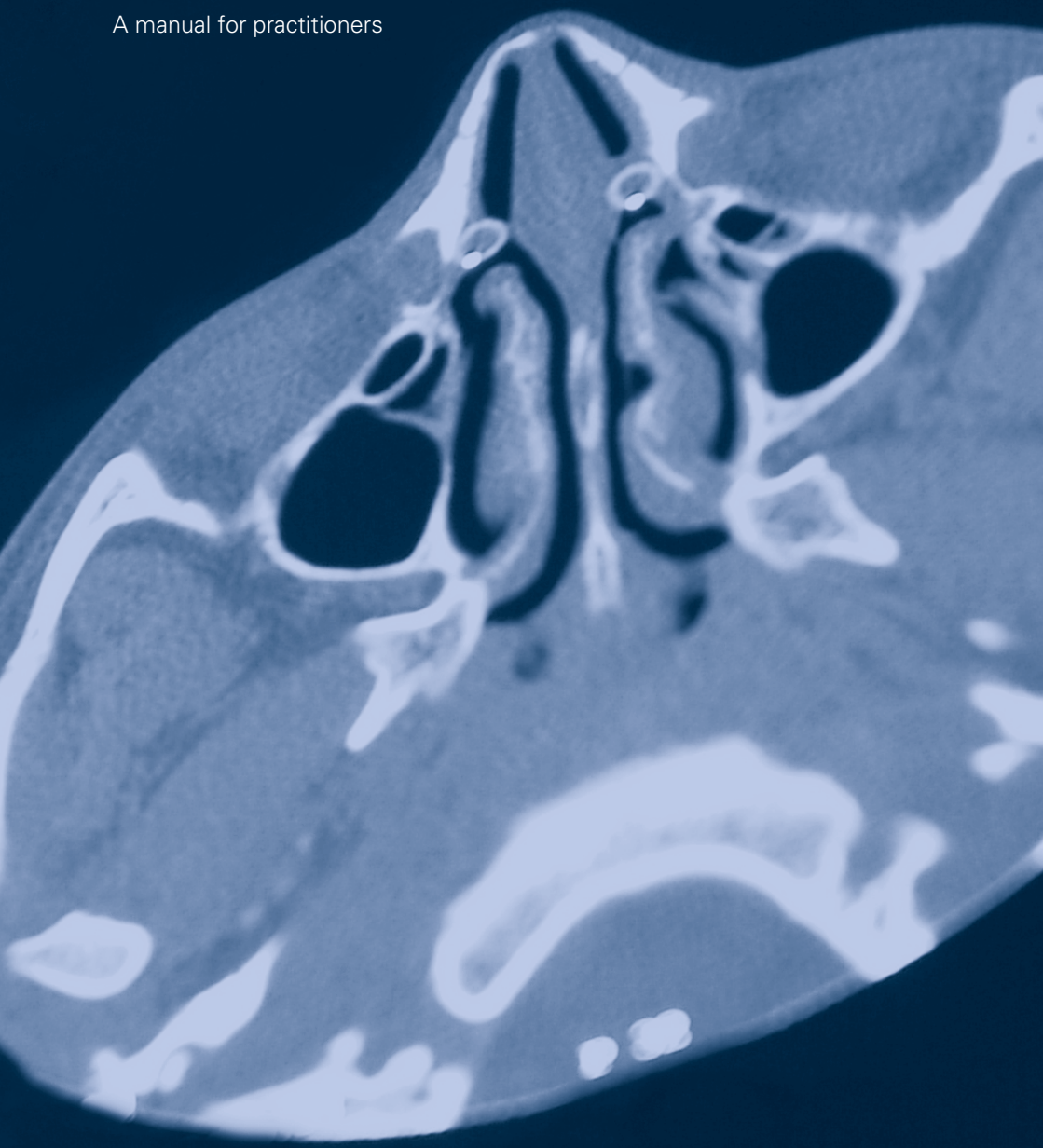
Research with human subjects

A manual for practitioners



2nd edition, revised and adapted in accordance with the Human Research Act
Issued by the Swiss Academy of Medical Sciences

The Swiss Clinical Trial Organisation and the Swiss Ethics Committees on research involving humans (swissethics) support this booklet and recommend it as an important manual for practioners.

swissethics

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Preface

Just as scientific progress is inconceivable without research, so too, if medical research could not be conducted with human subjects, medicine itself would degenerate into slavish adherence to traditional authorities or mere trial and error. However, if research is to enable medicine to develop for the benefit of patients and society, two fundamental requirements need to be met. Firstly, valid results can only be obtained via sound scientific methods; secondly, the regulatory framework for human research must guarantee that participants are duly protected. History has shown that neither of these conditions can by any means be taken for granted.

For this reason, the Swiss Academy of Medical Sciences (SAMS) first issued guidelines for "Research studies in human subjects" in 1970. Since then, the density of regulations in this area has steadily increased. In 2008, with the prospect of comprehensive legislation being introduced – including a new constitutional article and a federal act – the guidelines were withdrawn. For an area largely governed by legal regulations, ethical guidelines forming part of a professional code no longer appeared appropriate.

In their place, the manual entitled "Research with human subjects" was first published in 2009. Its aims are twofold. Firstly, it is designed to give researchers and members of research ethics committees a clear overview of the complex regulatory framework within which research projects now have to be conducted and evaluated. But, secondly, it is also intended to convey the basic ethical attitude which is required if researchers are to be perceived as trustworthy by potential research participants, regulatory authorities, policymakers and the public.

Since 2014, medical research in Switzerland has been comprehensively regulated by the Human Research Act (HRA) and the three associated implementing ordinances. It was clear from the outset that, while the new regulations would not render the SAMS manual superfluous, extensive revision would be required.

The revised manual is addressed primarily to researchers and to members of research ethics committees; however, it will also be of interest to physicians and other medical professionals who do not conduct research projects themselves but who provide care for patients participating in studies. Since not all target readers have to deal with the same questions, the individual chapters can be read independently; a certain amount of duplication is thus inevitable.

While the HRA refers to "research *involving* human beings"[1], the title "Research *with* human subjects" has been retained for this edition of the manual. This represents an explicit appeal for an approach to medical research based on partnership. Even if scientific methods require human individuals to become the objects of research, ethics and the law call for priority to be accorded to the rights of the persons concerned to autonomy and to respect as human subjects. This also applies in cases where individuals are involved in research projects not physically, but only through their samples or personal data.

The SAMS thanks all the existing and new authors and experts without whose contributions it would not have been possible to revise this manual. Particular thanks are due to Michelle Salathé, the deputy General Secretary of the SAMS, who performed the lion's share of the work with great dedication and persistence at every stage – from reconception, coordination of contributors and preparation of texts, right up to the final editing.

Professor Christian Kind,
President of the Central Ethical Committee, SAMS

1 The scope of the HRA is defined as "research concerning human diseases and concerning the structure and function of the human body" (Art. 2 para. 1). The Act covers research activities involving persons, cadavers, embryos and foetuses *in vivo*, biological material and health-related personal data, but also studies of the function of the human body or of human diseases in the humanities and social sciences.

CHAPTER 1

History of research with human subjects

Medical[2] experiments involving human beings are known to have been performed in ancient times, but they only became more widespread from the second half of the 18th century onwards. At that time, clinical/therapeutic tests were first carried out systematically. The view that the practice of medicine amounted to "a continued series of experiments upon the lives of our fellow creatures" gradually began to be accepted around 1800.[3] But it was also argued that patients "should benefit from the trials to which they were subjected, and ... must not be put in danger for the sake of scientific curiosity."[4] These quotations indicate the two different conceptions of "experiment" existing in medicine at that time: for most physicians, it was a matter of testing a new method with the hope of producing a direct benefit for the patient. In contrast, only a few physicians sought to compare a new approach with the conventional method in the largest possible number of patients with the same disease. Here, according to the traditional understanding of scientific experiments, the benefit for the patient arises indirectly, from the reduction in uncertainty regarding the beneficial or harmful effects (or lack of effect) of an intervention. This type of benefit is not readily predictable – otherwise there would be no need to conduct the experiment at all. Some physicians insisted that appropriate measures should be taken to prevent trial-related harm. They also called for the results – negative or positive – to be published.

2 The term "medical" encompasses the activities not only of physicians but also of nurses and other healthcare professionals. In a historical context, however, "medical" is generally taken to refer to physicians.

3 Cf. Maclean C. Results of an investigation respecting epidemic and pestilential diseases. Vol. 2. London: Underwood; 1818, pp. 500–4.

4 Cf. Maehle AH. Drugs on trial: Experimental pharmacology and therapeutic innovation in the eighteenth century. Amsterdam, Atlanta GA: Rodopi; 1999, pp. 268–9.

For many years, hospital and dispensary patients and soldiers served as trial subjects.[5] This raised ethical problems. In Europe's highly class-conscious societies, hospitals were used by the lower classes, while the well-off were treated at home; soldiers had to obey orders. Thus, as early as 1840, human trials were condemned as exploitation of the poor. From today's perspective, patients were indeed frequently exploited, since nobody provided them with information or requested their consent. At the same time, some academics argued that experimentation was indispensable for scientific progress. What did the suffering and death of individuals matter compared to the prospect of universal gains? Among those who warned against this attitude were leading researchers and physicians of the latter half of the 19th century, such as the French physiologist Claude Bernard and the British-Canadian internist William Osler. Their warnings were evidently justified, but little heeded: reports of human trials that would never be approved by a research ethics committee today were published without demur in medical journals[6]. In the 1890s, however, Berlin's daily newspapers carried sensationalist reports of experiments designed to test an antisyphilitic serum: this research was carried out in eight subjects – including minors and prostitutes – without their knowledge or consent. The professor responsible was reprimanded, and in 1900 the Prussian education minister issued what must have been the world's first official "Instructions for Clinic Directors". These related only to non-therapeutic trials – patients were expected to be grateful for therapeutic and diagnostic trials. The instructions called for the provision of information ("appropriate explanation") and consent, the exclusion of minors and those lacking full mental capacity, and detailed record-keeping. However, these instructions received just as little attention as the "Guidelines for New Therapies and for Undertaking Experiments on Human Beings" issued by the Imperial Ministry of the Interior in 1931. The latter distinguished between therapeutic and scientific (non-therapeutic) research and recommended that experiments in humans should be preceded by tests in animals. Typically, neither of these directives provided for sanctions in the event of non-compliance.

5 Cf. Tröhler U. "To improve the evidence of medicine": The 18th century British origins of a critical approach. Edinburgh: Royal College of Physicians; 2000.

6 Cf. Tröhler U. The long road of moral concern: Doctors' ethos and statute law relating to human research in Europe. In: Schmidt U, Frewer A (eds.) History and theory of human experimentation. The Declaration of Helsinki and modern medical ethics. Stuttgart: Franz Steiner Verlag; 2007.

After the Second World War, details emerged of the inhuman experiments conducted on inmates of Nazi concentration camps. Elsewhere, military necessity also served as a pretext for ethically unacceptable human experimentation.[7] At the Nuremberg trials held in 1946–47, it became apparent that a specific legal basis was lacking to convict the indicted doctors. This was only established in the course of the proceedings in the form of the *Nuremberg Code*. Among the ten points specified for ethically legitimate human experiments was the principle of informed consent, i.e. provision of comprehensive information on the goals, methods, potential benefits and risks of the experiment, and voluntary consent on the part of the subjects.

Among national medical associations, the reception of the Code varied: while it was rapidly adopted by the UK and the Netherlands, it was only implemented around twenty years later in most other European countries. The only country to accept all ten principles – incorporating them in the SAMS guidelines – was Switzerland. Two important principles of the Nuremberg Code were not, however, included in the 1964 *Helsinki Declaration*: the personal, non-delegable responsibility of each individual involved in research to ascertain the quality of the consent given and the right of the "human subject … to bring the experiment to an end".[8]

The past 50 years have seen a proliferation of similar guidelines issued by national and international professional associations and by governmental and non-governmental organisations. Triggered by scandals in the US and Germany in the 1960s, this wave of agreements reflected the growing awareness among physicians and the public of the urgent need to regulate medical research in human subjects. But there was also a need for the numerous guidelines to be standardised and simplified. After years of negotiations, this was achieved in 1997, with the adoption of a typical minimal consensus – the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine. This document, known as the Biomedicine Convention, is a legally binding international treaty.[9] Partly as a result of continued ethical and legal debate on research, the status of study participants has changed: research is now spoken of as being conducted *with* rather than *in* human subjects.

7 Cf. Schmidt U. The Nuremberg Doctors' Trial and the Nuremberg Code. In: Schmidt U, Frewer A (eds.). History and theory of human experimentation. The Declaration of Helsinki and modern medical ethics. Stuttgart: Franz Steiner Verlag; 2007, pp. 71–116.

8 Cf. Herranz G. Der Eingang der 10 Nürnberger Postulate in berufsständische Ethik-Kodizes. Ein internationaler Vergleich. In: Tröhler U, Reiter-Theil S (eds.). Ethik und Medizin 1947–1997: Was leistet die Kodizifierung von Ethik? Göttingen: Wallstein; 1997, pp. 171–88.

9 Cf. Tröhler U. The long road of moral concern: Doctors' ethos and statute law relating to human research in Europe. In: Schmidt U, Frewer A (eds.) History and theory of human experimentation. The Declaration of Helsinki and modern medical ethics. Stuttgart: Franz Steiner Verlag; 2007.

CHAPTER 2

Introduction to research ethics

The ethical dilemma posed by research with human subjects is evident: on the one hand, new findings enhance our ability to alleviate suffering; on the other hand, research is not primarily geared to the welfare of those who participate, but to the methodologically sound production of generalisable knowledge. Research serves the interests of a group of patients or society as a whole, and not – or not only – the study participants. These conflicting aims are most apparent when the roles of healer and researcher are combined in a single person.[10] While the healer is responsible for the patient's individual welfare, the researcher is obliged to test a hypothesis using scientific methods. In a situation involving conflicting aims and values, reflection is required: what are the responsibilities of the healer and the researcher, and how can they both be fulfilled at the same time?

