it. This might involve a test of a drug in patients. Just testing the drug is generally not enough. Your hypothesis will be supported more strongly if you show that mediator x actually changes in an appropriate way as disease y improves. It is even better if you can show that the extent of change of x correlates with the extent of improvement in disease y in individual patients. A common way to do this is to use 2 doses to show a gradient of improvement. The same principles apply with interventions *in vitro* or in physiology studies.
 - You must also consider that the intervention you choose (whether in a patient or a model system) might be acting in a completely different way to what you thought. One way to get around this is to intervene in two ways (e.g. drug and gene manipulation in an *in vitro* system) and preferably with

interventions that go in opposite effects (over express of gene and inhibit it). This is often easier to achieve in laboratory or animal experiments than human ones.

- Mechanistic studies. If you show that mediator x produces effect y, you will want to know how this occurs. Does it occur in a single cell and if so, what are the signalling pathways? You can ask similar questions nowadays in tissue obtained from patients. In the past, because of the difficulty of doing multiple experiments on small tissue samples, this often involved measuring just one thing (mediator x) as described above (ii). Nowadays, you can quite easily go beyond this black box approach using techniques such as luminex beads that make multiple measures (e.g. a range of cytokines) on the same sample, PCR to detect changes in gene expression or gene array analysis to detect multiple effects - but beware of 'fishing' for a result that you did not actually hypothesize originally!

5. Important practical issues

Having a clear idea of exactly what you are testing and how your research might evolve over a couple of years is critical for careful planning. Imprecise thinking and poor planning result in poor, inconclusive research that ends up being a waste of time and effort.

6. Type of research: pragmatic or explanatory

A lot of (particularly laboratory) research, along the lines described above, is explanatory research. You want to know if mediator x causes phenomenon y . If your intervention doesn't actually change mediator x , it doesn't actually prove or disprove whether mediator x does or doesn't cause phenomenon y . You have devised new experiments that result in a change in mediator x . Quite often in clinical trials, the question is different: taking everything into account, including tolerability, compliance and differences in effectiveness in individual patients, it is pragmatically worthwhile to give treatment z to patients. Treatment z might do all the right things in explanatory terms but could fail as a realistic treatment because it only achieves this in a minority of patients or because its benefits are counterbalanced by side effects that cause patients to stop taking it. Being clear what you are doing is important in determining how you analyze your results. Pragmatic studies require intention to treat analyses: you analyze all those who have been allocated treatment. Explanatory studies require per protocol analyses: you analyze only interventions that effectively achieved what you intended. For clinical trials this means analyzing those where effective continuing drug exposure was achieved because the patients followed the protocol. For laboratory studies, this means only analyzing experiments that worked (but it is essential to take strong active steps to avoid bias).

7. Choosing a method of measurement

One of the big mistakes that researchers can make is not choosing the best measurement method. This can result in wasted time and ineffective research. In laboratory research, measurement methods that have been used before are often copied when methods that are faster, more sensitive, more accurate, more precise or more relevant are available. People often choose inappropriate methods because that is what they are familiar with. But technology advances fast. It's often a good idea to see if measurement methods that have been used in other fields would give your research an advantage over other approaches. In clinical studies, it's often a matter of making sure you have defined endpoints in an extremely precise and concrete way.

8. Proving the accuracy and reliability of your methods

Whatever method you choose, you will need to spend time to establish that the method is accurate, reliable, reproducible and valid. It's a fatal mistake to rush straight into your study without establishing the validity of your measurements.

In laboratory research you must show that you can measure what you know (e.g. authentic standards) accurately and that when you add known amounts of these standards to one of your samples the increase in what you measure is an accurate measure of what you actually added. In both clinical and laboratory research, you need to show that you get similar results when you measure the same experimental sample or do the same technique on different occasions, and also when you measure the result of identical experiments done on different occasions. A good way of validating a clinical endpoint such as an endoscopic finding is to do an inter-observer variability study to prove that reproducible results can be obtained.

Reproducible measurement requires you to think carefully BEFORE you do the experiment: your protocol should be so clear that when you actually make measurements you don't have to think but rather work like a machine. If your measurements are not accurate and reproducible your research is guaranteed to fail and you need to choose and validate a different measurement approach if necessary.

Optimizing your methods can take a long time, and you will feel impatient to get real results. But don't cut corners. No-one will believe research that does not contain report method validation nor will they believe negative results from a method that is so inaccurate that its reproducibility is minimal.

9. Confirming previous results

As mentioned above, reproducing existing results is not a good research aim in itself but it is a good way of illustrating that the more original data you produce are believable. It's therefore a good component of a research project.

10. Comparisons and control groups

Most experiments involve a comparison, whether in the laboratory or in populations. You may have to decide whether this is against placebo or (in case of a trial) against best existing treatment.

11. Bias

Although sometimes difficult to achieve, you should ensure that clinical studies are blinded. In general a double (subject and investigator) blind approach is best. There are very few circumstances where you should be prepared to depart from this. If you can't for example get matching placebos, perhaps you shouldn't do the study. It is highly unlikely that you will be able to publish in a good journal without blinding. If the endpoint is an objective assessment (eg histology) you can avoid bias from a more open study if the person making the assessment knows nothing about when the sample was taken or what the subject received.

Avoiding bias in laboratory research is more difficult because blinding is less common. You may well need to exclude the results of bad experiments and/or ones that produce "outlier" results, but the rules on this must be decided in advance, not when a result that you don't like turns up. This should be on the basis of your initial experiments to validate your methods and their reproducibility. Your rule might be to exclude results that are more than 2 standard deviations from expected, but you should get experienced advice from your supervisor.

12. Primary endpoint

A hypothesis is a test of a single idea and you must decide in advance on the main (primary) endpoint that you are examining. If you don't, a natural tendency to bias will lead you astray so that you convince yourself that the only positive result of (say) ten things you look at is the one you were interested in all along, whilst the truth is probably that it is a chance finding. Making sure you have a primary endpoint and take the right approach to it is a good reason to involve a statistician in planning your research. A good statistician will show you to deal with having a range of secondary endpoints and how to handle results that you had not initially intended to study.

13. Dealing with unexpected results

A critical rule in approaching research is that you should care about asking the right question rather than getting the result answer you hoped for. Unexpected results should be exciting, because they take thinking forward, yet many people who do research feel inappropriately threatened by them. Bias will lead many to decide that these results must somehow be wrong. Remember, the whole point of research is to test how robust a hypothesis is. You will need intellectual flexibility to deal with unexpected results but rethinking your hypothesis will prove much more rewarding than doggedly sticking to one that has become invalid.

Special issues

Clinical trials

The explanatory/mechanistic approach can be applied to small scale clinical trials that are amenable to intensive investigation but are a mistake if your investigations concern a clinical evaluation in large numbers of people. Here it is important to make the study work and mechanistic studies often render such trials impossible to do and make them fail. For large scale pragmatic studies, simplicity of design and answering all relevant and no irrelevant questions is the goal.

Epidemiology

In epidemiological studies, remember that you can only show associations. Often these can arise because what you think is a cause of a condition can be a consequence of it. You need to think carefully how to avoid this. One way is to do studies where the causal connection is measured in as yet healthy populations and related to subsequent measurements of disease. A good example is studies of *H. pylori* infection in patients who subsequently developed gastric cancer. Many of these studies are cohort studies. You might be tempted to set one of these up prospectively but for most measurements, the time to event is likely to be impractically long. You need to identify the best database where the measurement of interest has already been made in the past. One way this can be done nowadays is using computerized databases of large populations of patients, which enable cohorts from many years ago to be identified and changes over time that have already occurred to be investigated.

