

Research Code

University Medical Center Groningen

Basic principles for
medical-scientific
research

July 2007



university of
groningen



umcg

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Colophon

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Foreword

In recent decades, scientific research has grown explosively. The importance of this research to society has also grown. The number of sponsored studies is increasing, external funding bodies want to control the results or the interpretation of the results, and the general public wants to be informed about new scientific developments. As a result, there is increasing pressure to publish and to achieve positive results. And because funding must often be obtained in competitive frameworks, the competition between scientists is increasing.

Due to these factors, the carefulness and independence of scientific research can be threatened. To prevent this and to preserve scientific integrity, the Board of Directors of the UMCG has drawn up a Research Code. The UMCG Research Code provides researchers and their supervisors with guidelines for conducting biomedical research in a correct and ethical fashion. The relevant councils – *CliëntenRaad Academische Ziekenhuizen (CRAZ)*, *the Stafconvent* and *the Onderzoek- en Onderwijsraad (O&O-raad)* – have responded positively to the Research Code.

All UMCG employees who conduct research at the UMCG or elsewhere in the world are expected to be familiar with the Code and to act in accordance with its rules of conduct. For third parties, such as clients, sponsors, patient organizations, politicians and societal organizations, the Research Code provides insight into the basic principles that the UMCG applies to its biomedical research.

The UMCG is grateful to the AMC for providing access to its own Research Code, which has served as the basis for the UMCG Research Code. We would also like to express our appreciation to the UMCG Research Code Committee for its work on the Code. A great deal of effort has been required to convert the Research Code from a printed document into a dynamic guideline that applies not only to research, but also to education and training.

The Board of Directors hopes that the common rules in this Research Code will make it possible for UMCG researchers to maintain their independence, and thereby their scientific integrity.

We wish you a great deal of success in this process!

Sincerely,
on behalf of the Board of Directors,

drs. L.C. Bruggeman, Chair

1. Background and aim

The University Medical Center Groningen (UMCG) is a leading center of medical research. The central tasks of the UMCG are patient care, scientific research and education/training; these three core tasks are inseparably bound to each other. Within the UMCG, research is conducted into the causes of disease and the application of acquired knowledge to patient care (including advanced clinical care). This research also takes place in close cooperation with the University of Groningen. This makes the UMCG an inspiring and stimulating working environment.

Every year, the American Office of Research Integrity publishes a report on scientific misconduct; in 2005, there were 114 new misconduct reports. Recent international cases of scientific misconduct and conflicts of interest (Seoul National University, Norwegian Radium Hospital, Alder Hey Children's Hospital, National Institutes of Health, University of Tokyo) indicate that the current system is not entirely failsafe. In addition, there is increasing competition for scarce means at the national and international levels. Extra funding (hundreds of millions of euros) has recently been allocated within a competitive framework to large public-private consortiums. These developments underline the need for clear rules and controls, i.e. a research code. The UMCG has therefore set down the basic principles for conducting medical research in the UMCG Research Code. During this process, the UMCG has gratefully made use of the AMC Research Code¹. The UMCG Research Code went into force on 1 January 2007. This Research Code frequently refers to codes of conduct and legislation drafted in the Dutch language; an inherent limitation for the English reader.

The research code applies to all individuals who are involved in research within the UMCG as well as staff of the UMCG who are involved in medical research elsewhere in the world. Although students (with or without scholarships) do not have an employment relationship with the UMCG, they are also expected to conduct their research activities in accordance with this code. In addition, the research code is intended to allow third parties, such as clients, sponsors, politicians, and social and patient organizations, to become acquainted with the principles that are applied by the UMCG when conducting medical research.

To a large extent, the UMCG Research Code is a "code about codes", or a metacode. This means that there are a number of de facto limitations, such as substantive discrepancies between underlying codes, readability for various target groups, consequences of new or amended legislation, new codes or codes of conduct², regulations, guidelines that have not yet been included in the UMCG Research Code, etc. Up-to-date and easily accessible information about these topics is crucial. In this regard, the UMCG Research Code Committee has been established under the leadership and responsibility of the Vice Dean of Research. This committee is responsible, among other things, for the keeping the research code up-to-date. The latest version of the UMCG Research Code is available at <http://www.rug.nl/umcg/onderzoek/research>.

2. Basic principles for biomedical research at the UMCG

In 2004, the Association of Universities in the Netherlands (VSNU) published the Netherlands Code of Conduct for Scientific Practice. This Code of Conduct³ formulates and elaborates on five principles. It describes the

¹ URL <http://www.amc.uva.nl/index.cfm?sid=84>

² In 2006, ZonMW implemented a Conflicts of Interest Code (Code belangenverstrengeling) for its evaluation procedures. URL <http://www.zonmw.nl> search for < belangenverstrengeling >

In 2006, the NWO implemented a Code of Conduct regarding conflicts of interest in research programming.

URL <http://www.nwo.nl> search for < gedragscode belangenverstrengeling >

³ <http://www.vsnu.nl>

desired behavior of researchers and has been applied by universities since 1 January 2005. It is not only important for the researchers themselves to take these principles into account, but also for the reputation of the institution⁴.

The five principles are the following:

1. *Due care*: Scientific activities are performed with due care, unaffected by mounting pressure to achieve.
2. *Reliability*: The reputation of science as being reliable is confirmed and enhanced through the conduct of every scientist. A scientist is reliable in performing and reporting on his or her research, and equally reliable in transferring knowledge through teaching and publication.
3. *Verifiability*: Presented information is verifiable. Whenever research results are publicized, it is made clear what the data and the conclusions are based on, where they were derived from and how they can be verified.
4. *Impartiality*: In his or her scientific activities, the scientist heeds no other interest than the scientific interest. In this respect, he or she is always prepared to account for his or her actions. In cases involving medical research with people, the interest of the patient must also be carefully considered.
5. *Independence*: Scientists operate in a context of academic liberty and independence. Insofar as restrictions of that liberty are inevitable, these are clearly stated.

3. Good mentorship⁵

Research is often done by junior researchers. This group comprises individuals with a wide range of functions, such as interns, students, analysts, PhD students (trainee research assistants, scholarship students, AIOS⁶/AGIKOs, medical PhD students) postdocs and university lecturers, all working under the supervision of a more experienced researcher (postgraduate or staff member) and ultimately under a professor. Supervising junior researchers properly is an important part of good scholarship, partly because they often depend on their supervisors. Within the UMCG, the relationship between supervisors and junior researchers is not only regulated in the graduate school, but also outside this environment, such as in the clinic, research centers, research facilities and laboratories. The tasks and responsibilities in these relationships are described below.

3.1 Duties of the supervisor

The duties of someone supervising a junior researcher can broadly be summarized under four headings:

- training the junior researcher;
- making the junior researcher enthusiastic and showing real interest in his/her work;
- helping to give concrete shape to the junior researcher's work;
- supervising the junior researcher with appropriate intensity and respect.

Here are some points for a supervisor to remember when performing these duties:

1. The supervisor should ensure that the junior researcher's proposed work is based on a well-defined plan. This may take widely differing forms, depending on the stage the research project (or module) has reached. A workplan may cover developing an idea, drafting a research protocol, doing a survey of

⁴ In this context, reference is made to "regulations to protect the integrity both real and perceived of the finest institution of the world". Bill Pearce, Dept. of Health and Human Services (HHS), Genetic Engineering News, April 2005 on integrity and the FDA.

⁵ Source: AMC Research Code.