Patients can also face ethical conflicts. They may possibly feel obliged to take part in a study suggested by their physician and therefore – despite being assured that participation is voluntary – have inhibitions about refusing. Or they may have to decide whether they wish solely to receive the best possible treatment themselves, or whether they feel obliged to express their solidarity with others in a similar position.

2.1 Principles of research ethics

What is now the most widely accepted formulation of the basic ethical principles underlying the conduct of research can be traced back to the Belmont Report,[11] which was prepared by a National Commission for the US Health Department in 1979.

The three principles identified are:

- Respect for persons (autonomy)
- Beneficence
- Justice

10 Cf. Marckmann G. The conceptual foundations of scientific research and medical practice. In: Boomgaarden, J. et al. (eds.). Issues in Medical Research Ethics. New York: Berghahn; 2003, pp. 9–14.

11 Cf. http://videocast.nih.gov/pdf/ohrp_belmont_report.pdf

Respect for persons entails two requirements: firstly, individuals should be treated as autonomous agents, capable of deciding for themselves about important personal matters. Accordingly, subjects should only be involved in research if they have given their voluntary consent and been fully informed about the nature, purpose and consequences of the study. Secondly, individuals whose autonomy is diminished as a result of external circumstances, or their physical or mental condition, require special protection. With regard to a research project, this protection needs to be adapted to individual circumstances, ensuring that the persons concerned are not involved in research which could be harmful for them.

Beneficence is the duty to ensure the welfare of the persons concerned. This means an obligation firstly to avoid harm and secondly to maximise possible benefits. But here a dilemma arises: to avoid risks, one needs to know what is harmful. This knowledge, in turn, depends on evidence obtained from studies. Thus, in order to discover what is actually beneficial for patients, it may be necessary to expose them to risks.

Justice is concerned with the distribution of burdens, risks, chances and benefits to different persons and groups, and with the question of what exactly is "owed" to an individual. The first element raises the question, for example, who should receive the benefits of research and who should bear its burdens. The second asks, for example, to what extent people whose condition may differ markedly should be recognised as equals and treated accordingly.

Answers to concrete questions concerning research projects cannot, however, be directly derived from these three abstract ethical principles. They are to be understood as fundamental guiding principles to be taken into account in the careful ethical evaluation of research projects. Their specific content emerges from an understanding and analysis of the particular case. The various principles may also conflict with one another. In cases where the interests of society in acquiring scientific knowledge are to be weighed against the interests of an individual participating in a study, priority should generally be accorded to the latter.

2.2 Ethical requirements for the planning and conduct of research projects

What conditions have to be met if research with human subjects is to be ethically justifiable and thus acceptable? To answer this question, the ethical principles need to be fleshed out and defined in operational terms. Having analysed the most important international guidelines published since the adoption of the Nuremberg Code in 1947, Emanuel et al.[12] propose seven requirements for the conception and implementation of studies which must be fulfilled if clinical research is to be ethical:

- A study must be socially valuable.
- A study must be conducted in a methodologically rigorous manner.
- The selection of subjects must be fair.
- The risk-benefit ratio must be favourable.
- There must be an independent review.
- Subjects must freely give their informed consent to participate.
- Subjects must be treated with respect throughout the study and after its completion.[13]

Evidently, informed consent alone is not enough to ensure the ethical acceptability of a study with human subjects – additional requirements must also be met. In addition, there are certain situations in which it is not possible for informed consent to be obtained and yet it is still fair and appropriate to carry out a research project. This means that informed consent is neither necessary nor sufficient for ethical clinical research.

12 Cf. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA. 2000; 283: 2701–11.

13 In a subsequent publication, these authors defined further benchmarks for research conducted in developing countries, e.g. "Respect the community's values, culture, traditions, and social practices." Emanuel EJ, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. Journal of Infectious Diseases. 2004; 189: 930–7. For a comprehensive examination of the ethical and legal issues involved, cf. Lenk C, Duttge G, Fangerau H (eds.) Handbuch Ethik und Recht der Forschung am Menschen. Heidelberg: Springer; 2014.

In giving concrete form to the ethical principles, the seven requirements listed above do not define the boundaries of what is prohibited or permissible in absolute terms. That would be the case if, for example, conditions were specified such as "non-therapeutic research involving subjects incapable of giving consent is prohibited" or "human embryos must not be created for research purposes". Thus, rather than promoting the moralisation of science, the requirements enable research with human subjects to take place within a culture of reflection. This culture, of course, still leaves room for moral reservations which are important to individuals and which in some cases – depending on the particular country – are reflected in regulations, thus placing further limits on what is legally permissible.

The seven requirements correspond to the globally accepted standards now enshrined in international guidelines. However, despite their fundamental universal validity, the requirements need to be adapted to specific features of the particular social and cultural context. In certain cultures, for example, it will be necessary – for reasons of respect – to consult family elders before an individual can give informed consent. To determine the ways in which the selection of subjects can be unfair, a detailed knowledge of local social conditions will be required.

2.3 Research ethics: a multi-stage process

The conception, review and implementation of research projects are based on a multi-stage discursive process. Each stage involves elements which serve as the pillars upon which ethical research with human subjects rests:

- ethical reflection on the part of researchers;
- independent review by a research ethics committee;
- voluntary informed consent given by study participants;
- ongoing critical public debate on research ethics procedures and regulations.

The first pillar underlying the process is the researchers' moral stance. When a project is first conceived, a variety of ethical aspects need to be considered, and because the researchers are best placed to recognise the possible implications of their study for the participants, they are responsible for identifying and resolving ethical problems at the planning stage. In other words, researchers can only gain the trust of participants by exhibiting an active concern for their welfare, based on an ethical attitude.

The second pillar consists of independent review by an interdisciplinary research ethics committee, evaluating the scientific quality of the study, the risk-benefit ratio and any ethical problems which could arise in connection with the study.

The third pillar is formed by the participants' self-determination. The researchers are responsible for informing participants about all relevant aspects of the study, so that they understand what kind of decision is involved. They must know what other treatment options are excluded if they participate, what chances and risks are associated with the study, what the study involves in practice, what responsibilities, rights and obligations they have, etc. In addition, they must be given the opportunity to ask questions, which are answered to their satisfaction in a comprehensible manner. Lastly, they must be able either to consent voluntarily or to refuse to participate without suffering any disadvantages. They must also be allowed to withdraw from the study at any time.

The fourth pillar of research ethics is the social underpinning of procedures and criteria in the form of transparent and openly debated regulations. Apart from federal and cantonal legislation, an important role is played not only by international agreements but also by "soft law" – in particular, the Helsinki Declaration of the World Medical Association. Circumstances can change, creating hitherto inconceivable challenges; scientific and technological developments raise new questions and enable different kinds of research projects. It is therefore essential that the established standards of research ethics should be subject to ongoing critical review, not only within the scientific community but also among the public.

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CHAPTER 3

Legal framework

Until recently, the field of human research was not consistently or fully regulated in Switzerland. With the entry into force of Art. 118b of the Federal Constitution ("Research on human beings") and the Federal Act on Research Involving Human Beings, Switzerland now has a uniform and comprehensive set of regulations. Under Art. 118b of the Federal Constitution (approved in a referendum held on 7 March 2010), the Confederation is responsible for legislating on research involving human beings where such research could pose risks to their dignity or privacy. In addition, this constitutional article specifies key principles for biological and medical research involving human beings.

3.1 International regulations

At the international level, various ethical guidelines for human research exist, which are of indirect legal significance for Switzerland insofar as reference is made to them in legislation or professional codes, or they are invoked in the application of the law by courts and authorities. Of fundamental importance are the Ethical Principles for Medical Research Involving Human Subjects adopted by the World Medical Association in Helsinki in 1964 (the *Helsinki Declaration*). Reference is made to the Helsinki Declaration (as amended in 2013) in Art. 18 of the Code of the Swiss Medical Association (FMH).

Also of particular relevance is the *Guideline for Good Clinical Practice* of the International Conference on Harmonisation (ICH Guideline), which was adopted in 1996 and is currently under revision. The ICH Guideline is designed to create internationally harmonised quality standards for the conduct of clinical trials of pharmaceuticals so as to facilitate mutual recognition of clinical research data. In Switzerland, the ICH Guideline is directly applicable, as reference is made to it in the Clinical Trials Ordinance. While the ICH Guideline refers to the principles of the Helsinki Declaration, it is much more detailed and comprehensive. It specifies the rights and duties not only of investigators but also of sponsors (who take responsibility for the management or financing of a clinical trial). Also of indirect relevance for Switzerland is the *Regulation on clinical trials on medicinal products for human use* (EU No 536/2014), which was adopted on 16 April 2014 and is to supersede the currently applicable Clinical Trials Directive (2001/20/EC). The new Regulation will apply no earlier than 28 May 2016.

Human research is also regulated by international treaties, notably the Council of Europe's Convention on Human Rights and Biomedicine, which was ratified by Switzerland in 2008. The Biomedicine Convention specifies minimum standards for biomedical research on persons and on embryos *in vitro*. However, following the entry into force of the Human Research Act and its associated ordinances, these standards are no longer of independent importance. The Additional Protocol to the Biomedicine Convention concerning Biomedical Research, adopted by the Council of Europe in January 2005, has not been signed by Switzerland to date.

3.2 Switzerland

The Federal Act on Research Involving Human Beings (*Human Research Act, HRA*), which came into effect at the start of 2014 together with three implementing ordinances (Clinical Trials Ordinance, ClinO; Human Research Ordinance, HRO; HRA Organisation Ordinance, OrgO-HRA), gives concrete form to the principles for the protection of human beings in research enshrined in Art. 118b of the Federal Constitution (see Section 3.3). Under the HRA, authorisation is mandatory for all research projects covered by the Act; the HRA specifies in detail the conditions for authorisation and the procedure to be followed by cantonal ethics committees.

In addition, for certain areas of research, special provisions apply. For *clinical trials of therapeutic products* (medicinal products and medical devices), it is necessary to comply with the Therapeutic Products Act[14] as well as the HRA. Here, authorisation is generally[15] required not only from the ethics committee but also from Swissmedic. For *clinical trials in transplantation medicine*, the Transplantation Act[16] generally requires authorisation from the Federal Office of Public Health as well as from the ethics committee. Finally, *research involving IVF embryos and embryonic stem cells* is regulated, not by the HRA, but by the Stem Cell Research Act[17].

Apart from the above-mentioned research-specific regulations, human research projects are also subject to general legal provisions concerning, in particular, personal and public liability, offences against life and limb (Art. 111 ff. Swiss Criminal Code[18]), professional confidentiality in medical research (Art. 321bis Swiss Criminal Code) and data protection (federal and cantonal legislation).

14 Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA; SR 812.21).
15 Under Art. 30 ClinO, Category A clinical trials are exempted from the requirement for authorisation from Swissmedic.
16 Federal Act of 8 October 2004 on the Transplantation of Organs, Tissues and Cells (Transplantation Act; SR 810.21).
17 Federal Act of 19 December 2003 on Research Involving Embryonic Stem Cells (Stem Cell Research Act, StRA; SR 810.31).
18 Swiss Criminal Code of 21 December 1937 (SR 311.0).

3.3 Federal Act on Research Involving Human Beings (HRA): purpose and scope

In the HRA, research is defined as a systematic search for generalisable knowledge, driven by scientific methods. The question of what is to count as a scientific method has to be answered with recourse to the standards of the scientific community.

The purpose of the HRA is threefold:

a) Protecting the dignity, privacy and health of human subjects

The primary aim of the HRA is to protect the "dignity, privacy and health" of persons involved in research (Art. 1 para. 1). For this purpose, the Act specifies various conditions which must be met if a research project is to be carried out. In particular, persons may generally only be involved in a research project if they have given their informed consent (Art. 16) and if the likely risks are not disproportionate to the expected benefits of the project (Art. 12 para. 2).

b) Creating favourable conditions for research

The HRA is also designed to create favourable conditions for research (Art. 1 para. 2 let. a). Before the introduction of the Act, provisions concerning human research were patchy and scattered across various federal and cantonal laws. The HRA now provides a uniform regulatory framework for human research in Switzerland and, by harmonising the administrative requirements, creates favourable conditions for research.

c) Ensuring the quality and transparency of research with human subjects

Finally, the HRA also aims to ensure the scientific quality and transparency of research with human subjects. The use of human beings as objects of research can only be justified if the research is of high quality and projects are conducted in a transparent manner. For example, the HRA stipulates that research must address a scientifically relevant topic (Art. 5) and meet certain scientific requirements (Art. 10). The Act also provides for mandatory registration of authorised clinical trials (Art. 56).

The scope of the HRA is defined as "research concerning human diseases and concerning the structure and function of the human body" (Art. 2 para. 1). The Act covers research involving persons, cadavers, embryos and foetuses *in vivo*, biological material and health-related personal data, but also *studies of human diseases in the humanities and social sciences*. Humanities or social science research projects which are not concerned with a disease or do not involve interventions or effects on the human body – e.g. employing only interviews or observations – do not fall under the HRA, although it is not always easy to draw such distinctions in particular cases. Also not covered by the HRA is research involving anonymised biological material or anonymously collected or anonymised health-related data (Art. 2 para. 2 let. b and c).

In some cases, it may be difficult to determine whether a research project falls within the scope of the HRA. Often, for example, research cannot be clearly differentiated from non-research – particularly in the case of quality assurance projects, practice experience reports or studies required for scientific qualifications (dissertations and Master's theses). Under the legislation, the decision whether an activity counts as research or not depends on both the goal and the method: whenever generalisable scientific knowledge is sought in a systematic, method-driven and verifiable manner, the activity is deemed to be research.