FROM RESEARCH PLAN TO GRANT PROPOSAL

R. Hulcrantz

FROM RESEARCH PLAN TO GRANT PROPOSAL



To do research, you need money! Sometimes the institute or university you work at will pay your research, and sometimes you will have to find industries that are willing and eager to finance your research. However, mostly you have to apply for a grant at for example national (governmental) organizations, funds or the European Union.

This is when you have to convince someone else that what you want to do is worth putting some resources, money in. You have to be able to show that what you want to do is

- Very important,
- New,
- Will lead to important findings,
- You are the right person to do it and
- You have the facilities and time to do it.

Make sure that all language and terminology is clear, and cannot be misinterpreted. Describe the research design in terms of consideration between methodologically the best solution and what is the best to do in practice. Most foundations will have their own request forms to send upon request.

In general, the content of a grant proposal includes:

Summary

You have to be able to communicate your ideas. Write a short summary of the plan. The summary should invite the readers to spend time on the rest of the proposal. Therefore, make it crystal clear what you want to do and make it interesting. Take good time in doing this and let someone else read it.

Background

The proposal has to contain relevant background information and clear aims, a work plan containing the methods and how you will pursue the study. Clarify what you will do and what other collaborators (labs) will do. State the importance of the study in a few sentences.

Network

Give names and expertise of your collaborators (network). This is important since it strengthens the proposal/application.

Management

Mention the site of the research and approval of the management. This gives the reader an impression whether you have the basic resources and will work in a good environment.

Experience

Your own CV is very important since it will help the reader to evaluate your capacities to get the things done.

Description of the study

This is a very important part and should be included in your summary and research plan. Just be sure to check whether it is all there:

- Describe which phase of the empirical cycle the research fits in.
- What type of research is it and why.
- Methodology and design: What type of measures are taken to be sure that the data are reliable, how can they be validated? Think also about describing in this the process of sampling, data collection, the instruments used and their validity, data analyses procedures, etc..
- What influences do methods and instruments used on the research, the finances and the time of the research?
- What alternatives to determine the outcome-parameters were chosen and why was chosen for this solution in this particular study?

Measurements for improvement of internal validity against feasibility of the research. Describe the possible confounders and what measures are taken to prevent the influence of these confounders.

Budget (Cost)

- All research must be financed and is expensive so provide realistic figures.

- Make a total budget and then consider what the actual institution/fund you apply for can give to you. It is not wise to apply for ten times the sum it is possible to get from the fund. Give in the proposal the names of all other sources you expect to get support from, so that anyone who reads your proposal can evaluate the possibility that you get the complete budget funded.
- It is generally accepted that if you are in a research institute, some basic facilities like chairs, desks, paper and pencils are available.
- Make sure to include all costs for all parts of the research in the budget (see budget specifications). Do not forget the cost for administration in your institution (charges, overheads), which can be 10-30 percent of the budget.

Budget specifications:

- Personnel (including brut costs)
- Data collection, data entry and analyses
- Equipment, for example, microscopes, computers and whatever is required to do analyses or to perform measurements
- Materials / analyses
- Travel, accommodation and other meeting expenses
- Medical ethical or animal ethical committees
- Insurance
- Reimbursement study subjects.

Make sure that all costs are mentioned, and try also to include unforeseen costs.

Planning

Time planning and progress control is essential in research. In planning make sure that you have enough time, it always takes more time than you think, or make plans together with an experienced investigator. Calculate the time you think to be necessary and add at least 50%. This seems to be a lot but has proven to be true. Think about sick leave, vacation, period bound activities, delay in time when other supervisors are enrolled or when there is cooperation between other research groups, analysing the data, which can lead to new findings and new analyses etc. It is better to make a time schedule you can manage and to that makes supervisors happy.

Communication

The most essential part of time planning and progress control is communication.

Take upfront in your planning enough time for meetings and indicate milestones for the major processes. Furthermore try to make the timetable as detailed as possible. For example, instead of giving deadlines for the total data collection you can agree upon a deadline for small parts of the data collection. In that way the data input and data formation can start earlier and adjustments can be made in between.

Take into account what the consequences are when the timetable has to be adjusted.

Try to include a test-phase in which you can test the time needed for all aspects of the research project. Make an excel sheet for the planning, including the tasks and the names of the responsible persons and the dates of the deadlines. Send it to everyone who is involved and update it on a regular base; otherwise it will lose its value.

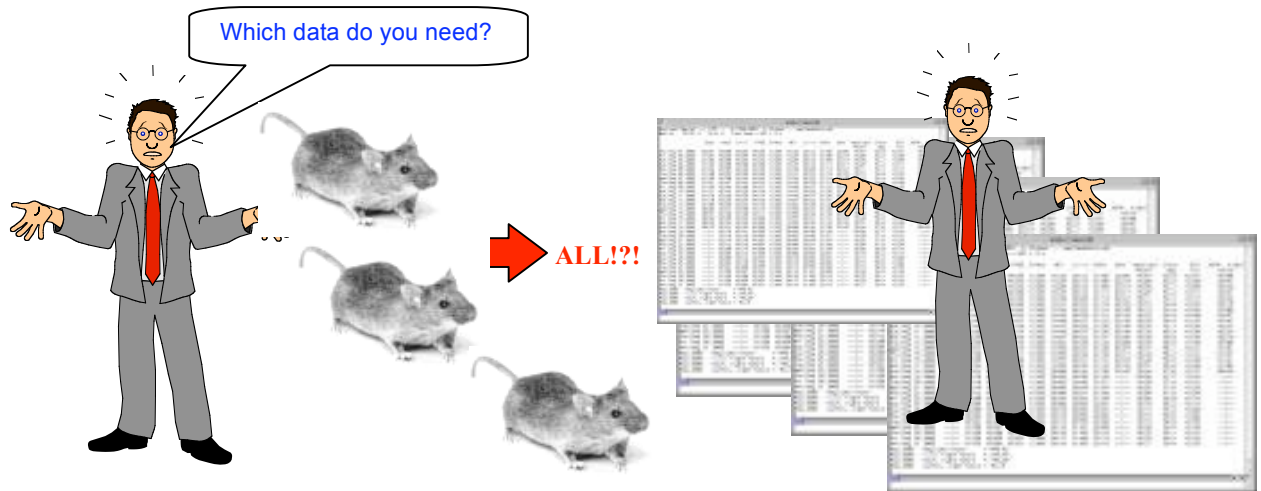
Connecting topics are:

- Hospital / institutional funds
- Regional funds
- Historic foundations
- Disease associated funds
- National research funds / institutions
- International grants
- European grants
- Educational grants from bio-medical industry
- Dedicated industrial grants.

COLLECTING DATA PERFORMING THE STUDY

D. Jonkers
M. Hesselink - van de Kruijs
K. Scheele

PERFORMING THE RESEARCH



T.G. started his thesis in 1990. He wanted to do research on the health of rats after administration of a specific drug. He wrote a research plan, which was approved by the animal experiments committee and started collecting data with 24 mice. After collecting data from 20 mice, he found more and more interesting questions, so another 24 mice were included in his research. After 30 mice, he found to have made a mistake with the first 24 mice. No problem, after 30 mice, the data collection was altered and another 24 mice were included. At the end of 1992, he had collected data of 72 mice. It took him until 1998 to analyse part of the data and finally the thesis was written. In 1999 he became a doctor on the behaviour of mice during experiments..... WHAT ARE IMPORTANT ITEMS? WHY DID THIS GO WRONG?

