

**Independence in scientific research**  
**AMC–VUmc Research Code**  
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**Table of contents**

- 1. Introduction**
- 2. Good mentorship**
- 3. Respect for human subjects involved in medical research**
- 4. Respect for laboratory animals involved in biomedical research**
- 5. Clinical research methods and good clinical practice**
- 6. Good laboratory practice**
- 7. Research data management**
- 8. Collaboration with third parties**
- 9. Ownership and valorisation of research findings**
- 10. The right to authorship**
- 11. Dealing with the media**
- 12. Conflicts of interest**
- 13. Careful reviewing of research proposals and manuscripts**
- 14. Scientific misconduct and how to prevent it**
- 15. When scientists go astray**

## 1. INTRODUCTION

Good research flourishes in a culture that is characterized by independence and integrity. Many depend on such integrity. University medical centres have a responsibility to society and patients. By means of scientific research, they aim to contribute significantly and distinctively to improving health and healthcare. Thus, users of scientific knowledge should be able to trust that what is studied rightly adds to the body of knowledge. Researchers themselves also benefit from a culture of integrity and constructive mutual relationships: if they can trust their colleagues worldwide, they will feel free to cooperate in a fruitful manner and will cherish creativity. Similarly, a research institute and the academic community as a whole are dependent on their reliability and honesty in the eyes of society.

In its [European Code of Conduct for Research Integrity](http://www.esf.org), the European Science Foundation ([www.esf.org](http://www.esf.org)) specifies the following principles:

- **Honesty** in presenting research goals and intentions, in precise and nuanced reporting on research methods and procedures, and in conveying valid interpretations and justifiable claims with respect to possible applications of research results.
- **Reliability** in performing research (meticulous, careful and attentive to detail) and in communicating the results (fair, full and unbiased reporting).
- **Objectivity**: interpretations and conclusions must be founded on facts and data that can be substantiated and withstand secondary review; there should be transparency in the collection, analysis and interpretation of data, and verifiability of the scientific reasoning.
- **Impartiality and independence**: independent of commissioning or interested parties, ideological or political pressure groups, and economic or financial interests.
- **Open communication** in discussing the work with other scientists, in contributing to public knowledge through publication of the findings, and when communicating with the general public. This openness presupposes the proper storage and availability of data and their accessibility for interested colleagues.
- **Duty of care for participants** in and the subjects of research, be they human beings, animals, the environment or cultural objects. Research on human subjects and animals should always rest on the principles of respect and duty of care.
- **Fairness** in providing proper references and giving due credit to the work of others, and in treating colleagues with integrity and honesty.
- **Responsibility for future generations of scientists**. The education of young scientists and scholars requires binding standards for mentorship and supervision.

In order to consistently promote, facilitate and ensure that scientific research is conducted according to these principles in and across the university medical centres in Amsterdam, this joint Research Code was established on behalf of the executive boards of the Academic Medical Center (AMC) and the VU University medical center (VUmc). This code aims to be a stepping stone between the general principles outlined above and the specificities of daily scientific practice. It was prepared by experienced investigators and expert support staff members from both alliance partners. The Research Code covers the main issues in conducting medical, biomedical and health research. The focus is on good mentorship, respect for research subjects, good clinical and laboratory practices, data handling, collaboration with external partners and external parties, ownership of research findings, authorship, dealing with the media, conflicts of interest, the prevention of scientific misconduct, and what to do when scientists do not work according to the established rules and regulations.

This Research Code applies to all units operating within the AMC and the VUmc organizations. All scientific practitioners – from principal investigators to junior researchers, as well as research support staff – should know of this code and be familiar with its content. This Research Code is, however, not a research handbook, nor a ‘cookbook’ covering all regulations in detail. Instead, and because the process of evolving possibilities and questions is crucial in scientific research, the code provides a framework to guide researchers in living up to the values of independence and integrity. It introduces the main relevant issues and

topics, and where useful or necessary refers to further reading. By making clear the conduct that is expected and considered effective, this code contributes to an atmosphere of openness and a culture in which doing research is an enjoyable and productive experience.

The Research Code is not a fixed and definite document. Both science and scientific conduct develop and innovate. For example, biomedical and health research are increasingly dependent on multidisciplinary collaborations – frequently in large, often international consortia that include public–private partnerships – that use extensive data from a variety of sources. Such developments will most probably necessitate further changes to the Research Code. In the same vein, emerging technological possibilities, cultural norms about privacy and safety, changing legal frameworks and new modes of scientific communication urge us to constantly rethink how researchers can maintain their scientific integrity. This Research Code is therefore a living document that will be updated on a regular basis. The most up-to-date version can be accessed on the intranet at [Research/Researchcode](#).

The AMC–VUmc editorial team

## 2. GOOD MENTORSHIP

Junior researchers usually carry out research under the supervision of a more experienced researcher, namely their supervisor (a postdoc, staff member or professor). Supervising junior researchers is an important part of good scholarship. The duties of someone who is supervising a junior researcher – duties that constitute good mentorship – can be summarized as follows:

- Providing day-to-day guidance and feedback.
- Encouraging the researcher and showing a keen interest in his/her work.
- Supervising the junior researcher's work with the appropriate intensity and respect.
- Supervising the junior researcher in all relevant phases of the research project.
- Monitoring progress and critically reviewing the raw research data together with the junior researcher.
- Monitoring and promoting quality assurance and control.
- Monitoring the researcher's integrity in relation to the studies, data handling and submission of publications.
- Checking whether claims to authorship are justified.

Junior researchers may be Master or even Bachelor students, postgrads or PhD students. They are generally referred to below as 'researchers' as opposed to 'mentors' or 'supervisors'. The following guidelines apply to all forms of mentorship and supervision.

### 2.1 Duties of all supervisors

The goal of the working relationship between researcher and supervisor should be clear and explicitly agreed upon, as should the tasks of the researcher and the responsibilities of the supervisor with regard to the project.

1. A good supervisor acts as a mentor, a confidante, an advisor and a voice of reason for his/her researcher. Researchers want and need supervisors they can believe in and trust, and whose work they find exciting.
2. The supervisor should ensure that the project is based on a well-defined plan. The supervision may take diverse forms, depending on the stage the research project has reached. The supervisor should give the researcher the opportunity to develop his/her own ideas and plans, within the limitations of any agreements with a funding agency. The supervisor should provide alternative ideas and plans particularly if the researcher gets into a difficult or deadlock situation.
3. In the research project, any special requirements regarding access to research infrastructure and facilities should be taken into account.
4. The supervisor should ensure that the researcher has access to the infrastructure needed to carry out the research project, appropriate backup, adequate physical facilities and, if necessary, assistance from staff from both within and outside the researcher's own department.
5. The researcher should get regular help with, advice on and support for his/her research work. Such can be provided at scheduled times, but there should also be room for ad hoc consultation in the event of unexpected developments.
6. The intensity and form of the supervision may vary widely, depending on the people involved. It should be based on the researcher's level and approach. Mentorship given to a novice, for instance, may well differ in form and intensity from that given to a PhD student who is in the last stage of his/her research.

7. Regular consultations should take place on the progress the researcher is making. Such consultations should cover at least the progress of the project and any problems the researcher has encountered. The next steps in the research may also be discussed during these consultations. The consultations should preferably result in specific agreements on short-term and, if necessary, medium-term goals. During these consultations, the supervisor should go through the raw data with the researcher, so as to ensure that the final data are produced in a fashion that is in accordance with all aspects of the research code, such as proper data acquisition, processing and statistics, proper handling of patient material, etc.
8. The supervisor should set aside time to provide and receive critical feedback. This includes returning within an acceptable time corrected manuscripts, reports, etc. written by the researcher.
9. Feedback benefits from open, clear and structured communication, and from a discussion of both positive and negative elements of the research and the supervision.
10. The supervisor and the researcher should hold a performance appraisal interview at least once a year in order to review their respective performances.
11. The supervisor and the researcher should reach an agreement upon the publication of research findings and/or their presentation in the form of a lecture. As authorship is a particularly important issue, it is advisable to reach explicit agreement upon this in advance.
12. Both supervisor and researcher should have an open, critical attitude – irrespective of the hierarchical relationship between them – towards the academic goals as originally formulated by the supervisor. They should realize that the original hypotheses could turn out to be incorrect on the basis of their own or other people's findings. If this is the case, the supervisor should not push the researcher towards the expected results.

## 2.2 Specific duties of the PhD supervisor (*promotor*)<sup>1 2</sup>

A doctorate or PhD is the highest academic degree awarded in the Netherlands. It is proof that the researcher is capable of conducting independent research of a very high standard.

Any researcher who wants to obtain a doctorate must prepare a PhD thesis. He/she will do so under the guidance and supervision of a full professor, who will act as PhD supervisor (*promotor*).<sup>3</sup> This professor has overall responsibility for the PhD trajectory and has specific duties pertaining to this role. The regulations stipulate that any qualified researcher can approach a full professor and ask him/her to act as PhD supervisor. The PhD supervisor may

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<sup>1</sup> AMC Graduate School

The AMC Graduate School enhances the quality of PhD studies by organizing the doctorate level academic training of AMC PhD students, supporting students and their supervisors. See [AMC Graduate School](#). \*Niet beschikbaar bij VUmc\*

<sup>2</sup> UvA Doctorate regulations

These can be downloaded from <http://www.uva.nl/en/research/phd/procedure>  
Additional specific provisions issued by the AMC can be found on [AMC Graduate School](#).  
\*Niet beschikbaar bij VUmc\*

<sup>3</sup> The procedural rules for PhD candidates are laid down in the [Doctorate Regulations \(Algemeen Promotiereglement\)](#) issued by the UvA's Doctorate Board (College voor Promoties). VUmc: [http://www.vu.nl/nl/Images/Promotiereglement-webversie%201-4-2010\\_tcm9-147637\\_tcm9-198605.pdf](http://www.vu.nl/nl/Images/Promotiereglement-webversie%201-4-2010_tcm9-147637_tcm9-198605.pdf)

delegate his/her duties as a supervisor to one or more co-supervisors, but retains responsibility.

1. It is a personal decision of the professor whether to accept the researcher as a PhD student (*promovendus*).
2. When making a decision about supervision, the professor checks whether the conditions for successfully completing a PhD programme are available. This applies not only to the formal requirements (the PhD student must hold a Master's degree in a subject relevant to his/her proposed research), but also to the conditions for successfully completing a PhD programme of additional training and research.
3. Agreeing to act as PhD supervisor for a young researcher is an important decision that has far-reaching consequences. Both the student and the supervisor must confirm the request and the decision by signing a document.
4. The duty of the PhD supervisor is to supervise the PhD student in his/her research and in all aspects of the training related to that research. The supervisor is also expected to help the student to identify appropriate skills training and to undertake it.
5. After a professor has agreed to act as a PhD supervisor, he/she develops the content of the personal training programme. This programme has two sections: training and research. The PhD supervisor develops a plan and a schedule for coursework, training and other activities aimed at developing the knowledge and skills of the PhD student to the level of that of an independent researcher. The second part of the PhD programme is supervised research. The PhD supervisor creates or facilitates conditions for high quality research and for adequate day-to-day guidance and supervision of the PhD student, as specified earlier.
6. By the end of the first trimester, the PhD student and the PhD supervisor are expected to have reviewed and discussed the student-supervisor agreement and to have a signed training and supervision plan.<sup>4</sup> The PhD supervisor then ensures that a timetable is in place that will lead to a timely upgrade and progression to completion and submission of the PhD thesis.
7. The PhD supervisor may delegate the day-to-day supervision, or the supervision of specific elements of the PhD programme, to a colleague (e.g. an assistant professor), who may ultimately become a co-supervisor of the PhD student. However, final responsibility for the PhD thesis remains with the PhD supervisor (*promotor*). If PhD supervision is shared, a clear understanding of the allocation of duties (including the procedure to be followed in the case of diverging opinions) must be reached and communicated to the PhD student.
8. The PhD supervisor monitors the progress of both the training and the research part of the personal PhD programme. This is arranged during regular meetings. A PhD supervisor should maintain regular contact with his/her PhD students: it is not unusual in the early and closing stages for a PhD supervisor to meet with his/her PhD student on a weekly basis or even more frequently.
9. It is the PhD supervisor's responsibility to monitor the integrity of the PhD student in relation to performing the research studies, handling the data and submitting manuscripts.
10. In the case of conflicts, the PhD supervisor must ensure that the PhD student has access to an independent and qualified third party. In general, shared supervision (by two supervisors, a supervisor and a co-supervisor, or a supervision team) is

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<sup>4</sup> The AMC Graduate School uses a standard Training and Supervision Scheme (*Opleidings-en Begeleidingsplan*; OBP), which is available on their website [www.amc.nl/graduateschool](http://www.amc.nl/graduateschool).

preferable, considering the potentially vulnerable relationship between a PhD supervisor and a PhD student.

### **2.3 Duties and rights of the PhD student**

Doing PhD research should be a pleasant and valuable experience. Good mentorship assists PhD students to enjoy their research work and training. A PhD student also has certain primary responsibilities pertaining to the relationship with his/her supervisor, namely:

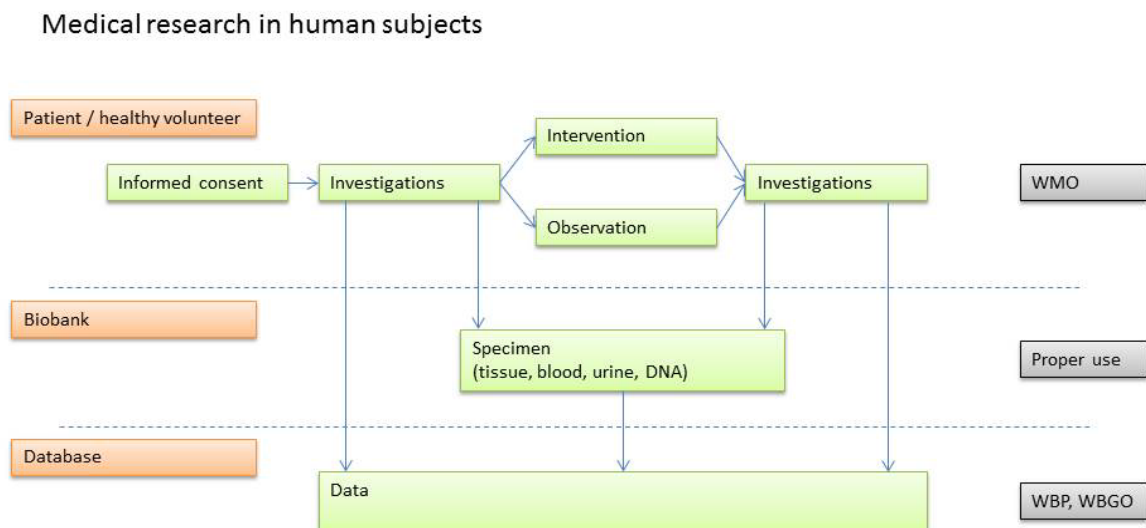
- To act as a professional and assume responsibility for his/her own scientific work.
- To function as member of a team and to be accountable towards the PhD supervisor.
- To be critical of his/her own work and that of other team members.
- To follow mutual arrangements regarding the design and execution of the work.
- To accept guidance related to the personal PhD programme.
- To follow mutual arrangements related to the organization of the work, including work hours and presence.
- To submit or deliver agreed work packages on time.
- To conduct the research with care.
- To handle data properly (e.g. not to omit or falsify data).
- To check for errors.
- To take great care when dealing with patients and laboratory animals and their data, and to obey the rules such as those stipulated in this Research Code.
- To ensure that his/her reporting is complete and transparent.

The PhD student has the right to consult an independent and qualified third party with regard to the functioning of his/her supervisor.

### 3. RESPECT FOR HUMAN SUBJECTS INVOLVED IN MEDICAL RESEARCH

In any type of scientific research, an absolute prerequisite is to respect the participants and their rights. In medical research, this prerequisite is fundamental. It is also enshrined in the law in various ways; for example the rights that research subjects have to protect their physical and mental integrity and their privacy are laid down in law. Lastly, respect for subjects involved in research is essential if the trust and cooperation of potential participants is to be secured for the future.

Respect for the persons or participants cannot be fully captured in rules or procedures. This means that respect for participants is not only a matter of obeying rules and following verification procedures: it is also a state of mind. Researchers need to be open to and feel responsible for those interests of participants that could be affected by the research, and to ensure that the participants are aware of this.



**Figure 1 Medical research in human subjects**

Medical research can be broadly divided into three types according to the degree of the subjects' involvement (Figure 1):

1. Research on human subjects, that is, research in which patients are subjected to certain interventions or investigations, for example administration of a trial drug (medicinal product) in order to compare it with a well-known registered drug, or taking samples of body material for analysis.
2. Research on body material (blood, tissue, urine, spinal fluid, DNA, etc.) that is already available for one reason or another (e.g. material that was taken in the course of diagnosis or treatment).
3. Research on other data that are already available from patients' medical records or elsewhere, or that is collected directly from the subjects.

#### 3.1 Research on human subjects

'Medical research that includes subjecting persons to interventions or imposing a particular course of conduct upon them' is subject to the Medical Research Involving Human Subjects Act ([Wet Medisch-wetenschappelijk Onderzoek met mensen; WMO](#)).



For research that is subject to the WMO, the research in question can be carried out only if a detailed research protocol has been approved by a certified Medical Ethics Committee (MEC). In some cases, approval has to be given by the Central Committee on Research Involving Human Subjects ([Centrale Commissie Mensgebonden Onderzoek: CCMO](#)) in The Hague. A step-by-step approach with respect to the choice of an accredited MEC is provided on the [CCMO website](#).

Both the AMC and the VUmc have their own MEC, as do all other university hospitals and several other hospitals and institutes in the Netherlands. Most of the criteria used by the committee are laid down in international documents, for example [the Declaration of Helsinki](#) (revised in Seoul in October 2013) and the [Good Clinical Practice guidelines](#) (which are applicable to interventional clinical research with medicinal products in the EU, the USA and Japan). In essence, the legal requirements are as follows:

- The research must be worthwhile and should lead to medical progress as regards the question it sets out to answer, be sound as regards design and execution, and be reasonable, that is, its value must be in proportion to the burden on and the risks to the subjects.
- The subjects (or their legally acceptable representatives) must have been properly informed in writing and have given their written consent. The information provided must include the purpose, nature and duration of the research and the risks and problems it could entail for subjects.
- The subjects must be adequately insured (specific WMO insurance).
- More stringent requirements apply in the case of minors, incompetent adults and subjects who are dependent in some other way.