In differentiating between quality assurance and research projects, the following criteria are helpful:[19]

	Quality assurance	Research
Aim	– Based on project management principles and methods, existing operations are reviewed in order to optimise processes and increase efficiency – Improvements should directly and primarily benefit the institution in line with operational strategy – Project results are to be implemented as rapidly as possible – Generally, object-related (e.g. hospital)	– Search for generalisable knowledge in accordance with scientific principles and methods – Targeted gain in knowledge: object-independent and open outcome
Scope of consent of persons involved in the project	As a rule, only consent to use of data	As a rule, consent to involvement in the research project (including use of data)
Risk for participants	No risk or no greater than in routine operations	Minimal to high, depending on the project
Publication in a scientific journal	Not envisaged. However, the results may prove to be of such medical or public interest that a decision to publish is subsequently taken	Publication is the rule, whenever possible in a recognised scientific journal
Applicable law	– Data protection legislation – Health Insurance Act	– Human Research Act – Therapeutic Products Act and associated implementing ordinances – Data protection legislation – Health Insurance Act

19 Cf. swissethics, Clarification of responsibility: www.swissethics.ch/doc/ab2014/Zustaendigkeit_e.pdf

Compassionate use or experimental treatment in individual cases[20] is only considered to be research falling within the scope of the HRA if at least one of the following criteria is met:

– Data concerning several patients[21] is prospectively collected and analysed.
– The type of treatment and mode of administration are determined not only by the needs of the patients but also by the requirements of the research project.
– Additional data, not required for treatment purposes, is collected, or additional investigations are carried out.

The expressions research concerning human diseases and structure and function of the human body used in the HRA are imprecise and may give rise to uncertainty – especially in the case of research projects in fields such as psychology, nursing science or sociology – as to whether the HRA is applicable or not. In the Dispatch concerning the HRA, the following explanation is given:[22] "'Research concerning the structure and function of the human body' relates in particular to general basic research in the areas of anatomy, physiology, pathophysiology and genetics of the human body. It is covered by the present draft Act even if it has no bearing on a disease, and is therefore to be distinguished from 'research concerning diseases' as described above. In contrast, basic research in other areas, e.g. concerning the human mind or its development, only falls within the scope of the Act if, in accordance with [Art. 3] let. b, it generates knowledge on the causes and pathogenesis of (frequently mental) diseases. Research on the normal structure, function and development of the human mind, as undertaken for example in educational sciences and in basic psychological research, is not included in the scope. In addition, the scope encompasses any research which, outside of the prevention, diagnosis, treatment and epidemiology of diseases, involves interventions and effects on the body." Imaging procedures and direct measurements of brain function are deemed to be research concerning the function of the human body and thus always fall within the scope of the HRA, even if they are conducted in the field of the humanities or social sciences.

20 "Experimental treatment in individual cases" refers to a treatment which differs from the standard treatment, or is employed in the absence of a standard treatment; cf. the SAMS Guidelines "Distinguishing between standard treatment and experimental treatment in individual cases" (2014): www.samw.ch

21 Here, the Zurich Cantonal Ethics Committee (KEK) has defined an upper limit of 5 patients.

22 Cf. Federal Council Dispatch of 21 October 2009 concerning the Federal Act on Research Involving Human Beings, BBl 2009, p. 8094, Sect. 2.1.1.3.

In case of doubt, a decision on responsibility must be taken by an ethics committee. Increasingly, however, universities and other higher education institutions are establishing Institutional Review Boards to evaluate research projects in the fields of nursing science, psychology, etc. which do not fall within the scope of the HRA.

Literature

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CHAPTER 4

Scientific requirements for research projects[23]

4.1 Relevance of the topic

It is in the public interest that research projects should be carried out which increase our knowledge of individual and public health; accordingly, society invests public funds for this purpose. For the participants, however, involvement in a research project may entail risks and burdens which are only offset by comparable benefits in some cases – and this is never guaranteed for the individual subject. Participation in studies is therefore usually based on altruistic motives, especially the idea of helping future patients. In general, researchers appeal implicitly or explicitly to motives of this kind when they seek to recruit patients or healthy volunteers. When clinical studies are designed, therefore, at least as much attention must be paid to their potential for generating knowledge with the maximum possible benefits for future patients as is paid to the interests of researchers in high-profile publications or to those of industry in profitable products. While researchers and sponsors do have legitimate interests of their own, these must not compromise their honesty and fairness vis-à-vis study participants.

Although researchers have a right to academic freedom,[24] this is not unlimited. In particular, researchers are accountable for their goals, their behaviour and their use of resources. Irresponsible conduct can damage the credibility and undermine acceptance of research. Recent years have seen growing criticism of the waste of resources arising from fruitless, unnecessary and poorly planned biomedical research.[25] Professionals agree that studies which expose the participants to needless risks and burdens are not ethically justifiable. Article 5 of the HRA specifies that research involving human beings may only be carried out if it addresses a topic of scientific relevance concerning the understanding of human diseases, the structure and function of the human body, or public health. However, assessing in advance whether or not a topic is relevant is not always easy and poses difficulties for ethics committees in particular.

23 Cf. Part III: Methodology.
24 Freedom of research and teaching is guaranteed under Art. 20 of the Federal Constitution.
25 Macleod MR, Michie S, Roberts I, Dirnagl U, Chalmers I, Ioannidis JPA, Salman RA, Chan A-W, Glasziou P. Biomedical research: increasing value, reducing waste. Lancet. 2014; 383: 101–4.

4.2 Scientific quality[26]

If research is scientifically unsound, it will produce unusable results and thus needlessly expose study participants to risks or burdens and abuse their trust. Studies must therefore be designed and conducted in such a way that the results can be expected to be reliable and valid. Researchers are also responsible for ensuring that the study which they are planning can yield generalisable knowledge and addresses a question which is not already answered by existing solid data. The obligation to record authorised clinical trials in a public registry (Art. 56 HRA) helps to avoid unnecessary repetition of studies. In addition, registration makes it easier to find ongoing, discontinued or unpublished studies and can provide insights into conflicts of interest.

According to the literature, the following criteria should be reviewed in order to ensure scientific quality:

Research topics should be selected in such a way as to maximise the potential benefits for future users of the results:

- Before a study is planned, an overview of the current state of research based on a complete literature list should be prepared so as to avoid unnecessary repetition.
- Patients, physicians and other health professionals can provide valuable information on the practical relevance of the research topic (patient organisations, professional associations or focus groups can also be involved in preliminary investigations).
- Research groups working on similar topics should be identified via study databases and contacted so as to facilitate synthesis of the results through mutual agreements or direct collaboration.

26 Under Art. 10 HRA, research involving human beings may only be carried out if scientific quality requirements are met and the persons responsible have appropriate professional qualifications.

The methods must be selected so as to ensure that the research question can be reliably answered by the study:[27]

- The number of study participants must be in accordance with the chosen research method; in particular, it must enable a clinically relevant difference to be detected with a high degree of confidence (power analysis).
- Appropriate attention should be paid to the avoidance of bias (i.e. distortions due to methodological factors).
- A small number of predefined outcomes should be measured, which are as relevant as possible for patients.
- Planning, data collection and data analysis must be performed by qualified professionals not subject to conflicts of interest of any kind.
- The study protocol must be sufficiently detailed and made publicly accessible to allow the study to be replicated.

All results of clinical studies must be made accessible to the public, irrespective of their content:[28]

- All studies, including those with negative results, must be published in a suitable form.
- The publication should comply with recognised standards (for an overview of reporting guidelines see: www.equator-network.org). It must be sufficiently complete to allow the results to be reproduced and to ensure transparency and comprehensibility.
- The results obtained should be interpreted and assessed in the light of the current state of research.
- The primary data should be made available to other researchers for further investigation and meta-analyses.

27 Cf. Part III: Methodology.
28 Cf. also Chapter 11.

Literature

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Salman RA, Beller E, Kagan J et al. Increasing value and reducing waste in biomedical research regulation and management. Lancet. 2014; 383: 176–85.

4.3 Scientific integrity[29]

In accordance with its goal of seeking the truth and its methods based on truthfulness, research depends for its very existence on the fulfilment of certain fundamental requirements. These can best be defined and, in particular cases, evaluated by those who are themselves involved in the scientific process. Scientific misconduct is not a new phenomenon, although it should be noted that the current research environment (shortage of time, competitive pressures, lack of mentoring, etc.) increases the temptation to use questionable means to secure greater attention and more rapid scientific success. Universities and research-funding institutions are responsible for raising awareness of scientific integrity and taking appropriate measures to support a scientific culture which promotes honesty in research. They are also required to establish appropriate procedures for sanctioning scientific misconduct. The Swiss Academies of Arts and Sciences have drawn up recommendations concerning the design of such procedures.[30] Most Swiss universities and the Federal Institutes of Technology (ETH, EPFL) have now issued regulations for dealing with scientific misconduct and have appointed an ombudsperson, who serves as an advisor and arbitrator and is to be contacted in the event of suspected scientific misconduct.[31] If suspected cases are reported by a whistleblower, the individual concerned must be protected from any reprisals or other adverse consequences.

29 Cf. Art. 10 para. 1 let. a HRA, which specifies that the recognised regulations concerning scientific integrity must be complied with. In Art. 3 ClinO, reference is made to the Principles and Procedures for Integrity in Scientific Research issued by the Swiss Academies of Arts and Sciences.

30 Cf. Integrity in scientific research: Principles and procedures (2008); Authorship in scientific publications: Analysis and recommendations (2013): www.akademien-schweiz.ch/en/index/Schwerpunktthemen/Wissenschaftliche-Integritaet.html

31 Cf. Overview of regulations/guidelines concerning scientific integrity issued by Swiss higher education institutions: www.akademien-schweiz.ch/en/index/Schwerpunktthemen/Wissenschaftliche-Integritaet.html

In particular, the following types of misconduct, inter alia, are contrary to the rules of scientific integrity:

- Causing harm to other researchers (e.g. through sabotage, breaches of confidentiality, retaliation against whistleblowers, or unjustified allegations of misconduct);
- Causing harm to patients, trial subjects or the public (e.g. through questionable research goals or methods);
- Practising deception, which makes scientific progress impossible: deception with regard to data (fabrication, falsification or suppression) or the origin of texts or ideas – either without the consent of the actual author (e.g. in the form of copyright violation or incorrect omission of an author's name) or with the author's consent (e.g. in cases of ghostwriting or incorrect listing of an additional author). Other examples include deception regarding personal details, such as failure to disclose personal interests or misrepresentation of qualifications and awards, but also incorrect attribution of qualifications to third parties – e.g. in fraudulent expert opinions.

Literature

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European Science Foundation/ALLEA. European Code of Conduct for research integrity. Strasbourg. 2011. www.esf.org/fileadmin/Public_documents/Publications/Code_Conduct_ResearchIntegrity.pdf

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Swiss Academies of Arts and Sciences. Integrity in scientific research: Principles and procedures. 2008. www.akademien-schweiz.ch/en/index/Schwerpunktthemen/Wissenschaftliche-Integritaet.html

4.4 Management of conflicts of interest

The financing of research projects can give rise to a conflict of interest which may undermine confidence in the researchers' integrity. It is therefore essential to disclose the financial aspects of research activities and to eliminate any existing conflicts of interest. Payments should not exceed the level required to compensate for the additional work actually arising as a result of the study. Funds should never be paid into a personal account, but into an institutional account for third-party funding. Sound research requires the greatest possible transparency in the financing of studies.

However, transparency is only of limited use in remedying a loss of confidence since it does not alter the conflict of interest itself – it merely reveals it. In a sceptical essay on this topic, Carl Elliott[32] concludes that "Disclosure is an empty ritual designed to ease the consciences of academics." Accordingly, transparency should not distract attention from the real issue of eliminating conflicts of interest themselves. What is ethically problematic about conflicts of interest is not primarily the fact that they are invisible, but that they can influence the behaviour of medical researchers and other medical professionals at the treatment/research interface in a way that runs counter to patients' best interests. For example, researchers might be led to manipulate the results of studies or to expose participants to risks, e.g. by withholding information on certain exclusion criteria for a study. Nonetheless, financial ties between researchers, their institutions and sponsors must be fully disclosed to the research ethics committee. Only then can the committee assess whether the agreements are acceptable and whether certain precautionary measures are required.

32 Eliott C. Pharma goes to the laundry: Public relations and the business of medical education. Hastings Center Report. 2004; 34(5): 18–23.

The following questions are to be answered:

- Where do the funds come from, and what interests are being pursued by the sponsor?
- Where do the funds go to, i.e. who benefits financially from the study, and how much is being paid for what services?
- Who is vulnerable due to a lack of funds or a desire for income, and what form do study-related vulnerabilities take?
- What medical decisions can be influenced by financial motives related to the study, and in what ways (e.g. manipulation of study results in the interests of the sponsor)?

Literature

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CHAPTER 5

Selection of study participants

The selection of potential study participants encompasses all decisions concerning who is to be included in a study. Important elements are thus not only the specific inclusion and exclusion criteria but also the strategy adopted for recruitment of participants.

The selection criteria have a substantial influence on the interpretation of the results and their applicability in practice. The criteria are often narrowly defined so as to obtain a study population which is as homogeneous as possible. This increases the likelihood that the fundamental efficacy of an intervention can be demonstrated; in addition, the risks associated with the study are reduced by the exclusion of vulnerable persons. However, the price paid for the advantages of this approach is the limited generalisability of the results. In other words, the effectiveness of the intervention is not guaranteed for widespread use in practice, and adverse effects in certain patient groups may remain undetected. In contrast, if the selection criteria are more broadly defined, while on the one hand the external validity of the results is considerably increased, on the other hand larger study populations are required in order to obtain reliable results in spite of greater random variation and more numerous confounding factors. The generalisability of results can also be reduced if the rate of consent to participate in a study varies widely among different patient groups.

Ethical pitfalls are also associated with the choice of recruitment measures (e.g. advertisements, call centres, personal contacts). For example, the voluntariness of participation can be affected by high levels of compensation or by advertisements extolling the benefits of the drug which is to be investigated.[33] A checklist issued by swissethics provides an overview of the requirements to be complied with when advertising is used to recruit participants.