➤ The data should answer the hypothesis

The purpose of a data collection plan is to ensure that proper data are collected in the right amounts and the right ways. The data must be sufficient to answer your hypothesis and are predefined in your study plan.

➤ Gather only the necessary data

Just gather the number of data that you need. Do not create an overload, or you will drown in the flood of data, which may have been gathered without being used in the end, wasting time and money.

Before collecting data, you should ask yourself:

- Which data (and how many data) do I need to answer the hypothesis?
- What is the best way to collect the data I need (questionnaire, medical exam, laboratory analyses)?
- What materials (and how many) do I need for collecting the data (disposable (laboratory) materials, questionnaires, computer, palmtops)?
- Is the method I want to use accurate and reliable?
- What are the costs of collecting the data in this way, and is there a cheaper possibility without losing quality?
- What time will it take to collect these data, including eventual laboratory analyses.

Data collecting by using the computer diminishes the risk of human mistakes (filling in forms, reading from form and typing into the computer) and prevents loss of time: data are available from the input on.

Try to be SMART: Do not use charts from which you have to retrieve the data needed, but make a form (preferably in Excel or some other data sheet program) to be used while collecting the data and make sure that

this form is being used during the research! In this way no data can be forgotten and data are immediately gathered in a uniform way. Try to make a connection for all the laboratory data to the excel sheet you are using.

➤ Use a pilot

Always test your methods and the way you are collecting your data before starting the “real” study. This pilot can lead to more insight in the procedure and to adjustments in the methods used or in the data collection plan! The pilot is not only a test, but also a learning curve.

Whether you are collecting the data yourself or others are collecting the data, you all have to be trained. Take time and money for training and evaluation of the first results before starting the actual research. Who will train the data-collectors? What materials must be used, who is responsible for the performance?

➤ Include the required sample

In normal life, it is not easy to get more mice for your research or to extend your research in any other way (time, money). Every missing experiment endangers the significance of the final results! Try to be as complete as possible and to prevent mice from dying, missing an experiment, both for patients and for samples.

➤ File the data properly

Will all information be collected in one file, or will adjustments be necessary to make one file out of several? At what level do you need the information and does it have consequences for the files? In what format are the data filed? Where are the data filed?

Use one file as a working file which is up-to-date. Give every file a following number. Make sure to have extra copies of your data-file.

➤ Standardise the method and regularly check this method

All research (also in the laboratory) must follow standardised protocols and must be checked on a regular base whether the method is still following this standard. Document every deviation and follow the Guidelines for Good Laboratory Practices and Good Clinical Practices (further in this chapter).

➤ During the research, motivate your co-workers and control them

Since you possibly cannot do all the work yourself, keep your co-workers informed and motivated. This does not mean that they must work on their own until the end of the research: control them in between also, whether they are keeping the right track also. This keeps them motivated as well. Realise that without these co-workers, your research would not exist! Therefore, make them part of your success. This will also help you for a possible next research.

Data to answer your hypothesis can be collected for example using questionnaires, medical exams and laboratory analyses. Therefore, guidelines for using questionnaires, and for good clinical practice and laboratory practice will be discussed in this chapter.

I. Using questionnaires: be smart before creative!

Before starting to create questions, verify whether already existing valid questions or validated (parts of) questionnaires are available. This facilitates comparison between your questions and existing questionnaires or other research populations. If you want to do so, do NOT alter these validated questionnaires!

A questionnaire is valid when a test of validity is performed in the language it is used in.



Kind of questions

In general, there are two types of questions one can ask, open format or closed format.

- *Open format* questions are those that ask for unprompted opinions. There are no predetermined set of responses, and the participant is free to answer. Analysing open format questions takes a lot of work and time, but can be useful when exploring a (new or unknown) situation.
- *Closed format* questions usually take the form of a multiple-choice question. They are easy for the respondent, give statistical possibilities and take less time.

Response category

- The response categories as well as the questions should be in a uniform mode.
- The answers have to be distinctive from each other, the answers should not be suggestive and the order of appearance has to be logical.
- In general: offering three-, four- or five-point scales is usually sufficient to obtain a reliable response.
- 'I don't know' or 'other': the careless respondent can use these response categories as an escape to avoid giving an answer.

Keep in mind that:

- Questionnaires are quite flexible in what they can measure, but they are not equally suited for measuring all types of data. The validity of data from a questionnaire relies on the sincerity of the respondent.
- A questionnaire should be considered when resources and money are limited. If a questionnaire is self-administered, potentially several thousand people could respond in a few days or weeks.
- The researcher should define precisely the information needed and should attempt to write as few questions as possible to obtain this information.
- The language must be adjusted to the group of respondents. Everyone in this group must be able to understand every single phrase in the questionnaire.
- A question should be explicit and not possibly be interpreted in more ways.
- Try to limit the number of referral questions: these are questions which refer to a question or part in the questionnaire and allow respondents to skip a part of the questionnaire.
- Include control questions such as 'What is your date of birth?' and 'What is your gender?'.
- In case of the use of a control group the questions in the questionnaire need to be adjusted to this group of respondents. Be aware that the questions for both groups (control group and research group) have to be identical and comparable (open-ended or closed, used scale).
- The introduction letter has to be clear and informative. It contains information about the purpose of the study, clarification how the results will be used and by whom the results will be used. Also the respondent should receive information about confidentiality and how this is guaranteed. Directions to complete the questionnaire must be short but clear and can best be included in the questionnaire.

When a questionnaire has been developed, a small but representative group of respondents should answer the questions as a test case to reveal any problems in answering the questions and to determine the relevance of all questions.

Response

- The results of a questionnaire will have a fair chance to be biased when the response rate is low. After sending a questionnaire, the researcher could send postal reminders and contact respondents with a telephone reminder to enhance the response.
- To improve the response rate, it is of help to send an introduction letter first (even when the respondent already agreed upon the research). If some intended respondents are not willing to fill in a questionnaire, a request for completing a small part of the questionnaire (possibly by telephone) can be made.
- Include a few specific questions to justify whether the groups of respondents and non-respondents are comparable. The sample will probably be representative if the answers to the questions of both groups are similar.
- Make sure that the Lost-To-Follow-Up is well documented.
- For most questionnaires it is necessary or desirable to check for non-response and to compare data of non-responders with data of responders.

Lay-out of the questionnaire

- The appearance of the questionnaire should be attractive and clearly printed.
- The questionnaire should be arranged uniformly.
- The use of italic and underlines should be avoided.
- Do not use codes or response categories after a question.
- The layout of the questionnaire should comply with the demands of data entry. If the questionnaire will be processed with an optical mark reader, the layout has to be adjusted to the capability and characteristics of this way of data entry.

Anonymity

Researchers should always inform the responders that confidentiality (but not anonymity) is guaranteed. Anonymity implies that data, as soon as they are collected will not be traceable to a responder.

Psychometric qualities of a questionnaire

The usefulness of a questionnaire is determined by the psychometric quality of the questionnaire.

- Reliability: a questionnaire is reliable if the results are constant with repeated measurements under the same conditions.
- Validity is determined by the extent in which a questionnaire is able to measure what it is supposed to measure.
- Responsivity: a questionnaire is responsive when it is able to measure actual improvement. To be able to determine responsivity an external criterion will be used to compare the questionnaire to.