On 1 March 2006, the WMO law was changed, implementing the international Good Clinical Practice guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ([ICH](#)); see also Chapter 5. This implies that clinical research with either registered or nonregistered medicinal products must be conducted in compliance with these guidelines. Other research that is not subject to the WMO should preferably also be conducted in the spirit of the ICH Good Clinical Practice guideline. This is not a regulatory requirement, but a common sense approach.

For research that is not subject to the WMO, less stringent requirements apply: in principle oral informed consent written down in the file of the patients is adequate and there is no need for specific insurance.

For research with healthy volunteers there are additional requirements at both the AMC and the VUmc: employees are not allowed to participate as subjects in research carried out by their own department; see the [Uitvoeringsrichtlijnen Goedkeuring medisch wetenschappelijk onderzoek door de RvB en Deelname van wetenschappelijk personeel en studenten aan medisch wetenschappelijk onderzoek](#) of the AMC and *Informatie over proefpersonen METc* of the VUmc: [http://www.vumc.nl/afdelingen/METc/wmo-beoordeling/indiening/pif\\_oordeel/](http://www.vumc.nl/afdelingen/METc/wmo-beoordeling/indiening/pif_oordeel/)

### **3.2 Research on body material**

The statutory rules concerning research on body material are still under development. In recent decades, hospitals and the research community have put a lot of effort into establishing *de novo* biobanks (prospective collections of patient material) for broad research goals, especially to enable future studies. All Dutch university medical centres participate in the collaboration on these biobanks, for example in the [String of Pearls initiative](#). The statements below apply both to these biobanks and to other kinds of research on stored patient specimens.

According to the Code for Proper Secondary Use of Human Tissue ([FMVV](#), 2011), research on anonymous (i.e. untraceable) body material is permitted unless the person in question has at any time indicated that he/she objects to this further use. For storing and using human tissue for research that is not anonymous (such as encoded tissue), the written informed consent of patients is required, unless this is impossible (e.g. the patient is deceased) or

reasonably impracticable (e.g. very large cohorts of patients). Explicit informed consent should always be obtained before material is taken specifically for the purpose of research. In most cases, consent can be of a broad nature.

If there is a substantial likelihood of findings being produced that are of clinical value to the health or wellbeing of the person concerned and are actionable ('individual research findings'), this issue should be specifically mentioned to potential research participants. They should be informed about the 'reporting back policy' of the researcher/biobank, the possibility to indicate that they prefer not to be informed about new findings, and that this preference can be overruled if serious harm to themselves or their family members can be prevented. If patients find this policy difficult to accept, they should not participate.

The MEC of the AMC or the VUmc is always involved at an early stage in the procurement and use of body material for research purposes. At the AMC, a dedicated committee ([\*Biobanken Toetsings Commissie; BTC\*](#)) evaluates the legal and ethical aspects of existing and new biobanks according to a standard procedure, including rules with respect to the supervision of the biobank. The MEC of the VUmc intends to install a similar committee.

It is important to realize that even research that only entails analysing blood, tissue or other material can interfere with people's interests and rights, as it produces information about them that could be of value to themselves and/or others. The key points described in the Code for Proper Secondary Use of Human Tissue are:

- *Safety*

Biological material obtained in the course of diagnostic tests on or treatment of patients should be processed and kept in accordance with the guidelines for specific diagnostic requirements (microbiology, clinical chemistry, pathology, etc.), taking current health and safety standards into consideration. This includes paying attention to deterioration, the risk of infection, encoding and the risk of mix-ups.

- *Carefulness*

The fact that patient material is involved means that carefulness is required in the sense of accurate identification and storage, as well as confidentiality.

- *Responsibility*

The hospital (and specifically the head of the department where the specimens are stored) where the patient is being treated is responsible for storing patient material and laying down rules on the matter. The patient should sign an informed consent document during the first consultation.

- *Traceability*

Records of patient material should be encoded, that is, they should be traceable to the patient only through an encrypted code. The head of department oversees access. Material obtained for research purposes can also be filed in other database systems; here, the head of the research team oversees traceability.

- *Informed consent*

Informed consent from the patient is required if the results of analyses of body material carried out for research purposes can be traced to the patient. Completely anonymous archival material can be used for research purposes provided this does not conflict with the permissible storage period and the purpose for which it was originally taken, and provided the patient has no objection.

- *Storage periods*

Patient material obtained for diagnostic purposes must be kept as long as is deemed necessary for proper care. Proper care may indicate that this is extended to the family of the participant, and even to his/her offspring, which may extend the period during which samples will be stored. Material that is obtained specifically for future research can be kept as long as agreed upon in the informed consent document. Guidelines on storage periods are generally drawn up by the professional association of the medical specialty.

### 3.3 Research on other data

Of the three types of research identified, research on data other than those indicated in 3.1 and 3.2 is, in principle, the least intrusive. Two comments need to be made, however. Firstly, some types of data research are potentially more burdensome than others, for example research in which the data has to be collected from the subjects by means of, for instance, interviews or questionnaires, as compared to research that is based on patient information that the doctor/researcher already has at his/her disposal in his/her capacity as practitioner. Second, a particular study of data could be more intrusive in terms of burden and risks than a relatively 'harmless' study using body material or humans.

The protection of the rights of participants in data research is a subject of continuous debate in the Netherlands and other countries. This reflects not only the fact that the casuistry is sometimes complex, but also the potential tension between the importance of protecting privacy on the one hand and the interests of scientific research on the other. Quality control and the proper documentation of the data management are important for safeguarding scientific integrity as well. More information can be found in Chapter 7.

### 3.4 Research in developing countries

The ethical principles that apply to research in Europe naturally also apply to research in developing countries. Research with partners in developing countries, just like research with partners in the Netherlands or elsewhere in Europe, is based on trust, collaboration, taking pleasure in the work, complimentarily and a shared goal. Both partners have something to offer and can learn from each other: together they can achieve more and move further ahead. Basic research and research that does not have an immediately apparent application are important in developing countries too, but in many cases applied research will be more appropriate because of the limited availability of resources and the scarcity of staff and funds. Neither the AMC nor the VUmc wishes to support research in developing countries that benefits only the Western researcher: medical tourism and exploitation need to be avoided. The following are a few points that merit special attention.

#### Review

The research question and research plan are subject to scientific scrutiny. Proposals for research involving humans or materials taken from humans should also be submitted to a Medical Ethics Committee (MEC). Such committees do not exist in all institutions and in all countries, but where they do exist the proposals should be submitted to them. If there is no such committee, the project may provide a good opportunity to initiate a debate within the local institution by, for instance, trying to set up an ad hoc committee and discussing the research within the institution. The research protocol should be approved by the MEC of the [AMC](#) or the [VUmc](#) <http://www.vumc.nl/afdelingen/METc/> and by that of the local institution.

Research done by AMC or VUmc researchers in developing countries remains the responsibility of the institution. If it cannot be reviewed locally, the MEC of the AMC or the VUmc can be asked to issue a certificate of no objection. It is not possible for these MECs to verify compliance of the research in developing countries with the Dutch legislation ([the Medical Research involving Human Subjects Act; WMO](#)), as the act applies only to the Dutch situation and the MECs cannot be expected to be aware of local rules and regulations. They can, however, carry out an unofficial check based on general principles and issue a certificate of no objection, if appropriate. In addition, local institutions or partners often want the proposal to be reviewed in the Netherlands. The name of the institution that is sponsoring (and is therefore legally responsible for) the project must be clearly stated.

#### Patient consent

Patients need to give their informed consent to participation in the project. The information must be provided in the patient's own language, which usually makes it impossible for the researcher to check it. On top of this, oral consent is often accepted, which is not ideal because in such cases there is no documented evidence of the consent. The information should preferably be provided in the presence of a witness who speaks the language in

question (as well as a language in which the researcher can communicate); the name of this witness should be documented on the written informed consent form that is signed by the patient, the researcher and the witness. The use of a fingerprint or another mark to indicate consent is considered acceptable.

### **Informing the authorities**

The local partner should ensure that the regulatory and other competent authorities concerned are informed about the project. These authorities include the board and management team of the district hospital where the work is to take place, the district medical officer, the provincial medical officer, representatives of the local population, etc. Whether the Ministry of Health or one of its departments needs to be informed will depend on various factors, for example the country and its rules, the nature of the research and the local institution. As this is best decided by the partner, it is wise to discuss it with the latter.

### **Personal and cultural factors**

Each organization in the Netherlands and Europe has its own culture when it comes to dealing with one another and with research, and this applies equally in developing countries. The researcher should be prepared for this. Patience is often called for, and talent for improvisation and a contemplative disposition can help; one can ask oneself, for instance, why something is done in a particular way, and it will often turn out that there are good local reasons. Anyone who cannot handle uncertainty may be better off not doing research in or in collaboration with developing countries. But for someone who is keen to gain new impressions and experiences, and is willing and able to improvise, research in developing countries is both a challenge and rewarding. It is often more demanding but it has more to offer – ideally to both parties.

Table 1 Laws and regulations. All these laws can be found at [www.wetten.nl](http://www.wetten.nl)

<b>Law</b>	<b>Remarks</b>
WMO	The Medical Research involving Human Subjects Act ( <a href="#">Wet Medisch-wetenschappelijk Onderzoek met mensen</a> ) is the research law governing all interventional trials.
WGBO	The Medical Contract Bill ( <a href="#">Wet Geneeskundige Behandelingsovereenkomst</a> ).
WBP	Data Protection Law ( <a href="#">Wet Bescherming Persoonsgegevens</a> ).
GW	Medicine Law ( <a href="#">Geneesmiddelenwet</a> ).
WBIG	Law for the Qualifications and Accreditation of Medical Professions ( <a href="#">Wet Beroepen in de Gezondheidszorg</a> ).
KWZ	Quality Law for Health Institutions ( <a href="#">Kwaliteitswet Zorginstellingen</a> ).

## 4. RESPECT FOR LABORATORY ANIMALS INVOLVED IN BIOMEDICAL RESEARCH

This chapter reiterates the demand formulated by politicians and supported by society to accord respect to laboratory animals. The Netherlands has strict legislation on the treatment of laboratory animals. In Dutch university medical centres (UMCs), laboratory animals are to be treated 'humanely' and must be housed, cared for and handled in accordance with the [European Directive of 22 September 2010](#).

### 4.1 Legal framework

Respect for laboratory animals is enshrined in the 1977 Experiments on Animals Act ([Wet Op de Dierproeven; WoD](#)). It is forbidden to carry out an animal test to achieve something that could be achieved in another way or by using a test that involves fewer animals and/or causes less discomfort. In addition, the scientific value of the test must be in proportion to the discomfort caused to the animal. The act includes licensing regulations. The licensee is the executive board. Responsibility for legal enforcement of the regulations rests with the chairman of the executive board.

With regard to the competence of persons who are permitted to perform animal experiments, Section 9 of the act prescribes that in order to plan and supervise animal tests, researchers must have undergone preparatory training as set out in the Animal Tests Decree (the training comprises at least 500 hours of academic study of basic biology) and must have taken a compulsory course on laboratory animal science. These researchers are referred to as 'Section 9 officers'. Section 12 states that the people who look after the animals and those who carry out the actual experiments must be specially trained technicians/biotechnicians and animal attendants ('Section 12 officers'). With regard to supervising the welfare of the animals, Section 14 states that each licensee must have a laboratory animal science specialist ('Section 14 officer'), a person with preparatory training as set out in the decree and experience of carrying out animal tests followed by a postgraduate course in laboratory animal science. An animal experiments committee (usually referred to internationally as the Institutional Animal Care and Use Committee; IACUC) must be asked to examine the discomfort for the animals and the importance for society and science of proposed animal tests. The act states that the inspectorate (Nederlandse Voedsel en Waren Autoriteit; [NVWA](#)) ('Section 20 officer') is responsible for enforcing the act.

### 4.2 Ethical principles

According to the [Code of Practice](#) of the Dutch Association for Animal Science (Nederlandse Vereniging voor Proefdierkunde; [NVP](#)), researchers are required to learn and observe in practice. This is also stated in the Experiments on Animals Act. The general principle the act provides and that must be taken into account in any proposed animal test, is the 'recognition of the animal's intrinsic value'; in other words, an animal must not be used purely as a means to an end, but must be protected and respected for its own sake. The wording reflects the ethical principle that an animal has more than just instrumental value, that is, its value is not identical to its utility to mankind. This intrinsic value is not earned by the animal; it is not the result of our appreciation of the animal, whether based on ideology or not. On the contrary, it is the reason why animals are appreciated and treated with respect. Recognition of the intrinsic value of animals implies that mankind has direct moral obligations towards them. The intrinsic value of animals also means that when designing an experiment, a researcher must endeavour to take account of the animals' species-specific behaviour and their self-sufficiency. The aim must be to keep the animals as 'intact or whole' as possible.

[The Experiments on Animals Act](#) is available at: <http://wetten.overheid.nl>

The website of the Food and Consumer Product Safety Authority (Nederlandse Voedsel en Waren Autoriteit; [NVWA](http://www.vwa.nl)) provides information about animals, animal welfare and experiments on animals. See <http://www.vwa.nl>

For information on experiments on animals at the AMC, see: [intranet/Research/](#) and for the VUmc see: <http://www.vu.nl/nl/over-de-vu/profiel-en-missie/uitgelicht/proefdieren/index.asp>

The annual report of the inspectorate (NVWA) '[Zo doende](#)', with data on the use of animals for experiments, can be downloaded from: [www.nvwa.nl](http://www.nvwa.nl)

### 4.3 Animal experiments committees

A proposal for research on laboratory animals is made by the responsible Section 9 officer using a detailed application form. The animal experiments committee considers the application and advises the licensee accordingly. The committee provides an assessment of the value of discomfort caused by the experiment that is as objective as possible. The committee can also put forward fresh ideas and correct shortcomings in, for instance, the design or implementation of the experiment. Establishing the scientific quality of proposed research is an important prerequisite of ethical review. As the committee may not be sufficiently equipped to assess scientific quality in the various fields of research it has to deal with, proposals require prior review by the scientific review board of the respective department or institute.

The researcher is required to keep the effects of the interventions to a minimum, based on the three R's: refinement, replacement and reduction. When considering an application, the committee pays careful attention to the effects of the intervention on the animal and to its discomfort. The committee assesses this against the social and scientific benefit to humans, animals and/or science. There are exceptions: not all experiments can be justified in terms of special benefits to mankind. In order to prevent extreme discomfort, careful consultation and appropriately binding agreements between the committee and the researcher, keeping a welfare journal for each animal experimented upon, and supervision by and advice from the laboratory animal science specialist are important. Every year, each licensee (AMC or VUmc) sends the data on all the animal experiments for which it is responsible to the inspectorate (NVWA). The inspectorate compiles an overview from all the registration forms and publishes it in its annual report (entitled '[Zo doende](#)').

### 4.4 Animal experiments course

According to the [Experiments on Animals Act](#), anyone who wishes to do research on laboratory animals must take the Laboratory Animal Science course. This course teaches the careful and justifiable use of laboratory animals in biomedical research. It is a three-week course covering such areas as the legal, ethical and social aspects of animal experiments; the comparative biology and zoo technology of commonly used laboratory animals; animal accommodation and welfare; pathology; genetics; anaesthesiology; experimental techniques; trial design and statistics; aspects of stress and immunological research; and alternatives to animal experiments. The course is run jointly by the licensee of the University of Amsterdam (UvA), VU University Amsterdam (VU), the Royal Netherlands Academy of Arts and Sciences (Koninklijke Nederlandse Akademie van Wetenschappen; KNAW) and the Netherlands Cancer Institute (Nederlands Kanker Instituut; NKI).

Laboratory [Animal Science Course](#): For information on this course in Amsterdam, please contact K. van den Oever, email: [cursuspdk@amc.nl](mailto:cursuspdk@amc.nl), tel. 020-5666479.

## 5 CLINICAL RESEARCH METHODS AND GOOD CLINICAL PRACTICE

### 5.1 Introduction

The Medical Research Involving Human Subjects Act ([WMO](#)) covers medical scientific research in which people are subjected to interventions or have to follow established behavioural rules. The main purpose of the act is to protect research subjects (patients and healthy volunteers) against the risks and burdens of biomedical research involving human subjects without unnecessarily hampering the progress of medical–scientific research.

All clinical researchers, including PhD students doing research covered by the WMO, are obliged to follow the foundation course Legislation and Organization for Clinical Researchers (BROK course). The aim of this course is to provide clinical researchers with knowledge of the laws and regulations covering clinical research and their practical consequences. The course is completed by sitting an official national examination for the certificate of the NFU (Nederlandse Federatie van Universitair Medische Centra). The AMC and the VUmc provide the BROK course on a regular basis.

BROK course AMC, see:

<http://www.amc.nl/web/Onderwijs/PhD/PhD-Course-Program/BROK.htm>

BROK course VUmc, see:

<http://www.VUmc.com/branch/internalmedicine-cru/qualityassurancecru/brokcourseVUmc>

In line with the WMO, this chapter explains the requirements for clinical research methods and good clinical practice in all stages of the study.

### 5.2 Clinical research methods and good clinical practice

It is good practice when planning a research project to formulate the goal of the research transparently, following a critical analysis of the available literature and any other data that are available. In the case of clinical research involving subjects, the goal should comprise particulars of the sample to be taken, the intervention, diagnostic test or aetiological factor, and the outcome measures that will be used. An appropriate research design should be chosen, and the actual number of participants in the study should be ascertained, as this almost always turns out to be smaller than originally hoped for or expected. Precise formulation of the research question effectively selects the design of the project. Proper planning is absolutely required for a number of reasons: a researcher who knows what he/she wants and why, and who is able to formulate a clear motivation and design, has a greater chance of having his/her research proposal accepted by a grant-giving body. When starting out on a project, the researcher does not yet know the answer to the question, but it is essential for him/her to envisage what type of answer it could be. A researcher who cannot surmise what the answer may be is not asking the right research question.

For the reasons given above, a protocol summary should be drafted in the design phase of the research project containing the following elements:

1. Rationale. Study background and hypothesis (if applicable).
2. Objective. The main and secondary objectives of the study.
3. Study design. For example, randomized controlled trial, case-control study, etc. In this paragraph attention should also be paid to the sample size calculation (the minimal number of subjects needed to confidently answer the main study question).
4. Study population. For example, healthy human volunteers, 18–55 years old.