Fair selection of study participants means that no groups are to be subjected to discrimination – i.e. no group of persons is to be overrepresented in or wholly excluded from research without good reason (Art. 6 HRA).[34] After all, the results of research should be generalisable to all those who could benefit from the intervention under investigation. Fair selection also means that those groups and

33 Cf. Recruitment of study participants by means of advertising: www.swissethics.ch/doc/ab2014/Inserat_Checkliste_e.pdf; cf. also the recommendations concerning recruitment measures issued by the Working Group of Research Ethics Committees in Germany (AKEK): www.ak-med-ethik-komm.de/documents/RichtlinienfuerRekrutierungsanzeigenVersion10112012.pdf

34 Cf. also Art. 8 para. 2 of the Federal Constitution, which prohibits discrimination, in particular on grounds of origin, race, gender, age, language, social position, way of life, religious, ideological, or political convictions, or because of a physical, mental or psychological disability.

individuals who shoulder the risks and burdens of the research should enjoy the benefits. In addition, those who share in the benefits should also bear a proportion of the risks and burdens.

Fairness in the selection procedure thus demands that the recruitment of participants should be based primarily on the scientific goals of the study, rather than on whether certain groups happen to be readily available. Nor should selection be determined by privilege or other factors not related to the goals of the study. The exclusion of particular groups of persons (e.g. based on criteria such as age, sex, multimorbidity) is only justifiable from an ethical and legal perspective if it is required by the research question, or if participation in the study would involve disproportionate risks for the group concerned. Often, however, the inclusion of vulnerable groups can be made possible by special precautionary measures.

5.1 Concept of vulnerability

Vulnerability is a basic human characteristic, which also has to be taken into account in the research context in particular. Even if the boundaries cannot always be clearly defined, certain people are particularly vulnerable and thus require special protection. Children and people with cognitive impairments are vulnerable because their capacity for autonomy is limited or wholly lacking. Older people and those with physical impairments are particularly vulnerable if they are dependent on care and support. Patients who are invited by their physician to participate in a study may possibly be susceptible to deliberate or unconscious efforts to influence their decision. Vulnerability is also increased when people feel obliged to do their physician a favour. This also applies to people who, as employees, are dependent on the investigator.

In the research context, particular vulnerability arises in situations involving:

- limited or absent capacity for autonomy;
- social discrimination;
- stigmatisation;
- dependency or other impairment; and
- increased physical or psychological sensitivity to the planned interventions.

In cases where vulnerable groups are to serve as participants, their particular vulnerability must therefore be taken into account throughout the study. If persons partly or wholly lack the capacity for autonomy, this needs to be considered in the assessment of potential benefits and risks. In particular, the procedure for providing information about the study will also have to be adapted.

Research projects involving particularly vulnerable participants are only ethically justifiable and permissible[35] if the principle of subsidiarity is respected: particularly vulnerable persons may only be involved in a research project if equivalent findings cannot be obtained by other means. Thus, for example, a research project involving children may only be carried out if, for scientific reasons, the knowledge sought can only be obtained with children – and not with adults who have capacity; a case in point would be an investigation of the effects of medicines in children, who have a different metabolism from adults and show a different spectrum of disease. The subsidiarity principle is designed to prevent the exploitation of circumstances which increase a group's vulnerability to facilitate recruitment for a study (e.g. prisoners' dependency, children's lack of capacity or marginalised groups' need for integration).

It should be borne in mind that the avoidance of research with vulnerable persons further increases their vulnerability: the systematic exclusion of vulnerable groups leads to their being disadvantaged, owing to the lack of evidence-based knowledge concerning treatment methods and drug dosages appropriate for these patients. For example, evidence-based guidelines are frequently lacking for the treatment of children and adolescents. Many drugs used in paediatrics have not been tested in children and are thus prescribed off-label or in unlicensed applications. The effects of drugs in women are also less well known, as they tend to be excluded from studies because of the risk of pregnancy. In paediatrics, a research network known as SwissPedNet[36] has recently been seeking to promote clinical trials in children. Further impetus should come from the National Programme on Orphan Diseases.[37]

In the HRA, additional requirements are specified for research projects involving the following particularly vulnerable groups:

- children;
- adolescents (legal minors aged 14 years or more);
- adults lacking capacity;
- pregnant women;
- prisoners;
- persons in emergency situations.

35 Cf. Art. 11 para. 2 HRA ("Subsidiarity"): "A research project involving particularly vulnerable persons may only be carried out if equivalent findings cannot be obtained by other means."
36 Cf. www.swisspednet.ch
37 Cf. National Programme on Orphan Diseases: www.bag.admin.ch/themen/medizin/13248/index.html

The requirements vary depending on whether the research project is likely to improve the participants' health (expected direct benefit), or no such benefit is expected (non-therapeutic research).

The distinction between *therapeutic* (i.e. with an expected direct benefit) and *non-therapeutic research* has, however, been called into question by some authors.[38] Kleist and Zerobin summarise the development of the debate in this area as follows: "The original 1964 version of the Helsinki Declaration distinguished between therapeutic research (clinical studies), offering the patient a potential personal benefit, and non-therapeutic (experimental) biomedical research involving human beings. [...] However, with the establishment of the randomised, placebo-controlled study in the 1970s, the boundaries grew increasingly blurred and it became evident that therapeutic research also comprises non-therapeutic elements. The differentiation appeared increasingly illogical. In addition, ethical problems arise as a result of the possible undermining of the informed consent process, since the concept of therapeutic research encourages assignment to an established treatment and pushes the risk-benefit assessment of a study into the background. After intense controversy, the distinction between the two types of research was abandoned in the amended version of the Helsinki Deklaration adopted in 2000. At the same time, the processes of risk-benefit assessment and subjects' informed consent were strengthened, and the protection of patients in control groups was accorded high priority."[39]

Studies with persons belonging to a vulnerable group not listed in the HRA – e.g. those who have psychological disabilities, are unemployed, lack knowledge of the national languages or are refugees – may only be carried out if special consideration is given to the specific vulnerability profile. In order to assess the ethical aspects of a study, awareness of these specific vulnerabilities is essential.

38 Cf. Kind C. "Fremdnützige" Forschung mit Kindern – ist die scharfe Abgrenzung zu "therapeutischer" Forschung adäquat und zweckmässig? Bioethica Forum. 2007; 53: 2–5.

39 Cf. Kleist P, Zerobin Kleist C. Historische Meilensteine der Guten Klinischen Praxis von Heilmittelstudien. Teil 2: Von der Helsinki-Deklaration bis heute. Schweizerische Ärztezeitung. 2009; 90(14): 589–93.
The distinction is, however, reintroduced in the currently applicable Helsinki Declaration (2013): Article 28 specifies that, if research involving subjects incapable of giving informed consent has no expected direct benefit, it must be intended to promote the health of the relevant group, comply with the subsidiarity principle and entail only minimal risks and burdens.

5.2 Children, adolescents and adults lacking capacity

This group is extremely heterogeneous. On the one hand, it comprises persons who have never had capacity, e.g. young children, but also adults who were either born with a severe mental disability or suffered incapacitating brain damage in infancy. On the other hand, it comprises persons who, before losing their capacity, e.g. as a result of an accident or illness, were fully capable. It should also be borne in mind that, in many cases, the range of decisions for which capacity exists does not remain constant: while it becomes broader with increasing age in children and adolescents, it becomes more limited in progressive disease, e.g. in patients with dementia, and may also fluctuate. According to the definitions given in the HRA, the transition from childhood to adolescence occurs when a child reaches the age of 14 years (Art. 3 let. j and k).

Children and adolescents are particularly vulnerable for a number of reasons: they are less able to protect themselves against adults' actions and decisions; they are dependent on adults; they react particularly sensitively – both physically and psychologically – to certain events; with regard to the adult world, their capacity for judgement is not yet – or not fully – developed, and any damage can affect them for the rest of their lives. Even so, as mentioned above, it is very important to carry out studies with children, given the lack of evidence-based guidelines for their treatment in many areas.

If *adults lacking capacity* participate in research projects, they require special protection and care, as they are not (fully) able to safeguard their own interests. Separate issues arise in the case of persons who as a result of an *emergency situation* are not fully conscious and who require immediate medical treatment, without it being possible to obtain their consent or the agreement of their legal representative before a study begins (cf. Sect. 5.5).

Whereas in the case of children and adolescents, for example, the legal representatives – generally the parents – are readily identifiable, for many adults lacking capacity it first needs to be established whether they have written an advance directive, and who is authorised to represent them in medical matters.

Studies with children, adolescents and adults lacking capacity have to meet particularly stringent requirements. To ensure that these vulnerable persons are protected in the context of research, compliance with the special requirements has to be carefully evaluated by ethics committees.

In summary, the following conditions must be fulfilled (cf. also the swissethics checklist for research on and with children and adolescents[40]):

- Equivalent findings could not be obtained from a study carried out on adults with capacity (subsidiarity).
- Studies involving children, adolescents or adults lacking capacity which do not offer a prospect of direct benefit can only be carried out if the risks and burdens are minimal and if the findings, on subsequent application, will primarily benefit children, adolescents or adults lacking capacity who have the same disease or disorder or are in the same condition (so-called group benefit).
- Children, adolescents and adults lacking capacity are to be granted the greatest possible say in decision-making. They are to be involved in the informed consent process in accordance with their capacity for understanding and self-determination.
- Consent has been obtained from the legal representatives of children and adolescents (generally the parents), from children with capacity (Art. 22 para. 1 and 2 HRA), and from adolescents with capacity (Art. 23 para. 1 HRA).[41] Consent has been given in writing by the legal representatives and adolescents with capacity.
- In the case of adults lacking capacity, either consent has been granted by the person concerned while in a state of capacity and duly documented (e.g. advance directive), or consent has been given in writing by the legal representatives, a designated trusted person or the next of kin (cf. Art. 378 Swiss Civil Code) (Art. 24 para. 1 HRA).

Opposition to participation in a study on the part of children, adolescents or adults lacking capacity must always be respected. In the case of research projects in connection with medically indicated treatment, a distinction is to be drawn between opposition to interventions which are necessary for therapeutic purposes, and thus still have to be undertaken in the patient's best interests, and opposition to interventions which are designed solely for research purposes and are therefore to be dispensed with.

40 www.swissethics.ch/doc/ab2014/AGEK_Kinder_Checkliste_e.pdf

41 In the case of a research project involving only minimal risks and burdens, adolescents with capacity may give their consent to participate independently of the legal representative (Art. 23 para. 1 let. b HRA).

5.3 Pregnant women

Medical knowledge of the treatment of diseases during pregnancy is limited. In particular, many drugs have not been adequately investigated for their effects on the pregnant organism or teratogenic potential (i.e. risks to the embryo). Consequently, pregnant women who have to take medication because of a specific condition may possibly expose themselves and their child to unknown risks. Conversely, pregnant women may – for fear of harming their child – discontinue or refuse to take medication and thus increase the risks to their own health and possibly that of the foetus. For these reasons, there have long been calls for research also to be carried out on the optimisation of diagnostic and therapeutic standards for pregnant women, especially since they can themselves decide autonomously on whether to participate in a research project.

In the case of research projects investigating a maternal disease or a foetal disease or malformation, possible risks both for the mother and for the unborn child need to be taken into consideration. Also to be considered are the risks associated with non-treatment. In order to minimise the risks, the safety of the intervention should be adequately demonstrated in non-pregnant women before a study is carried out with pregnant women. Depending on the study design, it may also be necessary – with the mother's consent – to continue monitoring the child after the end of the study.

Research projects with an expected direct benefit for a pregnant woman or for an embryo or foetus may only be carried out if the foreseeable risks are not disproportionate to the expected benefit (Art. 26 para. 1 HRA).

If a research project has no expected direct benefit, it may only be carried out if it entails minimal risks and burdens for the embryo or foetus and it can be expected to yield substantial findings which could be beneficial for pregnant women or for embryos or foetuses (Art. 26 para. 2 HRA).[42]

42 Cf. also the swissethics Guidelines (in German) on the inclusion/exclusion of pregnant women in scientific studies involving magnetic resonance imaging (MRI) and spectroscopy (MRS). www.swissethics.ch/doc/swissethics/20110906_KEK_MRI.pdf

5.4 Prisoners

It is important for studies to be carried out in the special prison situation, in order to improve medical care for this group of persons. It needs to be borne in mind that prisoners' relationship to the institution is one of dependency, and that they are therefore vulnerable. For this reason, particular attention has to be paid to the voluntary nature of participation in a study and to the protection of privacy. For data obtained in this context, the same regulations are applicable as for data collected from persons at liberty. In particular, it must be ensured that data is stored in such a way as to prevent prison staff from accessing it. In contrast to other particularly vulnerable groups, research projects involving prisoners which offer the prospect of a direct benefit are not subject to the subsidiarity principle (Art. 28 para. 1 HRA). The assumption here is that adult prisoners with capacity should decide for themselves whether they wish to participate in a research project of this kind. However, a research project with no expected direct benefit may only be carried out if it entails no more than minimal risks and burdens (Art. 28 para. 2 HRA).

5.5 Persons in medical emergency situations[43]

The fact that a study is carried out in the emergency department does not automatically make it a study involving persons in emergency situations. Instead, the decisive factor is whether, in an emergency situation, it is essential – for methodological reasons – to enrol participants so rapidly that it is not possible for informed consent to be obtained in advance. It must be determined whether participants are in a position to give informed consent or not. In most emergency situations this is not the case, since capacity is limited by shock, medication, etc., or the pressure of time is such that patients are unable to consider a decision on informed consent with the necessary calm and attention to detail. If the patient's condition permits and the study is not overly complex, it may be useful to provide participants with verbal information or a concise written explanation of the research project. However, this is not to be equated with informed consent and does not have to be signed by the patient. The criteria for research carried out under Art. 30 HRA are not met if enrolment in the study can be delayed until the patient has regained capacity, or there is sufficient time to obtain informed consent from the legal representative. In such cases, the standard procedure for informed consent is to be applied.