Do's and don'ts of Questionnaires

1. Ask only what you need to know, i.e., get information to answer your hypothesis.
2. Will the respondent be able to answer your question: i.e. do they know the answer or understand the question?
3. Will respondents *want* to answer the question: i.e. are the questions not too private, or embarrassing?
4. Ask one question at a time!
5. Do not use negative questions.
6. Avoid leading questions: A leading question is one that forces or implies a certain type of answer.
7. Avoid prestige bias: prestige bias is the tendency for respondents to answer in a way that make them feel better.

More general information on interviews can be found:

<http://www.mapnp.org/library/evaluatn/interview.htm>
[CASAnet's overview of interviewing principles](#)

II. Ethics and Good clinical practice

Ethics

Ethical principals are very important when doing research. Therefore, in 1964 the declaration of Helsinki has been developed, defining 'ethical principles for medical reserach involving human subjects'. The guidelines state that the importance of the objectives of the research has to be in proportion to the possible risk for the trial subjects. The research has to meet scientific quality and the concern for the subjects must always prevail over the scientific interest. Furthermore, it has been stated that detailed information should be given to the trial subjects, that they have to sign a written informed consent and always have the right to withdraw from a study without giving a reason and whitout consequences for eventual further treatment. Furthermore, all obtained data have to be treated with confidentiality.

In most countries, medical ethics committees check the compliance with these guidelines and also journals want you to comply with these guidelines.

Detailed information on these guidelines is available on the following websites:

www.wma.net/e/
www.nihtraining.com/ohsrsite/guidelines/helsinki.html

Good clinical practice

International guidelines have been formulated for 'good clinical practice' (GCP), which are mandatory for all studies with medication.

The major aims of good clinical practice are *to protect the trial-subject* (i.e. adequate information, written informed consent, right to withdraw, and data confidentiality) and *to obtain reliable results* (i.e. accurate, complete and verifiable). The guidelines deal with:

- The declaration of Helsinki
- The contents of a protocol
- (Un)-blinding and randomization procedures
- Main players and their responsibilities, tasks and requirements
- Costs, resources
- Insurance
- Data handling
- Adverse events
- Monitoring, audits.

In several institutions, GCP courses are organised. Further information is available at:

<http://www.fda.gov/oc/gcp/guidance.html>

http://www.efpia.org/6_pub/document/clinical.pdf

<http://www.wma.net/e/ethicsunit/helsinki.htm>

<http://www.wma.net/e/policy/b3.htm>

III. Good Laboratory Practice

Not everybody is familiar with performing laboratory analyses. Sometimes technicians may help you to do the analyses but you may also have to do the analyses yourself. As written in chapter 5, it is important to have the proper lab facilities, back up of an experienced person in the lab and good contact with your colleagues (research fellows and technicians) as they might have to replace you if you are absent.



Some general points are important to keep in mind when analysing biological samples, doing in vitro research or performing animal studies:

The collection of samples

- What kind of sample do you need:
For example: whole blood, serum or plasma? Faecal water or whole faeces? etc.
- Have the samples to be analysed immediately?
Can samples be kept at room temperature or at 4°C without affecting the analyses and for how long?
Can samples be frozen and how should they be frozen (at -20°, -80°C or in liquid nitrogen)? Should they be frozen immediately?
- Be aware that freezing and thawing of samples mostly influences your assay and thus the test results. If you have to perform several assays on one sample, you should freeze your samples in several smaller portions.
- Do you need a special medium to collect, to keep or to freeze your samples?
- Do you have to collect and keep your samples under sterile, DNA or RNA free conditions?
- Handle all your samples in the same way:
If some samples have to be frozen, all samples have to be frozen;
If you expect a time delay before samples can be analysed, keep this the same for all samples, etc.
- Be sure to have enough room available to keep your samples and archive them in order
- Number your samples and write down day and time of collection.

The assay

- Find the best assay to analyse your samples and to obtain the right outcome parameter (read the literature and contact experts in the field or at your institution).

- Perform (get experience) and validate the assay (inter- and intra-test assay, what is the detection limit) before you start with the study.
- Always check your assay with a positive and a negative control.
- Make a protocol of the assay and stick to this protocol during the total study period as well as in subsequent studies if you want to compare the results.
- Work accurate.

Performing the assays

- Be sure that all samples will be analysed in exactly the same way. Stick to the protocol and write down all deviations you cannot prevent.
- Think about possible influences of temperature and humidity of your environment, the batch of chemicals or solutions you use, etc.
Sometimes analyses performed in winter may be different on a hot sunny day. Use of different batches (regarding chemicals, media, drugs, etc) should be limited as much as possible. Everything that might influence your assay should be kept constant!
- Keep in mind that for many if not most of the assays it is important to take positive and/or negative controls or markers each time that you perform the assay.
- For many assays it is required to analyse samples in duplicate or triplicate.
- Be sure that samples of one study will be analysed as much as possible in one run to limit the influence of inter-test variations. If this is not possible, think about how to limit this influence. For example, if you want to compare several (frozen) samples of one person over time, you can analyse these in one run.
- Be accurate in your work and take care not to switch samples.

Lab-journal

Write down in a lab-journal all the experiments you did, all the results you obtained, all variations you tried and possible deviations from the protocol. Date all notations.

If your results are unexpected regarding the values or the differences between groups, you have to be able to check for all possible factors, which might have influenced them.

In many laboratories, working according to protocols and writing down all possible deviations from these protocols has been standardised and formalised. In analogue to Good Clinical Practice this is defined as Good Laboratory Practice and often requires official certification. This GLP can be found in several languages at the website of the OECD:

<http://www.oecd.org>

Animal experiments

In most countries, animal experiments are regulated by law and experiments have to be approved by local 'animal experiment committees'. Apart from a relevant research question, respect for animals is important and thereby you have to consider:

Replacement: can animal experiments be replaced by in vitro assays?

Reduction: reduce the number of animals as much as possible.

Refinement: preferably use rats, mice etc. instead of dogs, sheep or monkeys.

In summary

Always be sure that you use a validated and standardised method and perform a pilot to test your methods in advance.

When performing the study: do what you write and write what you do!

DATA ENTRY AND PREPARATION OF ANALYSES

G. van Zeijl

DATA ENTRY AND PREPARATION FOR ANALYSES

According to the principles of knowledge management the road to knowledge starts with data and leads via information to knowledge and ultimately to wisdom. (Gene Bellinger, Durval Castro, Anthony Mills: Data, Information, Knowledge, & Wisdom, <http://www.systems-thinking.org/dikw/dikw.htm>)

This chapter describes activities situated on the route between data collecting and information. Activities such as data entry, transform paper data into computer datasets and data preparation of all types including data cleaning and data transformations. The goal of these activities is to come to information, i.e. data with context. In other words information sets are research databases or statistical files ready to use for describing a cohort or to start statistical analysis.



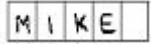
Scale

Activities as data entry and data preparation are costly and time consuming. Therefore the scale of a project matters. With a clinical trial for 30 patients overviews can be kept by the researcher. For a cohort study of 3000 participants experts are needed. For larger studies it is of utmost importance to include data entry and preparation into budgets and planning.