⁶ The term AIOS was introduced in 2005 and stands for "physicians in training as a medical specialist"; this position was previously known as AGIO (assistant physician in training). See the NFU *visiedocument* "OOR-zaak en gevolg" (October 2005). URL http://www.nfu.nl/fileadmin/documents/NFU_Oorzaak.pdf

- the literature, performing experiments or collecting data, analyzing data which has already been gathered, or preparing an article or lecture.
2. The goal of the partnership between the junior researcher and supervisor should be clear and explicitly agreed to. This can be to produce a thesis, article, report or lecture. In some cases the ultimate goal is simply to do part of the research for a project.
 3. The supervisor should ensure that adequate facilities and appropriate backup are available to the junior researcher in accordance with the regulations⁷ (e.g. good clinical practice (GCP), good laboratory practice (GLP), good manufacturing practice (GMP), regulations of the coordinating committee to promote quality assurance of laboratory research involving health care (CCKL), etc.). This concerns not only facilities in the physical sense, but also the assistance of other staff with relevant expertise, inside and outside the department (if necessary).
 4. The junior researcher can expect regular help, advice on and support for his/her research work. These can be provided at scheduled times, but there should also be scope for ad hoc consultation in the event of unexpected developments.
 5. The intensity and form of the supervision may vary widely depending on the people involved. It should be based on the junior researcher's level and approach. For example, the mentorship given to a novice research may well differ in form and intensity from that given to a PhD student in the last stage of his/her research. In the clinical setting, the interest of the patient should also be considered when supervising the junior researcher.
 6. Regular consultation about the progress of the junior researcher's research work will be provided. Besides discussion about research progress, there should also be scope for consultation in the event of unexpected problems. The next steps in the research may also be discussed at these consultations. There should also be regular consultations on progress in terms of achieving the ultimate goal of the partnership (see 2), e.g. producing the thesis⁸. The consultations should preferably result in specific agreements on short-term goals, and if necessary medium-term goals.
 7. The junior researcher should have as much access as possible to the supervisor. He or she must make time available for providing proper, critical feedback. This includes returning corrected manuscripts, reports and other work written by the junior researcher within an acceptable period of time.
 8. The junior researcher and supervisor should hold a performance appraisal interview at least once a year during which they have an opportunity to review each other's performance as junior researcher and supervisor.
 9. In the case of doctoral research, before the junior researcher starts work, the supervisor should, if possible, offer the junior researcher a concrete, phased plan of study that will enable him or her to explore and study a somewhat broader field than that covered by the project itself. The plan of study should take into account any special requirements the junior researcher may have.

⁷ For example, the GCP Directive 2005/28/EG, 8 April 2005 of the European Parliament;

URL http://europa.eu.int/eur-lex/lex/LexUriServ/site/en/oj/2005/l_091/l_09120050409en00130019.pdf

⁸ In accordance with the Higher Education and Research Act (October 1992), the Executive Board has established the Regulations of the Conferral of a Doctorate, which arrange matters involved the preparation for and conferral of a doctorate. Article 8 of the Regulations of the Conferral of a Doctorate state that the promoter supervises the doctoral student and provides regular consultations as well as ensuring the correct procedures involving the thesis and doctoral conferral. A new Higher Education and Research Act is currently being addressed in Parliament.

URL <http://www.rug.nl/bureau/expertisecentra/abjz/abjz/producten/index>

10. The supervisor and the junior researcher should reach proper agreement on the publication of research findings and/or their presentation in lecture form. Authorship⁹ is a particularly important issue, so it is advisable to reach explicit agreement on this in advance.
11. Irrespective of the hierarchical relationship between them, the supervisor and junior researcher should both maintain an open and critical attitude towards the academic goals as originally formulated by the supervisor, and 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 original hypotheses, goals and plans should be revised.

3.2 Responsibilities of parties involved in research

An overview of the responsibilities of the various parties involved in scientific research is given below. Although different responsibilities can be allocated to different parties, in many cases this may concern the same individual. The following parties are distinguished: researcher and junior researcher, project supervisor, project leader, PhD supervisor and director of the graduate school.

1. The researcher bears primary responsibility for:
 - a. conducting the research with care;
 - b. checking for errors;
 - c. handling data correctly (e.g. not omitting or falsifying data);
 - d. taking due care when dealing with patients and laboratory animals and their data, and observing the applicable rules;
 - e. correct reporting.
2. The project supervisor bears primary responsibility for:
 - a. day-to-day supervision of the researcher: in other words he or she must be available on a more or less daily basis;
 - b. on-the-spot checking that the research is conducted with care;
 - c. on-the-spot monitoring of the progress of the research.
3. The project leader is primarily responsible for:
 - a. the quality of the research topic, design, analysis and reporting;
 - b. a coherent research program for the line of research;
 - c. monitoring the progress of the line of research;
 - d. quality assurance policy;
 - e. the training of researchers and career policy;
 - f. checking that claims to authorship are justified.
4. The PhD supervisor is responsible for making sure that:
 - a. the thesis is of sufficient quality to merit defense.
5. The director of the corresponding graduate school is responsible for:
 - a. the study process and the total course of study followed by the junior researcher.
6. The human subject¹⁰
 - a. Recruitment: during recruitment, test subjects will be treated with respect.

⁹ Various institutions, scientific associations and periodicals have developed guidelines for authorship. The International Committee of Medical Journal Editors describes the minimum requirements for authorship as follows: "Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3. Source: Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication; updated February 2006.
URL <http://www.icmje.org/#author>

¹⁰ In scientific research, *Het Handboek Patiëntenparticipatie* – the Patient Participation Handbook – (2006) offers background information about the rights of patients who are involved in scientific research.
URL: http://www.zonmw.nl/fileadmin/cm/nieuws/documenten/handboek_pp_.pdf

- b. Agreements: agreements with human subjects involved in medical-scientific research will be complied with.
- c. Informative materials: in cases where there is informative material and/or reports for the human subjects, these will be written in an understandable fashion.
- d. The human subject has access to an independent physician¹¹ for any questions about the research.
- e. For children, the Patient Information Leaflet concerning the presented research protocol will be tested separately based on a modified standard operating procedure of the Medical Ethical Committee (METc). In addition, the METc will ensure that the children as well as their legal representatives can refer their questions to the treating physician and/or researcher. Human subjects younger than 12 will be informed orally in an appropriate fashion. The above procedures are generally in accordance with the "minimum requirements for Patient Information Leaflet" as proposed by the Vereniging Kind en Ziekenhuis (Child and Hospital Association)¹².

4. Scientific integrity

In 2001, the Royal Netherlands Academy of Arts and Sciences (KNAW), the Association of Universities in the Netherlands (VSNU) and the Netherlands Organization for Scientific Research (NWO) collectively published the "Notitie Wetenschappelijke Integriteit" (Report on Scientific Integrity)¹³. Scientists from various disciplines often have different mores; as a result, a detailed factual and normative description of scientific research that applies to all disciplines cannot be given. A transparent operational method is the most important collective starting point in this regard. The report gives the following examples of violations of scientific integrity:

- obtaining research commissions or funding through deception (feigning expertise, deliberately misrepresenting previous results and/or creating false expectations);
- falsifying data obtained from literature research, observation or experiment;
- selectively providing results, especially disregarding undesired results;
- presenting fictional data as the results of observations or experiments;
- intentionally applying statistical methods incorrectly to achieve other conclusions than those justified by the data;
- incorrectly interpreting the results and conclusions of research, either deliberately or due to negligence;
- plagiarizing the publications of other researchers by not citing the source of the text or the research results;
- encouraging the incorrect interpretation of research results by the media due to careless conduct;
- improperly approaching colleagues and subordinates with the aim of influencing their research results;
- deliberately conveying the results and research reports of others in an incorrect or biased fashion or pretending to be the author or co-author of an article without having contributed significantly to the design or implementation of the reported research or to the interpretation and description of the methods and findings;
- during publication, omitting the names of co-authors that made a significant contribution to the

¹¹ The WMO (Medical Research Act) stipulates that in every study an independent physician must be available for questions (orally or in writing) from human subjects. The Central Committee on Research Involving Human Subjects (CCMO) has established a subcommittee to improve the quality of patient information, including extensive attention for the role of the independent physician in relation to the human subject. The State Secretary has expressed the intention (TK 29 963, progress report resulting from the evaluation of the WMO, letter from the State Secretary VWS, 25 October 2006) to more clearly establish the role of the independent physician by making an amendment to the Act.

¹² URL http://www.kindenziekenhuis.nl/content_118.asp

¹³ *Notitie Wetenschappelijke Integriteit, over normen van wetenschappelijk onderzoek en een landelijk orgaan voor Wetenschappelijke Integriteit*. KNAW, NWO en Vereniging van Universiteiten (VSNU) ISBN 90-6984-335-8. URL <http://www.knaw.nl/publicaties/pdf/20011082.pdf>

- research, or presenting individuals as authors or co-authors who did not contribute to the research, or contributed insufficiently;
- carelessly conducting research yourself, having careless research conducted by others or omitting actions with which carelessness could come to light;
- disregarding established rules of conduct with respect to dealing with data and human subjects;
- copying experimental designs or software without permission.

4.1 Forms of fraud and plagiarism¹⁴

The pressure on scientists, for example to publish, to save a line of research or to ensure financing, can lead to the temptation to present research results as better than they are, to make them up or to plagiarize them.

Examples of fraud and plagiarism are listed below:

Research

- misleading applications for grant aid or job applications;
- making up data;
- adding fictitious data;
- wholly or partly failing to observe the inclusion and exclusion criteria in the protocol;
- selective and unreported omission of unwanted results.