5. Treatment (if applicable). For example, one group receives twice daily a 10 mg tablet of product X and the other group receives twice daily a placebo tablet. It also could be a surgical intervention or any other intervention.
6. Investigational product. This paragraph is applicable to research on the effects of any product (e.g. medicinal product, food product, medical device or other).
7. Non-investigational product. This paragraph is applicable for any other product that is used in the study. For example rescue medication, or challenge agents or products (e.g. medicinal product or chemical compound) used to assess study endpoints.
8. Methods. A description and operationalization of the main study parameters/endpoints (e.g. the percentage change in the number of events from baseline to endpoint, or the difference in genetic profile between patients and controls). This paragraph also details the procedures subjects will undergo (e.g. the amount and number of blood samples, the number of site visits or questionnaires that have to be filled in).
9. Safety reporting. Clinical researchers are required to report serious adverse events through the web portal [ToetsingOnline](#) to the Medical Ethics Committee that approved the protocol. When the research is determined to be high risk, a data and safety monitoring board ([DSMB](#)) is required to monitor the safety of the participating research subjects.
10. Statistical analysis, including power analysis, how missing data will be handled, and how data will be presented and analysed.
11. Ethical considerations. A description of recruitment and informed consent procedures. If applicable, a risk–benefit analysis can be given. If a non-therapeutic study is carried out with minors or incapacitated persons, it should be specified whether the risks are negligible and the burden minimal, and why the study is group related (i.e. can only be done using these patient groups).
12. Administrative aspects. Data should be handled confidentially and, if possible, anonymously. The handling of personal data should comply with the Dutch Personal Data Protection Act ([De Wet bescherming persoonsgegevens](#)).
13. Structured risk analysis. This consists of a number of steps to determine the direct risks for the research subjects in the study.

Summary of the research protocol.
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This summary is derived from the revised template published in 2012 by the Central Committee on Research Involving Human Subjects (CCMO). See <a href="http://www.ccmo.nl">www.ccmo.nl</a>
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### 5.2.1 Obtaining approval

Research covered by the WMO and/or the [Embryos Act](#) must be submitted to an accredited Medical Ethics Committee (MEC) for approval before it can be conducted. Studies are subject to the WMO if they meet the following criteria:

- It is medical scientific research.
- Research subjects are subjected to procedures or are required to follow rules of behaviour.

Examples of clinical research that does not entail subjecting research subjects to procedures or require them to follow rules of behaviour, and is therefore not subject to the WMO, are retrospective studies on patient records and prospective research with patient data.

The MEC reviews research protocols in accordance with the rules laid down in the WMO. The MEC can only provide positive judgement of a research protocol if (Article 3 of the WMO):

- The scientific research will contribute to new insights in the field of medicine.



- There is no simpler or less burdensome alternative (e.g. ideally no incapacitated study participants).
- The significance of the study is proportionate to the inconvenience (burden) and risk to which the research subject will be exposed.
- The study meets the scientific criteria for research.
- The study is to be carried out by or under the supervision of qualified investigators.
- Any payment made to the research subject must not have been a decisive factor in his/her decision to take part in the study.
- The protocol states the extent to which the scientific research might benefit the research subject or, in the case of group-based studies, the group to which the research subject belongs.

Research that is subject to the WMO cannot be carried out without a positive decision from the MEC. In some cases (e.g. for experimental interventions such as gene therapy) the Central Committee on Research Involving Human Subjects (CCMO) acts as the MEC. See '[Besluit centrale beoordeling medisch-wetenschappelijk onderzoek met mensen](#)'.

The protection of research subjects is the key issue in the WMO. Therefore, the law prescribes that:

- Research subjects must be given written information about the study.
- An independent expert who is not directly involved in the study must be available to give research subjects information.
- Research subjects must give their written consent prior to taking part in the study.
- Insurance must be taken out to cover any damage suffered by research subjects as a result of the study (liability insurance does not suffice).

The law imposes requirements on how the study must be reviewed, and additional requirements on research involving minors (persons under the age of 18) and incapacitated adults. MECs must follow these legal rules when reviewing studies. Consult the WMO for the full text.

After giving a positive decision, the MEC must still be informed of the following aspects: start and end dates of the study, protocol amendments, and amendments of other essential documents like the patient information. In the case of studies that are subject to the WMO, all serious adverse events (SAEs) and serious adverse device effects (SADEs) should be reported through the web portal [ToetsingOnline](#). Suspected unexpected serious adverse reactions (SUSARs) should be reported through the web portal [ToetsingOnline](#) in the case of trials of medicinal products.

'Besluit centrale beoordeling medisch-wetenschappelijk onderzoek met mensen'.  
[MEC / WMO](#)

### *5.2.2 Additional requirements applicable to trials of medicinal products*

For clinical research with medicinal products, an additional marginal review is necessary, in addition to the review by the MEC. This second review of whether there are grounds for non-acceptance concerning the study, is performed by the Competent Authority (CA). The CA examines whether there are motivated objections to the study. To this end, it checks the European database ([EudraVigilance](#)) for previously reported side-effects of the medicinal products that may lead to unacceptable risks to the study subjects.

In a trial with medicinal products for which the MEC is the reviewing ethics committee, the CCMO will act as the CA. If the CCMO is the reviewing ethics committee, the minister of health, welfare and sport will act as the CA. The investigator has to submit the same documentation package to the CA as to the MEC in order to obtain a statement of no objection. For details, see the [CCMO website](#).

The CA remains involved after the approval(s). The investigator/sponsor is obliged to notify the CA in the following cases: substantial amendments, SAEs (serious adverse events) and

SUSARs (suspected unexpected serious adverse reactions) in the case of investigator-initiated studies through the web portal [ToetsingOnline](#), annual safety report, end of study, and submission of the final study report.

Other obligations for interventional trials with medicinal products are:

- Studies and end results must be registered in the EudraCT database (European Union Drug Regulating Authorities Clinical Trials), which is the European database of all clinical trials. A request for a EudraCT number can be arranged via the [EudraCT website](#).
- Planning and conducting the research should be in line with the ICH Good Clinical Practice ([GCP](#)) guideline for trials with medicinal products.
- Manufacturing of the investigational medicinal product (IMP) should be in line with the [European Union Good Manufacturing Practice \(EU-GMP\) guidelines](#). This is also mandatory for placebos.

### 5.2.3 Manufacturing of study medication

In studies that with medicinal products as IMPs – either products under investigation (nonregistered) or medicinal products with a marketing authorization (registered) – the products (or ‘study medication’) must be manufactured, labelled and packed in compliance with the EU–GMP guidelines. To manufacture IMPs, a licensed GMP-manufacturing facility is required and a qualified person has to be appointed and registered at the Dutch health authority. The VUmc has an EU–GMP manufacturing licence for the packaging and labelling of study medication and for the production of radiopharmaceuticals. The AMC does not have a GMP licence.

The IMP, including placebo and comparator medication, should be labelled according to the [EU-GMP annex 13 guideline](#). The label should provide at least the following information:

- Name, address and telephone number of the sponsor or investigator
- Pharmaceutical formulation and number of dose units
- Batch number and/or production code
- Trial reference code
- Identification number of trial subjects
- Name of investigator
- Instructions for use
- The words ‘*Uitsluitend bestemd voor gebruik in klinisch onderzoek*’
- Storage conditions
- The words ‘*Buiten bereik van kinderen houden*’ (when used outside the hospital)
- Expiry date or retest date.

Labels must be approved by the MEC.

### 5.2.4 Investigational medicinal product dossier

The investigational medicinal product dossier (IMPD) contains all the information about an IMP with regard to the active pharmaceutical ingredient (raw product), other compounds, the production process, quality control of the product, stability studies and clinical pharmacology. A template is available on the website of the [CCMO](#). It is also obligatory to have an IMPD for the placebo and comparator medication. If the comparator is a registered drug, however, a summary of product characteristics (SPC) is sufficient (i.e. an IMPD is not needed). The SPCs of registered products can be downloaded from the website of the Medicines Evaluation Board ([College ter Beoordeling van Geneesmiddelen - CBG](#)) or the European Medicines Agency ([EMA](#)). The IMPDs must be approved by the MEC.

### 5.2.5 Storage and distribution of study medication

According to the Dutch Medication Law ([Geneesmiddelenwet](#)), only pharmacies and wholesalers of medication may store drugs. Investigators may store medication only with the

pharmacy's authorization. A prescription issued and signed by a physician is required in order to distribute study medication to the patient. Study medication transactions (receipt and distribution) are registered on drug-accountability forms. The investigator is responsible for the drug-accountability of returned medication. For all these issues, the pharmacy should be contacted at an early stage. It is recommended to make an agreement with the pharmacy and to document the arrangements.

EudraCT <a href="https://eudract.ema.europa.eu/">https://eudract.ema.europa.eu/</a> Good Clinical Practice (GCP) <a href="http://www.ccmo-online.nl/hipe/uploads/downloads_cato/richtsnoer%20GCP%20mrt%202003.pdf">http://www.ccmo-online.nl/hipe/uploads/downloads_cato/richtsnoer%20GCP%20mrt%202003.pdf</a> EU Good Manufacturing Practice (GMP) <a href="http://ec.europa.eu/health/files/eudralex/vol-4/2009_06_annex13.pdf">http://ec.europa.eu/health/files/eudralex/vol-4/2009_06_annex13.pdf</a> College ter Beoordeling van Geneesmiddelen (CBG) <a href="http://www.cbg-meb.nl">http://www.cbg-meb.nl</a> European Medicines Agency (EMA) <a href="http://www.ema.europa.eu/ema/">http://www.ema.europa.eu/ema/</a>
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#### 5.2.6 Registration of the trial

Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions in order to evaluate the effects on health outcomes should be registered in a public protocol registry; this also applies to early phase uncontrolled trials (phase I) in patients or healthy volunteers. This is both a recommendation of the WHO and the policy of the [International Committee of Medical Journal Editors \(ICMJE\)](#). If in doubt, registration is recommended. Studies can be registered with the [Netherlands Trial Register](#), [Clinicaltrials.gov](#) or [Current Controlled Trials](#). The Netherlands Trial Register and the CCMO have agreed to explore a merger of the Netherlands Trial Register and the CCMO register. The submission of the study protocol should be arranged prior to the start of the study, that is, before the first patient has signed the written informed consent.

International Committee of Medical Journal Editors (ICMJE) <a href="http://www.icmje.org">http://www.icmje.org</a> Netherlands Trial Register <a href="http://www.trialregister.nl/trialreg/index.asp">http://www.trialregister.nl/trialreg/index.asp</a> Clinicaltrials.gov <a href="http://www.clinicaltrials.gov">http://www.clinicaltrials.gov</a> Current Controlled Trials <a href="http://www.controlled-trials.com">http://www.controlled-trials.com</a>
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#### 5.2.7 Data management

Before starting the research, a number of activities must be planned regarding the data management. Essential steps in data management are: developing a case record form (a paper or electronic document designed to record all the information for an individual study subject required by the study protocol), building a database, defining a procedure for data entry, defining and programming validation checks to ensure the consistency of the dataset, and, if applicable, setting up a randomization procedure, web questionnaire and/or logistic module. In clinical studies with medical products, the database must permit data to be changed in such a way that these changes are documented; it must also prevent the deletion of entered data (i.e. it must maintain an audit trail). It is also necessary to set up and maintain a security system that prevents unauthorized access to the data. There should always be an adequate backup of the data.

### 5.2.8 Monitoring

At the AMC, all investigator-initiated studies with medicinal products or medical devices, and studies with a high risk level, should be monitored. At the VUmc, monitoring is mandatory for all mono-centre investigator-initiated studies and all high-risk multicentre studies. The purpose of study monitoring is to verify that the rights and wellbeing of human subjects are protected, that the reported research data are accurate, complete and verifiable from source documents, and that the conduct of the study is in compliance with the currently approved protocol/amendments, with GCP and with the applicable regulatory requirements. In general, onsite monitoring should be carried out by an independent monitor before, during and after the trial.

In line with international recommendations, the Netherlands Federation of University Medical Centres (NFU) recommends that clinical research projects should be categorized according to the level of risk that they pose to the research subjects, investigators and the health service. The three levels of risk are: negligible, moderate and high. Accordingly, monitoring procedures in terms of frequency and intensity should be adapted to reflect the degree of risk. This recommendation has been adopted by both the AMC and the VUmc.

Revised NFU guidelines.

In 2012 the Netherlands Federation of University Medical Centres (Nederlandse Federatie van Universitair Medische Centra; [NFU](#)) developed guidelines on the quality control of medical research with human subjects. These guidelines can be [downloaded](#) as a PDF file.

### 5.2.9 Doing the research

Patients can be enrolled in a study only after the researcher has planned the clinical study, been granted funding, obtained approval from the MEC, received the notification of no objection from the CA (if applicable), and received the hospital board's formal approval. It is also necessary to register the study in a public registry before enrolling the first patient.

An overview (the enrolment log) must be kept of all eligible and consenting research subjects. A subject identification list must also be maintained by the researcher. This document is a confidential list of the names of all enrolled subjects along with their allocated study numbers. It allows researchers to establish the identity of any subject, if necessary. Subject study numbers should be used instead of identifying information. When study data are to be transferred to a party outside the hospital (e.g. pharmaceutical industry, physicians at other hospitals, other institutions), only subject study numbers may be used. Any subjects who are screened but are found not eligible to participate must be documented on a screening log.

A document containing instructions for data entry should be created. The data must be processed digitally in an error-free manner and checked (digitally) for completeness, correctness and consistency. Data analysis planning begins before the researcher has collected all the data. The statistical analysis plan should be drawn up and approved by a statistician.

For clinical studies with medicinal products, the MEC, CA and the EudraCT database in London should be informed after the last patient has received the last treatment according to the study protocol. A specific 'declaration of end of study' form is available on the [EudraCT website](#). The requirements for EudraCT are valid only for clinical studies with medicinal products (both nonregistered experimental products and marketed products).

When a clinical study lasts longer than one year, the investigator should at least once a year submit a summary of the progress of the trial to the MEC by completing the 'annual progress report' template available on the website of the [MEC](#) or the [CCMO](#). This report should be submitted within 60 days after the first approval in the first country of the European Economic Area has been obtained.

The MEC must always be informed of the end of the study by completing the 'end of study report' available on the website of the MEC or the CCMO. For studies with a shorter duration, the annual progress reporting may coincide with the reporting of the end of study.

For clinical research with medicinal products, once a year throughout the study or upon request, a complete overview of all safety information that became known from the study and, if applicable, from all other studies with the same medicinal product performed by the same investigator, must be submitted together with a critical overview and a statement regarding the risk/benefit ratio to the MEC and the [Competent Authority](#) (CA). This is called the 'annual safety report'. Within one year after the end of the study, the investigator should submit the 'summary report' with the results of the study to the MEC and the CA.

#### 5.2.10 Statistical analysis plan

After finalizing the protocol, the statistical analysis plan (SAP) should be drawn up and dated, approved and signed by the study group and a statistician. The SAP should contain a detailed description of the following:

- Study objectives and design, including primary and secondary outcome measures.
- The sample size calculation and power considerations.
- If applicable: randomization procedure, including methods and logistics.
- Study populations: which participants will be included in the analyses (intention to treat versus per protocol considerations).
- List of relevant sample, patient and/or procedural characteristics that will be tabulated.
- All statistical methods to be used to estimate effect sizes and/or to test the study hypotheses regarding the outcome measures, including pre specified subgroups.
- The safety parameters and how they will be tabulated.
- If applicable: the timing and stopping rules of interim analyses/safety analyses.

Data validation, cleaning and analysis should be performed in line with this plan and begin during data collection. When deemed necessary based on a review of the data/blinded data, the SAP may be formally updated. If changes involve sample size considerations or changes in primary outcome definitions, the protocol should be amended and the MEC should approve the amendment. These kinds of amendments are only possible as long as the study is on-going. Each deviation from the original statistical plan should be recorded in the SAP and noted in the final study report. Once all data have been collected, validated and cleaned, the database can be locked and the SAP finalized. When applicable, the blinding can be broken and the final analysis be performed.

All data analyses should be performed by persons who are sufficiently trained in the required statistical methods. When data types and/or the amount of data prevent the medical researcher from performing the necessary statistical analyses on his/her own, collaboration with epidemiologists or biostatisticians should be sought to ensure that the study conclusions are based on valid analyses.

#### 5.2.11 Reporting on the research

Articles and any abstracts for conferences should be drafted. They must accurately reflect the original topic in the protocol and include additional analyses wherever such is useful, necessary and/or of interest. The researcher should state honestly where the question preceded the data and where *post factum* speculations take over. More and more journals demand transparent and full reporting of the essential components in the design and conduct of the research. Various checklists can be used to establish whether an article contains adequate information on every point. For example, there are the [CONSORT guidelines](#) for randomized controlled trials, and the [STROBE](#) and [STARD](#) guidelines for observational and diagnostic accuracy studies.

After reporting the findings, the researcher should archive all essential investigator documents (including data files, statistical syntax, etc.). The NFU recommends archiving essential documents for at least 5 years in the case of a study with a negligible risk, and for at least 15 years in the case of a study with a moderate or high risk. For investigator-initiated clinical studies with medicinal products, essential documents should be retained for at least

15 years, irrespective of the risk level of the study. These guidelines have been adopted by both the AMC and the VUmc.

Guidelines for health research reporting, see:  
<http://www.equator-network.org/resource-centre/library-of-health-research-reporting>  
Study documentation (AMC), see:  
<http://www.amc-cru.nl/klinischonderzoek.aspx?panel=ARC>  
Study documentation (VUmc), see:  
<http://intranet/afdelingen/thema/crb/6979188/7103445/7091925/>

### 5.3 Research support

The Clinical Research Unit (CRU) supports clinical research at the AMC. The CRU provides methodological support to researchers who are writing grant proposals or starting new clinical research projects. Its helpdesk can answer questions related to statistics. The CRU website provides detailed instructions on how to plan, execute and report clinical research. The website also provides various statistical tools (e.g. Wiki Biostatistics and the e-learning course Practical Biostatistics) and a set of standard operating procedures for clinical research can also be found in Kwadraet. With regard to data management, the CRU offers a range of products. ICT specialists and data managers can build GCP-proof databases, design and construct data warehouses, and set up randomization procedures. The CRU can also provide monitoring services and help researchers to set up a data safety monitoring board. For further details, see the [CRU intranet site](#).