Data Entry

Data entry is the activity of getting data gathered with paper forms or paper questionnaires into a computer format. Depending of scale and type of questions and layout there are several techniques available to get data digitised. The two main categories for data entry are:

- Manual data entry: A person types the data straight from paper into a computer. This can be done into a spreadsheet like Excel but professional programs exist that help the data typist to reach very high productivity, such as computerized medical files and laboratory analyses. Out of quality consideration, professional data entry service enters the data twice by different persons and compares the data sets. Differences are resolved.
- Scan solution: Paper forms are scanned into digital pictures. A recognition program automatically finds the answer but is followed by a human verification to resolve problems. Data are exported into datasets. Depending on the type of questions, the amount of forms and the layout of forms, a scan solution is more (cost) efficient than manual data entry. Scanning puts constraints on the layout of the forms to be scanned. At considering a scan solution, contact an expert data entry group at design time of forms or questionnaires. In every case contact these groups before sending forms or questionnaires to press for printing!

Technique	Example	Solution	Description
Barcode	 http://www.seeingwithsound.com/barcode.gif	Scan 100%	Barcode is often used for identification numbers on forms while at the same moment guaranteeing anonymity. Questionnaires with name and address are often not processed by data entry groups because of privacy laws.
OMR - Check box		Scan 100%	Most used on questionnaires.
OCR - Machine print	Printed text	Scan 100%	Letter types like Verdana and Ariel are better recognised than others.
ICR – Hand print		Scan 95% Manual	Computer recognition is not 100% therefore a verification is necessary. The programs for ICR are very expensive. Therefore not all data entry centres offer this service.
Handwritten text		Manual 99%	Labour intensive. For high correctness professional organisations use the double entry method.

Data preparation and data cleaning

Can a male give birth? Can people be born in the future? If one has to believe raw data sets from many research projects the answer is yes. Of course these examples are obvious errors made somewhere in the process of gathering the data. Errors in dataset, also called “noise”, are a fact of life. They can upset statistical analysis and make it hard to find the right answer on your hypothesis. Therefore a check is needed and the right moment is just before statistical analysis. This process is called “data cleaning”.

Furthermore it is information you need at this level, not just data. That means that during analysis it is clear to what question a column of data refers and what the meaning is of the numbers that represent the answers. We are talking about variable labels, value labels, logic variable names, and a good codebook. All these things set data in their context and make the data understandable.

Depending on the size of datasets the help of a data manager or computer expert can be cost effective to clean a dataset. These experts need input though. They need to know the logic and rules that is assumed to be in the dataset. A well-documented form or questionnaire design is most helpful at this stage of your research. For large cohorts it can be cost effective to look at questionnaire design software. One of the outputs of these programs are checking routines to clean the data at this stage of the research.

Cleaning and preparation activities

- Check if answers are in expected range and introduce a code for missing value. For example: question 1, what is your gender? (0 male / 1 female) All values for this question should be 0 or 1 other values are not allowed. Empty answer is coded to missing value "9". The researcher should decide what to do in case other values are found in the dataset.
- Are routing rules followed correctly? For example: If you are female please answer question 2 till 32, if you are male please skip to question 33. It is simple to check for all male that indeed questions 2 till 32 are left empty. The researcher decides what to do if not.
- Statistical packages like SPSS need integer answer values like (0,1,2,3,4). They can not handle alphanumeric characters like (a,b,c,d,e). One example for the need of recoding. Sometimes coding of similar answers to a question is not done in a similar way. For example question 8 (0=no / 1=yes) and question 9 (1=yes / 2=no). It is wise to standardise the coding. Obviously many recoding actions can be avoided at design time of forms and questionnaires.
- Introduction of calculated fields. For example: the quality of life is measured with a validated set of 16 questions included in a larger questionnaire. With these 16 answers and the provided calculation method, a quality of life score can be calculated. Before starting analysis one adds the quality of life variable to the dataset and computes all the scores for participants.
- Date formats are risky. Computers cannot see that '01-28-2004', '28/1/2004' and '28-jan-04' is referring to the same date. Data entry personnel or scanners will not change data to a similar format. It is at data cleaning and preparation time that this can be done. A reason for the introduction of different date formats is often the helpful programs of Microsoft like Excel which automatically put dates in the format that belongs to the language preference of the computer. Many universities work with English installed computers as well with computers installed in their home language. Practical experience learns that checking of dates is necessary, even when giving thought to this issue at design time.
- Introduction of age calculated from birthdates. Best done by one person during data preparation. The problem is that age is always calculated with reference to a certain moment. For example, the age of participants at 01-JAN-2004. Obviously, the introduction of items like 'age at onset' or 'disease time' are complicated because different reference moments for different patients. Be very careful with time elements and their definitions.
- Labels and value labels are making information sets from datasets. This information makes data understandable and thus speeds up the analysis.
- File formats. Not all programs can easily talk with each other. Much time is spend, in transforming datasets from one file format into another. Talk early to people that will help with data cleaning, preparation and statistical analysis and make this a topic.

Archive and backup

It is almost unnecessary to stress the importance of regular back-ups of your computer files. The two main reasons for back-up are 1) Computer breakdown or technical problem, 2) unintentional change of data (and hitting the save button at the moment you realise it is wrong). Programs like Excel or SPSS do not prevent you from changing data even in a dataset that is ready. Some tips for organising back up are: Keep important files on a network directory. System manager makes back-ups of network directories. Back up of files on local hard disk (C: or D:) or your own responsibility. Burn your raw data set and your cleaned dataset on a CD-rom. Files on CD-rom are read only and cannot be changed.

Archive key files of your research in case you get question after publication. Check at your organisation and funding organisation how long key files should be available. Important issue is where these key files should stay when you leave the organisation for a new job after finishing your PhD.

Privacy

Patient data and names and addresses are in most countries subject to privacy laws. Apart from some bureaucracy depending on the research you do, most important issue is to be aware that you are handling privacy data. Some key issues when working with privacy data are:

- Do not have forms, questionnaires or computer files lying around. Keep them behind lock and key. In case of computer files this means have files on a network directory rather than on local hard disk. The network directory is password protected while the local hard disk is mostly not. Use screensavers with password lock. In case you leave your room while working with patient data, after 5 minutes the screensaver will lock your computer. Do not send patient data over email. Email is like a letter in an open envelope.
- Keep track of who s handling forms or data and why and when. A logbook is a good method to do this. Ask the same from the data entry unit, data managers and statisticians helping you.

COMMUNICATION AND MONITORING

M. Revivo
N. Arber

COMMUNICATION AND MONITORING

Purpose

In epidemiological studies the purpose is to discover the patterns and the causes of diseases and to gather data from a group of people in order to develop comprehension on health or problems. Populations are the cores of epidemiological research.

Aim

The aim of many epidemiological studies is to see whether a specific agent or exposure is likely to cause the investigated disease. There are studies where the investigator examines different people who exposed to one factor for a period of time. If it is a prospective study, the investigator assemble the study population and then follow them over a period of time to check if the people who are the most exposed to the risk factor are those who develop the investigated disease. We are dealing with retrospective study, when there is a use of data that was gathered from records that are already known and check what we know regarding the risk factor. In this way the investigator is trying to determine which risk factors are involved



" He has excellent communication skills. "

In order to conduct a successful and fertile study it is recommended to assign a monitor for the study.

The most important subject, when conducting a clinical trial is having a good **communication** between the co-workers. When the co-workers has an open channel of communication it is easier to oversee progress of the trial and to ensure that the study is conducted and data are handled in accordance with the protocol, Good Clinical Practice, and applicable ethical and regulatory requirements.

The best way to assure the quality of the trial there should be a monitor assigned to the trial.