43 Cf. also the following swissethics templates (www.swissethics.ch): Schriftliche Bestätigung durch einen nicht am Versuch beteiligten Arzt, der nicht in die nachstehend genannte Studie involviert ist und unter Wahrung der Interessen der Versuchsperson deren medizinische Behandlung sicherstellt (HFG Art. 30) (English version forthcoming); Mutmassliche Willensäusserung des Patienten für die Teilnahme an der klinischen Studie durch einen Angehörigen (English version forthcoming).

For ethical and legal reasons, research projects in emergency situations are only permissible if a direct benefit, or at least a group benefit, can be expected. A study which "merely" offers the prospect of a benefit in the long term for patients in the same situation (group benefit) must not entail more than minimal risks and burdens (Art. 30 para. 2 HRA). In addition, as a protective measure, a physician who is not participating in the research project must ensure that the interests of the patient concerned are safeguarded. In particular, this physician must assess the implications of the study for the patient. In certain study settings, however – such as investigations in the preclinical emergency situation, e.g. to optimise the resuscitation procedure – it is difficult for technical reasons to involve an independent physician in advance. Here, the ethics committee is responsible for weighing up the interests concerned in individual cases.

Even if it is not possible for consent to be obtained, researchers are still obliged to determine the wishes of participants as rapidly as possible. For example, if patients indicate verbally or by their behaviour that they are opposed to participation, then they must not be included in the study. Post hoc consent must be obtained from the patient (or, in the event of prolonged incapacity, from the patient's legal representative) as soon as possible, and the procedure for obtaining post hoc consent is to be defined in the protocol. In general, data collected from the patient concerned should only be evaluated after consent has been given. In exceptional cases, data may be evaluated before consent has been obtained if this is necessary for the sake of the participants' safety and health, or if biological material is only utilisable for a limited period (Art. 17 para. 2 ClinO).

If consent to participate in a study is withheld post hoc by the patient or by the legal representative, the patient is to be excluded. Biological material already sampled in the course of the study must be destroyed and the data may no longer be used for the research project (Art. 31 para. 2 HRA, Art. 15–17 ClinO). However, if the validity of the study would thereby be compromised in essential respects, failure to evaluate data already collected and publish the results would be ethically problematic. In such circumstances, it is therefore permissible, by way of exception, to use the data in spite of refusal of consent, although the data and any biological material must be anonymised without delay (Art. 17 para. 4 ClinO).

Particularly delicate cases are those where the patient dies in the emergency situation and a decision on the use of data and samples collected in the study has to be taken by the next of kin (Art. 16 ClinO).

5.6 People in low- and middle-income countries

People in low and middle-income countries are particularly vulnerable as research subjects if it is primarily a lack of access to healthcare which leads them to participate in a study. Research projects are only ethically justifiable if they offer the prospect of a direct benefit for participants or a group benefit. The involvement of participants in randomised controlled trials is controversial if the standard of care provided in the control group differs substantially from that in the intervention group. However, if it were made a requirement that control groups in every country should also receive world-class care, it would be practically impossible to carry out studies in low- and middle income countries. Lower-quality care for control groups is, however – according to almost all international guidelines – only justifiable if the research projects concerned (a) are scientifically relevant, (b) provide local social benefits and (c) have a favourable risk-benefit profile for the individual participants. Whenever possible, access to treatment should also be assured after the completion of a study.[44]

Research projects designed in Switzerland and carried out abroad are not covered by the HRA and thus do not fall within the remit of the Swiss research ethics committees. Nor are these committees in a position to evaluate local conditions, in particular the procedure for recruitment of subjects and informed consent, insurance cover, the adequacy of infrastructure and the qualifications of non Swiss research personnel. The Swiss research ethics committees are, however, prepared to evaluate other points (scientific validity, risk-benefit ratio, etc.) in accordance with the ICH GCP guidelines and to confirm that the project is acceptable in these respects.[45] Researchers are still obliged to submit their project for evaluation by the ethics committee responsible for research at the site where the study is to be carried out.

44 At the national and international level, various organisations such as the Berne Declaration seek to promote the rights of these groups. Individual pharmaceutical companies also undertake to comply with these standards through corporate policies.

45 Cf. swissethics templates: Example of a positive statement for a research project that will be carried out abroad. www.swissethics.ch/doc/templates/Nord_Sued_Template_e.pdf

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CHAPTER 6

Assessment of the risks and benefits of a research project

Switzerland's human research legislation – like most ethical guidelines for research – requires that the risks and burdens for the participants of a study should not be disproportionate to the chances which it may offer. Under the Human Research Act (HRA), researchers are first required to minimise the risks and burdens for participants as far as possible (Art. 12 para. 1). This means that the scientific methods associated with the lowest risks and burdens are to be used[46]. In addition, the foreseeable risks and burdens for participants must not be disproportionate to the expected benefits of the research project (Art. 12 para. 2).

A risk is to be understood as the harm to be expected, or the extent of such harm, and the likelihood of its occurrence. The risks in question are those arising directly from the interventions involved in the study – i.e. not the individual risks associated with a disease and/or an established standard treatment.

Burdens are taken to be the temporary detrimental effects on a participant's well-being caused by the study.

A chance is a potential benefit and the likelihood of its occurrence. In particular, what is considered to be a benefit of participation in a study is an improvement in the course and prognosis of a disease. However, involvement in a study is rarely associated with a benefit for all of the participants. More often, a direct benefit of this kind is only experienced by a proportion of the study population. Chances are to be seen not only in relation to the health of individual participants. Many persons or patients assume that, by participating in a study, they are rendering a service to society or other patients. Without this altruistic motivation, clinical research would scarcely be conceivable. It would, however, be ethically questionable to suggest to healthy subjects or to patients that they should make sacrifices for the sake of society or fellow sufferers, as is occasionally proposed in the Anglo-American literature. The question is: to what risks and burdens can an individual reasonably be exposed for the sake of others, or to what extent can a person or patient be permitted to assume risks and burdens voluntarily? This question cannot be answered in a general way. What is important, however, is that the motivation of study participants should remain comprehensible.

46 BBl 2009 8104.

6.1 Evaluation of risks and burdens

As is apparent from the above considerations, the evaluation of chances, risks and burdens has to steer a course between society's interests in gaining knowledge and the welfare of individual participants. Here, in order to strike an appropriate balance, a two-step procedure is required. First, study planning must be optimised so as to make the risk-benefit ratio as favourable as possible. It should then be assessed whether study participants can reasonably be subjected to the results of this optimisation.

Thus, before the acceptability of risks and burdens is evaluated, the following conditions need to be met:

- The risks and burdens of the study have been reduced to the lowest possible level, i.e. minimised.
- The participants should have the greatest possible chances of benefiting; in other words, the likelihood of individual benefits is maximised.
- The potential benefits for the individual and society outweigh the risks.

The risks and burdens of participation in a study are not absolute values, since life also involves risks and burdens for people not taking part in a research project. If they are to be evaluated, therefore, the risks for persons participating in a study need to be compared with those to which individuals are exposed who also meet the eligibility criteria but do not participate. For healthy subjects, the risks accepted in daily life need to be taken into consideration.[47] This has been criticised because the everyday risks encountered, for example, in sport or in car trips may be substantial. However, the fact that individuals accept high risks for personal motives cannot be used as an ethical justification for exposing them to comparable risks for altruistic purposes.[48] A pragmatic approach would be to take as a reference the risks and burdens which an average, reasonable person not participating in a study would be exposed to during the period that would be required for participation in the study.

47 Wendler D, Belsky L, Thompson KM, Emanuel EJ. Quantifying the federal minimal risk standard. Implications for pediatric research without a prospect of direct benefit. JAMA. 2005; 294: 826–32.

48 Ross LF. Children in medical research. Access versus protection. Oxford: Oxford University Press; 2006.

Essentially the same applies for patients who receive treatment as participants in a research project. Here, in the case of serious or even life-threatening conditions, the risks and burdens – but also the potential benefits – are naturally much higher. It should be borne in mind that patients who are seriously ill face substantial risks and burdens even if they do not participate in a study. Therefore, in order to evaluate a research project, it is necessary to weigh up only the risks and burdens additionally arising from the study – such as adverse effects of the experimental treatment compared to standard (non-study) treatment, or additional diagnostic investigations – against the potential benefits of the experimental treatment in the form of a more favourable prognosis.

Apart from the objective components (e.g. magnitude and likelihood), there is also a subjective aspect to risks and chances, which is relevant when it comes to assessing the acceptance of a study and its proportionality. Patients are vulnerable if hopes are raised that their prospects of recovery will be improved by their participation in a study. In providing information for patients, one must therefore avoid arousing inflated expectations with regard to novel treatments, and downplaying or even failing to mention the risks.[49] Thus, both in the evaluation of research projects with healthy subjects and in the assessment of therapeutic studies with patients, the risk-benefit ratio of participation needs to be compared with that of non-participation and the additional burdens associated with the research need to be addressed. To this end, the following questions should be answered:

- What consequences will participation in a study have for an individual, and how does this compare with the position of a person who also meets the eligibility criteria but does not participate? In other words, what are the net risks of participation?
- What additional burdens will arise for persons who choose to participate, rather than not to participate, in a study?

49 In the literature, this issue is discussed under the heading of *therapeutic misconception*. Cf. also Article 14 of the Helsinki Declaration (2013): "Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects."

6.2 Evaluating the acceptability of risks and burdens

Researchers and research ethics committees have a duty to ensure that study participants are not exposed to unacceptable risks (and burdens). The problem is to draw the line between what is excessively risky and what can still be regarded as acceptable. Whether a risk is acceptable and can thus be countenanced should be carefully assessed by the research ethics committee, rather than simply being left for the participants to decide. With regard to risks, the research ethics committee thus operates with a degree of paternalism. An important factor in the decision whether the participants can reasonably be expected to accept the net risks and burdens identified in the assessment is their capacity for judgement and informed consent. In principle, adults capable of consenting may also, given their right to self-determination, accept high levels of personal risk. For this reason, incentives for participation in a study must not be such as to induce people to take disproportionate risks. Excessive payments, promises of additional medical services, or an overly optimistic portrayal of the chances of successful treatment are to be avoided. Otherwise, there is a danger that the individuals concerned will accept unreasonable risks if their situation is sufficiently desperate or the remuneration sufficiently enticing. This applies in particular also for research projects in low- and middle-income countries, where even relatively modest incentives can motivate people to accept substantial risks.

In the case of persons who lack mental capacity and thus cannot give informed consent, consent to participate in a study must be granted by a representative. In principle, however, the latter cannot make decisions on highly personal matters which do not promote the welfare of the person represented. This would also include the acceptance of risks "in the service of science". For this reason, non-therapeutic research involving subjects incapable of giving consent is open to criticism. However, avoiding research projects of this kind would mean forgoing further progress on medical problems which only concern patients incapable of consent, such as children or those in emergency situations.

Even if the involvement of persons incapable of consent in non-therapeutic research cannot be justified merely by the calculus of benefits, good reasons can be identified from another perspective. For example, the desire to help and benefit others is not dependent on the capacity to consent but is already apparent in early childhood. Fostering such desires is recognised by society as one of the tasks to be performed by the parents of young children. However, to protect those who are incapable of giving consent, the risk deemed acceptable must be set at a very low level; here, the concept of "minimal risk" is generally used. The guidelines issued by the Royal College of Physicians[50] are based on the definition of risk given by the Council of Europe's Steering Committee on Bioethics: "research

50 Royal College of Physicians. Guidelines on the practice of ethics committees in medical research with human participants. London. 2007.

bears minimal risk if it is to be expected that it would result, at the most, in a very slight and temporary negative impact on the health of the person concerned". This definition was also adopted for the application of the HRA. In practice, however, it is difficult to define the minimal risk threshold in absolute terms[51]. Interventions involving minimal risks and burdens are specified in the ordinances associated with the HRA. They include surveys and observations, peripheral venous or capillary blood sampling and skin punch biopsies of limited extent, removing or collecting bodily substances without invasive interventions (in particular, saliva, urine and stool samples), taking swabs, and magnetic resonance imaging scans without a contrast medium, ultrasound examinations or electrograms.[52]

In summary, the threshold of admissibility for the risk-benefit ratio of research projects can be defined as follows:[53]

For persons capable of giving informed consent

Both the net risks of study participation and the associated burdens must be of acceptable proportions – i.e. the participants must not, in all likelihood, fare worse to an unreasonable extent during and after the study than if they were not to participate.

For persons incapable of giving informed consent:

The net risks of study participation must be minimal and the associated burdens must be of acceptable proportions – i.e. the participants must not, in all likelihood, fare worse as a result of their involvement in the study than if they were not to participate, and the burdens associated with participation must, in the judgement of reasonable and caring parents/relatives/representatives, be tolerable and acceptable.

51 Cf. Wendler D, Belsky L, Thompson KM, Emanuel EJ. Quantifying the federal minimal risk standard. Implications for pediatric research without a prospect of direct benefit. JAMA. 2005; 294: 826–32.

52 Art. 2 let. b ClinO and Art. 7 para. 3 HRO.

53 Kind C. Evaluation of risk in research with children – it's time to clear the misconceptions. Bioethica Forum. 2009; 2: 74–9.

6.3 Risks and justifiability of placebo-controlled clinical trials

A placebo-controlled trial carried out with patients in a therapeutic context is a study with an expected direct benefit. However, the participants assigned to the control group are at risk of having their health indirectly compromised, as they only receive sham treatment and cannot benefit from the new therapy.