Reporting

- distorted interpretation of data or distorted conclusions;
- manipulating data to obtain better results;
- improper use of statistical techniques to produce different conclusions;
- incorrect or distorted representation of other people's findings (misquotation), failing to acknowledge other people's original observations (under-citation);
- exaggerated self-citation to artificially enlarge one's own index of citations.

Submission for publication

- unreported multiple submission or publication;
- unreported offer or publication, where the sample size increases with each subsequent publication and new data are repeatedly added to previously published data, and where the results do not change;
- unreported conflict of interest.

Criticism of articles¹⁵

- use of original ideas by abstractors or editors.

Published literature

- plagiarism of results, parts of articles or whole articles;
- misquotation and under-citation (see Reporting).

¹⁴ Source: AMC Research Code

¹⁵ In 2005, the World Association of Medical Editors made recommendations concerning the ethics of publishing for medical periodicals, with the request to the periodicals to implement the recommendations. Topics discussed: study design and ethics, authorship, conflict of interest, peer review, editorial decisions, originality, media relations, plagiarism, advertising, scientific misconduct and the relationship with the sponsor. Source: WAME Recommendations on Publication Ethics Policies for Medical Journals, URL <http://wame.org/pubethicrecom.htm>

4.2 Rules of conduct

When it comes to integrity in research, the best safeguards against fraud are cooperation between researchers, evaluation of research and a policy on publication that includes a thorough, independent peer review. The most important principle is that every study must take place within a clearly defined research framework or theme.

The following rules of conduct apply:

1. Establish a research protocol with provisions about the aims, operational method, etc. of a scientific study.
2. If the scientific study involves human subjects, the research protocol must be evaluated – before the research begins – by a review committee (METc or the Central Committee on Research Involving Human Subjects (CCMO)). Changes in a research protocol must also be examined by the review committee. The best guarantee is when the research takes place according to good clinical practice procedures. Before the study begins, the research plan for a clinical trial (with the exception of phase 1 and phase 2 research) must be placed in the Netherlands Trial Register, which is publicly accessible and can be consulted at no cost¹⁶. This is mandatory to qualify for publication in a number of medical periodicals, including the New England Journal of Medicine and the Lancet, in accordance with the recommendations of the International Committee of Medical Journal Editors¹⁷.
Most research at the UMCG is done by a project team. Although there can be a clear division of labor within a project team, it is important for the team to work as a unit when deciding how the data is to be collected, assessed and interpreted and how the results are to be reported. Regular checks on one another and feedback reduce the risk of fraud. This also applies to writing articles: provide proper supervision and feedback, ensure that the rules on citation of other authors are observed and prevent plagiarism.
3. Document the various stages and decisions in the research process. If a logbook is kept of the various decisions made during the research process, the argumentation can be properly reconstructed after the event. This provides a good understanding of what went on during the project, both for the researcher and for outsiders.
4. Encourage regular critical feedback by setting up a steering committee. For larger clinical studies, an external committee is advisable. The risk of fraud is reduced if the progress of the project is discussed and the results are presented to outsiders on a regular basis. The participation of UMCG staff in research supervisory committees is therefore extremely valuable for the quality and integrity of the research conducted at the UMCG.
5. Publish findings in journals which have a peer-review procedure. Besides providing worthwhile feedback on content, peer review helps to detect misleading representation of data and plagiarism before it is too late.

4.3 Rules for authorship

According to a recent British study of 119 institutions in higher education, one out of every six British students admits to copying information from the assignments of friends¹⁸. Clear rules for authorship are therefore

¹⁶ The data that are registered by the CCMO only partly overlap with that of the Netherlands Trial Register. URL <http://www.trialregister.nl>. The Trial Register focuses primarily on randomized intervention studies (e.g. randomized controlled trials), while the CCMO register contains all the research that is subject to the provisions in the Medical Research Act. URL <http://www.ccmo-online.nl/main.asp?pid=2&sid=9>

For all research that is subject to the provisions in the Medical Research Act, beginning on 1 March 2006 the data must also be registered in the EUdraCRT database in order to acquire a EUdraCRT number. The WHO is striving for a single, worldwide unique trial number. The 2005 annual report of the CCMO provides more background information about these new developments.

URL http://www.ccmo-online.nl/hipe/uploads/downloads_catc/ccmo-jv2005.pdf

¹⁷ URL <http://www.icmje.org/>

¹⁸ The Times Higher Education Supplement, March 17, 2006

essential, certainly for the practice of science, which continually builds upon the work of scientific predecessors. Consequently, in scientific articles it is customary to indicate how the theories and research results of others have been used. This must be done scrupulously. On the one hand, an excess of references can make a text stilted and unreadable, or can the author can irritate the reader due to a large number of self-citations. On the other hand, neglecting to cite references can lead to the risk of plagiarism. As with fraud in general, it is difficult to ascertain exactly where the border lies between deliberate plagiarism and carelessness. The role and responsibilities of the research supervisor are essential to this process (see Section 5).

The following rules of conduct may help to avoid problems:

1. Give a reference if your text describes a theory, a standpoint or findings taken from someone else. References are usually reported as part of the introduction, materials and methods and the discussion sections of an article. The introduction usually indicates the relevance of the subject matter under consideration and refers to other people's theories, standpoints and findings. The materials and methods section refers to the procedures that have been developed by others. The discussion section usually compares the author's findings with other people's. References need to be given in all these cases.
2. Try to make your references as accurate as possible. Most references are to articles, where the rules are fairly explicit. The matter is often more complicated when it comes to books and reports: page references should be given to enable interested readers to find the information, especially when your text refers to a particular theory or position. It is insufficient to link a single proposition to an entire book.
3. Try to refer to the article or book in which the theory or proposition was first published, and check all the references yourself. Especially when writing the introduction to an article, it is very easy to use references that have been previously cited in other articles. However, you should understand that other authors might have made mistakes and that every author is expected to be conversant with all the references in his or her own article. References should as a rule be to source articles, but referring to review articles is becoming increasingly common practice, given the limitations journals often impose on the length of manuscripts. In this case, however, the author should be conversant with the content of the source articles.
4. Indicate clearly in the text when you are quoting and where each quotation begins and ends. The suspicion of plagiarism can be aroused if the source article is mentioned once, but a check reveals that whole sections have been copied almost word for word. Lengthy quotations are certainly not forbidden, but it must be clear which parts of the text are quotations (with references including page numbers) and which are your own work. If a scientific publication makes substantial use of quotations, it is prudent to consult the original author(s) first: not only could there be copyright issues, this could also prevent problems later on.
5. Researchers must report their interests, financial or otherwise, in their scientific articles, in accordance with the recommendation of the International Committee of Medical Journal Editors.

4.4 Dealing with complaints about alleged scientific misconduct

The following regulations for dealing with complaints about alleged scientific misconduct are based on, and complementary to, the existing procedure at the University of Groningen; it applies to everyone who is involved in research and is employed¹⁹ at the UMCG. Everyone who is involved in scientific research has an

¹⁹ URL <http://www.rug.nl/bureau/expertisecentra/abjz/abjz/producten/pdf/wetenschappelijkWangedrag.pdf>

individual responsibility regarding the prevention and detection of scientific misconduct. Anyone who believes that an individual employed at the UMCG is not acting in accordance with the generally accepted principles for professional scientific conduct can report this to the Ombudsman of the UMCG²⁰ (ombudsmanresearch@umcg.nl)²¹. Consequently, the Ombudsman is the first contact point in the case of alleged scientific misconduct. As an intermediary, the Ombudsman contacts both the complainant and the accused. If the investigation initiated by the Ombudsman leads to the conclusion that there is possibly a situation involving scientific misconduct, then the Ombudsman will report this to the Dean of the UMCG²² and to the accused party. The Dean reports the complaint in turn to the Rector. The Rector then evaluates the admissibility of the complaint; he takes account of the trustworthiness, reputation and status of both the complainant and the accused party²³. Together, the Dean and the Rector, along with a professor to be appointed, form an investigation committee. This committee then makes a recommendation and writes a report that is sent to the accused party, the Gemeenschappelijk Beleidsorgaan (GBO – joint policy body) and the Ombudsman. If the investigation committee recommends that a resolution be made to take additional measures, then the GBO will inform the accused party, the Rector and the Ombudsman about this recommendation within four weeks. The Board of Directors of the AZG then accepts the GBO resolution, informs the parties involved, and implements the additional measures, if any.