The responsibilities of the monitor are:

- The connecting link between the co-workers and controlling adherence to the protocol
- Ensuring that data are correctly and completely recorded and reported, and confirming that informed consent is being obtained and recorded for all

The monitor should therefore follow a predetermined written set of standard operating procedures. The monitor should be appropriately trained and fully aware of all aspects of the drug under investigation and the requirements of the protocol, including any annexes and amendments. The monitor should have adequate medical, pharmaceutical, and scientific qualifications, and clinical trial experience. Any errors or omissions should be clarified with the investigator, corrected, and explained.

- The investigator must ensure the safety of the trial subjects. This includes providing the best possible care for subjects experiencing any trial-related

adverse events and conducting a thorough investigation to determine causality.

- The occurrence of adverse events must be monitored carefully and recorded in detail during the course of the clinical trial. The trial protocol should clearly state the method by which adverse events will be monitored.
- The aim of record keeping and handling of data is to record, store, transfer and, where necessary, convert efficiently and accurately, the information gathered on each trial subject into data that can be used in the report.

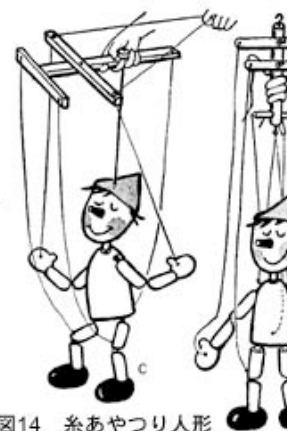


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- All steps involved in data management should be documented in order to allow step-by-step retrospective assessment of quality of the data and the performance of the clinical trial. Documentation is facilitated by methods such as the use of checklists and forms giving details of action taken, dates, the individuals responsible, etc.

INTERPRETATION OF THE RESULTS

D. Jonkers

INTERPRETING THE RESULTS

Before interpreting the results:

- check for mistakes at data-entry
- be sure that your database is complete and
- be sure that the right (statistical) analyses have been performed!!

Always start with the results answering your hypothesis (primary, secondary outcomes) and know your data:

- What are the values obtained? Are they in the expected range?
If results are not in the expected range, you have to check for possible mistakes in the analyses or possible reasons which may contribute to these values.
For example have the biological samples obtained been handled and analysed correctly in the laboratory? Did unforeseen factors occur?
- Have statistically significant differences been found?
- Are the observed differences expected and/or logic?
Sometimes findings may demonstrate the opposite as expected in your hypothesis (*increase instead of decrease or vice versa*).
- Think about the possible mechanism behind your findings (discuss with colleagues and experts in the field, look in the literature for possible explanations)
- Compare your findings with the results in the literature in similar or comparable studies (animal vs. humans, other patient group, other substrate, etc.). Are your results and those reported in the literature in line? If not, try to find possible explanations for the different findings?
- What are the possible consequences of your findings (for example regarding knowledge about a biological mechanism, clinical consequences or the generation of new hypotheses)?

Please also read the following lines!

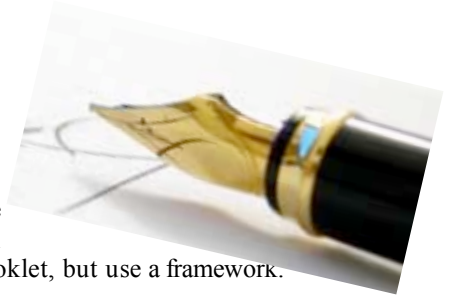
- Negative findings or lacks of association are also important to report.
- When interpreting your results, always keep in mind the limitations of your study and of the methods used (for example the study design, number of subjects, drawbacks because of practical limitations, the lab-assay or questionnaire you used, etc.).
- When you have several results belonging to the same hypothesis, check whether they all point to the same direction or not. If not, try to find explanations.
- Know your data. For example:
 - What kind of values did you find (range)
 - Do the very high or very low values occur in specific subjects
 - Are there differences in age, gender, etc.?

After you have analysed the results related to your hypothesis, you can have a look at all the data. Are there other remarkable or unexpected findings? Also these results should be compared with findings in the literature, try to find explanation, discuss the limitations and possible consequences, etc.

WRITING AN ARTICLE

P. Ferenci K. Scheele

WRITING AN ARTICLE



Now, you've done some research and you've decided to write an article on it. But maybe you cannot decide what to write, where to start or how to get the words together to make a coherent article. You need to make a few decisions on "what", "who" and "how". Do NOT just start writing as if it is a romantic booklet, but use a framework.

What

Try to write down what you want to tell. Write it down in no more than two sentences as a start of the summary. From these basic sentences you can start your article.

Who

Who are your readers? Make sure that the language of the article corresponds with the comprehension level and specific interests of the target reader.

How

All the information you want to tell about is inside your head. Create an outline to get your thoughts together. Use main points and categories on paper to arrange all the information you have. This also helps you to decide on which information you are going to use or not.

Have a critical look at the outline:

- Does it make sense?
- Does it flow logically?
- Is the appropriate information being included for the target audience?
- Is there anything that is not necessary, off-topic, or redundant that can be removed?

Writing

Writing, review and revision is an ongoing process. There are no shortcuts, and you will probably even want to throw it aside a couple of times, too. Some helpful hints that might help you in writing the article:

- Find a quiet area to write so you won't be interrupted.
- Keep a dictionary handy.
- Keep the relevant references close by.
- Avoid giving information that is not to the point of the heading or subheading you are writing about. Read back what you have written: is the information given coherent with the (sub)heading?
- Avoid slang or street terms.
- Don't write a whole article before asking a reviewer to read it and comment on it.
- In case English is not your native language, ask a native speaker for comments.

Rules of English Grammar

Because most articles will be written in English, some short grammar rules are given. A good computer program usually is very helpful to correct spelling and to alert you to grammatical problems.

Agreement and Sentence fragments: Make sure that all parts of the sentence corroborate with each other. Do not use sentence fragments without noun and verb.

Tense: Decide in what tense (time) you are going to write the article and stick to it.

Spelling, punctuation and use of words: Spell checkers on your computer may be a first help, but you better find a good dictionary and a native speaker to help you. Be sure that you use the right words for what you want to say!

Run-on-sentences: Don't make your sentences too long, or you will lose your reader. Make two or more short sentences, which will make your statement more clear and powerful.

The scientific research article

A standard format is used for scientific articles, in which the author (you!) presents the research in an orderly, logical manner. This does not necessarily reflect the order in which you did the work or thought about it.

General rule:

After completing the manuscript the first person to see it will be the journal editor and the peer reviewers. They will decide the fate of your paper! But they have limited time and try to grasp the importance of your contribution as quickly as possible. Thus, be clear, precise and highlight the importance of your study. Please check the instructions for authors of the journal you like to submit your paper.

The standard format includes:

Title: Make the title specific and attractive enough to describe the contents of the paper, but not so technical that only a few will understand. The title usually describes the subject matter of the article.

The title and abstract of your article permit potential readers to get a quick overview of your study and to decide if they wish to read the article itself. Titles and abstracts are also indexed and compiled in reference works and computerized databases. For this reason they should accurately reflect the content of the article and include key words that will ensure their retrieval from a database. You should compose the title and abstract after you have completed the article and have a firm view of its structure and content.

The recommended length for a title is 10 to 12 words. It should be fully explanatory when standing alone and identify the theoretical issues or the variables under investigation. Because you will not be able to mention all the features of your study in the title (or even in the abstract), you must decide which are most important.

Authors: The person who did the work and wrote the paper is generally listed as the first author of the article (you!). Other people who made substantial contributions to the work and the article are also listed as authors. Ask your mentor's permission before including his name as co-author.