The Clinical Research Bureau (CRB) at the VUmc (<http://intranet/afdelingen/thema/crb/>) offers an infrastructure by providing guidance and advice mainly on investigator-initiated studies to ensure quality compliance. The services offered by the CRB include:

- Training and education for research staff.
- Monitoring of investigator-initiated studies that are subject to the WMO.
- Data safety monitoring board in the case of high risk studies.
- Advice and guidance regarding several legal aspects and supporting the contracting process for clinical trial agreements.
- An intranet site providing advice and instructions on how to plan, execute and report clinical research according to GCP.

CRU  
For more information about the AMC Clinical Research Unit, see  
<http://www.amc-cru.nl/welkom.aspx> (intranet)  
<http://os1.amc.nl/wikistatistiek>  
<http://www.elearningbiostatistics.com>

CRB  
For more information about the VUmc Clinical Research Bureau, see  
<http://intranet/afdelingen/thema/crb/> (intranet)

## 6 GOOD LABORATORY PRACTICE

### 6.1 Introduction

Both the AMC and the VUmc aim to carry out basic and translational research of the highest quality. The regulations described here are intended to improve the reliability and reproducibility of basic and translational biomedical research, and to prevent scientific misconduct.

### 6.2 Good laboratory practice

Basic and translation biomedical research is performed in dedicated laboratories following strict rules, regulations and laws. In addition:

- The research performed should be of a high standard and quality, should be ethical, and should respect laboratory animals, healthy volunteers and patients.
- The personnel should be knowledgeable and well trained.
- The laboratories should be well equipped and the apparatuses should be maintained properly.
- Procedures should be well described, validated and up to date.
- Findings should be recorded properly in a laboratory notebook.

Scientific research is performed in the framework of projects that should contain a transparent formulation of the aim of the research, following a critical analysis of the literature and any other relevant data. The principal investigators are responsible for the quality, accuracy, traceability and reproducibility of all research findings obtained within their research projects.

Many different diagnostic laboratories at both the AMC and the VUmc have adopted quality control systems and are accredited according to, for example, [CCKL](#) or ISO 15189 standards. Although it is not mandatory for basic and translation biomedical research laboratories to comply with these CCKL standards and obtain accreditation, it is very useful to organize the research according to those rules and regulations. Imposing these rules and regulations in the laboratory facilitates patent applications and increases funding opportunities from national and international foundations and consortia, and from biopharmaceutical companies.

Strict rules for basic and translational research have been laid down in specific acts. These comprise, for example, strict rules for the use of radioactive material and genetically modified organisms, and the handling and use of laboratory animals.

Radioactive material, see: [www.agentschapnl.nl](http://www.agentschapnl.nl)

Genetically modified organisms, see: [www.rivm.nl](http://www.rivm.nl)

Laboratory animals, see: [www.minvws.nl](http://www.minvws.nl)

General information on applicable laws and government acts, see: [www.rijksoverheid.nl](http://www.rijksoverheid.nl)

### 6.3 Project administration

In order to keep track of the research performed, biomedical research laboratories should maintain a proper project administration. The project administration must include at least the following items.

1. An overview of all current and past projects.
2. An identification tag (e.g. a project number).
3. A record of changes that have been made since the project was granted/started.
4. The name and function of the principal investigator and scientific and other personnel involved in the project.

5. Expected start and end dates of the project.
6. Information on parts of the research that will be outsourced.
7. Information about materials to be stored for prolonged periods of time.
8. Information on the validation of apparatuses and processes.
9. Justification of research processes.
10. Information on handing materials and unpublished data to third parties.
11. Quality control.
12. Mid-term and end report to the financing parties, foundations, consortia and/or industries.
13. Information on co-authorships of publications resulting from the research.
14. Ownership of findings, patent filing.

The [CCKL rules](#) and regulations can serve as a guideline for proper project administration.

#### **6.4 Keeping a laboratory notebook**

- A laboratory notebook is primarily kept to record all the steps taken during experimental procedures.
- Keeping a good laboratory notebook prevents loss of data, enables easy continuation of the research when laboratory staff leave, and prevents misinterpretation of data and possible fraud.
- A laboratory notebook should have a permanent binding; loose-leaf, spiral-bound or other temporary binding systems are not recommended.
- The laboratory notebook should contain an index, and the pages should be numbered and dated.
- Paper and (permanent) ink should be of sufficient quality.
- The entries in the laboratory notebook should be legible and complete.
- Procedures must be described in full detail (or reference must be made to standard operating procedures), including the equipment that is used.
- Printouts and photographs should be glued (not stapled) inside the notebook.
- All results, observations and detailed calculations should be written down.
- Any subsequent data added to the notebook should be entered on a separate page with reference to the original entry.
- The principal investigator is responsible for the quality of the laboratory notebook and should check it on a regular basis.
- Old laboratory notebooks should be stored in a safe place at the institute where the research was conducted, and should be kept for 10 years after the last publication derived from the results indicated in the laboratory notebook.

Alternatively, electronic laboratory management systems may be used. For such an approach, do *not* use computer programs, like Word and Excel, which allow entries and dates to be altered without traceability. For information about electronic laboratory notebooks (ELNs), see for example:

<http://www.labarchives.com/index.php>

[http://download.cnet.com/iPad-ELN/3000-2654\\_4-10901569.html](http://download.cnet.com/iPad-ELN/3000-2654_4-10901569.html)

<http://www.cambridgesoft.com/>

#### **6.4 Standard operating procedures**

In addition to keeping a laboratory notebook in which all protocols are written down, it is recommended to keep a database of/binder containing all standard operating procedures (SOPs) that are followed in the laboratory. A SOP is defined as a 'detailed, written instruction to achieve uniformity of the performance of a specific function'. In basic and translational research, this often refers to a detailed protocol on how to perform a specific experiment. A SOP should address the following items:

1. Aim
2. Application
3. Definitions



4. Principle of the test
5. Safety
6. Reagents and solutions
7. Equipment
8. Samples
9. Standard procedures
10. Results
11. Report
12. Quality control (procedure/samples)
13. Disposal of chemicals and samples
14. Additional documentation
15. Remarks
16. Literature references
17. Appendices.

All SOPs should be numbered and stored both in a central place (or on a website) and in the laboratory. SOPs should be approved by the principal investigator and receive regular updates.

### 6.5 Accreditation of laboratories

Some 20 years ago, clinical laboratories began setting up an accreditation system to guarantee and demonstrate the quality of their processes and the results of their tests. The Foundation for the Promotion of the Quality of Laboratory Work and the Accreditation of Laboratories in the Health Service (Coördinatie Commissie ter bevordering van de Kwaliteitsbeheersing op het gebied van Laboratoriumonderzoek in de Gezondheidszorg; CCKL) was initiated for this purpose. The [CCKL rules](#) require the implemented quality system to be laid down in a manual that briefly sets out the laboratory's activities and organization, procurement of resources, quality of the facilities, initial and subsequent training of staff, servicing and calibration of apparatus and equipment, and how results are reported. All this has to comply with ISO 15189, an international standard for laboratories. The CCKL explains how this applies to Dutch laboratories in its Practice Guide ([Praktijkrichtlijn](#)).

Even though accreditation is an option for both translational and basic science laboratories, the guidelines and rules can be a great aid when organizing your research efforts.

For more information: [www.cckl.nl](http://www.cckl.nl)

### 6.6 Examples of laboratory notebook guidelines

The following examples are taken from [www.bookfactory.com](http://www.bookfactory.com) and [www.vwr.com](http://www.vwr.com).

#### Introduction

Recording ideas, inventions, experimentation records, observations and all work details in a notebook is a vital part of any laboratory process. Careful attention to how you keep your notebook can have a positive impact on the patent outcome of a pending discovery or invention.

The following are some general recommendations to help you keep more efficient and accurate notebook entries. Remember, however, that these are simply a suggested set of guidelines. Only your attorney can supply the exact guidelines you should follow in order to satisfy specific legal requirements. That is why we recommend that you consult your legal counsel.

#### Recording data

Your notebook is a vital record of your work whether it is for patent purposes, legal records or documenting drug research under FDA guidelines. The notebook can help you prove:

- a. Exact details and dates of conception
- b. Details and dates of reduction to practice

- c. Diligence in reducing your invention to practice
- d. Details regarding the structure and operation of your invention
- e. Experimentation observations and results
- f. A chronological record of your work
- g. Other work details.

#### **Follow a few simple rules of thumb**

1. Always record entries legibly, neatly and in permanent ink.
2. Immediately enter into your notebook and date all original concepts, data and observations, using separate headings to differentiate each one.
3. Record all concepts, results, references and other information in a systematic and orderly manner. Language, charts and numbering systems should be maintained consistently throughout.
4. It is acceptable to make your entries brief. Always, however, include enough details for someone else to successfully duplicate the work you have recorded.
5. Label all figures and calculations.
6. Never, under any circumstances, remove pages from your notebook.

**Remember to treat your notebook as a legal document:** it records the chronological history of your activities. The following guidelines should help you maintain the consistent and accurate entries needed for future legal purposes.

1. Start entries at the top of the first page, and always make successive, dated entries, working your way to the bottom of the last page.
2. After completing a page, sign it before continuing to the next page.
3. Make sure that you record the date of each entry clearly and unambiguously.
4. Never let anyone other than yourself write in your notebook (excluding witness signatures, which are discussed later).
5. Never leave blank spaces, and never erase or remove material you have added. Simply draw lines through any blank spaces while you are making your entries.
6. Do not erase errors. Just draw a single line through any erroneous entry, and then add your initials. Enter the correct entry nearby.
7. You can supplement your entries with supporting material (e.g. test result printouts and other documentation). But you must permanently affix the material onto a page in its proper chronological location.
8. Never rely solely on any supplemental attachment. Always include your own entry describing the attachment and add any conclusions that you might draw from its substance.
9. Occasionally, secondary sources might be too large or inappropriate to attach directly to your notebook. In this case, you can add all secondary sources to an ancillary record maintained precisely for this purpose. However, always remember to write a description of these secondary sources, clearly and unambiguously, in your notebook.

#### **Documenting patent activities**

A primary purpose of a notebook is to document work that may be patentable. To support patent activities, it is necessary to provide clear, concise, chronological entries with specific dates. To rely on these dates, you must have at least one non-inventor corroborate that the events actually happened and that he/she understood your invention by signing and dating the 'Disclosed to and understood by' signature blocks.

Your notebook should help you document and prove:

1. *Conception date*—the date that you knew your invention would solve the problem.
2. *Date of reduction to practice* – the moment that you made a working embodiment of your invention.
3. *Diligence in reducing your invention to practice* – diligence refers to your intent and conscious effort to make a working embodiment. You are not required to rush, or even to take the most efficient development strategy. But your notebook must include details relating to your diligent activities. These are dates and facts that show the activities that you have conducted to reduce the invention to practice, and when such activities were conducted. Since you may still be diligent despite periods of not

working on reducing your invention to practice, always remember to provide reasonable explanations for these periods of inactivity by supplying facts relating to why there was no activity during the period in question. (e.g. unavailability of test conditions or equipment).

4. *How to make and use your invention* – provide sufficient details to teach a colleague how to make and use your invention.
5. *The best mode of practicing your invention* – document the best way to practice your invention.

A non-inventor colleague should corroborate each of these events/facts by signing the 'Disclosed to and understood by' blocks on the relevant pages.

## 7 RESEARCH DATA MANAGEMENT

### 7.1 Design

All research protocols must meet professional standards. Protocols that are subject to the [Medical Research Involving Human Subjects Act](#) (WMO) must be examined by the MEC of the AMC or the VUmc (<http://www.vumc.nl/afdelingen/METc/>); see also Chapter 5. All other protocols should be examined by an institutional or departmental committee of peers. Examination must be carried out prior to the actual conducting of the study.

### 7.2 Permissions, privacy and data protection

The collection of data for medical research is subject to both the Data Protection Act (Wet Bescherming Persoonsgegevens; [WBP](#)) and the Medical Contract Bill (Wet Geneeskundige Behandelingsovereenkomst; [WGBO](#)).

The WGBO does not require the patient's consent for research using data the researcher already has at his/her disposal in his/her capacity as practitioner, but it does require consent to supply patient information to other researchers (including examination by them of patients' medical records).

The WBP, however, requires the participant's explicit permission for the use of their data. This consent does not need to be in writing, but it must be explicit. For example, if a researcher presents a person with a questionnaire and the person completes the questionnaire and gives it back, the act of handing the questionnaire to the researcher grants the researcher permission to use the data. There are a few situations in which permission is not needed, for example if the request for consent would entail a heavy burden of mental stress for the data subject in view of the subjects' condition, or if a long period has elapsed between the treatment and the request for consent. An important factor when deciding if consent is required is whether the data are encoded in such a way that they reasonably cannot be traced to the patient by the researcher who receives them. These conditions are described in a Code of Conduct for the Use of Data in Health Research ([Code Goed Gedrag](#)), which was approved by the Dutch Data Protection Authority ([College Bescherming Persoonsgegevens](#)). It is now under revision and will be resubmitted to the Dutch Data Protection Authority in 2013. Consult a specialist, like the security and privacy (protection) officer of the AMC ([b.franken@amc.nl](mailto:b.franken@amc.nl)) or the VUmc ([michel.paardekooper@vumc.nl](mailto:michel.paardekooper@vumc.nl)), for guidance on these, sometimes complicated, situations.

The following principles are important:

- The results of data research must not be traceable to the subjects; direct or indirect reducibility to the natural person in publications is absolutely forbidden. This is only allowed with the written consent of the person.
- The infringement of subjects' privacy must be minimized. This means that, for instance, (a) information must not be collected from subjects if sufficient secondary data are available; (b) traceable data must not be used if the research could be carried out using anonymous data; and (c) if it is not possible to use anonymous data, encoded data must be used. Prior to data analysis, data must be converted into the least identifiable forms. Data that are not strictly necessary for answering the specific question should be removed from the analytical dataset. This must be done without losing the analytical value of the data. Examples are the conversion of birth dates to the age of a person, aggregation of data or reduced postcodes.

The whole process of data collection, processing and storage must be properly shielded. The relevant regulations can be found in the official guidelines of the [Data Protection Authority](#) (Richtsnoer beveiliging van Persoonsgegevens, CBP 2013). Practical guidelines can be

found in the [Quality Handbook of EMGO+](#), the Institute for Health and Care Research of the VUmc and the VU in Amsterdam. This electronic quality assurance handbook has been created to help researchers set up and conduct research on data. It covers the various stages of preparation, data collection, data processing, data analysis and archiving, and contains tips and examples.

The use of third parties in data collection, management and storage is only allowed when agreements are made between the AMC/VUmc and the third party (see Chapter 8). These contracts must fulfil the requirements of the Data Protection Authority.

### **7.3 Traceability and reproduction**

A study or research project must be well documented in order to meet the increasing demand for open and transparent research (see the reports [Zorgvuldig en integer omgaan met wetenschappelijke onderzoeksgegevens](#), KNAW 2012 and [Vertrouwen in de wetenschap](#), KNAW 2013). This means that:

- All important decisions must be documented in an understandable and accessible way. All decisions that affect the content or execution of a research project are important. Logbooks and notes of work meetings are key documents that allow these decisions to be retrieved.
- Study documentation should be filed in a clear way that makes it accessible to all team members who have the necessary authorization. Also, the study documentation should be filed under the AMC or VUmc backup regime.
- Raw data should be shielded against any changes and be available for later retrieval.
- The entire data management process, from data definitions (code book) to data collection, cleaning and transformation, must be well documented.
- Reported results must be reproducible for each AMC or VUmc author or co-author. This can be achieved by maintaining a good folder structure, clear file names and annotated data analysis. Also, agreements, including oral agreements, should be made between the project members, for example to hand a copy of the dataset, syntax and manuscript to the responsible principal investigator before submitting it for publication.

The [Quality Handbook of EMGO+](#) provides guidelines for documentation throughout the research process.

### **7.3 Data sharing**

Data from a research project may be made available to third parties, such as fellow researchers who might use the data for additional analysis and publications. Prior to the delivery of the anonymous data, however, an agreement must be made. The agreement should stipulate what the third party may and may not do with the data, and detail the arrangements regarding co-authorships and the safeguards against possible identification of research subjects.

## 8 RESEARCH COLLABORATIONS WITH THIRD PARTIES

### 8.1 Introduction

The AMC and the VUmc collaborate with a broad spectrum of partners, such as academic parties, industries, national governmental agencies, charities and the European Commission. Both UMCs encourage such collaborations as an important part of scientific research. Sharing experiences, knowledge and resources is crucial for advancing scientific knowledge and innovations.

These collaborations impose on the UMCs the task of carefully weighing the interests of their collaborating partners against their own academic teaching and research obligations, as well as the interests of their patients and of society. In all collaborations with third parties, conflicts of interest should be avoided. The general principles of research integrity, transparency and independence must be respected. It follows from this that collaborations with third parties should be open or controllable, that the research aim and questions should serve a scientific purpose, and that the methods applied and the results reported are truthful and timely rather than serving commercial or political interests.

### 8.2 Ruling principles

When one of the UMCs enters into research agreements with third parties, certain principles should be adhered to in order to safeguard academia's role and responsibility:

#### *1. Reasonable efforts*

Since the course of state-of-the-art research is by its nature unpredictable and research results are inherently uncertain, UMC research is generally conducted on a reasonable efforts basis, performed at a standard that is consistent with research at the UMC.

#### *2. Work plan*

This is by far the most important part of the agreement. The work plan is attached to the agreement as an appendix.

In drafting the plan, the parties must work together closely. The plan should have a section stating the project's scientific objectives. Each objective should be followed by a description of the methodologies and approaches to be used to address the scientific questions involved. Further, each objective must detail what each partner (the institute scientists and the company scientists) will be doing, both separately and collaboratively.

Another point to consider is to quantify the work that is to be done. It may not be necessary to quantify this exactly, but do insert general guidance about the size and scope of the research project.

Benchmarks are important to help measure work progress. They specify that at a certain point both parties expect certain data to have been generated, certain parts of the experiments to have been completed and/or certain questions to have been answered.

#### *3. Conflicting obligations*

The UMCs do not knowingly enter into research agreements that involve commitments and obligations that are in conflict with those accepted under other research agreements of the UMCs. Special procedures for dealing with actual or potential conflicts may, in appropriate cases, be included in research agreements. The UMCs do not, however, accept blanket provisions that preclude the principal investigator or the UMC from performing research for other sponsors in related areas.

#### *4. Publications*

Disseminating results through scientific publication is the way in which the UMCs fulfil their obligation to share research results with society. By publishing results, they can be tested by other researchers and, in the case of certain type of results, be applied in the medical treatment of patients. In addition, scientific publication through journals and conferences is important to the career prospects of all UMC researchers.