The procedure at the National Organization for Scientific Integrity (LOWI)

If the complainant or the accused party cannot agree with the decision of the Board of Directors, they can request the National Organization for Scientific Integrity²⁴ (LOWI) to evaluate how the complaint was dealt with. If the LOWI believes that the complaint was not handled with due care, it will advise the institution to take the complaint under consideration a second time. If there is a reason to do so, the LOWI can also investigate the complaint itself.

5. Respect for human subjects involved in medical research

In any type of scientific research, regardless of the degree to which the participants are involved, respect for the persons and rights of participants is an absolute prerequisite. During the research process, researchers must comply with the relevant legislation (see below). In the first place, researchers must be open to the interests of the participants in medical research. They must realize that as researchers they are partly responsible for protecting these interests (to the extent that these interests are unaffected by medical research). It is also the task of the researchers to communicate this sense of responsibility to the participants in medical research.

²⁰ See the KNAW, NWO and VSNU *notitie Wetenschappelijke Integriteit* (report on scientific integrity–2001) for a description (footnote 16)

²¹ The background (scientific or otherwise) position and operational method of the Ombudsman will be described in detail in a separate regulation.

²² Source: AMC Research Code. Scientific Research Ombudsman. URL <http://www.amc.nl/index.cfm?pid=1623>

²³ The frame of reference regarding the complainant is the "whistleblower" regulation of the Tabaksblad Commission.

²⁴ The National Organization for Scientific Integrity (LOWI) was established in 2003 by the KNAW, VSNU and NWO. Its aim is to advise the Executive Board of a university and the administrations of the NWO and KNAW regarding complaints about violations of scientific integrity. The LOWI only takes complaints into consideration about which the relevant institution (where the violation has allegedly taken place) has already made a decision. If requested to do so, the LOWI can advise the administration of an institution before it makes a decision regarding a complaint about which the confidential adviser of the institution has made a recommendation.

URL http://www.knaw.nl/cfdata/adviesraden/adviesraden_detail.cfm?orgid=690

The task of the LOWI is comparable to that of the US Office of Research Integrity, established in 1989. URL <http://ori.dhhs.gov/>

One of the core interests of those involved in research is protection of their privacy. This means protection of their medical data and comprises the protection of personal details for medical research and body material for later use. The first rule is a strict separation of patient information and research data. After this, researchers must make as much use as possible of anonymous research data and anonymous or coded human body material. Researchers who are registered as part of the Individual Health Care Professions Act (Wet BIG) have an obligation to observe confidentiality regarding everything that is entrusted to them as confidential or about which the researchers must understand its confidential character. If this is not evident from specific and explicit permission from the subject, researchers cannot assume that he or she has agreed to the publication of research results concerning the subject that reveal his or her personal details.

Besides ethical and legal considerations, respect for the interests of human subjects is also essential to motivate potential participants, now and in the future, to take part in medical research.

In medical research involving people, a general distinction can be made between the following three types of research:

- Medical research with people, i.e. research where people are subjected to certain treatments or are required to engage in specific behavior. This concerns, for example, research into the effect of an experimental medication or taking blood for research purposes.
- Medical research on the body material of people (blood, tissue, DNA etc.) that is already available, for example because it was taken during patient care.
- Medical research using data that is already present in a patient file or that must still be collected from people.

These three forms of research and the applicable laws and norms are described in detail below.

5.1. Medical research involving people

The Medical Research on Humans Act²⁵ (WMO) applies to "medical research that involves subjecting people to treatments or requiring them to engage in specific behaviors." Research that involves testing a new drug, taking blood or extra blood, testing new diagnostic methods, investigating new medical aids or new surgical techniques are examples of medical research that are subject to the provisions in the Act.

A prerequisite for such research is a positive evaluation of the research protocol by a review committee that is certified by the Central Committee on Research Involving Human Subjects (CCMO) or – for specific types of research – by the CCMO itself. The UMCG has its own review committee (the METc) that has been certified by the CCMO. The structure and operational method of this review committee is set down in a guideline from the CCMO, which is based on the Medical Research on Humans Act²⁶.

The criteria used by the committee are initially laid down in the WMO, but also in international documents such as the Declaration of Helsinki of the World Medical Association, and for clinical drug testing, the Good Clinical Practice Guidelines²⁷. These documents also state the minimum requirements for a research protocol and the written information for human trial subjects, as well as aspects such as the demands that are placed on research involving minors or incompetent adults. In addition, the Medical Treatment Contracts Act (WGBO), included in Book 7 of the Dutch Civil Code (BW) and the Personal Data Protection Act (Wbp) both contain provisions that can apply to medical research involving people.

²⁵ The amended Medical Research on Humans Act went into force on 1 March 2006. URL <http://www.minvws.nl>
As a result of the amended Act, the Netherlands now satisfies the new European regulations for evaluating clinical drug testing. The UMCG will soon establish a single contact point for questions concerning the Medical Research on Humans Act.

²⁶ URL http://www.ccmo-online.nl/hipe/uploads/downloads/CCMO-richtlijn_org-werk.pdf

²⁷ URL <http://www.wma.net/e/policy/b3.htm>

A review committee can only make a positive evaluation about a research protocol under the following conditions:^{28,29}

- a. it can be reasonably assumed that the research will lead to new medical insights;
- b. it can be reasonably assumed that the insights referred to in the above provision cannot be attained through other forms or methods of research than research involving human trial subjects or by conducting research that is less interventional;
- c. it can be reasonably assumed that the interests served by the research are in proportion to the objections and the risks for the human trial subject;
- d. the research satisfies the requirements of correct methodology for scientific research;
- e. the research is conducted under the leadership of people with expertise in the relevant field of the scientific research, where at least one of these leaders has expertise in the area of the interventions that will take place on the human trial subject;
- f. it can be reasonably assumed that the compensation paid to the human trial subject was not disproportionately influential in acquiring his or her permission to participate in the research;
- g. the research protocol clearly indicates to what extent the research can benefit the human trial subject involved;
- h. the research itself also satisfies reasonable demands.

In addition, the ethical review committee ensures, among other things, that:

- the correct insurance has been acquired for the participating human trial subjects;
- the privacy of the participating human trial subjects will be adequately protected (e.g. protecting information that can be traced to the subjects);
- easily-understood written information for human trial subjects (including minors) is available that indicates the aim of the research, what is expected from the participating human trial subjects and what the objections to and risks of participation can be.

Minors have additional legal protection during medical research.

- A European work group has been recently established and has published a working document³⁰ about the ethical aspects of clinical trials involving children, which is complementary to the Good Clinical Practice guidelines.

Additional recommendations regarding clinical research with children were published in 2004 by the Confederation of European Specialists in Paediatrics³¹ and concern the protection of the integrity of the child, timing the involvement of the child, heterogeneity (for example stratification according to age), risk-benefit analysis, minimization of risks/discomfort, and informed consent followed by assent. These recommendations are also included in the evaluation research involving children conducted by the METc of the UMCG ; in this context, one of the members of the METc is an expert pediatrician (see also Section 5.2, item 6).

²⁸ Source: Toetsingshandleiding (review handbook) CCMO. The handbook for reviewing medical research involving humans was published in September 2002. With this document, the CCMO aims to give a positive impulse to the quality of the review of research in the Netherlands that is subject to the WMO. URL <http://www.ccmo-online.nl>

²⁹ Evaluatie Wet medisch-wetenschappelijk onderzoek met mensen, ZonMW, NIVEL; December 2004
ISBN 90-5763-071-0;
URL http://www.zonmw.nl/fileadmin/upload/33096/evaluatie_wmodef.pdf

³⁰ Ethical Considerations for Clinical Trials Performed on Children, 4 October 2006. RFC deadline 31 January 2007.
Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. URL http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/paeds_ethics_consultation20060929.pdf

³¹ Gill, D. Ethical principles and operational guidelines for good clinical practice in paediatric research: Recommendations of the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP). Eur. J. Pediatr. 2004. vol. 163. pp. 53-57. Prof. dr. P.J.J. Sauer, pediatrician at the UMCG, is a member of this working group.

The External Review Guideline (*Richtlijn Externe Toetsing*³²) of the CCMO applies to multi-center research and the external review of mono-center research. A model document on local feasibility must be signed on behalf of the Board of Directors. A signed model document means that the expertise and skill of local practitioners and support staff is adequate, that all individuals who will contribute to the research have been sufficiently informed, that the facilities and the institution are suitable for the correct implementation of the research and that simultaneous implementation of other research projects in the same institution will not hamper the research under question.