Such studies are ethically justifiable if no effective treatment exists, or if there is uncertainty as to whether the treatments currently used offer more benefits than risks (clinical equipoise). However, if an effective standard treatment is available, the question of ethical justifiability is more difficult to assess. Opponents of placebo-controlled trials argue that it is generally not justifiable to withhold an existing effective treatment from participants and to administer a placebo instead[54]. In their view, comparative studies may only be undertaken versus an active-control treatment. At the same time, society has an interest in well-investigated, innovative treatment options and, in many cases, placebo-controlled trials are essential if valid conclusions are to be drawn concerning the efficacy and safety of a new therapy.[55]

This is because many drugs considered to be effective have not been shown to be superior to placebo in up to 50% of all trials conducted; if drugs with inconsistent and only modest effects are used as a control, an ineffective new treatment cannot be recognised as such and will be rated as "non-inferior". For this reason, EMA guidelines – e.g. for the approval of antidepressants – strongly recommend that studies should be designed with a placebo and an active-control arm, so as to avoid the introduction of ineffective products.

Based on these principles of research ethics, placebo-controlled trials may be justifiable – even in cases where an effective treatment exists – under the following conditions:[56]

- A placebo control is necessary for methodological reasons.
- The participants have been clearly informed about the advantages and disadvantages of placebo treatment and have given their consent.
- The participants' interests are safeguarded.

54 Cf. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. New England Journal of Medicine. 1994; 331: 394–8.
55 Cf. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. Annals of Internal Medicine. 2000; 133: 455–63.
56 Cf. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials – a middle ground. New England Journal of Medicine. 2001; 345: 915–9.

Article 13 of the HRA specifies that, in research projects with an expected direct benefit, the use of a placebo or non-treatment is only permissible if no additional risk of serious or irreversible harm is to be expected for the persons concerned and no standard treatment is available, or the use of a placebo is required for compelling, scientifically sound methodological reasons, in order to establish the efficacy or safety of a treatment method.

6.4 Risk categorisation under the HRA

Under the human research legislation, the inherent risks of research projects are categorised using an assessment procedure, with due consideration being given to the vulnerability of participants and the specific circumstances.[57] The procedure is largely based on legally established and internationally recognised assessment methods.[58] The aim of the categorisation is – by easing the administrative burden, dispensing with mandatory authorisation (Swissmedic, FOPH) and reducing liability coverage requirements – to eliminate obstacles for low-risk research projects.

The legislation distinguishes between clinical trials of medicinal products and other research projects involving persons. Clinical trials or research projects are divided into Categories A, B and C, with A representing the lowest and C the highest risk potential. The categorisation reflects the varying degrees of risk associated with different research methods and procedures. Categorisation is thus only envisaged for research projects involving persons – projects involving cadavers, embryos, etc., or existing biological material, are not classified by risk.

When a research project is submitted by applicants, it must already be assigned to a risk category, and this categorisation is to be reviewed by the ethics committee. The Coordination Office for Human Research (www.kofam.ch) provides an online wizard for classifying and determining the risk category of a research project.

57 Goldenberger R. Bemessung von Risiken in der Humanforschung. In: Zaugg H, Schläpfer L (eds.). Recht und Gesundheit. Junge Rechtswissenschaft Luzern. Zurich: Schulthess; 2013, pp. 87–108.

58 Explanatory Report of 21 August 2013 on the Ordinances associated with the Human Research Act, p. 9.

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CHAPTER 7

Independent review by the research ethics committee

It is part of international standard practice – and a fundamental requirement of contemporary human research legislation – that biomedical research projects should be reviewed in advance by an independent ethics committee. The constitutional basis is provided by Art. 118b of the Federal Constitution. For trials of medicinal products, this procedure has long been widely accepted. Since 1975, submission of medical research projects to an ethics committee has also been required under the Helsinki Declaration.

In Switzerland, all research projects falling within the scope of the HRA (cf. Sect. 3.3) require prior authorisation from the responsible cantonal ethics committee. By authorising a study, the ethics committee confirms that it complies with the legal requirements. Mandatory authorisation for research projects restricts the freedom of research guaranteed by Art. 20 of the Federal Constitution and thus calls for special justification. This substantial restriction of academic freedom is designed to ensure that the participants' dignity, privacy and health are protected. In addition, the review should ensure that research meets the relevant scientific and ethical requirements.

History has shown that, if the safety of medical research is to be assured – and public confidence maintained – it is not sufficient to rely exclusively on researchers' individual sense of responsibility, or on self-regulation by the medical community. It is thus also in the interests of researchers themselves to have a study protocol evaluated by an ethics committee with appropriate expertise. While researchers still have to assume responsibility for the safety of participants and comply with scientific and ethical requirements, an independent review means that responsibility for the evaluation of benefits and risks is shared ("two pairs of eyes"). Lastly, for many scientific journals and funding bodies, approval of a study by a research ethics committee is a prerequisite for the publication of results.

7.1 Duties and responsibilities of the ethics committee

Ethics committees perform two (partly overlapping) duties: firstly, they assess whether the protection of participants (patients, subjects) is assured; secondly, they evaluate compliance with the scientific requirements for research projects, and the scientific relevance of the topic. The key question is whether the risks for the human subjects are disproportionate to the expected benefits of the project. A research project will only be authorised by an ethics committee if it meets the ethical, scientific and legal requirements specified in the HRA (cf. Sect. 7.2).

In addition, ethics committees monitor ongoing research projects. For this purpose, information is obtained from researchers' notifications concerning safety and protective measures taken or serious adverse events observed, and from other reports (Art. 46 HRA). If participants' safety or health is at risk, the ethics committee may revoke the authorisation or make the continuation of the research project subject to additional conditions (Art. 48 HRA), with researchers being required to provide further information and documentation.

Ethics committees' primary responsibility is towards study participants and the public. However, they can also advise researchers on ethical questions and comment on research projects not subject to the HRA (e.g. projects carried out abroad, Art. 51 para. 2 HRA).

Appeals against ethics committee decisions may be submitted to the competent cantonal authorities (e.g. administrative court) and subsequently to the Federal Supreme Court.

7.2 Components of the review

Ethics committee decisions are based on the application dossier. The extent of the documentation to be submitted depends on the type of study and the risk category. For research projects with human subjects, the following review areas are of crucial importance (Art. 4 ff. HRA and in particular Art. 15 HRO):

– Review of the informed consent documentation for comprehensibility and completeness, with particular attention being paid to the planned procedure for providing information and obtaining consent.

– Assessment of whether the subsidiarity principle is complied with, the criteria for selection of study participants are fair, the safety and precautionary measures are adequate (e.g. emergency planning), and the ratio between the likely risks and burdens and the expected benefits is acceptable.

– Evaluation of scientific requirements – in particular, the relevance of the topic, scientific integrity (e.g. handling of conflicts of interest on the part of researchers), scientific quality, compliance with Good Practice guidelines for research, researchers' professional qualifications and, in the case of clinical trials, registration.

– Definition of the risk category for the research project, based on the researchers' own assessment. Ethics committees review dossiers under conditions of uncertainty: they have to evaluate future events on the basis of as yet incompletely known facts – otherwise, there would be no need for research in the area concerned. Here, ethics committees operate within the complex web of – partly opposing, partly overlapping – interests of researchers, participants and the public. Put simply, wishes for recovery collide with the pursuit of knowledge. The situation is further complicated by the interests of third parties – e.g. society, industry, hospitals or relatives. Ethics committees are guided by the principle that the interests of individuals are to be accorded priority over those of science and society (Art. 4 HRA).

While research ethics committees can evaluate the ethical, scientific and legal aspects of a study, they only get to see it "on paper". They are not present when participants are enrolled or privy to the interactions occurring between study personnel and participants – i.e. the aspect which, from the latter's perspective, is decisive for the ethical quality of the study.

– Detailed information concerning submission procedures can be found on the various ethics committee websites.
– Also available online are the swissethics checklists for application documentation → www.swissethics.ch/templates_e.html

7.3 Structural requirements

Responsibility for authorisation lies with the ethics committee of the canton where the research is conducted. If a research project is carried out according to a standard protocol, but in different cantons (multicentre research project), the lead committee function is assumed by the ethics committee which is responsible at the site where the project coordinator works (Art. 47 HRA). Having sought the opinions of the local ethics committees, the lead committee authorises the research project for Switzerland as a whole. The local committees simply assess whether the professional and operational requirements are met at the site in question (e.g. researchers' training and experience, or the suitability of premises and facilities); they do not evaluate the informed consent documentation or compliance with scientific requirements.

The ethics committee's decision must be available within two months after submission of an application (Art. 45 para. 2 HRA). In the relevant ordinances, shorter periods are specified (30 days for single-centre, 45 days for multicentre research projects), calculated from the date when receipt of the formally correct application is acknowledged by the ethics committee.

For Switzerland as a research centre, expeditious authorisation procedures are of great importance. Accordingly, to ensure that research is not unduly delayed, ethics committees must reach a decision as rapidly as possible – without the quality of the review being compromised as a result. Each ethics committee is supported by a scientific secretariat. Ultimately, the cantons – which appoint and assure the financing of ethics committees – are responsible for ensuring that the necessary resources (time, personnel, funding) are available (Art. 54 HRA).

Ethics committees are integrated into a supervisory system. They reach decisions in a professionally independent manner but are otherwise subject to cantonal supervision (Art. 52 and 53 HRA). Responsibility for general supervision of medical research activities lies with the cantonal health authorities. This is supplemented by the authorisation and inspection activities of Swissmedic in the area of therapeutic product safety, and of the FOPH in the area of transplantation research. The latter authority is also responsible for the operation of the public registry of clinical trials (Art. 56 HRA).

The members of ethics committees must have the requisite professional skills and experience, representing the disciplines of research-focused medicine, psychology, nursing, statistics, pharmacology, law or ethics. Those members who represent the disciplines of medicine, psychology or nursing must have already acquired experience in the conduct of research projects. Depending on the canton, patient representatives may also be included.

Ethics committees operate on the "militia principle", with their members serving in a part-time capacity. Committee members are obliged to disclose their interests in a publicly accessible register. In the event of any doubts as to their impartiality (in particular, due to direct involvement in a study, financial interests or institutional ties), they are required to absent themselves from the committee's deliberations (Art. 52 HRA).

The Swiss ethics committees for research involving humans have formed a joint working group – swissethics. This organisation has been assigned the following tasks by the Conference of Cantonal Directors of Public Health (GDK):

- coordination and standardisation of working methods;
- representation vis-à-vis external partners: Swissmedic, FOPH, industry, GDK, SCTO, EURECNET;
- education and training of committee members.

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CHAPTER 8

Information and consent

Informed consent is a fundamental ethical requirement for research with human subjects. This is based on the consideration that it cannot be wrong to expose someone to a risk if the person concerned voluntarily accepts it. Underlying this is the moral ideal of self-determination, which involves not merely independent decision-making, but "principled autonomy".[59] Respect for autonomy involves not only duly informing potential participants about the study but also respecting their right to consent – or refuse – to participate, and to subsequently withdraw from the study at any time.[60]

Consent can only be *freely given* if the person has capacity and decides independently (i.e. free of deception and coercion). Consent is only *informed* if the person has received and also understood all the relevant information. It must also be expressly formulated and certified by the person's signature.

Freely given informed consent places high demands on study participants, which – as medical laypersons and possibly as patients – they may only be able to meet in part. The information provided must be comprehensive; however, complete equivalence in knowledge between the non-medically trained participants and the researchers is not possible. From the participants' perspective, it is therefore essential that they should be informed in a comprehensible manner about all aspects of the study which are important to them personally. From the researchers' perspective, the main consideration is often the content of the information – the question of what is being investigated. What is more crucial from the participants' viewpoint, however, are the consequences of their participation and how researchers provide information and communicate on the subject of the study.

Studies have shown that it is difficult to provide appropriate information about a research project for the persons concerned. Many explanatory documents are too long, the content is pitched at an inappropriate level and elementary rules of communication are disregarded.[61] As fully informed consent remains an ideal, what is more relevant from an ethical viewpoint is the informed consent process. From the participants' perspective, the way in which the information is presented is of greater importance than formal aspects such as the requirements for written information and consent. Here, recent research in ethics has yielded

59 O'Neill O. Autonomy and Trust in Bioethics. Cambridge: Cambridge University Press; 2002.

60 Cf. Art. 7 and Art. 16 para. 1 HRA; see also Art. 5 in conjunction with Art. 16 of the Biomedicine Convention.

61 Cf. Position paper issued by the Swiss Academy of Medical Sciences (SAMS) and the Swiss Association of Ethics Committees for research on humans (AGEK): Provision of written information in connection with research projects (available in French/German). SÄZ/BMS. 2012; 93(36): 1299–301.

important insights. Informed consent is to be understood as a process of communicative action, which is initiated prior to the actual granting of consent. A fair informed consent process is characterised by dialogue – both partners speak and listen to each other, thus also becoming aware of what participation in the study means for them personally.

8.1 Content of information to be provided

Potential participants receive written information on the planned study, but it is also explained to them verbally. The information for study participants is to be written in language which is comprehensible and takes their situation into account. Rather than being an abridged version of the study protocol, it should include those elements which are necessary to permit a decision on participation.

In its guidelines for the drafting of participant information,[62] swissethics notes that the description of the study which is to be distributed to potential participants must be guided by their specific needs and interests and should therefore focus on the essentials, giving due consideration to participants' cognitive abilities. To achieve this goal, attention should be paid to the following points when the information is drafted:

- The scientific content of the research project is presented in a form appropriate for the participants, comprising only what is necessary for them.
- The information includes a table of contents.
- The sequence of individual sections is based on the participants' needs. Priority is accorded to information on the following aspects of the research project: Why should I participate? What advantages and disadvantages should I expect? What will change if I take part in this study?
- The participant information comprises a core document, which includes only the information which is essential for participants, and an accompanying document, including more detailed information.

62 Cf. swissethics guidelines for drafting participant information including declaration of consent for human research projects. www.swissethics.ch

If necessary, information can also be provided in stages, or spread out over a number of appointments. This applies in particular for studies extending over a prolonged period.[63] In the case of research projects in special (e.g. emergency) situations, or involving persons with restricted cognitive abilities (e.g. children, adults lacking capacity), pictures, pictograms, films, comics or other suitable media can also be used to ensure that the persons concerned understand the essential elements of the information provided.