It is fundamental to the UMC that the scientific publication of results is guaranteed. On the other hand, there may be a need to protect sensitive information and intellectual property (IP) rights. Therefore, it is necessary to determine at an early stage of the negotiations how a proposed publication may be amended and how long it may be delayed in order to accommodate the needs of all parties. Delay should be for a reasonable period and in general not be longer than 90 days from first submission to the reviewing party (thus including the review period).

#### *5. Intellectual property and economic valorization*

It is important to verify whether it is necessary to give the contracting partners access to the UMC's existing know-how, materials and/or IP rights, and whether access can be granted and, if so, under what conditions. On the other hand, researchers must ensure that no IP right licensed to the UMC by a third party outside the scope of the project (including materials obtained under a MTA) will be used in the project without the third party's prior consent.

While the UMC customarily grants a royalty-free license to the sponsor to make internal use of any written reports and data that arise from the research project, in principle the UMC retains ownership of all inventions and discoveries arising from UMC-conducted research whether or not patentable (see also Chapter 7). The UMC will grant a sponsor a first right to negotiate a reasonable commercial license to use the technology arising from the research, which may include the right of the sponsor to obtain exclusive rights.

In appropriate cases, more favourable conditions may be agreed with respect to IP rights. Such agreements should always be negotiated in good faith between the parties and be based on current market conditions. The basic objectives of the UMC's IP policies are to promote the progress of science and technology, and to ensure that discoveries and inventions are utilized in ways that are most likely to benefit the public. Therefore, such agreements should contain clear anti-shelving clauses, that is, obligations to further develop the results created by the UMC. The UMC will always retain the right to use any results for research and educational purposes.

#### *6. Funding and pricing*

The UMCs' sponsored research projects are generally conducted on the basis of full cost recovery, including payment of indirect costs at the UMCs' established rate and IP fees. Prepayment or early payment may be necessary since the UMC does not utilize its working capital to finance large expenditures incurred in the course of sponsored research.

#### *7. Confidentiality*

The UMCs encourage open discussion and exchange of ideas. At times, however, it may be necessary to provide an umbrella of protection to preserve or maintain the confidentiality of disclosed information. This will then be arranged in a confidentiality agreement.

#### *8. Warranties, liability and risks*

The UMCs are generally unable to accept contractual provisions that establish rigid deadlines or deliverables, impose penalties for failure to progress at a certain pace, or provide for the withholding of payment if the sponsor is not satisfied with the results. The UMCs' research agreements will have express provisions disclaiming liability and indemnification obligations, including without limitation liability for sponsor business losses, such as lost profits.

### 8.3 Types of research agreements

Depending on the nature of the research and its scope, duration and degree of formality, tailored agreements are required to address the different needs of the parties. In general, six types of research collaborations with third parties can be distinguished. Each represents a step in a continuum from basic, curiosity-driven research to targeted, application-driven research.

- 1) Research grant
- 2) Collaborative research agreement
- 3) Sponsored research agreement
- 4) Research service agreement
- 5) Clinical research agreement
- 6) Consultancy/advisory agreement.

#### 8.3.1 Research grant

A research grant is a funding agreement typically focusing on basic, curiosity-driven research. Grants typically come from government or charity granting councils, but there are also industrial research grants. Especially research grants provided to consortia of research groups with commercial parties face complex financial, legal and intellectual property regulations.

Typical features:

- Research proposal and project control lies with the researcher.
- Rights to publish research results not restricted.
- Payment in advance or based/partly based on deliverables.
- Ownership of any intellectual property resides with the UMC.
- Granting body is provided with a copy of the final research report.

#### 8.3.2 Collaborative research agreement

Collaborative research agreements cover collaborative or joint research of mutual interest to the UMC and the collaborator. The research can be fundamental or applied in nature. This type of research arrangement is often co-funded by industry.

Typical features:

- Defined scope of work/research plan.
- Publication is not restricted, but the agreement generally allows the company to preview any publications prior to public disclosure in order to remove any confidential information or to allow for a reasonable delay for patent protection (90 days maximum).
- Payment may be made tied to milestones/deliverables.
- Background intellectual property and ownership are clearly defined. The UMC retains ownership of new intellectual property, although the sponsor is given rights to use results for non-commercial purposes and the sponsor is granted the option to acquire a license (on terms negotiated in good faith and appropriate to the industry sector).
- The UMC retains rights to use results for research and education (non-commercial) purposes.
- Termination provisions are included.
- Insurance and indemnification provisions are included to protect the UMC and the persons involved in the research (researchers, visiting scientists, students and interns).
- Indirect cost assessment varies according to the nature of the project and a reasonable compensation based upon market conditions for the use of UMC intellectual property needs to be paid by the sponsor to the UMC.



### 8.3.3 *Sponsored research agreement*

Sponsored research agreements cover well-defined research of specific interest to the sponsor. The research is performed solely by the UMC (no collaborative research) but the sponsor often has input or directs how the project is to be conducted. The project is usually initiated by the UMC but the sponsor provides a financial contribution to the UMC and/or provides access to the sponsor's proprietary IP rights, materials, software or other valuable background IP. The research is more often applied in nature and is directed at answering questions that are of interest to the sponsor. Sponsored research agreements have the same general terms as collaborative research agreements; however, there is more room for negotiation, particularly with respect to the ownership of research results and the financial contribution to be provided by the sponsor.

### 8.3.4 *Research services agreement (contract research)*

This is an agreement that facilitates the delivery of specialized services, the use of the institution's equipment and the reporting of results to the sponsor. The service provided by the UMC might include the testing, evaluation or analysis of materials owned by the sponsor. There is little or no research involved and the service seldom leads to publishable results. Therefore, a due balance of interest should be stipulated in the agreement. If the service encompasses advisory activities only, this may be a consulting agreement (see 8.3.6).

Typical features:

- Use of existing know-how and/or IP rights to provide the service.
- Use of UMC facilities, resources and time.
- Start and end dates of the project are defined.
- Payment can be made after the services are rendered or tied to deliverables; holdback often required.
- Service results are the property of the sponsor; UMC has the right to use the results for teaching and non-commercial research projects.
- The UMC owns any know-how it developed for or utilized in the provision of services.
- Insurance and indemnification provisions are included to protect the UMC and the persons involved in the research (researchers, visiting scientists, students and interns).
- Indirect cost assessment varies according to the nature of the project and a reasonable compensation based upon market conditions for the use of UMC intellectual property needs to be paid by the sponsor to UMC.

### 8.3.5 *Clinical trial agreements*

Clinical trials might be investigator initiated (sponsored by direct or indirect government funding or charities) or sponsored by for-profit parties. A clinical trial agreement (CTA) is a legally binding agreement that manages the relationship between the sponsor, which might be providing the study drug or device, and the UMC performing the clinical research project. CTAs can be industry initiated or UMC investigator initiated.

It is important to have a CTA in order to allocate risks, responsibilities, funds and obligations, and to protect academic, legal, intellectual property and integrity. For the general rules and regulations on clinical research, see Chapter 5.

### 8.3.6 *Consultancy agreement (advisory agreement)*

A consultancy agreement is a contract under which advisory activities are provided by UMC employees to third parties (e.g. participation in an advisory board). See section 12.4 about the rules on external employment (*nevenfuncties*) and the regulations in Article 9.3 of the Collective Agreement for University Medical Centres (CAO, 1 March 2011–1 April 2013).

## 8.4 Supporting agreements in research collaboration

Material transfer agreements (MTAs), confidentiality or non-disclosure agreements (NDAs) and visiting scientist agreements are supporting agreements that are designed to ensure protection of your research or to protect confidential information or materials shared with a third party.

### 8.4.1 *Material transfer agreements*

Biological materials can have substantial commercial value. Therefore, it is important not to provide such material to third parties unconditionally. A material transfer agreement (MTA) is a legal document that defines the basis upon which you transfer or obtain access to biological or chemical compounds (ranging from specific molecules – such as pharmaceuticals, nucleic acids or proteins – to biological research tools, such as cell cultures, cell lines, plasmids, transgenic plants or animals). The MTA controls the use of transferred materials when material is sent or received by UMC.

MTAs regulate the terms of material exchanges, in particular:

- What the recipient is allowed to do with the material.
- What the property situation is.
- Who is liable for damages.
- How to proceed in the case of publications and inventions.

Human material derived from patients may be transferred to academic collaborators under MTAs. The UMCs do not transfer human material derived from patients to companies under an MTA. If researchers want to set up a research collaboration involving human material derived from patients with a company, a collaborative research agreement is necessary

### 8.4.2 *Confidentiality agreements (non-disclosure agreements)*

Before entering into a collaboration, a level of trust between the parties must be established. This trust is the basis for a confidentiality agreement (CDA), which is often the first step in developing mutually advantageous relationships.

CDAs obligate the receiving party to keep the information confidential and thus enable the parties to discuss the outlines of the collaboration and to share information regarding project proposals, budgets and IP matters. A non-patented research discovery may be disclosed to another person, organization or company provided there is a CDA between the UMC and the organization/person to which/whom the invention is disclosed.

### 8.4.3 *Visiting scientist agreement*

A visiting scientist agreement is intended to safeguard the IP rights and duty of confidentiality with regard to confidential information for temporary scientific staff and scientific trainees (see also Chapter 7).

## 8.5 How to prepare for collaboration with third parties

All research agreements are executed by the executive board, which is authorized to sign agreements on behalf of the UMC. Any agreement should be signed in accordance with the institutional authorization procedures (*bevoegdheidsregeling*). Discussions between sponsor representatives and UMC researchers are preliminary only and no understandings or agreements are legally binding until reflected in a duly-executed written agreement. Researchers are therefore not entitled to be a party to such agreements.

When considering collaboration with third parties, researchers must ask themselves whether the research objectives and questions pertain to relevant and new medical/scientific insights. Regarding the research project itself, the researcher needs to verify that the performance of

the project and the commitments stipulated in the contract with the third party do not conflict with other commitments of the UMC that are already in place. A researcher who is to perform research that is part of a protocol drawn up by other people is still responsible. He/she must determine whether he/she agrees with all details of the intended research. Researchers are responsible for the analysis of data, even if this is done elsewhere, and must have insight into the manner in which the data are processed.

First draft agreements are often proposed by collaborators; however, to speed up and facilitate the process of research-related agreements, the UMCs' research contract and IP lawyers have developed template contracts which could be used as a starting point for the negotiations. [Innovation Exchange Amsterdam](#) (IXA, previously Technology Transfer Office TTO) will assist you with the preparation and with selecting the best contract model and negotiating your research collaboration. A business developer will collaborate with an internal research contract lawyer during the contract negotiations. To process agreements promptly, researchers will be requested to complete an agreement intake form that helps to determine what type of agreement, IP proposition and budget is best suited to the needs in a particular set of circumstances. Questions to be addressed include:

1. Who is the funding party?
2. What type of research will the project undertake?
3. Who contributed to the development of the protocol/research plan?
4. Is the funding sufficient to cover all costs related to the project?
5. Does the project conflict with other projects?
6. Is the focus of the project the testing or analysis of the sponsor's information, data, materials and/or IP rights ('background IP')?

## 9 OWNERSHIP AND VALORIZATION OF RESEARCH RESULTS

### 9.1 Introduction

Academic research is aimed at creating new knowledge, which can manifest itself in many ways, ranging from technological inventions and new methods, to social scientific insights. New knowledge is the basis for future research, education and responding to societal challenges such as the optimizing of healthcare. Specific laws and regulations are applicable to the ownership and commercial use of knowledge. Clear agreements about the availability and use of new knowledge are therefore of vital importance in enabling the UMCs to perform their principal tasks.

The AMC and the VUmc have adapted the NFU guideline [Naar een goede waarde](#) and have a separate set of IP regulations that are applicable to any person involved in research within the UMCs: for the VUmc [Regeling Kennis, Intellectueel Eigendom en Participatie](#) and for the AMC [Remuneration and incentive system](#). This chapter sets out general principles on intellectual property and the treatment of research findings. Please check your local intranet site for more information.

Innovation Exchange Amsterdam (IXA, previously Technology Transfer Office TTO) is the central point of contact for UMC inventors/ researchers who have questions regarding any aspect of economic valorization as well as for industry representatives and entrepreneurs who are interested in particular UMC technologies or in collaboration in general. Please check the [IXA website](#) for more information. IXA helps researchers to protect and exploit IP. Its services cover activities ranging from handling confidential disclosure agreements and material transfer agreements, the patenting of inventions, the management of IP, and negotiating research and licensing contracts with industry, to creating start-up companies based on UMC technologies.

### 9.2 Ownership of research results and IP rights

#### 9.2.1 Ownership of knowledge

Under Dutch law and internal regulations, all research results – including without limitation data, computer software, apps, computer databases, prototype devices, and biological materials (cell lines, plasmids, etc.) – developed by a UMC employee in the course of his/her employment are the property of the UMC. In addition, the UMC owns any IP rights in respect of the foregoing.

According to the Dutch Patent Act 1995, all inventions made by employees of universities and research institutes are owned by the employer, regardless of whether the invention is in a different field or made outside office hours. If an inventor works for multiple employers, it may be the case that the invention is jointly owned. In any case, partial employment of a UMC employee with another legal entity does not preclude ownership by the UMC, unless the UMC has specifically agreed otherwise with that other legal entity.

Employees are obliged in such cases to inform their employer of a potential invention at the earliest possible stage. The UMC also has the ownership rights to knowledge generated by academic staff working on projects with third parties. Clauses on IP rights and the use of IP are often an important element in contracts with external parties (see Chapter 8).

Individuals may have an association with the UMC other than being an employee, for example visiting academics and students (hereinafter 'academic visitors'). These academic visitors are required to transfer to the UMC any IP they create in the course of their activities as though they were UMC employees.

If research is subject to a contract with a third party, the parties can make specific arrangements about the ownership of IP (see Chapter 8).

Laboratory notebooks are essential in order to demonstrate how the invention came about (see Chapter 6). The UMC also needs to be prepared to have the research audited for quality assurance. All data should therefore be stored appropriately and be accessible to internal or external auditors. When a staff member leaves his/her employment at the UMC, the laboratory notebooks should be handed over to the head of department. In the case of a project that is externally funded, it can be agreed contractually that a copy of the data and the results is to be transferred to the funding party.

### 9.2.2 *Human material*

Following the donation of human material, the person donating his/her bodily material is no longer the legal owner: through the donation, the ownership is transferred to the UMC, which can use the material for scientific research in a certain field. Patients or healthy volunteers thus renounce their power of decision and potential financial revenues resulting from the research performed with their material. A certain say regarding their material is retained, however, such as the right to have the material destroyed if so wished, and the possibility for the donor to indicate that he/she does not want to be informed about individual research findings (right to 'not know'; however, this right can be overruled if the donor or a relative is at serious risk).

The primary use of human material at the UMC is scientific research, but it may also be transferred to third parties, provided that it is used in accordance with the objectives for which it was originally donated. For the transfer of human material to a third party, as a rule the UMC and the third party must have agreed on a collaborative project for which the transfer is required. Before any transfer can take place, a collaborative research agreement between the UMC and the recipient should be signed. The agreement should stipulate, for example, the subject of the collaboration and which party will own the results yielded by the collaborative project, and safeguard UMC's rights to use the human material for further research purposes. Obviously, all arrangements with third parties should be in accordance with applicable legislation on the use of human material, informed consent, privacy regulations, etc. Databases that contain data related to human material are also covered by the Copyright Act and/or Database Act.

Further details on the use of human material in research and the specific rules and regulations that apply are presented in Chapter 3.

## **9.3 Protection of knowledge**

It is essential to protect potential research results through the proper legal means (e.g. a patent) in order for new UMC technology to eventually benefit the patient. Due to the high costs associated with the development and marketing of, for example, a new drug or medical device, companies will only make such large investment if a temporary monopoly position through a patent can be obtained. Technologies that are not protected by a patent will therefore not be commercialized and consequently not reach the market or become available to patients. The way in which this knowledge will be protected, for example by applying for a patent or confidentiality agreement, depends on the nature of the knowledge or invention.

Premature disclosure of knowledge in the form of articles and publications, presentations at public events such as conferences, but also in discussions with non-employees in which the confidentiality is not safeguarded in advance in writing, seriously endangers the possibility of knowledge protection in the form of a patent. Prior to any disclosure it is therefore obligatory to verify whether it is wise to protect the knowledge. Once a patent has been applied for – which in most cases can be done within a period of a few weeks – the protected knowledge can be published in whatever form preferred.

#### 9.4 Patentable Inventions

In the course of his/her work, a researcher is confronted with various types of IP rights, for example patent rights, copyrights, rights in designs, database rights and trademarks. This chapter covers patentable inventions in general. More information can be found for VUmc in the [Regeling Kennis, Intellectueel Eigendom en Participatie](#) and for AMC in the [Remuneration and incentive system](#).

A patent is a form of IP. It consists of a set of exclusive rights granted by a sovereign state to an applicant for a limited period of time in exchange for the public disclosure of an invention. It is important to realize that a patent right is not a right that allows the applicant to perform the invention, but a right to prevent a third party from copying or using the invention without permission or from bringing the invention to the market (i.e. it provides monopoly rights). The period of protection afforded by a patent is generally 20 years.

As mentioned, bringing a new invention to the market is a costly and risky process, and companies will only be prepared to make the necessary investments if they are confident that they will be able to prevent others from copying the innovation and competing against them. A patent allows a company the time to recoup the costs associated with the design, development and marketing of the innovation (return on investment). Therefore, as an inventor interested in seeing your innovation become a product in the market, it is essential that it is properly protected. A successfully filed patent can represent a great financial and social value if there is a market for the product it describes. Thus, even if you are not interested in bringing an innovation to the market yourself, you should think of seeking protection for the benefit of patients and society in general and to capture the value the innovation may represent.

Patentable inventions include new processes, products, apparatuses, compositions of matter, and living organisms, or improvements to existing technology in those categories.

A process is a method of producing a useful result. A process can be an improvement on an existing system, a combination of old systems in a novel manner or a new use of a known process. A machine is an apparatus that performs a function and produces a definite result or effect. It can range from a simple device to a complicated combination of many parts. A manufacture is an article that is produced and has usefulness. Compositions of matter include chemical compounds, mixtures such as drugs and, more recently, living matter.

Abstract ideas, principles, and phenomena of nature cannot be patented.

What are the criteria for a valid patent? In Europe, as well as in most other territories outside Europe, patentability is determined by: 1) novelty, 2) industrial applicability and 3) inventive step:

1) Novelty: an invention is novel if nothing identical previously existed. How does your invention differ from what already exists?