The Vice Dean of Research signs the statement of local feasibility on behalf of the Board of Directors based on the positive recommendation of the department head, which in turn takes account of the advice of the sector management as well as the positive recommendation of the METc. A statement of local feasibility is equivalent to approval by an Institutional Review Board, as referred to in non-European legislation, for example as part of the frameworks of cooperation in research with North American institutes and companies.

Not all medical research is evaluated by the METc. There are various specific disciplines, including behavioral and social science research, but also some forms of epidemiological research, to which the Medical Research on Humans Act does not apply. For this type of research, a VSNU code of conduct has been in force since March 2006: "Code of conduct on the use of personal details in scientific research" (*Gedragscode voor gebruik van persoonsgegevens in wetenschappelijk onderzoek*). In terms of concept definitions, this code of conduct is complementary to the Code of Conduct for the Biomedical Sciences (*Code Goed Gedrag binnen de Medische Wetenschappen*) and is also based on the Personal Data Protection Act. Important components of this code of conduct include the following: range of application, points of departure and principles, security and conditions for provision of data to third parties. If there is doubt about the application of the Medical Research on Humans Act to a research proposal, for example from the above-named disciplines, then the researcher must first have the proposal reviewed by the METc office.

The UMCG also has a Clinical Research Desk, where researchers can take all their questions about clinical research. In this way, researchers can obtain effective and timely solutions to problems such as study design, contract agreements with external funding sources before a project is reviewed by the METc or before final contracts are signed with external funding sources, etc. (see Section 8).

5.2 Medical research on human body material

The use of body material from patients (taken during diagnosis and/or treatment) for the purposes of medical research is subject to regulations. Art. 7:467.1 of the Dutch Civil Code states that *anonymous human tissue* can be used for medical research (statistical or otherwise), if the patient from whom the tissue originates does not object and if the research is conducted with due care³³. Article 9.1 of the Requirements for Human Tissue Decree (*Eisenbesluit Lichaamsmateriaal 2006*) states that it is the responsibility of the relevant institutions to ensure that data which can be consulted by third parties, including genetic information, can no longer be traced to individuals³⁴.

³² URL <http://www.ccmo-online.nl/hipe/uploads/downloads/RET.pdf>

³³ The present government will make a decision about the Control of Human Tissue Act (*Wet zeggenschap lichaamsmateriaal - WZL*) (kamerstuk 27428, nr79, January 2007).

³⁴ The Requirements for Human Tissue Decree 2006 (*kamerstuk 30338*) is a draft law to implement the corresponding EU directive (2004/23/EG). The Safety and Quality of Human Tissue Act (*Wet veiligheid en kwaliteit lichaamsmateriaal – WVKL*) has also been amended in accordance with this EU directive (December 2006).

At the UMCG, research with human body material must also meet the legal requirements in the WVKL and the Organ Donation Act and its interpretation in documents such as the Requirements for Body Material Decree, the draft norm NEN 8016 "Chain quality norms for body material" *Ketenkwaliteit lichaamsmateriaal*³⁵ and the Proper Secondary Use of Human Tissue Code (*Code Goed Gebruik* – see below).

In 2001, the Dutch Federation of Biomedical Scientific Societies (*Federatie van Medisch-Wetenschappelijke Verenigingen* – FMWV) established a code for the proper secondary use of human tissue³⁶ with rules of conduct for using human tissue (obtained during diagnosis and/or treatment) for scientific research. In 2004, the same federation also developed a practical questionnaire for researchers in order to promote the readability/use of the codes of conduct. The METc of the UMCG has also developed a brief guideline for removing and storing human tissue³⁷.

The Proper Secondary Use of Human Tissue Code makes a distinction between

- a. *directly traceable human tissue*: tissue which is linked to information that can be used to determine, either directly or very easily, the identity of the individual from whom the tissue originated;
- b. *anonymous human tissue*: human tissue which is not linked to such information;
- c. *coded human tissue*: human tissue that is anonymous for the researcher, but by means of a code – which is controlled by the donor of the tissue – can still be traced back to the individual from whom the tissue originated.

The use of *directly traceable* human tissue requires the written permission of the individual from whom the tissue originated. *Anonymous human tissue* and *coded human tissue* can be used for scientific research to the extent that the individual from whom the tissue originated does not object to this use.

Research with human tissue must take place in accordance with a research protocol. Such a research protocol (with several exceptions) must be submitted for evaluation to a medical ethics review committee. Human tissue can only be made available for research based on a conveyance agreement with the party who removed and stored the tissue for its original purpose (diagnosis and/or treatment).

With patients at the UMCG, human body material is often removed as part of diagnosis and/or treatment, such as blood, urine, cells or tissue. Once the diagnostic tests or the treatment have been completed, the material is kept as long as is necessary for good clinical practice. As a rule, the human body material or tissue is destroyed if it is no longer needed for good clinical practice. During this process, patients at the UMCG are informed about the use of human body material and tissue for medical research by means of information booklets or the website; they are also informed that they have a right to object to the use of their human body material or tissue (anonymized or coded) for scientific research. If a patient objects to the use of their human body material or tissue, it of course cannot be used.

³⁵ NEN 8016 specifies requirements concerning the organizational responsibility and technical procedures focusing on an optimal operational method for dealing with human body material that is intended for use in medical treatment. The basic principle is that these actions, from the recognition of the donor through the use of the material, are considered to be a chain of actions. Within this chain, various institutions and individual care providers are involved, such as organ banks, organ centers, institutions from which human tissue originates and institutions where human body material is used.

URL: <http://www.nen.nl>

Please note. This proposed set of norms is a product of the Netherlands Organization for Standardization (*Centrum voor Normalisatie* – NEN) and is available upon payment.

³⁶ URL <http://www.fmwv.nl>

³⁷ Source: Intranet UMCG, Research and Medical Education Section, Medical Ethical Committee, Special Topics Section, document "removing and storing body material" (*sectie Onderzoek en Med. Onderwijs, Medisch Ethische Toetsingscommissie, sectie Speciale Onderwerpen, document "afnemen en bewaren van lichaamsmateriaal"*).

5.3 Medical research with data

The Wbp and the WGBO have regulations concerning the acquisition, storage and use of data (medical or otherwise). Using data from a patient's records for medical research requires the written permission of the patient. This permission must be based on written information about the nature and aim of the research. Such permission is also required for providing patient data to other researchers and for allowing other researchers to view medical records³⁸.

If specific data must be collected for the purposes of medical research, and this data is not yet available, it can be acquired by means of interviews or surveys. However, interviews or surveys (single or in series) can be very taxing or even hazardous for a patient. This is not only due to the time required for participation, but also due to the content of the items being studied. Medical research comprising interviews or surveys (single or in series) that can be taxing and or hazardous for participants is also subject to the provisions of the WMO.

For the purposes of research with data (medical or otherwise) that are already available and for which professional confidentiality applies (for example in medical records), the Dutch Federation of Biomedical Scientific Societies has published a code of conduct for medical research (also known under the title *Code Goed Gedrag*³⁹). In 2004, a practical questionnaire for researchers concerning this code was also developed to promote its readability/use.

Regarding the 2004 version of the Code of Conduct for Medical Research (*Gedragscode Gezondheidsonderzoek*), the Personal Data Protection Authority has stated⁴⁰ that this is a correct interpretation of the Wbp and other statutory provisions concerning the processing of personal data. This Code of Conduct for Medical Research states among other things that medical research with data, if this concerns identified or identifiable individuals, must be based on a research protocol that is approved beforehand by a medical ethics review committee.

6. Relationship of the researcher with external funding bodies

Research at medical teaching and research institutions has traditionally been funded by universities, hospitals, the NWO, KNAW etc⁴¹. However, scientific research is increasingly being financed by other sources. We have gradually come to take funding by charitable organizations and industrial and venture capital organizations – known in the Netherlands as third-party funding – for granted as part of the income of many research groups. Research projects that are funded, wholly or in part, by third-party funding must be reported beforehand to the *Bureau Derde Geldstroom* (Third Party Funding Office) of the UMCG. It is crucial that clear agreements are made with bodies that fund scientific research. In the past it has turned out that inadequate agreements about the design, implementation and reporting of research can lead to conflicts. This is true for both basic and applied research. The KNAW has written a memo on this topic for the Minister of Education, Culture and Science which recommends drawing up a "statement of independence"⁴² that is signed by the client and researcher⁴³.

³⁸ Researchers can deviate from this permission requirement only in very exceptional cases. The possible traceability of the data plays an important role in this consideration.