Abstract/Summary: An abstract or summary gives the reader a preview of what's to come. The abstract should contain 100-250 words, summarizing the article and following the headings of the article: introduction, materials and methods, results and conclusion. Do not use footnotes or references in the abstract. The abstract should be able to stand alone.

Introduction. The introduction summarizes the relevant literature used, so that the reader will understand the interest in this specific research topic and the hypothesis you have been studying. Include:

- General background.
- Identify areas where further research is needed.
- What is known so far (be sure to quote all relevant studies -the authors may be the reviewers!). Summarize and analyse (define gaps, new insights, consequences, methodological limitations, etc.) the most important findings from the literature with regard to your research topic.
- Formulate your question.
- Why do we want to know the answers on the questions?
- Why was the question not solved so far (methodology.....).
- Formulate your null hypothesis (=primary outcome variable)

Materials and methods. How did you collect evidence for the hypothesis? There should be enough information here to allow another scientist to repeat your experiment. Include a diagram, table or flowchart to explain the design used. Describe accurately which materials (obtained from...), methods and which outcome parameters were used. Also give information on the reliability and validity of the methods chosen. If you used a standard method (ie. a chemical procedure) without modification, it is sufficient to quote the reference. If you used a commercial assay identify the supplier. If you modified a method or developed the method yourself, you have to describe it in full detail and provide information how this method was validated.

Describe the used statistical methods, which statistical tests were used and explain the power of the study. If this is standard, describe it briefly (e.g., "All data were analyzed by two-way analyses of variance with sex of participant and mood induction as the independent variables"). If the analysis is unconventional or makes certain statistical assumptions your data might not satisfy, however, discuss the rationale for it.

Discuss problems and other difficulties encountered in executing the study and explain whether they might have affected the validity or the interpretation of your results (or not).

After presenting the methods you employed in your study, mention used ethical issues such as informed consent, declaration of Helsinki, medical ethical committee, animal experimental committee.

Results. Present in this part the results you have obtained. Use graphs and tables if appropriate, but also summarize your main findings in the text. Do NOT discuss the results or speculate. Make sure that the results given are accurate, comprehensive and mention the significance of the results. The clearest way to present distribution of data is to give the mean and the 95% confidence interval (SD or SE are appropriate but hide a view to the applicability of the data – especially of the number of experiments is small). If the data are not normally distributed, give the median and the range!

Whenever possible, state a result first and then give its statistical significance, but in no case should you ever give the statistical test alone without interpreting it substantively.

Do not try to manipulate the data to make it look like you did more than you actually did, or to make the results look better than they are. This will be noticed and will affect your future career.

Tables and Graphs. Graph or table or just text? Select the most appropriate. Avoid duplication of information text vs the table or figure and use a logical ordering and sequence.

- Graphs give an optical info (to be used to highlight large differences, good correlations, large scatter of data).
- A table gives the opportunity to show a large number of data with lot of numbers. By selecting rows/columns carefully, the reader should be able to grasp and understand the info easily.
- Just text: either very few very important data which are essential to give an answer to your question (ie. response in group a 80% in group B 20%, $p < 0.0001$) or less important data in conjunction with a graph or a table.

In the text explain shortly the content of a graph/table (ie. Table 1 summarizes the baseline data of the two study groups). Refer to each table or figure in the text.

Include a title describing what's in the table or graph. For graphs, you should also label the x- and y-axes. Give data rather than percentages, or: data (x %).

Figures and tables must be titled and labeled clearly and completely, even if that means constructing a very lengthy title or heading ("Mean number of tears produced by two affective films as a function of affect valence, participant sex, parental observation, and self-esteem").

Discussion. Start the discussion with a separate paragraph which answers the question raised in the introduction (ie: The results of this study shows that a well designed study is the best way to get a paper published).

Highlight the most significant results, but don't repeat what you have written in the results section. State which of your findings are new (this study shows for the first time...), what is confirmatory (the results confirm the observations by Everybody et al...), and what is conflicting with the current understanding of the subject (In contrast to Dumb et al, we found....)

Try to answer (some of) the following questions:

- How do these results relate to the original hypothesis? Was your method appropriate to derive the answer to the question (sufficient number of observations, validated methodology)?
- Are your results consistent with what other investigators have reported?
- If your results were unexpected, try to explain why. Always mention what further research would be necessary or wanted to answer (new) questions raised by the results.
- It is also appropriate to compare your results with those reported by other investigators and to discuss possible shortcomings of your study, conditions that might limit the extent of legitimate generalization or otherwise qualify your inferences.
- Outlook: consider questions that remain unanswered or that have been raised by the study itself, along with suggestions for the kinds of research that would help to answer them.

Acknowledgement. This section is optional. You can thank those who helped with the experiments, or made other important contributions, such as statistic help, providing the patients, etc.

Helpful sites:

www.dictionary.com This site searches several dictionaries at once, including Cancer WEBS' On-line Medical Dictionary. The home page also has links to Roget's Thesaurus, resources for grammar and style, a translation tool, and other dictionaries.

www.stedmans.com This site contains all medical terms.

effective presentations: <http://www.kumc.edu/SAH/OTEd/jradel/effective.html>

REVIEW AND CRITICISM

P. Ferenci
K. Scheele

REVIEW AND CRITICISM

Moral

For many authors revising their article is unmitigated agony. Even proofreading is painful. And so they don't. So relieved to get a draft done, they send it off to the journal thinking that they can clean up the writing after it has been accepted. Some may find solace in the belief that the manuscript probably would have been rejected even if it had been extensively revised and polished; after all, most of our journals accept only 15-20% of all manuscripts submitted. *Moral*: Don't expect journal reviewers to discern your brilliance through the smog of polluted writing. Revise your manuscript → Polish it → Proofread it → Then submit it.

Rewriting is difficult for several reasons

- It is difficult to edit your own writing. You will not notice ambiguities and explanatory gaps because you know what you meant to say and you understand the omitted steps. One strategy for overcoming this difficulty is to lay your manuscript aside for awhile and then return to it later when it has become less familiar. Practice the art of taking the role of the nonspecialist reader. As you read, ask yourself, "Have I been told yet what this concept means?" "Would I know what the independent variable is at this point?" Good writing is good teaching.
But because this is not easy, you should probably give a fairly polished copy of the manuscript to a friend or colleague for a critical review. The best readers are those who have themselves published, but who are unfamiliar with the subject of your article. If your reader finds something unclear, accept that the writing is unclear.
- Rewriting is difficult for a second reason: It requires a high degree of attention to detail. The probability of writing a sentence perfectly the first time is vanishingly small, and good writers rewrite nearly every sentence of an article in the course of polishing successive drafts. For journal articles in particular, get the first draft done as quickly as possible without agonizing over stylistic niceties. But once it is done, compulsiveness and attention to detail become the required virtues.
- And finally, rewriting is difficult because it usually means restructuring. Sometimes it is necessary to discard whole sections of an article, add new ones, go back and do more data analysis, and then totally reorganize the article just to iron out a bump in the logic of the argument. Don't get so attached to your first draft that you are unwilling to tear it apart and rebuild it. A badly constructed article cannot be salvaged by changing words, inverting sentences, and shuffling paragraphs.