2) Industrial applicability: an invention is useful if it produces an effect, if the effect is the one claimed and if the effect is desired by society, at least in principle. This criterion is considered met if an invention has at least one possible industrial use.

3) Inventive step: namely the degree to which an invention differs from the totality of previous knowledge, and the degree to which an invention could not have been anticipated from that knowledge. At the time it was conceived, why might your invention not have been obvious to people reasonably skilled in the field? Are there ways in which it might be an evolutionary step? What is the difference between the proposed invention and what previously existed?

#### 9.5 Valorization of research results

Intellectual property may lead to new products or processes for which a licence can be granted to a company or institution. In some cases, further development of the IP through a

limited spin-off company can be the preferred route. The choice between external licensing or setting up a spin-off company is determined by the question which of these routes to exploitation offers the best chance of a successful market introduction. [IXA](#) will assist researchers to ensure that the UMC's academic and commercial interests are safeguarded. Its staff has the knowledge and expertise to select the appropriate way for knowledge transfer and can help researchers to take the necessary formal steps.

If a company is interested in obtaining the right to use (license) certain UMC intellectual property, IXA will conduct negotiations regarding the conditions and a licensing agreement will be drawn up. In the process, certainty is provided that the knowledge can continue to be used for the UMC's own research and teaching. The licensing agreement will also contain a compensation arrangement. This may take the form of payments linked to concluding the agreement, achieving particular development objectives, income generated from sales of sub-licences, or a combination of these.

New entities such as foundations and companies that involve UMC knowledge, staff or resources can only be founded with the explicit approval of the executive board. It is not permitted in the context of subsidy applications or the acquisition of other resources to make any proposals or commitments relating to jointly (or otherwise) founding a new entity, without the abovementioned approval. If employees or others consider setting up a new company that will involve staff and knowledge or other IP of the UMC, approval has to be given in advance, both by the department concerned and by the executive board. If there is an intention to establish a spin-off company to commercially exploit UMC intellectual property, the executive board will make the final decision.

Revenues may be generated by licensing rights to results to market parties, or through the founding of a spin-off company that is based on the underlying technology. Taking into account the NFU guidelines and the UMC conflict of interest guidelines (see Chapter 12), such revenues will be divided according to the remuneration and incentive system, see for VUmc the [Regeling Kennis, Intellectueel Eigendom en Participatie](#) and for AMC the [Remuneration and incentive system](#).

## 10 THE RIGHT TO AUTHORSHIP

Publishing is the ultimate way of presenting the results of original scientific endeavours and discoveries to the outside world and thus contribute to the body of knowledge. Authorship is a researcher's main instrument to gain credit for scientific work, and it represents a benchmark for scientific status, sometimes with far-reaching personal implications.

This chapter is based on the uniform requirements for manuscripts submitted to biomedical journals drawn up by the International Committee of Medical Journals Editors ([ICMJE](#)). The AMC and the VUmc endorse these requirements. All persons designated as authors should fulfil the requirements for authorship, and all persons who fulfil the requirements for authorship should be offered authorship. Each author must have participated sufficiently in the project to be able to take responsibility for the content of the entire article. The term 'authorship' refers both to sole and first authorship, and to co-authorship.

### 10.1 Authorship

An 'author' is generally considered someone who has made substantive intellectual contributions to a published study, and authorship continues to have important academic, social and financial implications. An author must take responsibility for at least one component of the work, should be able to identify who is responsible for the other components, and should have no reason to doubt his/her co-authors' ability and integrity. Some journals request and publish information about the contributions of each person named as having participated in a submitted study, at least for original research. Editors are now strongly encouraged to develop and implement a policy on identifying who is responsible for the integrity of the work as a whole.

While contributorship and guarantorship policies obviously remove much of the ambiguity surrounding contributions, they leave unresolved the question of the quantity and quality of contribution that qualify the researcher for authorship. The right to authorship is based on whether each of the following three points applies:

1. Substantial contribution to at least one of the following:
  - conception and design
  - data acquisition
  - analysis and interpretation of data.
2. Drafting the manuscript or critically reviewing it.
3. Final approval of the version to be published.

Group authorship: when a large, multicentre group has conducted or contributed to the work, the group should identify those individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above. When submitting a manuscript authored by a group, the corresponding author (the author to whom correspondence relating to the manuscript should be directed) should clearly indicate the preferred author citation and identify all individual authors, as well as the group name. Journals generally list other members of the group in the acknowledgments or as collaborators.

It follows from the foregoing that:

- Acquisition of funding, collection of data or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be offered authorship.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.



- Intentionally and unjustifiably presenting oneself as author or co-author (guest or honorary authorship), or omitting qualified researchers (ghost authorship), qualifies as scientific misconduct (see also Chapter 14)

### **Types of authorship**

With respect to specific positions on the author list, there are interdisciplinary differences in the significance of the various positions. For the biomedical field, as well as several other fields, the following general guidance applies:

- **First author:** it is customary for the researcher who did the majority of the work and prepared the first version of the manuscript to be listed as the first author. If the first and second authors contributed equally, this should be mentioned in a footnote ('these authors contributed equally to this study'). In rare cases, a similar construction is used for last authors ('joint last authorship').
- **Last author:** the researcher who is most broadly involved in the successive components of the project (conception and design, data acquisition, and analysis and interpretation), and who has taken on most responsibilities with respect to supervision of the first author(s), is usually appointed as the last author. In other words, the last author is usually the person with the strongest role in the overall scientific conception and interpretation and organizational supervision of the project and the project members' scientific performance. This role is project related and not determined by 'seniority' or 'departmental hierarchy'.
- **Corresponding author:** the first author is usually also the corresponding author. There might, however, be good reasons to decide differently, for example if the first author will be leaving the group soon after publication.
- **Other authors:** the remaining authors are listed in order of contribution. In some cases, however, the order is based on other principles (e.g. it might be alphabetical or balancing authors from different contributing disciplines). The order in which the authors are listed should be a joint decision, in which the last author lists the final order after consulting all authors (see below). If there is disagreement with this decision, the last author decides after consulting the person who is formally in charge of the research line, or the head of the department.
- **Guarantors:** some journals now also request that one or more authors, referred to as guarantors, be identified as the persons who take responsibility for the integrity of the work as a whole, from inception to published article, and publish that information. If guarantors are mentioned, this has no consequences for the aforementioned requirements applying to other authors.

There are advantages in drawing up an agreement during the initial phase of the project that states how the list of authors is to be decided, and how changes are to be made once the actual contributions made by the co-authors are known. In practice, things may turn out differently from what was anticipated, so it is prudent to start out by designating a supervising researcher (principal investigator, usually the anticipated last author) involved in the project as responsible for deciding on any problems concerning authorship.

#### *Contributors listed in the acknowledgments or as collaborators*

Contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include a person who provided purely technical help or writing assistance, or a department chairperson who provided only general support. The corresponding author has to declare whether contributors had assistance with study design, data collection, data analysis and/or manuscript preparation. If such assistance was provided, the authors should disclose the identity of the individuals who provided this assistance and the entity that supported it in the published article. Financial and material support should also be acknowledged.

Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under such headings as 'collaborators', 'clinical investigators' or 'participating investigators'. Since their names are also displayed in, for example, PubMed, their function or contribution should be described (e.g. 'served as scientific advisors,' 'critically reviewed the study proposal,' 'collected data' or 'provided and cared for study patients'). As a reader could infer that they concur with the results and conclusions, all these people need to give written consent to being mentioned in the acknowledgements. It follows that along with the right to be mentioned goes a duty to accept mention, as is the case with authorship.

Financial and other substantial material support for the project should always be mentioned in the acknowledgements. In the case of experiments that involve humans, this is laid down in the Medical Research Involving Human Subjects Act ([Wet Medisch-wetenschappelijk Onderzoek met mensen; WMO](#)). This obligation also applies to the sponsorship of journal supplements that contain original or review articles. This prevents potential conflicts of interest (which do not occur when publishing in regular peer-reviewed issues of periodicals) being obscured. Sponsors and parties with whom sponsorship has been agreed (authors, editors of periodicals and others) have a mutual responsibility to mention this.

## **10.2 Professional considerations when preparing for publication**

Manuscripts should be prepared for publication by the research team in complete openness and in accordance with the agreements made. However, rules such as those outlined above cannot be written in stone. The system has flexibilities, as it should. In some cases, for example, first and last authorships may be shared (e.g. if two junior researchers performed most of the work together, or if one supervisor wrote the protocol and the other did much of the supervision).

Members of the group must not prepare separate publications without the prior consent of the other members. Any proposal to use the results of a project for special publications (e.g. theses) not envisaged at the start of the project should be put to the research team as a whole. Here again it is prudent to start out by designating a senior researcher to be responsible for resolving any conflicts.

## 11 DEALING WITH THE MEDIA

### 11.1 Introduction

Of all the sciences, biomedical research attracts the most attention from the press. This media interest undoubtedly has its benefits. By explaining the results of research in the media, scientists and their institutes are able to justify the spending of public and private funds. Favourable reporting can also speed up fund raising and, if it is sustained, give research institutes a reputation for solidity and expertise. In addition, the media are so influential in society that researchers' personal careers sometimes benefit from favourable media attention. These benefits are countered by risks that do not always make it easy to communicate the message in an undiluted form. The media increasingly represent an arena in which commercial interests play a major role.

#### Parties involved

When they are trying to attract publicity, researchers should realize that commercial or political interested parties are almost always dependent on the researchers' cooperation. This is what gives them the opportunity to communicate research findings independently and with integrity.

Major parties in the publicity surrounding scientific research are:

- Commercial companies
- Government/public sector
- Funding agencies
- Patients' organizations
- The media themselves.

#### *Commercial companies*

Pharmaceutical companies, biotechnology companies, suppliers of biomedical equipment and any other parties in the private sector (often operating internationally) utilize the results of scientific research in their marketing – and hence their commercial objectives. They try to generate and steer positive publicity for their products by, for example, approaching researchers and asking for their cooperation. This can include a variety of forms: from inviting researchers to collaborate on audio-visual productions of the company to asking for quotes for a press release.

The paradox is that scientists' contribution is requested because of their academic independence, while at the same time this independence could become compromised by their involvement.

#### *Government*

The public sector at the local, national and European level 'steers' the publicity about scientific research in the direction of political goals or policy principles that are not always explicitly formulated. Research results that are not consistent with those goals, can then be marginalized or left out.

#### *Funding agencies*

Government funds and charitable funds depend on political and societal support. This means that they have to substantiate their *raison d'être*. The results of research they sponsor are also used for their own profiling and branding.

#### *Patients' organizations*

Patients' organizations often rely on financial support from commercial companies that supply drugs or medical devices for the patient group. This puts the independence of such a patient organization at risk. Researchers who attract publicity together with patients or patients' organizations should keep this in mind.

## *Media*

The media themselves are not devoid of commercial self-interest. News is surprisingly often related to acquisition and the possibility to earn advertising revenue. The linking of advertising space and editorial coverage is common. Even such reputable scientific journals as *The Lancet*, *Science*, *The New England Journal of Medicine* and *Nature* bombard the media with weekly press releases in order to uphold their authority.

### **11.2 Conflicts of interest**

It should be stressed that the publicity interests of researchers and industry, government and funding agencies might coincide. If, however, a researcher's contribution to publicity statements becomes part of the marketing of third parties, scientists must always be vigilant. The scientific independence of both the researcher and the institution can be compromised by:

- One-sided presentations of scientific results, making them appear too rosy.
- The selective presentation of results.
- Stretching the implications of the results beyond the scope of the study.

#### *11.2.1 New media*

Researchers must take into account the institution's rules on the use of social media. Note that the laws on privacy, research and patient data also apply to publication through social media.

New media characteristically present information to the public without intermediaries. This involves some risks. News sites, blogs and social media accounts of opinion makers are not bound by, or do not always keep to the principles of fair journalism. Moreover, the dividing line between news and opinion is thin. If the integrity of a researcher or institution is questioned in these media, it is recommended not to react individually. Researchers can contact the department of communications for assistance.

#### *11.2.3 Rules and recommendations*

When they are trying to attract publicity, researchers should realize that there are pitfalls – and that 'personal attention' or 'public recognition of expertise' appeals to the ever-present vanity of scientists (who, after all, are humans).

The following guidelines will help to avoid publicity pitfalls. Special attention is paid to publicity in which industry plays a role. This is because, firstly, companies can often benefit from a very large marketing and PR machine. Second, because the relationship between the private sector and the healthcare sector is increasingly put under the magnifying glass of journalistic productions, and the relationship between science and commerce and the interests of scientists are the prominent themes.

By complying with the guidelines, conflicts of interest – and even the suggestion of non-transparent relationships between the UMC/the researcher and interested third parties – can be avoided.

**1. Publicizing your research, as well as contacts with the media about research, should always be done through the communication department** of the institute; this also applies to publicizing initial research outcomes on the internet and social media. The independent nature of the research is emphasized by the institute's seal of approval.

**2. The independent status of their institutes enables researchers to resist media pressure** from bodies that provide all or part of the funding. Examples of commercial influence are:

- A fully sponsored symposium related to a PhD thesis or a major publication, with the publicity in the hands of a commercial PR agency.

- Sending out press releases to speed up the registration of a drug or to facilitate the introduction of a young biotech company on the stock market.
- Loaning equipment on the condition that favourable publicity is generated.
- Funding the printing of a thesis or book in exchange for including the company logo, or printing special copies for customers and journalists.
- A sponsored meeting with media with expert opinions about a new treatment, product, drug or therapy.

In the case of government-commissioned research, researchers frequently find that the ministry or municipal authority, as the commissioning body, would like to arrange publicity itself. The golden rule here is to let the institute (i.e. the communication department) arrange the reporting or, in the case of an official presentation, at least demand the right to see and approve press releases before they are issued.

3. To avoid suspicion of conflict of interest, **researchers are not to feature in any media production** (whether AV, web or other) **created by a company** that is the manufacturer of the investigated product/therapy.

4. There should be **openness regarding the funding of research** unless it has been entirely funded from the institute's own research budget. Transparency can prevent suspicions arising and aspersions being cast. It is important to inform the communication department fully in this respect, not only to avoid undesirable publicity but also because charitable funds and research organizations – such as the Netherlands Organization for Scientific Research (NWO), the Netherlands Organisation on Health Research and Development (ZonMw), the Top Institute Pharma and the Center for Translational Molecular Medicine (CTMM) – insist on being mentioned so as to be accountable to the community for their expenditure.

5. **Popularizing expectations** about or the findings of research in a responsible way can entail risks. The media almost always gauge the importance of basic research in terms of potential clinical applications. Many a 'medical breakthrough' is broadcast into our living rooms because the researcher allowed him-/herself to be led more by exciting theoretical vistas than by the actual significance of his/her findings. A classic example is the scientist who, without beating about the bush, predicts that good results from in vitro or animal tests mean that the drug will probably be effective in humans. The same care is called for when presenting the results of clinical trials. Here, the danger of overgeneralization is more that of identifying over-large categories of patients who will potentially benefit from a new or modified form of diagnosis or therapy. Caution is always called for as regards the actual availability to patients of a new test or drug. In all these cases, the researcher should be acutely aware that overenthusiastic pronouncements can excite expectations among patients that cannot be met, resulting – understandably – in disappointment or anger.

6. Extreme caution is also called for when **interim findings** point to a successful outcome: there is a great temptation to release results prematurely. The urge to make positive noises halfway through may also be fuelled by uncertainty about the funding of follow-up research that has been identified. Researchers who anticipate their final results in situations of this kind are playing with fire: there are far too many documented cases where the final outcome was disappointing.

7. It may be advisable to **take the initiative yourself if it can be expected that the media will be interested** and if the research (findings or subject matter) could easily result in misunderstanding or touches upon a hot topic in society. In many such cases, an effective approach is to issue a press release in collaboration with the communication department (to 'set the tone') or to present the news in the institute's magazine, where there is more scope for careful argumentation.

8. **Premature publicity is undesirable** if an article on the project has already been offered to a scientific journal. The top journals in particular have strict rules on this, with sanctions that can go as far as refusal to publish the article or the issuing of a reprimand. Their regulations are not always clear, however, when it comes to taking part in conferences while the work is in progress or participating in promotional ceremonies prior to publication. Again, it is

advisable to contact the communication department, which in borderline cases can reach a firm agreement with the editor of the journal in question. Prior consultation may also be desirable if the article is mentioned in a press release on the forthcoming issue of the periodical; the point here is usually to set the precise date when the embargo expires.

**9. When using a press release or advertisement to recruit trial subjects, take care to describe the conditions accurately.** The phraseology is absolutely critical when it comes to describing the potential effects of the drug, especially in trials involving patients. Information about possible side effects and uncomfortable tests must not be veiled, and the likelihood of being assigned to a placebo group must be indicated clearly and the reasons stated. The publicity on these important points must tally completely with the research protocol. In the case of a multicentre trial not coordinated by the institute, the researcher is still responsible (also to the institute) for recruiting subjects correctly.

**10. Publishing in non-editorial (commercial) sections issued with newspapers is undesirable,** because they are produced and published by a commercial party, not under the responsibility of the editor-in-chief. They are in fact advertisements or the content is related to advertisements.

### 11.3 Epilogue

This chapter does not claim to be exhaustive: the situations that occur in contact with the media (including the internet) differ too widely. If questions about publicity arise that have not been dealt with here, please contact the department of communication.

Additional information:

[De regeling nevenwerkzaamheden AMC](#)

[De Gedragscode Integriteit AMC](#)

[Richtlijn Gunstbetoon door bedrijven \(NFU\)](#)

The AMC's communication department can be contacted directly during office hours (020–566 2421). Outside office hours, it can be contacted through the switchboard (020–566 9111).

Additional information VUmc:

Regeling omgaan met de media (VUmc)

<http://intranet.vumc.nl/27557/39299/7561455/Mediarichtlijn-volledig>

Richtlijn social media (VUmc) <http://intranet.vumc.nl/afdelingen/dienst/communicatie/social-media/richtlijn-vumc-social-media/richtlijn-social-media/#selected>

Regeling nevenwerkzaamheden (VUmc)

<http://intranet.vumc.nl/direct/arbeidsvoorwaarden/nevenwerkzaamheden/meldennevenwerk/mh/>

The VUmc communication department can be contacted directly during office hours (020–444 3444). Outside office hours, it can be contacted through the switchboard (020–444 4330)

## 12 CONFLICTS OF INTEREST

### 12.1 Introduction<sup>5</sup>

Members of the research staff are expected to apply the knowledge and expertise for which they were appointed in the interest of their institute, namely the AMC and the VUmc, respectively. They need to guard against conflicts of interest, as defined below. Lack of independence can result in substandard science, damage the reputation of the researcher and that of his/her research group, reduce transparency and diminish the institute's standing, and ultimately even adversely affect patient care. The increasing need to acquire external funding and the significant interests that the funding bodies have in the research carried out at academic medical centres can jeopardize researchers' independence. The AMC and the VUmc endorse the [Code for the prevention of improper influence due to conflicts of interest](#). This chapter discusses the principles and procedures in situations where conflicts of interest might arise, specifically when collaborating with external parties and when working under external employment.