³⁹ URL <http://www.fmwv.nl>

⁴⁰ *Besluit CBP*, 19 April 2004. URL http://www.cbpweb.nl/downloads_gedragscodes/gedr_FMWV_gkvk.pdf?refer=true&theme=purple

⁴¹ *Basic funding*: funds that are made available directly to the universities by the Ministry of Education, Culture and Science. *Governmental funding*: funds that are made available to researchers by the Netherlands Organisation for Scientific Research (NWO) and Royal Netherlands Academy of Arts and Sciences (KNAW). *Third-party funding (contract research)*: funds that are made available to researchers by charities such as the Dutch Cancer Society and Heart Foundation and by companies and ministries other than the Ministry of Education, Culture and Science.

⁴² URL: http://www.knaw.nl/nieuws/pers_pdf/wetenschappelijke_onafhankelijkheid.pdf

⁴³ Source: *Wetenschap op bestelling - Over de omgang tussen wetenschappelijk onderzoekers en hun opdrachtgevers*, September 2005. URL <http://www.knaw.nl/publicaties/pdf/20051083.pdf>

6.1 General guidelines

The statement of independence drawn up by the KNAW (see above) provides the general guidelines regarding relations with external funding bodies; these guidelines are described below. Additional conditions apply to specific medical disciplines and professional associations⁴⁴.

- The research is not designed to achieve results that may be desired by the sponsor.
- The sponsor and researcher jointly formulate the assignment and the aim of the assignment.
- Monetary compensation and other forms of appreciation must never depend on the results or interpretation of the research.
- Scientific research results will be published whether they are beneficial or non-beneficial for the sponsor.
- The scientist always has the freedom to publish findings within a specified length of time, where two months is assumed to be reasonable and six months is the maximum (to be figured from the moment the final results are delivered to the sponsor). An exception must be made here for issues of intellectual property: in that case, a maximum period of 12 months will be accepted.
- The method of publication is agreed to in the contract. Publication in a scientific journal takes place in consultation with the sponsor. However, the researcher always has the final word about the content, authors, form and venue of scientific publication.
- The names of external funding bodies and/or other sponsors are included especially in publications and other forms of publicity.
- The relevant interests and/or advisory relationships of the researcher(s) are reported in publications and in other forms of publicity.
- The text of the contract is available for confidential inspection by the National Committee for Scientific Integrity (LOWI).

6.2 Checklist for agreements

If scientific research is financed by a source other than the UMCG itself (for example industry, charitable institutions, government agencies etc.), a number of matters must be set down in a written agreement. This goes without saying for contract research on behalf of a pharmaceutical company, for example, but it also applies to cooperative projects (such as investigator-initiated, multicenter research) or when exchanging research material. Governmental and third-party funding bodies often have terms and conditions that are automatically accepted when a funding proposal is submitted. Third-party funding bodies often use a written agreement that stipulates mutual rights and obligations. The parties must always determine whether the proposed rights and obligations can be reasonably applied to both of them⁴⁵.

Below is a checklist of a number of important topics that must in any case be addressed in the agreement⁴⁶. Transparency of the relationship between the researcher and the funding body and the independence of the researcher are the points of departure of this agreement. "Loose ends" must not appear in agreements or model agreements. Various model contracts are also available to support this process⁴⁷. The checklist is emphatically not complete, but must be seen as a guideline for evaluating and committing to agreements. The Clinical Research Desk is the first contact point for questions about legal agreements.

⁴⁴ The American Society of Clinical Oncology recently amended its policy on conflicts of interest with a clear guideline about the relationship between researcher and sponsor. Ref. ASCO: Revised Conflict of Interest Policy, J. Clin. Oncol. 24, 3, Jan 20, 2006, pp 1-3, 517-518

URL: <http://www.plwc.org/portal/site/ASCO>, see menu heading "Legislative and Regulatory Issues".

⁴⁵ Source: AMC Research Code, Chapter 6.

⁴⁶ Source: AMC Research code. This concerns an adaptation of the Contracting section

⁴⁷ The Legal Office of UMCG uses a model contract for clinical trials. The General and Administrative Affairs Office uses a general model contract. URL: <http://www.rug.nl/Bureau/expertisecentra/abjz/abjz/producten> <section "Third-party funding" >

1. *Parties and authorized signatories*

A contract is entered into by two or more parties. These parties must be correctly defined in the contract, including particulars of legal status and domicile. Anyone signing a contract on behalf of a contracting party must be explicitly authorized to do so. If there is any doubt about the particulars, a copy of the entry in the register of the Chamber of Commerce can be requested.

The Board of Directors of the AZG is authorized to sign research agreements and third-party funding contracts. The Board of Directors of the UMCG is also authorized to sign third-party funding contracts from sources outside the UMCG. With clinical trials, the researcher (as the investigator or principal investigator) co-signs the agreement to indicate approval of provisions in the agreement that apply specifically to him or her. A researcher cannot sign an agreement on behalf of the UMCG/AZG. A researcher who still does so can be held personally liable, and there is a serious likelihood that any loss or damage arising from the research project will not be covered by insurance.

2. *Considerations*

The considerations indicate what the parties' intentions are with regard to the contract and what interests are involved. If there is a difference of opinion, the considerations are taken into account when interpreting the contract.

3. *Project/Study*

The project or study is usually described in a research protocol or project description that is appended to the contract and forms part of it. As a rule, the contract merely refers to the appendix. But this appendix is extremely important. The researcher should make sure in advance that everything set out in the research protocol or project description can actually be realized. The agreement must also include a statement that the research institution cannot guarantee the usability of the results of the research.

4. *Best effort*

In scientific research, there usually cannot be an obligation in the agreement to produce specific results. After all, if the researcher knows in advance what the results are going to be, the research is not needed. Consequently the only obligation in the agreement is to give the research one's best effort. This also applies to the number of patients and/or healthy volunteers to be included in a study. The researcher can do his/her utmost to include a certain number of patients, but cannot guarantee what number will ultimately turn out to be feasible. Therefore the specifications in these agreements must also address the possibility of terminating the research project prematurely; the possible financial consequences of such premature termination must be covered.

It is very desirable for the researchers to be involved in drawing up the research protocol; in this way the parties can mutually consider the exact research question(s), the research design and the proposed analyses. Preferably, the researcher draws up the protocol. However, if the research protocol has already been realized, the researcher must carefully determine whether he/she can agree with all details in the proposed research. In a clinical setting, it is possible that the researcher may also act as the treating physician. This can lead to tension between the study design and the interests of the individual patient. An important assurance before beginning the study is the risk-benefit analysis conducted by the METc. However, these situations cannot always be avoided by a strict evaluation process. From the perspective of the treating physician/researcher or patient, a conflict of interest can also take place after a study has begun (for example during the inclusion process)⁴⁸. The integrity of the supervisor and treating physician and the role of the independent physician remain essential in this context (see Section 5.2 and Section 6).

⁴⁸ See Sugarman, J., Ethics in the design and conduct of clinical trials. *Epidem. Rev.* Vol 24, no 1. pp. 54 – 58, 2002.

If applicable, it must be determined whether the research, in terms of its design and implementation, satisfies the conditions of good laboratory practice and/or good clinical practice (GLP/GCP). It must also be determined whether the research is subject to the provisions in the Medical Research on Humans Act (WMO), and the research must be evaluated by a certified Medical Ethical Committee⁴⁹ (see Section 7).

Good agreements must be made about the exact method for collecting research data, the transfer of research data to the funding body and the location and method of analysis. Key concepts in this process are the following: careful documentation, independent data collection and analysis – or at least an independent control on the data collection and analysis – an analysis plan drawn up in advance and protection of privacy if the research involves personal data. Finally, agreements must be made about the conditions under which the research can be terminated prematurely.

5. *Funding*

Before the research begins, a clear funding section must be drawn up by the sector management, in consultation with the department head. This section must contain details about which costs will be reimbursed: personnel, experimental animals, experimental and/or laboratory costs, and the time period for reimbursement. If the research is terminated prematurely, the agreement must also contain a provision that all costs in the contract that relate to the specified time period of the research project will still be reimbursed (for example, the costs of the researcher who has been hired for the entire length of the research project). Insufficiently detailed agreements must be avoided; otherwise this can lead to misunderstandings and manipulation. Personal reward is not permitted. Funding linked to the medical treatment of patients leads to unacceptable conflicts of interest.