The word processor

Its very virtuosity at making these cosmetic changes may tempt you to tinker endlessly, encouraging you in the illusion that you are restructuring right there in front of the monitor. Do not be fooled. A word processor--even in conjunction with a fancy "outline mode"--is not an adequate restructuring tool. Don't be ashamed to print out a complete draft of your manuscript, spread it out on table or floor, take pencil, scissors, and scotch tape in hand, and then, all by your low-tech self, have at it.

Outcome of the journal submission – editorial decision

1. Accepted → be happy, contact your teacher and co-authors and drink a beer!
2. Revisions are requested → be polite and follow all requests (even if they are silly!). Thank the reviewers for their constructive comments.
3. Rejection → NEVER ACCEPT AN UNFAIR REVIEW. Write to the Editor if you feel that the arguments of the reviewers are wrong (this occurs quite frequently), biased or both. Politeness is not always necessary.....In my experience there is always a way to convince the editor to give you a second chance, providing your arguments are correct.

SUBMITTING AN ARTICLE

P.W. de Leeuw

SUBMITTING AN ARTICLE

Provisionally accepted

If and when your article is provisionally accepted for publication "pending revisions in accord with the reviewers' comments," you should be deliriously happy. Publication is now virtually under your control. If your article is rejected but you are invited to resubmit a revised version, you should still be happy--if not deliriously so--because you still have a reasonable shot at getting it published.

But this is the point at which many authors give up. As one former editor noted,

In my experience as an associate editor, I thought a good deal of variance in predicting eventual publication came from this phase of the process. Authors are often discouraged by negative feedback and miss the essential positive fact that they have been asked to revise! They may never resubmit at all, or may let an inordinate amount of time pass before they do (during which editors and reviewers become unavailable, loose the thread of the project, and so forth). An opposite problem is that some authors become defensive and combative, and refuse to make needed changes.

Don't give up

So don't give up yet. Feel free to complain to your colleagues or rail at your poodle because the stupid reviewers failed to read your manuscript correctly. But then turn to the task of revising your manuscript with a dispassionate, problem-solving approach. First, pay special attention to criticisms or suggestions made by more than one reviewer or highlighted by the editor in the cover letter. These *must* be addressed in your revision--even if not in exactly the way the editor or reviewers suggest.

Next, look carefully at each of the reviewers' misreadings. Whenever readers of a manuscript find something unclear, they are right; by definition, the writing is unclear. The problem is that readers themselves do not always recognize or identify the unclarities explicitly. Instead, they misunderstand what you have written and then make a criticism or offer a suggestion that makes no sense. In other words, you should also interpret reviewers' misreadings as signals that your writing is unclear.

Think of your manuscript as a pilot experiment in which the pilot participants (reviewers) didn't understand the instructions you gave them. Analyze the reasons for their misunderstanding and then rewrite the problematic sections so that subsequent readers will not be similarly misled. Compared with the average journal reader, reviewers are almost always more knowledgeable about your topic, more experienced in writing manuscripts themselves, and more conscientious about reading your article. If they didn't understand, neither will that average reader.

Revised manuscript

When you send in your revised manuscript, tell the editor in a cover letter how you have responded to each of the criticisms or suggestions made by the reviewers. If you have decided not to adopt a particular suggestion, state your reasons, perhaps pointing out how you remedied the problem in some alternative way. In your response, be polite and thank the reviewers and the Editor for their comments; do not condemn them! Above all, remember that the editor is your ally in trying to shape a manuscript that will be a credit both to you and the journal. So, cooperate in the effort to turn your sow's ear into a vinyl purse. Be civil and make nice. You may not live longer, but you will publish more.

VALUE THE PUBLICATION

R. Stockbrügger

THE VALUE OF THE PUBLICATION – AND WHAT NEXT?

The day has come, your paper “.....” has been accepted after the few changes that the editor had proposed to you. Probably you can’t believe it yet: it is like getting a baby: you would like to tell it to everyone. Do that! But mainly to good friends, in order to avoid envy!

Like with getting babies, the world has suddenly changed in some way, future will be different. With your first publication, you have added a new dimension to your personal and professional options. Few will say “never again!”, most will like to repeat the success, and many will have started already on the next research leading to a further publication, either driven by new data and hypotheses originated by the work with the first study, or simply suggested by the teacher, who has discovered that a new star is rising on the firmament of science. Working on the second publication you will discover that it is at least 50% easier; you have already learned a lot of tricks. However, do not be too self-confident, it will still take years before you may become a master! Keep working with every detail, keep reading from the real masters, learn to write the different types of publications: short communications; reviews; editorials; etc.

One way of **evaluation of your publication** is the “impact factor”. “Impact factors” make part of a complicated system of international assessment based upon the frequency of quotation of your article in other articles published in scientific publications all over the world. If you want to know more about this system, follow this link: <http://www.ibpc.fr/~dror/jif.html>. Impact factors are utterly important not only for the assessment of a single scientists but even much for the fame and future of scientific journals and other publications. You will discover that your teacher will advise you to submit your articles to a journal with the highest possible impact factor. Why?



The further you climb the ladder of science the more you will discover that the “**impact factor**” reigns (nearly) everything: if you will apply for a scientific position, some or several of your auditors will already have gone to some of the assessment systems and have looked at your cumulated impact factor, comparing it with that of your competitors. When you will apply for a research grant on behalf of a group of investigators, you many times will be ask to quote your most important publications in the field were you are looking for support. Be sure, the impact factors of these publications will be looked up.

But not only individuals, also institutions are assessed in the same way: Nowadays universities, faculties, departments, research institutes are audited in an increasingly objective way: Impact factors play a crucial role in that quality-power-money play. Let’s face it like that: Impact factors are the **dollars/euros of science**. The comparison is right in many ways, as scientific quality in this way is connected to values partly non-scientific and rather “capitalistic”. Temptations to manipulate the impact factor systems are therefore always present and sometimes this really happens.

I will not tell you how, better forget it! For yourself, try to realize that not even the world of science is an ideal one, but keep looking for the objective evidence in your own research, accept the necessity of competition, and avoid corruption by looking at research dollars, “I.F.s” only.

The first publication of a young investigator always bears the risk be the last one, if you don’t like that way of working, or if teachers retire, or a different career is coming up. In the best of the cases (under the aspect of science!) that publication will become the first one in a long line of results and is the start of your career as scientist.

Most of the times, also **a career has to be planned!** There is a lot to say about this subject and probably that will make another ASNEMGE publications in the future (“How to become a Rising Star?”). For the purpose of the present manual, our career advice will be limited. Starting with a certain teacher, in a certain laboratory and with a certain topic, it is the most natural, “economic” and career-wise normal to continue for a while the research-line you have entered upon with your first publication: you have already a good knowledge of the subject and the literature around it; you have probably met other specialists in the field or listened to them; you might have non-used data to analyze and you certainly have been getting a lot of questions and/or hypotheses when you have discussed your first results in public or internal meetings. Pick up all of this and start on your next study/publication: possibly you will now even get the research grant you were refused before the first publication!

After a few papers, you will be asked to mentor other people during their first steps in research, you have become a teacher because you were doing well yourself. And now suddenly you understand that doing research is not anymore a task for geniuses alone in their study in the dark of the night, but a disciplined effort of an intelligent and motivated crowd to promote knowledge and skills in society, rather in the way of stafett than as a

marathon competition. Starting to publish in a good way will very soon give you the sensation that you have become part of that crowd. Believe me, no bad kick!

Links referring to the impact factor are also:

<http://scientific.thomson.com/free/essays/journalcitationreports/impactfactor/>

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=141186>

<http://www.ibpc.fr/~dror/jif.html>