### 12.2 Definition

A conflict of interest occurs when researchers or their institutes have financial or personal ties with other persons or organizations that influence their work. The extent of this influence ranges from negligible to very substantial. Financial relationships (such as appointments, consultancies, stock ownership, fees, paid advice) are the sources of conflict of interest that are the easiest to identify and the most likely to undermine credibility. A conflict of interest can sometimes exist without the researcher being aware of it.

Conflicts of interest are often associated with the interests of pharmaceutical companies, but they can also stem from personal relationships, academic competition and intellectual passion. Research sponsored by the government, semi-governmental bodies or other funding agencies can also give rise to conflicts of interest. Examples of situations that may give rise to conflicts of interest are given below.

### 12.3 Collaboration with commercial parties

The AMC and the VUmc advocate that, whenever feasible, the results of scientific research be rapidly converted into new diagnostic and therapeutic tools in order to allow patients to benefit from innovations as soon as possible. This usually involves a process that necessitates collaboration with commercial companies – and this is where the danger of conflict of interest arises. The collaboration may in no way cast doubt on the independence of the research performed at the AMC/VUmc. Such doubt threatens the academic careers of individual researchers, who could be barred from publishing in leading journals or not considered for particular forms of funding. In addition, funding bodies sometimes demand transparency on potential conflicts of interest of researchers applying for grants. The arrangements that can be made to safeguard independence when setting the research question, gathering and analysing data, and publishing the results of research in collaboration with external funding bodies are described in Chapter 8. See also the brochure [Naar een goede waarde](#) of the Netherlands Federation of University Medical Centres (NFU) and the [Richtlijn Gunstbetoon door bedrijven \(NFU\)](#). Financial relations between medical doctors working at UMCs and commercial parties can be consulted at the [Transparantieregister](#).

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<sup>5</sup> References for this chapter:

Online disclosure of physician–industry relationships. Perspective, *N Engl J Med*, 360, 2009, 325-327.

Sponsorship, authorship, accountability. Editorial, *N Engl J Med*, 345, 2001, 825-827.

## 12.4 External employment

Article 9.3 of the Collective Agreement for University Medical Centres ([CAO, 1 March 2011 - 1 April 2013](#)) includes rules on external employment (*nevenfuncties*) that apply to all employees covered by the CAO. External employment, remunerated or otherwise, is not permitted if these external duties are incompatible with the employee's responsibilities at the AMC/VUmc or could interfere with the interest or reputation of AMC/VUmc. The CAO therefore contains rules that require external employment to be reported, and in specific cases makes it subject to explicit approval by the executive board (see below). Further information on the application of the rules on external employment can be obtained from the business manager of the division or department, and from CAO article 9.3.

Article 9.3 of the CAO for University Medical Centres stipulates the rules that the parties to the CAO have agreed upon concerning the external activities of staff of teaching hospitals:

1. Employees do not require the employer's prior consent to accept or perform external activities, unless those activities could affect the interests of the university medical centre (UMC) and/or the proper performance of their job.
2. The employer shall grant permission to perform external activities if in its opinion the performance of those external activities cannot damage the interests of the UMC and/or affect the proper performance of the job. If it is in the interests of the UMC, the employer may agree to allow employees to perform their external activities wholly or partially during their working hours.
3. The employer shall grant permission for a fixed period or for an indefinite period and may attach further conditions to its consent. The employer may stipulate the condition that the employee must pay all or part of the income that he earns from external activities to the employer. This condition may be stipulated for income that exceeds €2,200 a year and is earned from activities that follow from the employee's job at the UMC.
4. The employer may withdraw the permission that has been granted if it considers that the circumstances under which the permission was granted have changed.
5. If it emerges that an employee is performing or has performed external activities without the permission required by virtue of the first paragraph, the employer shall still give the employee the opportunity to request the necessary permission. If the permission is not granted, the employer may, without prejudice to the provisions of Article 11.1 (dereliction of duty), instruct the employee to cease the activities and/or pay the income earned to the employer.
6. In consultation with the works council, the employer may lay down further rules for the administrative implementation of the provisions of this article.

### [De regeling nevenwerkzaamheden AMC](#)

De regeling nevenwerkzaamheden VUmc\*

## 12.5 Procedures for reporting potential conflicts of interest

Based upon the guidelines of the Netherlands Federation of University Medical Centres ([Nederlandse Federatie van Universitair Medische Centra; NFU](#)), the AMC and the VUmc have established the following procedures to handle potential conflicts of interest.

### • *Provide transparency*

In order to safeguard the independent position of the researcher and the standing of the AMC and the VUmc as research institutes, researchers should report any external employment that might lead to conflicts, including financial ones, of interest to their head of department or division, and disclose it on their personal page on the '[Who is Who](#)' section of the AMC's website or via the department website of VUmc (<http://www.vumc.nl/afdelingen/afdelingen-themas/>). They should also report the agencies that fund their research on this page. Although disclosure itself does not eliminate bias or conflicts of interest, it can make financial



relationships widely known and be used as a starting point for asking questions. Those who participate in the scientific process must clarify any relationships they have that could potentially give rise to a conflict of interest. This applies not only to situations where there is a demonstrable conflict of interest, but also to situations that could create that impression.

- *Discuss the matter during the annual interview*

Potential conflicts of interests must be an item during the annual interview (*jaargesprek*) between the researcher and his/her head of department or division. If there is any doubt whether there is a potential conflict of interest, the researcher must report this to the business manager of the division (*directeur bedrijfsvoering*).

- *Report to business manager*

Researchers are required to report immediately to the business manager of their division if they believe they might be caught up in a conflict of interest or are exposed to potentially conflicting interests outside the institute. The business manager will inform the head of the department of all such notifications. The examples given below of situations that could entail a conflict of interest can be used as a checklist.

The notification may be discussed with the legal advisor to the executive board, if appropriate. The researcher will be consulted as to how the situation can best be dealt with. The researcher can also initiate consultations of this kind. The executive board may decide to publish notifications. Both the notification and any approval granted by the executive board are recorded in the employee's personnel file. If no such notification is received, it will be assumed that there is no potential conflict of interest and that the employee can prove this if necessary.

## **12.6 Examples of situations that may give rise to conflicts of interest**

The [Association of American Medical Colleges](#) provides the following examples of situations that may give rise to conflicts of interest

### **Situations that may increase the potential for bias in research**

- Undertaking basic or clinical research when the investigator or the investigator's immediate family has a financial, managerial or ownership interest in the sponsoring company or in the company producing the drug/device under evaluation.
- Accepting gratuities or special favours from research sponsors.
- Entering into a consultancy arrangement with an organization or individual that/who has an economic interest in related research. Situations that may invoke inappropriate use of institutional assets and resources in research.
- Using students or employees of the institute to perform services for a company in which a faculty member has an ownership interest or from which he/she receives any type of remuneration.
- Unreimbursed or unauthorized use of institutional resources (e.g. equipment, supplies or facilities) for personal purposes or to support the activities of an independent entity in which an investigator holds a financial or other interest.
- Associating one's name or one's work with the institution in such a way as to profit monetarily by trading on the reputation or goodwill of the university or hospital, rather than on one's professional competence.

### **Situations that may lead to inappropriate use of information**

- Unauthorized use of privileged information acquired in connection with one's professional responsibilities.

- Accepting support for basic or clinical research under terms and conditions that require results to be kept confidential, unpublished or significantly delayed in publication.
- Providing privileged access to information that was developed with university resources or supported by independent sponsors to an entity in which the faculty member has a financial interest.

**Situations that may lead to self-dealing**

- Purchasing equipment, instruments or supplies for research or teaching from a firm in which the faculty member has a financial or other interest.
- Influencing the negotiation of contracts between the academic institution and external organizations with which a faculty has a financial interest or other relationship.
- Requiring or recommending one's own textbook or other teaching aids.

## 13 CAREFUL REVIEWING OF RESEARCH PROPOSALS AND MANUSCRIPTS

Reviewing research proposals and manuscripts is an important component of a researcher's work. This chapter discusses the principles and procedures in situations where conflicts of interest might arise when reviewing other researchers' grant proposals and manuscripts. A reviewer's verdicts on articles, research proposals and grant applications can have serious consequences. It is important, therefore, that these appraisals show high technical quality, respect and independence. The ownership of ideas and confidentiality should always be safeguarded.

### • *Factual quality*

In order to guarantee factual quality, observe the following guidelines.

- If one feels that one does not, on the whole, possess the expertise required to make a sound judgement on a manuscript or proposal offered for review, it is better to refuse the request.
- It is a good idea to begin a review with a concise summary of the research question, design and main findings. This shows that the reviewer has understood them properly.
- Any criticism should be factually correct; when in doubt, one should either refrain from making a judgement or check with the experts or in the literature. In such cases, one can state that one is not an expert on certain matters and therefore cannot make a judgement.
- Make any comments as specific as possible and clearly indicate what the authors should address or change.
- It helps the authors if the comments are backed by references to the literature.
- If the report or proposal sets out to test a hypothesis or principle that one does not agree with, be careful to use only scientific arguments.
- Clearly distinguish between matters of taste and scientific inaccuracies.

### • *Respect*

- Before submitting, the reviewer should read the review from the recipient's perspective.
- The authors or researchers will find it more useful to receive positive feedback as well as negative criticism. Mention the strong points of the reported or proposed project.
- If there are serious, fundamental shortcomings, there is not much point in criticizing details.
- The tone of the review should not be scathing: even negative criticism can be phrased constructively. Remember that it is the reported work that is under review, not the researcher, so it is not appropriate to demolish him/her personally; that criticism can be phrased as a belief; and that criticism could be phrased as a question.
- Suggestions for improvement will help the author to make a better job of his/her next manuscript or proposal.

### • *Ownership of ideas*

- It is only natural to acquire new ideas from the work one reviews, but it is wrong to take ideas from research proposals and present them as one's own.
- It is fraudulent to give a negative verdict on the proposal so that the grant-giving body will reject it and you will have more chance of being the first to come up with an answer to the question.

### • *Confidentiality*

- It is inappropriate to talk to outsiders about the content and/or quality of the reviewed work or about the authors. This is one reason why manuscripts submitted for review are sometimes presented anonymously. Even where the authors are anonymous one

may occasionally have a good hunch as to their identity or background; however, their confidentiality should be respected.

- Reviewers who need to contact the authors can do so through the organization requesting the review.

- *The worst case: suspicion of fraud*

There may be a suspicion of fraud, for example if the same article by the same authors has been published elsewhere (dual publication) or if plagiarism is suspected. A reviewer may also have the impression that the reported data are incorrect. It is in the interest of scholarship to inform the editor of the journal or the scientific advisory board of the grant-giving body about such suspicions and to do so in a detailed manner.

- *Independence/conflict of interest*

Participants in the research or the research team should turn down a request to review a manuscript reporting that research, as there is a conflict of interest. If the work is by a competing research team it is even more important to examine whether one's judgement is impartial. When reviewing grant applications, similar rules apply and reviewers are frequently requested to explicitly report on potential conflicts of interest to the granting organization (see [Gedragcode belangenverstrengeling NWO](#)). In such cases, one would be disqualified from being either a reviewer or a member of a granting committee, specifically for applications where such conflict of interest applies. Examples are:

- Prejudice (either positive or negative) towards the applicant; this includes family relationships, personal friendship, and previous personal or professional conflicts.
- Being an applicant or co-applicant or being involved in the writing of a competing application in the same reviewing round.
- Economic benefit following from the granting or rejection of an application.
- Professional involvement with an applicant, for example being the applicant's supervisor or co-supervisor, being a collaborator on research projects and publications in the previous three years, or being a direct colleague or supervisor of the applicant within a department or larger organizational entity (research school, faculty).

## 14 SCIENTIFIC MISCONDUCT AND HOW TO PREVENT IT

### 14.1 Introduction

*Research integrity requires honesty in presenting goals and intentions, in reporting methods and procedures and in conveying interpretations. Research must be reliable and its communication fair and full. Objectivity requires facts capable of proof, and transparency in the handling of data. Researchers should be independent and impartial and communication with other researchers and with the public should be open and honest. All researchers have a duty of care for the humans, animals, the environment or the objects that they study. They must show fairness in providing references and giving credit for the work of others and must show responsibility for future generations in their supervision of young scientists and scholars. [European Code of Conduct for Research Integrity, 2011](#).*

The basic premise for scientific research is indeed honesty. Or, as Schuyt puts it most simply: 'Do not lie, do not steal.'<sup>6</sup> Yet, unfortunately, scientific misconduct does occur. Scientific misconduct has large negative consequences, firstly for science itself. Results have to be trustworthy for science to have the possibility to advance our knowledge. Similarly, scientific misconduct has negative consequences for its users, patients and society. They have to be able to trust the methods followed and the results obtained. Especially in biomedical research, misconduct may result in damage to patients' health and to healthcare in general. Also, fellow researchers need to be certain of the absence of misconduct, as misconduct would render impossible both cooperation and progress. Likewise, institutions must be sure that the research conducted in their name is trustworthy. They must be able to present an image that is worthy of support and grants. Finally, for individual researchers there are enormous risks connected to committing fraud. Even though in the short run their embellished output and increased funding may have advantages, the long-term consequences can be disastrous, as was recently shown by several cases of misconduct in, for example, the Netherlands.<sup>7</sup>

At the same time, independence in research is under growing pressure as a result of external factors: the increasing need to publish and the researchers' dependence on external funding. Individual researchers may also be driven by internal factors such as a desire to be the first and to produce positive results. This may make them overlook the need to be careful and to respect the process and the time needed to conduct good studies. Therefore, in this chapter we more extensively explain the general principles of what scientific misconduct entails and what can be done to prevent it.

Research misconduct may appear in many guises. The major forms of misconduct are:<sup>8</sup>

1. *Fabrication* – making up results and recording them as though they were real.
2. *Falsification* – manipulating research processes or changing or omitting data.
3. *Plagiarism* – appropriating other people's material without giving proper credit.

Other forms of misconduct include:

- Failure to meet clear ethical and legal requirements, such as misrepresentation of interests, breach of confidentiality, lack of informed consent and abuse of research subjects or materials.

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<sup>6</sup> [Kees Schuyt, Hypothese \(NWO\), 2013, pp. 08–11](#)

<sup>7</sup> Such as the cases of Prof. D. Stapel (University of Tilburg) and Prof. D. Poldermans (Erasmus University). See also Simonsohn U. Science 2012; 337:21; Simonsohn U. The data detective. Interview by Ed Yong. Nature. 2012;487(7405):18-9.

<sup>8</sup> European Code of Conduct for Research Integrity, 2011 ([www.esf.org](http://www.esf.org)).

- Improper dealing with infringements, such as attempts to cover up misconduct and reprisals on whistle-blowers.

More specifically, Dutch Universities (VSNU, 2012) have stated in their [Code of Conduct for Scientific Practice](#) that scientific misconduct extends at least to the following:

1. Falsifying data
2. Entering fictional data
3. Secretly omitting unfavourable results
4. Deliberately misusing statistical methods to achieve conclusions other than those justified by the data
5. Deliberately interpreting results and conclusions falsely
6. Plagiarizing results or other authors' publications
7. Pretending to be an author or co-author
8. Deliberately ignoring or not recognizing the contribution of other authors
9. Failing to exercise due care when conducting research.

Dishonesty or a lack of integrity can pertain to the research itself, to the dissemination of scientific findings by publication (including reports, applications and articles), to reviewing, and to applications for funding and jobs. Scientific misconduct can relate to all stages of research.

## 14.2 Fraud in different stages of research

### Planning of the research:

1. Presuming the research question is scientifically driven while it is actually based on commercial or political interests, namely the interests of those granting the study.
2. Using other people's ideas in research proposals and applications for funding without permission and/or citation.
3. Making up data or pilot data for research proposals and applications for funding.
4. Consciously omitting relevant knowledge from research proposals and applications for funding.

### Data collection:

1. Fabrication of data.
2. Adding fictitious data.
3. Wholly or partly failing to observe the inclusion and exclusion criteria in the protocol.
4. Infringing the privacy of persons (patients as well as healthy subjects) taking part in the research.

### Analysis:

1. Massaging data to produce better results; adding and discarding data.
2. Selective and unreported omission of unwanted data (e.g. outliers) and results.
3. Improper use of statistical techniques to produce more desirable conclusions.
4. Distorted interpretation of data or distorted conclusions.

### Reporting:

1. Incorrect or distorted representation of other people's findings (misquotation).
2. Intentionally and unjustifiably presenting oneself as author/co-author (guest or honorary authorship) and leaving out qualified researchers (ghost authorship).
3. Intentional and unjustifiable referencing.
4. Failing to acknowledge other people's original observations (under-citation).
5. Exaggerated self-citation to inflate one's own citation index (even citing one's non-existent papers).
6. Plagiarism; self-plagiarism and slothing (copying of sentences without referencing)
7. Untrue mention of other information (e.g. CCMO/MEC or DEC permission; granting body; untrue acknowledgement).

### Submission for publication:

1. Unreported multiple submissions or publications.
2. Duplicate and redundant publications ('salami publication').
3. Unreported conflict of interest.
4. Unwarranted waiting for or omitting of reporting to serve commercial or political interests.

### 14.3 Fraud in judging others

#### Colleagues:

Colleagues are favourably or unfavourably judged on something other than scientific arguments.

#### Reviewing of articles and applications for grants:

1. Reviewing of manuscripts or grant applications in which one has too much interest (e.g. manuscripts written by friends or enemies, or grant applications from researchers whose work is too close to one's own field of research).
2. Stealing of original ideas by reviewers or editors.

### 14.4 Preventing fraud

Although there will always be persons who commit serious scientific misconduct for their own reasons, measures can be taken and a culture can be created in which misconduct is less likely to occur. Such measures can be divided into activities on an individual, a departmental and an institutional level. Here, we limit ourselves to the individual and the departmental or research programme level.