If research is being conducted on behalf of a company, then this company usually pays for the research. To determine the amount of the reimbursement, a budget must be drawn up which includes all costs that will be incurred as part of the research. Preferably, this budget should be drawn up by the researcher and the administration of the department where the research will be conducted. If the company makes a budget proposal itself, this proposal must be evaluated by the department in terms of its financial feasibility. If multiple departments are involved in the research, their corresponding administrations must also be involved. The amounts that the company will pay are specified in the agreement or an appendix to the agreement. The basic principle is that the amounts in the contracts are specified ex VAT. A budget can be based on various starting points, for example per unit of time or per patient, or related to the salary of the member of staff appointed to the project. Preferably, the funding is paid independently of the results achieved. If the research involves payment per patient, it must be stated clearly in the budget how much will be reimbursed for patients who withdraw from the study (drop-outs). For some research projects, payment takes place according to so-called milestones. The reimbursement then depends on achieving a series of specific milestones in the research. In that case, the researcher should first determine whether these milestones in the agreement are realistic. There can also be a situation where a company provides funding for research that has been initiated by UMCG researchers (the so-called unrestricted grant). The amount of such payments can vary greatly and does not have to be related to the actual costs of the research.

If staff must be hired for the purposes of the research, there can be no deviation from the terms and conditions of employment of the UMCG.

6. *Confidentiality*

In the case of research commissioned by a company, a unilateral obligation of confidentiality is agreed upon, under which the researcher and the UMCG agree to keep certain information secret. There is a difference between information obtained from the other party and information generated as part of implementing the

⁴⁹ In case of experimental animal research, the research protocol must be presented to the Laboratory Animal Committee of the University of Groningen (see Section 7).

agreement. In the case of information obtained from the company, such as specific formulas, an obligation may be given to keep this information secret for a longer period (usually five years). However, this confidentiality requirement should not apply to information generated in the course of the research. It may be in the interest of the UMCG not to publish its own information for a certain length of time. In that case, a mutual confidentiality obligation is advisable, under which the company is also required to keep UMCG information secret.

7. *Publishing rights*

In all agreements, it is extremely important to reserve the UMCG's right to publish the results of research carried out at the UMCG or commissioned by the UMCG and carried out elsewhere. The company has the right to see the draft of the article before it is submitted. During a specified period (e.g. 4-6 weeks), the company can make comments on the draft to the researcher. Often a company will have specific knowledge which is very useful when it comes to reviewing articles, so it is important to take the company's opinion seriously. However, the researcher's scientific integrity and the author's responsibility for the article should not be compromised by a company's right of veto. In addition, there must be caution about conditions requiring permission (written or oral) from a company for publication, because the lack of this permission can hamper publication at a later stage. Besides providing substantive comments, a company can also object to the publication because:

- it contains the company's confidential information (see above, under Confidentiality). In that case the UMCG may be required to remove this information from the publication.
- premature publication could jeopardize patent applications. In that case, the company is given time to protect this information. An acceptable time limit is 60 to a maximum of 90 days.

A passage stating that the company may have information removed to prevent "damage to its commercial interests" is not acceptable. Commercial interests must never stand in the way of publication.

Emphatic agreements must be made about the publication strategy. The basic principle is that the researcher always has the freedom to publish the findings within a reasonable term, but with a maximum postponement of no more than 12 months. In the research protocol, it is a good idea to specify who will prepare the manuscript and to describe the procedure for commentary and correction by the sponsor. Generally speaking, the sponsor is given a term of four to six weeks for this procedure. The responsibility for the final manuscript must always lie with the researcher. Strategic or patent interests must be respected, but these interests must never prevent publication. Comparable agreements should be made about presentations at scientific meetings.

In view of the desired transparency during both the publication and presentation of the research results, when planning the project it is advisable to make agreements about how the role of the external funding body will be reported. Agreements should also be made about reporting the relationship between the researcher and the funding body.

8. *Intellectual property*

Intellectual property rights fall under two headings, industrial property rights and copyright. Industrial property rights are those conferred by patent law, trademark law and designs and models law. Can intellectual property rights (patents, copyright) arising from the research be transferred to the commercial company (sponsor/funding body)?

The answer depends on various factors:

- In the case of clinical trials initiated by a company, it is fairly standard practice to transfer rights to any new inventions resulting from the trials to the company. This is because the likelihood of a new invention resulting from a trial is small (after all, the trial is designed to research an existing product), and because the invention is all the work of the company (it is the company that has developed the drug).
- In the case of basic research into the development of new drugs, the situation is completely different. Then it is important to consider carefully what the consequences of transferring property rights to this knowledge would be. Transferring patents, for instance, could mean that the researcher is no longer

able to use the technology he/she has developed. If commercially worthwhile developments could arise from the research, it is reasonable for the UMCG to have a share in the financial rewards. Whether transferring rights is a reasonable proposition also depends on the price the company is paying. Agreement on these matters should of course be reached before the research starts. The following criteria can be applied here: a) in principle, intellectual property rights to the results of basic research should not be transferred, b) only discoveries resulting directly from the project for which the company is paying may be transferred, c) discoveries made prior to the project, or outside the project, should not be covered by the contract, d) if patent rights are transferred, these should be licensed to the UMCG for the purposes of research, education and patient care. With basic research, there are various factors that determine whether or not the company can obtain patent rights. The ownership rights of the research data must be set down in writing. In a strict sense, these rights are held by the institution which employs the researcher, but in consultation they can be transferred to the funding body. In addition, agreements must be made about the time limit for storing the research data, in accordance with the applicable guidelines.

9. *Liability*

In all contracts the company should be liable for any loss or damage caused by fulfilling the contract unless there is intent or gross negligence on the part of the UMCG. If development (for example an apparatus or drug) is done by the UMCG, it is important that the company should indemnify the UMCG with respect to any loss or damage to third parties as a result of applying the results developed by the UMCG. The UMCG is also not liable for loss or damage due to a third party claiming, rightly or wrongly, that the results infringe upon its intellectual property rights.

Possible reimbursements for damage resulting from partial or complete non-compliance of the UMCG with the provisions in the agreement should be limited, for example to a maximum that is equal to the financial reimbursement to the UMCG for carrying out the complete agreement.

If a clinical trial is to be carried out for a company, the company should take out patient insurance in compliance with the Medical Research on Humans Act (Wet medisch-wetenschappelijk onderzoek met mensen). The medical ethics review committee (METc) will decide whether it is necessary to take out insurance for patients participating in the research, and if so, will check whether this has been done.

10. *Applicable law*

Foreign law is not acceptable as a rule, and contracts should be governed solely by Dutch law. Possible disputes can be decided only by the Dutch courts. This is defensible, given that the research is taking place in the Netherlands.

6.3 Outside employment and conflicts of interest

Employees of the UMCG may be expected to apply the knowledge and expertise for which they were appointed in the interests of the UMCG. All employees can have reasons to take on outside duties or appointments, remunerated or otherwise, and these activities may result in undesired conflicts of interest. In most cases, conflicts of interest can be prevented by means of transparency.

Outside employment

The public employment contract for University Hospitals (Academische Ziekenhuizen⁵⁰), a public law statutory salary regulation (Article 9.3), states that advance permission is required from the Board of Directors for taking on outside employment that can affect the interests of the hospital, harm the operation of the hospital and the employee, and that is incompatible with the function of the employee.

⁵⁰ URL http://www.nfu.nl/fileadmin/documents/CAO-UMC-2007_Ned.pdf

Conflicts of interest

The UMCG is greatly concerned that the results of scientific research are, whenever feasible, rapidly converted into new diagnostic and therapeutic tools to allow patients to benefit from innovations. However, this usually involves a long process during which collaboration with commercial companies is unavoidable. This type of collaboration is where the greatest danger of conflict of interest occurs because the independence of the research at the UMCG can be thrown into doubt. This could have harmful consequences for both the reputation of the UMCG and the academic careers of individual researchers.

Here are some examples of situations that can lead to conflicts of interest⁵¹:

Situations where bias can play a role in research

- Research funded by third parties if the researcher or his/her family have financial interests with the funding party.
- Accepting favors from parties funding the research.
- Working as a consultant for funding sources such as industry, government funds or charities.

Situations where facilities of the institute are being used

- Allowing students and staff to work for a company in which the researcher holds an interest.
- Improper use of facilities for personal gain or to support a company in which the researcher holds an interest.
- Associating one's name or one's work with the institute to benefit from the goodwill of the institute.

Situations which involve the use of information

- Improper use of confidential information.
- Accepting support for research under conditions that require the results to remain confidential or unpublished, or which lead to a serious delay of publication.
- Providing access to confidential information from the institute to an organization in which the researcher holds a financial interest.