The information for participants should include the following points[64]:

- general description of the study (including the sponsor);
- selection of participants (reasons underlying the invitation to participate in the study and the main eligibility criteria);
- information to the effect that participation in the study is voluntary and that – in the case of studies with patients – participants can withdraw from the study at any time without giving reasons and without suffering any disadvantages with regard to subsequent treatment;
- study design and schedule;
- other possible treatment methods;
- chances which participation may offer;
- risks, burdens and possible known adverse effects;
- duties of the participant and of the (principal) investigator;
- assurance that any new findings concerning the benefits and safety of participation – which could influence participants' consent – will be communicated without delay;
- agreements concerning confidentiality and data protection;
- reimbursement of the participant's expenses, details of remuneration, possibly division of costs between sponsor and health insurer;
- conditions for involuntary termination of participation;
- coverage of study-related damage;
- address and telephone number of a contact person.

63 Cf. Art. 7 para. 3 ClinO.
64 Cf. also Art. 16 HRA; Art. 7 ClinO; Art. 28–32 HRO; Principles 25–26 Helsinki Declaration.

When drafting participant information, one can generally assume that the persons invited to participate in a study are reasonable, interested and wish to know everything that is relevant for them about the study. On the basis of this information, they should be able to decide whether or not they wish to participate in the study. In addition, they should be granted an appropriate period to reflect on their decision.

8.2 Information for foreign-language speakers

Particular challenges arise when information is to be provided for potential participants who are not proficient in the language in which the participant information is written. As the verbal and written information on the study has to be comprehensible for the persons concerned, all the relevant information is to be translated in writing, and an interpreter should be called in when information is to be given verbally. As this involves substantial costs and is not always practicable, it is generally not possible to enrol foreign-language speakers in studies. From an ethical perspective, however, it should be borne in mind that patients may be disadvantaged if they cannot participate in a study. In 2012, a consensus paper[65] was prepared by swissethics and the Swiss Clinical Trial Organisation (SCTO) to provide guidance for these situations. According to this paper, participants who speak one of the three national languages (French, German, Italian) must receive written and verbal information in their own language. For speakers of other languages, this will not always be possible; however, as they may be disadvantaged by not being able to participate, assessments should be carried out on a case-by-case basis. In the absence of written information, enrolment in a study may still be justifiable if no equivalent alternative treatment is available, or if the attending physician considers the study to be the only or superior option for the patient from a medical viewpoint. Naturally, the patient must be provided with verbal information, with the aid of an interpreter. The decision to enrol the patient in the study must be documented in the medical records. In addition, provision for such a situation should be made and the procedure (involvement of witnesses/an interpreter, list of verbally translated documents, etc.) should be specified in the protocol authorised by the ethics committee, or enrolment should be approved by the ethics committee in individual cases.

65 Cf. Information for participants in foreign languages (available in French/German): www.swissethics.ch/templates.html

8.3 Incomplete information

For certain research questions, it may be advisable on methodological grounds to withhold information about essential aspects of a study from participants, or even to misinform them – e.g. by failing to disclose the true purpose of a study or the fact that subjects are randomly assigned to an intervention (randomisation). Traditionally, social scientific research has sometimes involved deception of participants; in such cases, were complete information provided, the study could not be performed, or the results would be biased to such an extent that the research would lose its validity.

However, what may appear methodologically plausible needs to be critically evaluated from an ethical perspective. Here, the participants' interests are subordinated to those of researchers. In addition, curtailment of informed consent jeopardises one of the fundamental principles of research ethics. Accordingly, incomplete information must be confined to exceptional cases.[66] Key requirements for such exceptions are a topic of high relevance and the lack of an alternative (conventional) study design where complete information is provided. One possible compromise worthy of consideration involves telling participants in advance that, for methodological reasons, they cannot yet be fully informed.[67] Participants must subsequently, however, be fully informed about the results – at the latest, when the study has been completed.

Moreover, participants must not be induced to give consent which they would not have granted if they had been fully or truthfully informed; this would be to treat them as research material. Deception over a prolonged period is thus scarcely justifiable. In a study involving patients, trust may be undermined if the physician is perceived by the patient as dishonest, having provided incomplete or misleading information; patients may be less able to cope with this than healthy subjects.[68]

66 Kleist P. Unvollständige oder fehlende Aufklärung von Versuchspersonen in klinischen Studien. Methodologisch notwendig – aber auch moralisch zulässig? Folia Bioethica. 2013; 37.

67 Boter H et al. Modified informed consent procedure: consent to postponed information. British Medical Journal. 2003; 327: 284–5.

68 Cf. Miller FG. Consent to clinical research. In: Miller FG, Wertheimer A (eds.). The Ethics of Consent. Theory and Practice. Oxford: Oxford University Press; 2010, pp. 375–404.

In connection with the provision of incomplete or misleading information, researchers have a particular responsibility to respect and safeguard the interests of study participants. Risks and burdens must be minimal. For patients, in addition, optimal medical care is to be assured. A study involving unpredictable risks or a potential loss of benefits is not compatible with the provision of incomplete information; this type of non-therapeutic research involving personal risks can only be justified if the participants fully exercise their right of self-determination, i.e. by granting fully informed consent.[69]

Under Art. 18 HRA, provision of incomplete information is permissible only in exceptional cases and under the following conditions:

- It must be essential for methodological reasons.
- The research project must entail no more than minimal risks and burdens.
- The participants must subsequently be fully informed as soon as possible. Having been thus informed, they are entitled to withhold their consent to the further use of their biological material or their data. Only when valid consent has been given in this regard may the biological material or data be used for the research project.

8.4 Consent

Once the consent form has been signed, the person's consent to participate in the study in accordance with the legal regulations and institutionally defined rules becomes effective and valid. The researchers are thus authorised to enrol the subject in the study on the previously specified terms and to conduct the research.[70]

Persons participating in a research project must indicate by their signature that they voluntarily consent to participate. Exceptions to this rule are a number of precisely defined situations in which it is not possible to obtain the written consent of participants.

69 Cf. Truog RD et al. Is informed consent always necessary for randomized, controlled trials? New England Journal of Medicine. 1999; 340: 804–7.

70 Faden R, Beauchamp TL. A history and theory of informed consent. New York: Oxford University Press; 1986.

For consent to be voluntary, the following conditions must be met.

Consent can only be freely given if it is granted by a person who
– has capacity with regard to this decision and

– decides independently.

Consent is only informed if the person
– has been provided with all the relevant information and

– has understood this information.

Consent is only granted if the person thereby
– expresses a wish to participate and

– this wish is apparent to others and is objectively documented.

In practice, however, informed consent is subject to a number of possible limiting factors:

– Capacity with regard to this decision may be limited because the person is ill and is unable to consider the decision in the requisite manner and detail.

– In the decision-making process, independent assessment may be impeded by the person's confidence in medicine or trust in the attending physician.

– The information provided for participants is often insufficient to ensure that the goal of the study is understood.

– The person may interpret certain details of the documentation in a way that was not intended by the investigators.

Consent therefore often amounts to an act of acceptance rather than an expression of wishes. Only the explicit and formally documented aspects of consent – the legally valid signing of the consent form – can be unequivocally verified. An additional difficulty arises from the fact that the research ethics committee only sees the documents used in the informed consent procedure (participant information and consent form) and is not privy to the actual communication process. It must therefore assume that discussions are conducted by the study personnel in an optimal manner, appropriate to the given situation. It assesses whether the documents will provide the best possible support for this process.

The written[71] participant information is at best a useful reference document for the verbal informed consent process. It is retained by participants for subsequent reference.

71 For exceptions to the requirements for information and consent in written form, see Art. 16 para. 1 HRA in conjunction with Art. 8 ClinO and Art. 9 HRO.

8.5 Use of (financial) incentives to promote participation

Consent to participate in a research project must be freely given. The decision to participate should be made on the basis of individual values, interests and preferences. In the case of research projects with an expected direct benefit, the participants may hope to experience beneficial effects on their health. In the case of research projects with no expected direct benefit, the key motives are altruistic: any knowledge gained from the research project will benefit third parties, rather than the participants themselves. It is therefore justifiable and appropriate that the participants should be compensated for their time and for the burdens involved. This remuneration should be appropriate and not so high as to induce persons to underestimate or to accept the possible risks involved for purely economic reasons (Art. 14 HRA). What is to be deemed appropriate must be assessed by the responsible ethics committee in particular cases.

8.6 Proxy consent

Particularly delicate from an ethical viewpoint are research projects where the subjects cannot themselves consent to participate because they lack (full) capacity. In these situations, consent for participation must be given by a duly authorised person (representative). This raises additional problems since it is possible that the values and interests of the representative do not coincide with the perspective of the person concerned. Traditionally, proxy consent for studies conducted in a therapeutic context has been viewed as less problematic than in the case of studies with no expected direct benefit for the participants' health (non-therapeutic studies). However, one should not overlook the fact that therapeutic studies may also involve serious risks, in view of which proxy consent would also be problematic. Here, the fundamental ethical question arises, under what conditions proxy consent for participation can legitimately be given. Under the HRA, in the case of studies with no expected direct benefit for the person lacking capacity, proxy consent is only permissible if the subsidiarity principle is complied with, a group benefit is anticipated, no more than minimal risks and burdens are entailed and no opposition is expressed by the person concerned.

All cases involving persons who lack capacity are covered by the provisions concerning advance directives, advance care directives, representation in relation to medical procedures and urgent cases. As the HRA is harmonised with the adult protection legislation, reference can be made to the latter.[72] For children and adolescents, the legal representatives (generally the parents) are entitled to give consent, and for adults lacking capacity responsibility lies either with the person appointed in an advance directive or advance care directive, the deputy (if one has been appointed), or the next of kin or cohabiting partner, if they regularly provide personal support for the person lacking capacity (cf. Art. 378 Civil Code).[73]

8.7 Rights of children and adolescents to be consulted

The rights of children and adolescents to be consulted are not dependent on their decision-making capacity or capacity to give consent. In the context of research, their capacity for understanding and self-determination is to be respected and promoted. Even though, in many cases, children and adolescents cannot independently give legally valid consent to participate in a study, they are certainly able to assume responsibility for their own body. The rights of children, adolescents and adults lacking capacity to be consulted (informed assent) stand alongside their representatives' authority to give informed consent.

Like informed consent in adults with capacity, informed assent in minors requires the involvement of the person concerned in the informed consent process. However, in the event of participation in a study, the minor's informed assent does not take the place of the legal representatives' informed consent. Consequently, regardless of their capacity for consent, children and adolescents need (and have the capacity) to be informed and have a right to be involved in the informed consent process. As children's decision-making capacity develops in a gradual and individual way, involvement in the informed consent process needs to be adapted to the developmental status of the child concerned. In studies with children and adolescents, therefore, their age and individual maturity need to be taken into account. Accordingly, a different approach needs to be taken for infants and toddlers than for preschool or school-age children.[74]

72 Art. 22–24, 30–31 HRA; Art. 15–17 ClinO.
73 Amendment of 19 December 2008 to the Swiss Civil Code concerning Adult Protection Law, Law of Persons and Law of Children, AS 2011 725 ff., in force since 1 January 2013.
74 Cf. Nos. 5 and 8 swissethics Checklist for research on and with children and adolescents; AGEK Research on and with children and adolescents under the age of 18: Guidelines for the provision of study information.

In the case of children under 14 years of age, the HRA specifies that – for studies with or without an expected direct benefit – both the child with decision-making capacity and the legal representatives are to be informed and to give their consent. The legal representatives' consent is to be given in writing, and the child's consent is to be documented. In the case of children lacking capacity, the legal representatives are to be informed and to give legally valid consent, although the child is to be involved in the informed consent process (Art. 21 HRA). If the child concerned is unwilling or unable to be involved in the informed consent process, the representatives are to be guided in their decision-making solely by the child's presumed wishes or welfare.

In later school age or adolescence, the consent of the legal representatives is not always required as well as the agreement of the adolescent concerned (see below). While adolescents may be interested in participating in studies, they are not always able to carry out a comprehensive risk assessment themselves. Rather, with regard to the adolescent concerned and in relation to the specific study, it needs to be evaluated whether the adolescent currently has the requisite decision making capacity. Here, in individual cases, conflicts may arise between the legal representatives' duty to provide protection, the responsibilities of the physicians and the autonomy of the adolescents concerned.

For studies involving adolescents with capacity, the HRA specifies that they are to give their informed consent in writing. The informed consent of the legal representatives is only additionally required in the case of research projects entailing more than minimal risks and burdens (Art. 23 para. 1). For research involving adolescents who lack capacity, the HRA specifies the same requirements as for children (see above). Adolescents lacking capacity are also to be informed and involved in the decision-making process as far as possible. They also have the right to oppose interventions.

The right to refuse to participate in a study should always be linked to the right to be involved in the decision-making process, since expressions of opposition by children and adolescents have a different quality if they are based on comprehensive information and consultation adapted to the understanding, maturity and individual situation of the persons concerned. However, in the case of younger children in particular, it may be difficult to determine whether they are opposed to a particular intervention or more generally anxious.

8.8 General consent[75]

A special type of consent is granted when a donor agrees to the further use of material and data for research projects which will only be specified in the future (so-called general consent). From an ethical and legal perspective, it may be objected that general consent undermines the principle of informed consent.[76] Comprehensive (informed) consent is not technically possible when the material and data is collected – because it not yet known how it will be used – but repeated procedures to obtain specific consent for each individual research project may impose excessive demands both on the person concerned and on researchers. As the SAMS notes in a position paper on personalised medicine:[77] "In cases where large amounts of data possibly relevant to health are to be collected in a single step and in the absence of a clearly defined medical question, the requirement that the subject should receive full, comprehensible information about the benefits and risks of the procedure must be seen in a new light." From an ethical and legal viewpoint, it must be ensured in the case of general consent that donors understand what they are agreeing to; their consent must be freely given and it must be possible to revoke it. In addition, to provide further assurances, a framework needs to be established – e.g. biobank regulations and technical and organisational measures for appropriate protection of data and samples – so that the donor can be confident that they will not be misused.