The basic premises of research integrity are transparency and independence. Of these, transparency is most likely to be influenced by the measures taken. At the same time, a culture in which the importance of research integrity is explicit and evident is also important. Measures can thus be promoted to stimulate a culture of decent scientific thinking and behaviour.

#### *1. Individual researchers*

An individual researcher should be aware of the high demands involved in science: carefulness, precision, readiness to be accountable. The individual researcher is ultimately responsible for the behaviour related to doing research, be it the design, data collection, data storage or result reporting.<sup>9</sup> The researcher should always keep in mind that everything he/she does should be amenable to an open discussion. If not – that is, if one believes that something is better not seen or heard – one should not proceed, but should start thinking about what is at stake and perhaps discuss the issue with others.

1. To be transparent, it is crucial that steps taken and decisions made are well documented. By doing this, the process of argumentation can be properly reconstructed afterwards. Moreover, data, arguments and decision should be documented in such a manner that they can be found and understood by others. It must be remembered that data and lab notebooks are the institute's property. Thus, they should be properly stored in a safe place. Also, the archiving of data should be transparent; that is, not only the data itself but also the ways of coding should be well documented (see Chapters 5, 6 and 7).
2. Research is usually not an isolated activity, and even if it is, it is important to organize collaboration and feedback. In this way, unclear actions and irregularities can be discovered more easily. Organize regular feedback. Discuss dilemmas with peers and supervisors in time. Realize that the ultimate aim is not competition but the progression of science and knowledge.

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<sup>9</sup> [Schuyt et al., \*Zorgvuldig en integer omgaan met wetenschappelijke gegevens\*. KNAW, Amsterdam, 2012](#)

## *II. The level of department or research programme*

At the level of the department or research programme, it is possible to create a culture in which science flourishes in a transparent manner. The heads of departments and leaders of research lines are responsible for organizing the working environment in such manner that adequate scientific thinking and behaviour is stimulated. Two issues are crucial: a safe environment and continuous attention to careful handling of the scientific endeavour.

1. A safe environment is helpful for scientists to be able to discuss dilemmas and possible errors. Young people especially should feel free to ask questions and express their concerns. This is possible only when the culture is such that doubts and temporary lesser performance are allowed and the pressure on people is not too heavy. Therefore, leaders of research lines or programmes are responsible for fruitful and honest scientific exchange within their research groups. Indeed, most important is the fair play of all collaborators involved.
2. The best safeguards against fraud are cooperation between researchers, mutual evaluation of research, and a policy on publication that includes a thorough, independent peer review.
3. Programme leaders can encourage cooperation among researchers by organizing a project team to do the research and internal reporting. Thorough discussions help prevent fraud.
4. Although there may be a clear division of labour within a project team, it is important for the team to work as a unit when deciding how the data are to be collected, assessed and interpreted, and how the results are to be reported. Regular in-group reporting/discussions, with the responsible leader as organizer, are essential. Regular checks of one another and mutual feedback reduce the risk of fraud. Isolated individuals are more prone to scientific misconduct due to the lack of social control. This also applies to reporting: proper supervision and feedback to ensure that the rules on citing other authors are observed prevent plagiarism. In other words, good mentorship also reduces the likelihood of misconduct.
5. Many research projects (especially those of larger research groups and consortia) have a steering committee in addition to the project team. Again, the risk of fraud is reduced if the progress of the project is discussed and the results are presented to the steering committee, and possibly outsiders, on a regular basis. The work done by staff members of research steering committees contributes substantially to the quality and integrity of the research as a whole, even if it does not immediately produce publication points for individual members of staff.
6. Regular audits of individual studies can be organized within the research group. See for example the audit procedures described in the [Quality Handbook of EMGO+](#).
7. The leaders of research lines or research programmes should introduce all PhD students to the rules of good scientific conduct. The mentors should discuss these issues at the start of a contract. Courses that deal with aspects of integrity can be taken by the PhD students elsewhere. Obviously, good scientific conduct and the occurrence and dangers of misconduct can also be discussed within research teams.

On scientific misconduct, see also <http://ori.hhs.gov/TheLab/TheLab.shtml>



## 15 WHEN SCIENTISTS GO ASTRAY

The executive boards of the AMC and the VUmc aim to prevent and, if necessary, correct scientific misconduct. For the independent judgement of possible allegations, they have appointed an ombudsman for scientific integrity who is independent of the board. This chapter describes the procedures taken when scientific misconduct is suspected. It is important to note that anyone suspecting scientific misconduct by persons involved in scientific research at one of the medical centres can report this to the [Ombudsman for Scientific Integrity](#) or <http://intranet/afdelingen/dienst/raadvanbestuur/7188274/> for the VUmc. The ombudsman will look into the matter in consultation with the plaintiff (whistle-blower) to see whether the suspicion is justified. The procedures to be followed will depend on the seriousness of the case and its consequences, legal and otherwise.

### The ombudsman's position

The ombudsman for scientific integrity holds an independent position. His/her tasks and the modus operandi are elaborated below.

- It is the ombudsman's task to investigate allegations of suspected scientific misconduct lodged against persons involved in scientific research at one of the medical centres, namely employees and external employees working under the responsibility of the medical centre (AMC or VUmc). In principle, anyone within or outside the medical centre who suspects scientific misconduct can inform the institute's ombudsman.

### Reports

- A report may relate to an AMC or VUmc employee who is involved in scientific research or to an external employee who is involved in scientific research under the responsibility of an AMC or VUmc employee.
- Reports may only relate to incidents or acts that took place no more than 5 years previously.

### Accountability and evaluation

The ombudsman makes an annual report to be presented to the dean, describing in an anonymous form the numbers and nature of the reports of all cases presented and the action(s) taken. The dean sends this report to the Works Council ('[Ondernemingsraad](#)') or <http://intranet/afdelingen/orgaan/OR/> for the VUmc to be discussed confidentially. The dean discusses the annual report with the UMC's supervisory board.

### Procedure in the event of alleged scientific misconduct

General principles are the following:

- The ombudsman judges scientific conduct in line with this Research Code. The ombudsman can ask advice from the integrity committee. As a next step, experts from within or outside the medical centre can be asked to give advice or become members of an ad hoc research integrity committee. If deemed necessary, a legal advisor may also be approached. The ombudsman reports his/her judgment to the dean, that is, his/her opinion on whether scientific misconduct has occurred and, if so, to what extent it is to be considered serious. The dean then arrives at a verdict based on the ombudsman's report and his own judgment concerning the alleged misconduct. The verdict may affect the legal position of employees. The dean reports his verdict within a reasonable time period.
- The ombudsman observes maximum care and confidentiality with respect to both the whistle-blower and the person(s) to whom the report relates.
- The whistle-blower, the person(s) to whom the report relates and any person assisting in any way the work of the ombudsman treat the matter and the findings as strictly confidential unless exempted therefrom by the board.

- All AMC/VUmc employees must assist with any investigation by the ombudsman immediately upon being asked to do so.

If a suspicion is reported to the ombudsman, the following steps are generally undertaken:

- 1) If the ombudsman decides not to investigate the allegation, he/she informs, in writing, the whistle-blower and the person against whom the allegation has been made. This decision is recorded in the ombudsman's annual report. If the whistle-blower does not accept this decision, he/she can inform the ombudsman of this in writing. The ombudsman may, after consultation, decide that further investigation is indeed desirable.
- 2) If the indications are sufficient to warrant a prima facie suspicion of misconduct, the ombudsman takes action.
- 3) In general, as a first step the ombudsman then hears both parties. He/she decides whether misconduct is likely to have occurred.
- 4) If so, the ombudsman decides whether an agreement between both parties might be reached. If possible, the ombudsman supports efforts to reach such an agreement. If agreement is reached, the case will be described as minor in the annual report.
- 5) If agreement is not reached, the whistle-blower presents his/her allegations to the ombudsman in writing, or the allegations are set down in writing by the whistle-blower and the ombudsman jointly. The allegations should be clear and succinct.
- 6) In cases of suspected serious misconduct, the ombudsman may decide that the allegation requires further investigation. Actions will then be taken depending on the nature of the allegation and on the circumstances. The ombudsman decides on a procedure that fits within the framework of the Research Code. This procedure is communicated to all parties involved.
- 7) If deemed necessary, the ombudsman may discuss the allegation with the members of the integrity committee. This committee may again hear both parties. On the basis of the collected written evidence, and possibly a hearing, it is decided whether there is sufficient reason to suspect scientific misconduct, which would require further investigation.
- 8) The ombudsman informs the dean and may suggest seeking advice from external experts or forming an ad hoc research integrity committee consisting of experts from within or outside the medical centre and, if deemed useful, a legal advisor. The dean nominates the committee, including a secretary. Depending on the seriousness of the case and the nature of the committee, the ombudsman can be advisor to or chair of the committee.
- 9) The ad hoc research integrity committee can meet separately with the whistle-blower(s) and the person(s) to whom the report relates. If required, other experts may be invited to attend a meeting. The minutes of the hearing pertaining to each party may be read by the relevant party, who may request the correction of any factual errors.
- 10) The investigation instituted by the ad hoc research integrity committee results in a written report, which includes the committee's conclusion whether scientific misconduct has occurred and, if so, to what extent such misconduct is considered serious. The ombudsman sends this report to the dean. Depending on the local situation (i.e. the AMC or the VUmc regulations), the ombudsman sends the final report either to the dean or to the dean and the parties involved.

- 11) The dean then arrives at a verdict and informs the ombudsman, the whistle-blower and the accused party. The final report is recorded in an anonymous form in the ombudsman's annual report.

Procedure for appeal

- If either the whistle-blower or the person accused of scientific misconduct disagrees with the dean's verdict, he/she can inform the dean of such, in writing, and express his/her motivated complaint about the verdict.
- If the dean agrees with the complaint, he can conduct a new, independent investigation into the alleged scientific misconduct.
- If the complaint is not honoured by the dean, either the whistle-blower or the person accused of scientific misconduct can request an investigation by the National Body for Scientific Integrity ([Landelijke Organisatie voor Wetenschappelijke Integriteit, LOWI](#)), a committee installed by the KNAW, VSNU and NWO (Royal Academy of Arts and Sciences, Association of Universities in the Netherlands, and Netherlands Organization for Scientific Research).
- The LOWI judges whether the procedure followed by the medical centre was justified and correctly executed. The LOWI procedure can be found on the [LOWI website](#).

Internet references	
European Code of Conduct for Research Integrity	<a href="http://www.esf.org">www.esf.org</a>
UvA doctorate regulations	<a href="http://www.uva.nl/en/research/phd/procedure">www.uva.nl/en/research/phd/procedure</a>
VUmc doctorate regulations	<a href="http://www.vu.nl/nl/Images/Promotiereglement">www.vu.nl/nl/Images/Promotiereglement</a>
Informatie over proefpersonen METc VUmc Research protocol	<a href="http://www.vumc.nl/afdelingen/METc/wmo-beoordeling/indiening/pif_oordeel/">www.vumc.nl/afdelingen/METc/wmo-beoordeling/indiening/pif_oordeel/</a>
Experiments on Animals Act	<a href="http://www.wetten.overheid.nl">www.wetten.overheid.nl</a>
Food and Consumer Product Safety Authority	<a href="http://www.vwa.nl">www.vwa.nl</a>
Experiments on animals, AMC	Intranet/research
Experiments on animals, VUmc	<a href="http://www.vu.nl/nl/over-de-vu/profiel-en-missie/uitgelicht/proefdieren/index.asp">www.vu.nl/nl/over-de-vu/profiel-en-missie/uitgelicht/proefdieren/index.asp</a>
Research involving human subjects	<a href="http://www.ccmo.nl">www.ccmo.nl</a>
European Union Drug Regulating Authorities Clinical Trials	<a href="http://www.eudract.ema.europa.eu/">www.eudract.ema.europa.eu/</a>
Good clinical practice (GCP)	<a href="http://www.ccmo-online.nl">www.ccmo-online.nl</a>
EU good manufacturing practice (GMP)	<a href="http://www.ec.europa.eu/health/giles/eudralex/vol-4/2009_06_annex13.pdf">www.ec.europa.eu/health/giles/eudralex/vol-4/2009_06_annex13.pdf</a>
College ter beoordeling van Geneesmiddelen	<a href="http://www.cbg-meb.nl">www.cbg-meb.nl</a>
European Medicines Agency (EMA)	<a href="http://www.ema.europa.eu/ema/">www.ema.europa.eu/ema/</a>
International Committee of Medical Journal Editors (ICMJE)	<a href="http://www.icmje.org">www.icmje.org</a>
Netherlands Trial Register	<a href="http://www.trialregister.nl/trialreg/index.asp">www.trialregister.nl/trialreg/index.asp</a>
Clinicaltrials.gov	<a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a>
Current controlled trials	<a href="http://www.controlled-trials.com">www.controlled-trials.com</a>
NFU guidelines	<a href="http://www.nfu.nl">www.nfu.nl</a>
Guidelines for health research reporting	<a href="http://www.equator-netwerk.cog/resouce-centre/library-fo-health-research-reporting">www.equator-netwerk.cog/resouce-centre/library-fo-health-research-reporting</a>
BROK course, AMC	<a href="http://www.amc.nl/web/onderwijs/PhD/PhD-Course-Program/BROL.htm">www.amc.nl/web/onderwijs/PhD/PhD-Course-Program/BROL.htm</a>

BROK course, VUmc	<a href="http://www.VUmc.com/branch/internalmedicine-cru/qualityassurancecru/brokcourseVUmc">www.VUmc.com/branch/internalmedicine-cru/qualityassurancecru/brokcourseVUmc</a>
CRU	<a href="http://www.amc-cru.nl/welkom.aspx">www.amc-cru.nl/welkom.aspx</a> <a href="http://www.elearningbiostatistics.com">www.elearningbiostatistics.com</a>
CRB	Intranet VUmc <a href="http://intranet/afdelingen/thema/crb/">http://intranet/afdelingen/thema/crb/</a>
Radioactive material	<a href="http://www.agentschapnl.nl">www.agentschapnl.nl</a>
Genetically modified organisms	<a href="http://www.rivm.nl">www.rivm.nl</a>
Laboratory animals	<a href="http://www.minvws.nl">www.minvws.nl</a>
General information on applicable laws and acts	<a href="http://www.rijksoverheid.nl">www.rijksoverheid.nl</a>
Laboratory notebooks	<a href="http://www.vwr.com">www.vwr.com</a> <a href="http://www.bookfactory.com">www.bookfactory.com</a>
Electronic laboratory notebooks	<a href="http://www.labarchives.com/index/php">www.labarchives.com/index/php</a> <a href="http://download.cnet.com/iPad-ELN/3000-2654_4-10901569.html">http://download.cnet.com/iPad-ELN/3000-2654_4-10901569.html</a> <a href="http://www.cambridgesoft.com">www.cambridgesoft.com</a>
Coördinatie Commissie ter bevordering van de Kwaliteitsbeheersing op het gebied van laboratoriumonderzoek in de Gezondheidszorg	<a href="http://www.cckl.nl">www.cckl.nl</a>
Preparing for publication	<a href="http://www.icmje.org/ethical_1author.html">www.icmje.org/ethical_1author.html</a>
Regeling Omgaan met de media	<a href="http://intranet.vumc.nl/27557/39299/7561455/Mediarichtlijn-volledig">http://intranet.vumc.nl/27557/39299/7561455/Mediarichtlijn-volledig</a>
Richtlijn social media, VUmc	<a href="http://intranet.vumc.nl/afdelingen/dienst/communicatie/social-media/richtlijn-vumc-social-media#selected">http://intranet.vumc.nl/afdelingen/dienst/communicatie/social-media/richtlijn-vumc-social-media#selected</a>
Regeling nevenwerkzaamheden, VUmc	<a href="http://intranet.vumc.nl/direct/arbeidsvoorwaarden/nevenwerkzaamheden/">http://intranet.vumc.nl/direct/arbeidsvoorwaarden/nevenwerkzaamheden/</a>
Scientific misconduct	<a href="http://ori.hhs.gov/TheLab/TheLab.shtml">http://ori.hhs.gov/TheLab/TheLab.shtml</a>
Ombudsman for Scientific Integrity, VUmc	<a href="http://intranet/afdelingen/dienst/raadvanbestuur/7188274/">http://intranet/afdelingen/dienst/raadvanbestuur/7188274/</a>
Ondernemingsraad, VUmc	<a href="http://intranet/afdelingen/orgaan/OR/">http://intranet/afdelingen/orgaan/OR/</a>
Transparantieregister	<a href="http://transparantieregister.brabers.nl/nl-NL/Home">http://transparantieregister.brabers.nl/nl-NL/Home</a>
Code of practice	<a href="http://www.proefdierkunde.nl/nl">http://www.proefdierkunde.nl/nl</a>
ToetsingOnline	<a href="https://www.toetsingonline.nl/">https://www.toetsingonline.nl/</a>

Code for the prevention  
of improper influence  
due to conflicts of  
interest

[https://www.knaw.nl/shared/resources/actueel/publicaties/pdf/code\\_digitaal\\_2012\\_e](https://www.knaw.nl/shared/resources/actueel/publicaties/pdf/code_digitaal_2012_e)

## Abbreviations

ESF	European Science Foundation
OBP	Opleidings- en Begeleidingsplan
WMO	Wet Medisch-wetenschappelijk Onderzoek
MEC	Medical Ethics Committee
CCMO	Centrale Commissie Mensgebonden Onderzoek
WGBO	Wet Geneeskundige Behandelingsovereenkomst
WBP	Wet Bescherming Persoonsgegevens
GW	Geneesmiddelen Wet
Wet BIG	Wet Beroepen in de Gezondheidszorg
KWZ	Kwaliteitswet Zorginstellingen
WoD	Wet op de Dierproeven
NVWA	Nederlandse Voedsel en Warenautoriteit
DSMB	Data and safety monitoring board
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good clinical practice
IMP	Investigational medicinal product
EU-GMP	European Union good manufacturing practice
IMPD	Investigational medicinal product dossier
CBG	College ter Beoordeling van Geneesmiddelen
EMA	European Medicines Agency
ICMJE	International Committee of Medical Journal Editors
NFU	Nederlandse Federatie van Universitair Medische Centra
CRB	Clinical Research Bureau (VUmc)
CRU	Clinical Research Unit (AMC)
SOP	Standard operating procedure
CCKL	Coördinatie Commissie ter bevordering van de Kwaliteitsbeheersing op het gebied van Laboratoriumonderzoek in de Gezondheidszorg
AAMC	Association of American Medical Colleges

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