Situations in which the researcher directly promotes his or her own financial interests

- Purchasing materials, instruments or supplies from a company in which the researcher holds a financial interest.
- Influencing the negotiation of agreements between the institute and the company in which the researcher holds a financial interest.
- Requiring the purchase of textbooks of which the employee is the author or co-author.

In such situations, permission for conducting outside activities will always depend on the individual circumstances.

⁵¹ Source: *Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research*. Report of the American Association of Medical Colleges (2002). URL <http://www.aamc.org/research/coi/>

7. Respect for laboratory animals

Besides people, animals can also be involved as the subject of biomedical research. Animal experiments for research and education can only be conducted if there are no suitable alternatives. The Animal Welfare Act (Wet op de dierproeven)⁵² states that an animal experiment can be conducted only if a certified laboratory animal committee makes a positive recommendation about the corresponding research plan. The Animal Welfare Commission (DierExperimentenCommissie⁵³) of the University of Groningen is a certified laboratory animal committee that is required to make a recommendation about all laboratory animals used in research at the University and the UMCG.

A research plan must in any case address the following topics:

- the research question;
- the importance of the research for the health or nutrition of humans or animals;
- the social and scientific importance of the research;
- the expertise of those who design and implement the experiment, including their experience in the relevant field;
- the name of the individual or committee who will evaluate the scientific quality of the research;
- why the research question cannot be addressed with fewer animals or without using laboratory animals;
- why the species and number of laboratory animals were chosen;
- the origin of the laboratory animals;
- the intended treatment and care of the animals – including their housing – before, during and after the experiment, as well as the expertise of the persons charged with this care;
- the nature, frequency and duration of the interventions to which the animals will be subjected;
- the degree of discomfort to which the laboratory animals will or can be subjected;
- the use of anesthesia or pain relieving medication and other methods to avoid discomfort;
- whether an animal has been previously used for an experiment;
- whether, and at what time, the decision will be made to conduct responsible euthanasia of the experimental animals involved, including the method that will be used;
- the destination of the animals following the experiment.

In addition, the Animal Welfare Commission (DierExperimentenCommissie) of the University of Groningen endorses the generally applicable standpoints from the Codes of Practice on diverse topics. These Codes of Practice are drawn up by experts and published under the auspices of the Laboratory Animal Inspectorate. Three Codes of Practice have been published:

- laboratory animals in cancer research⁵⁴ (1999)
- immunization of laboratory animals⁵⁵ (2000)
- assuring the welfare of laboratory animals⁵⁶ (2001)

⁵² Source: <http://www.rug.nl/fwn/faculteit/bestuur/dierenExperiment/dec/pdf/wetOpDeDierproefen.pdf>

This Act (dated 12 January 1977) was evaluated in 2005 (Kamerstuk 2005-2006, 30168). In 2006 public consultation began with the aim of updating the existing EU directive on laboratory animals (86//609/EG).

⁵³ <http://www.rug.nl/fwn/faculteit/bestuur/dierenExperiment/dec/index>

⁵⁴ <http://www.rug.nl/fwn/faculteit/bestuur/dierenexperiment/dec/pdf/CofPkankeronderzoek.pdf>

⁵⁵ <http://www.rug.nl/fwn/faculteit/bestuur/dierenexperiment/dec/pdf/CoPImmunisatie2000.pdf>

⁵⁶ <http://www.rug.nl/fwn/faculteit/bestuur/dierenexperiment/dec/pdf/codewelzijn.pdf>

8. Dealing with the media

UMCG researchers are often in the news. This is important for various reasons. A great deal of research is conducted at the UMCG. Publicity makes this research visible. This improves the reputation of the UMCG as a research institution.

Moreover, communication in the media can be used to account for the spending of public funds. Policymakers and scientific organizations have recently argued for a stronger dialogue between researchers, citizens and society. In its recent policy paper, the NWO refers to the essential role of science in solving societal issues, which is expressed in the strategy "science valued"⁵⁷. And the KNAW even wants to play a leading role in the public debate on science. This organization believes that activities focusing on popularizing science can make an important contribution to societal support for scientific research⁵⁸.

However, publicity and media attention can also entail risks. It is not always an easy task to present scientific results in an understandable fashion. Moreover, publicity is often driven by the interests of third parties. For example, a pharmaceutical company can have a commercial interest in publicity. And some media are more interested in the latest developments than in the limitations that are linked to a study.

Researchers must therefore realize that dealing with the media requires other skills than scientific ones. Professional support in this process is essential. Therefore publicity about research must always proceed through the Communications Office of the UMCG⁵⁹. In addition, the University of Groningen and the UMCG have made an agreement on joint communication about research.

8.1 Publicity by third parties

Researchers are regularly confronted with funding providers or clients who want to publicize the research themselves. This is usually undesirable. Publicity provided by third parties can sow doubt about the independent nature of the research. For instance, this is the case when the publicity is driven by commercial motives. Examples of unacceptable forms of publicity are the following:

- Sending out press releases to force the registration of a drug;
- Lending out apparatus in exchange for positive publicity;
- Financing the printing of a dissertation or book on the condition of placing the company logo on the cover.

The basic principle is that the researcher's own institution always provides the publicity. It is possible that the Communications Office can make an agreement with the clients about a division of publicity tasks. By placing the UMCG hallmark on the press release or publication, the independence of the research is emphasized. Clarity about funding can prevent possible suspicion or allegations. It is important to inform the Communications Office fully about these matters.

The UMCG has standing agreements with a number of charities. For example, the Dutch Federation of University Medical Centers (NFU) and the Association of Universities in the Netherlands (VSNU) have agreed that the relevant charities can emphasize their funding or co-funding of research in their publicity.

⁵⁷ *Wetenschap Gewaardeerd*. NWO-strategie 2007-2010. May 2006 ISBN 90-77875-093
URL <http://www.nwo.nl> zoekterm < wetenschap gewaardeerd >

⁵⁸ *Duurzame Wetenschap*. Strategisch Plan KNAW 2007-2010; May 2006. ISBN 90-6984-490-7
URL http://www.nwo.nl/nwohome.nsf/pages/NWOA_6PXJ9W_Eng

⁵⁹ The Communications Office of the UMCG can be reached by phone 24 hours per day, seven days per week. Outside regular office hours, the on-duty press information officer can be reached through the central telephone number of the UMCG, tel. (050) 361 61 61.

8.2 Due caution during media contacts

Responsible popularization of scientific research can be very difficult. This applies perhaps even more to biomedical research than to other branches of science. After all, nearly every biomedical study touches on the interests of patients. Researchers must be aware that overly enthusiastic statements can create unrealistic expectations with patients. Understandably, disappointment or anger can be the result.

Due caution is therefore required when making statements about possible clinical applications of basic research. Many "medical breakthroughs" have reached patients' homes because researchers allowed themselves to be led more by exciting, theoretical prospects than by the actual scope of the results. A classic example in this context is the scientist who indiscriminately applies the results of laboratory or animal studies to humans.

The same caution is required when presenting clinical research. In this type of research, generalization can lead to an excessively broad definition of the categories of patients that can benefit from a new drug or therapy. In addition, caution is always required regarding the actual availability of a new test or drug for patients.

Extreme caution is required when the interim research results point towards success. In this case, there is a great temptation to publicize the results. The urge to provide a positive signal halfway through a study can also be fed by uncertainty concerning the funding of a possible follow-up study.

8.3 Publicity about scientific publications

With important scientific publications, it is advisable to contact the Communications Office at an early stage. This applies especially if a great deal of media attention is expected, if the results of the research can be easily misunderstood or if the research touches on a controversial topic. The Communications Office can then distribute a press release ("setting the right tone") or present the news to the media by means of an article in Triakel, the magazine for professional contacts of the UMCG (this provides more space for careful argumentation).

If the manuscript is going to be published in a scientific periodical, publicity beforehand is often undesirable. Prestigious journals have strict regulations about this, which can even lead to the ultimate sanction of rejecting the article for publication. However, the regulations of these journals are not always very clear. For example, it is unclear whether participation in a conference or PhD defense ceremony are also forms of premature publicity. In this situation, it is therefore also advisable to contact the Communications Office; in case of doubt, it can make a binding agreement with the editorial board of the relevant journal.

Journals generally do allow a press release to be distributed (with a news embargo) several days before the publication date. These journals often distribute a press release themselves with a news embargo. In such cases, consultation beforehand with the Communications Office is always desirable.