If donors are to be appropriately informed so as to be able to grant general consent, they must know:

- that their samples and data may be used for research projects which are as yet unspecified at the time consent is given, and without them subsequently being informed in particular cases;
- that data protection is assured, and that they have the right to inspect their data at any time;
- that they can revoke their consent at any time, and that this right is not subject to any conditions;
- that their samples and data may be transferred to other biobanks;
- what will happen to research findings which directly affect the donor; and
- what is envisaged in the event of research findings leading to a commercial product.

75 Cf. also the detailed discussion in Chapter 12.
76 Cf. Büchler A, Dörr B. Medizinische Forschung an und mit menschlichen Körpersubstanzen, Verfügungsrechte über den Körper im Spannungsfeld von Persönlichkeitsrechten und Forschungsinteressen. Zeitschrift für schweizerisches Recht. 2008; 381–406.
77 Cf. Swiss Academy of Medical Sciences (SAMS) position paper: The potential and limits of personalized medicine. 2012. www.samw.ch/en/Publications/Statements.html

Templates for patient information and consent forms, as well as biobank regulations, are available on the swissethics website.[78]

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78 Cf. www.swissethics.ch/templates.html

CHAPTER 9

Respect for participants

Respect for participants is a basic attitude which is to be maintained throughout the study.

Particular mention should be made of the following obligations:

- maintenance of confidentiality;
- participants' right to receive information; [79]
- safety and protective measures;
- liability for damage arising as a result of participation in a research project.

It should be noted that medical research is frequently conducted within the context of therapeutic and nursing relationships which are essentially based on trust between the recipients and providers of care. If patients' trust is breached, their relations with the study team may be damaged. Breaches of trust can also, indirectly, have adverse impacts on other patients. Trust can have both a subjective and an objective basis: subjectively, trust rests on the conviction that third parties – persons or institutions – will act in one's best interests. [80] Objective grounds for trust may be the understanding that, within a given framework, it is also in the interests of the trusted institution to act in the truster's interests. [81] Conflicts of interest arising in connection with studies threaten in particular the objective aspect of trust.

9.1 Confidentiality

The maintenance of confidentiality with regard to information, i.e. data protection, is important because – both subjectively and objectively – it is a prerequisite for trust. In addition, data protection is a legal obligation for the protection of participants' privacy.

79 Cf. Chapter 10.
80 O'Neill O. Autonomy and trust in bioethics. Cambridge: Cambridge University Press; 2002.
81 Hardin R. Trust and trustworthiness. New York: Russell Sage Foundation; 2002.

Data protection is to be assured not only by technical means, such as electronic or mechanical protection and anonymisation, but also by organisational measures – e.g. separation of data and coding keys, and standardised procedures for data collection, processing and storage. This also applies to the research institution itself, which must not use the knowledge acquired to the detriment of the persons concerned. This is particularly relevant in cases where persons close to the participants are also involved in the research project (e.g. family members, employees within the same organisation, treatment and nursing staff, etc.). In such cases, it may be necessary to guarantee confidentiality not only vis-à-vis the public but also within the research environment.

Personal medical records and/or data obtained from biological material may, directly or indirectly, provide evidence of a person's physical or mental health and, for this reason, can only be used for research under clearly defined conditions. If there are fears that health-related personal data could be used – without consent – for research purposes or even passed on to interested third parties (e.g. insurers, businesses or employers), people will be less inclined to participate in studies and there will be a general loss of confidence in medicine.

If photographs are reproduced in publications or displayed at public presentations or teaching events, the subjects are to be anonymised. If this is not possible, the consent of the person concerned is to be obtained for this use (the "right to one's own image"). The aim is also to ensure that the individual's dignity is protected in photographic documentation.

In the case of topics investigated using qualitative methods, the problems arising in connection with data management are different from those associated with quantitative research.[82] Large surveys involving questionnaires are relatively easy to anonymise, even if delicate issues are covered. But in case studies and in-depth interviews, even if data is consistently anonymised, conflicts are more likely to arise between the persons involved and third parties. Especially in cases where behaviour, attitudes, personal experiences, etc. are studied, participants may feel threatened if there is a risk that their data will not be adequately anonymised. Researchers must therefore guarantee confidentiality for participants. Particularly if it is not foreseeable what information will be obtained, the consent form should include an explicit agreement (binding on the researchers) concerning the ways in which information can be used.

82 Cf. Hopf C. Forschungsethik und qualitative Forschung. In: Flick U, von Kardoff E, Steinke I (eds.). Qualitative Forschung: Ein Handbuch. Reinbek: Rowohlt; 2000, pp. 589–600.

It must always be ensured that personal information is used exclusively in such a way that identification by third parties is not possible. Of particular importance are consistent anonymisation of data which is published or transferred to third parties, secure storage of uncoded primary data, such as field notes, photographs, videotapes, audiotapes and increasingly also digital records stored and evaluated on computer systems. It is also important that the key, or the link between anonymised data and real names, should be subsequently deleted, and that sparing use should be made of contextual information in reports. Participants are entitled to be informed about all the personal data held in relation to them (Art. 8 para. 2 HRA).

9.2 Safety and protective measures

Highest priority is to be accorded to ensuring that participants are protected, both in the planning phase and during the project itself. If risks are involved, measures to ensure the safety of participants must be specified when the study is submitted to the ethics committee (e.g. pregnancy test prior to enrolment, hospitalisation during the study, 24-hour availability of a physician, etc.). Appropriate infrastructure must of course be available at the study site, and the research team must have the necessary expertise. If a (serious) adverse event occurs during a trial of a medicinal product, appropriate measures are to be taken and, if necessary, the ethics committee/Swissmedic is to be informed. Different reporting deadlines apply, depending on the severity of the event. If the safety or health of trial subjects is at risk, the research project may be suspended or its continuation may be made subject to additional conditions (Art. 48 para. 1 HRA).

Adverse events are considered serious if they are fatal, life-threatening, result in disability, or necessitate inpatient treatment not envisaged in the protocol.[83]

Adverse events (AEs) are events observed in a subject participating in a drug trial (irrespective of their association with the treatment). Prior to authorisation of a drug for clinical use, all harmful and unexpected reactions – regardless of the dose – are to be viewed as adverse drug reactions (ADRs) unless an association between the event and the study drug can be definitively ruled out. A reaction is unexpected if it is not listed as an adverse effect in the Investigator's Brochure. An AE which additionally satisfies the above-mentioned criteria for seriousness is known as a serious adverse event (SAE). If a causal link to the study drug is suspected, an unexpected serious ADR is known as a suspected unexpected serious adverse reaction (SUSAR).

83 Cf. Council for International Organizations of Medical Sciences (CIOMS). Reporting Adverse Drug Reactions. Definitions of Terms and Criteria for their Use. Geneva: CIOMS; 1999; US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, 2009.

The following table provides an overview of deadlines for the reporting of different types of events to the ethics committee.[84]

Type of event	Consequences and deadline	Consequences and deadline	Reporting to EC
Serious adverse events (SAEs) in clinical trials of medicinal products (cf. Art. 40 ClinO)	Fatal consequences Within 7 days	Others Within 15 days	Only local events to the local EC All events among participants in Switzerland to the lead EC
Suspected unexpected serious adverse reactions (SUSARs) (cf. Art. 41 ClinO)	Within 7 days	Within 15 days	Only local events to the local EC All events among participants in Switzerland to the lead EC
Serious adverse event (SAEs) in clinical trials of medical devices (cf. Art. 42 ClinO)	In Category C trials, SAEs where a connection is suspected with the investigational device or intervention, within 7 days		Only local events to the local EC All events among participants in Switzerland to the lead EC
Serious adverse events (SAEs) that may be related to the intervention under investigation in other clinical trials (cf. Art. 63 ClinO)	Within 15 days		To the responsible (i.e. local) EC; if appropriate, to the lead EC

84 Details of reporting obligations vis-à-vis Swissmedic are available online: www.swissmedic.ch/bewilligungen/00155/00242/00327/00343/index.html?lang=en. In the case of standard post, compliance with reporting deadlines is determined by the date of the postmark, i.e. the item in question must be posted before the last collection time. It should also be noted that different deadlines apply for the reporting of events by the investigator to the sponsor – generally within 24 hours after the event becomes known.
Source: swissethics. Notification and reporting to the ethics committee from 1 January 2014. www.swissethics.ch/doc/ab2014/Meldungen_Berichte_an_EK_e.pdf

9.3 Liability for damage

Persons participating in research are entitled to receive compensation for damage suffered by them in connection with the research project. Sponsors are essentially liable for all damage suffered by subjects in connection with a project (Art. 19 HRA),[85] and they are generally required to cover liability through insurance or in some other manner (Art. 20 HRA).[86] Liability requires a direct causal link between the damage suffered and the research project. Liability is excluded for damage which would also have occurred in the absence of the research project (e.g. deterioration of health due to a pre-existing condition) but coincides with it. Such damage is covered by the usual liability regulations.

Strict liability encompasses all damage due to death or personal injury and damage to property, but also damage arising from breaches of privacy (e.g. consequences of unauthorised transfer of personal data). In the event of damage, the persons concerned can submit their claims directly to the insurer. The latter is not allowed to cancel the insurance policy after a case of damage has occurred. This is a requirement of justice, ensuring that all persons participating in a trial have the same entitlement to compensation – not merely those whose claims are submitted most rapidly.

The following templates are made available by swissethics:

- General Insurance Conditions (GIC) for clinical trials in Human Research;
- General Insurance Conditions (GIC) for non-clinical trials/research projects pursuant to the Human Research Ordinance (HRO);
- Certificate of insurance (template) for clinical trials (valid for medicinal products, transplant products, medical devices and other clinical trials);
- Certificate of insurance (template) for sampling of biological material and collection of health-related personal data (within the scope of research projects that do not qualify as clinical trials); and
- Certificate of security in lieu of and equivalent to liability insurance

85 Cf. the exemptions from liability specified in Art. 10 ClinO and Art. 12 HRO.
86 Cf. the exemptions from liability coverage requirements specified in Art. 12 ClinO and Art. 13 HRO.

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CHAPTER 10

Information on study results and incidental findings

Those who participate in a study, thus making their personal data and biological material available for research, should not only have the right to be informed about study results which affect them directly, but also be entitled to forgo such information without giving any reasons (the "right to know/not to know"). These rights are indeed enshrined in the HRA (Art. 8). Consent to participate in a research project does not, however, confer a right to be individually informed about the overall results of the study. It is, nonetheless, recommended that investigators or sponsors inform participants in an appropriate manner about the progress and results of a study. Information can be provided, for example, via a regular newsletter or via references to scientific publications.

In practice, implementing the *right to know/not to know* involves certain difficulties: When and to what extent should information be passed on? Who should provide the information? How can the right not to know be guaranteed?

As a general rule, the more serious the (existing or expected) condition and the more conclusive the specific findings, the more pressing is the need to provide information. It must be borne in mind that it may be highly stressful to discover that one has a predisposition to a disease the onset of which is uncertain and lies in the future. Communication must be undertaken by a professional and be tailored to the person concerned. In particular, the latter must be informed about the nature and the reliability of the findings and the possible implications; here, consideration needs to be given not only to the individual health situation but also to possible psychological and social consequences.

The right not to know is also particularly relevant in the case of incidental findings – i.e. results which are not connected with the actual topic of the study but which could nevertheless possibly be important for the participant. As well as evidence of possibly treatable or avoidable conditions, the findings may take the form of abnormalities whose potential pathological significance cannot be reliably assessed, or genetic information of relevance for the whole family (hereditary diseases, paternity).

The more comprehensive the methods used for investigations, the higher the risk of detecting abnormalities whose potential pathological significance cannot be assessed with any degree of reliability. Particularly problematic are not only extensive genomic analyses but also imaging procedures, especially MRI, which not infrequently reveal so-called incidentalomas (incidentally detected space-occupying lesions of unclear significance).

In the case of research projects where incidental findings are likely to emerge, this must be explicitly addressed in the information provided, and the person's wishes regarding the handling of such results need to be determined. The management of incidental findings must be defined in the protocol – i.e. it is to be specified when information must be provided, how, by whom and within what timeframe.

CHAPTER 11

Publication of study results

In Art. 18 of the Code of the Swiss Medical Association (FMH), reference is made to the Helsinki Declaration. Accordingly, publication of study results is mandatory for FMH members: under Art. 36 of the Helsinki Declaration, researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. In the national legislation on human research, explicit mention is made of mandatory registration for clinical trials, but not of the obligation to publish the results. For industry-funded research projects, publication arrangements are generally governed by the contract concluded between the sponsor and investigator; these contracts are to be submitted to the ethics committee. Publication clauses which impose restrictions on the investigator (non-disclosure agreements, confidentiality agreements) are ethically problematic, as they impede public access to the findings of research. As a result of such clauses, information relevant for specific patient groups may not be disclosed (in a timely manner) and/or further research on the topic may be delayed or prevented.[87] Such public interests may run counter to the interests of industry in withholding study results while a patent application is processed. Although it would be unethical to accept a comprehensive ban on publication, it may be justifiable in individual cases for results to be held back for a limited period. If the overall results are not published within a reasonable timeframe, local investigators have a right to publish the results obtained at their site.

In addition to conventional publication in a peer-reviewed scientific journal, study results are increasingly also being made available in electronic databases and registries. Here, there is a need to distinguish between access to the results of statistical analysis (aggregate data, e.g. in study reports) and access to the underlying anonymised personal data. Under the Clinical Trials Regulation (EU No 536/2014) adopted by the European Parliament in 2014, it will be mandatory to publish the results of clinical trials in detail. In addition, efforts are being pursued (e.g. by the European Medicines Agency and the pharmaceutical industry) to allow anonymised personal data from clinical trials to be made available for secondary analysis.

87 Cf. Fangerau H. Publikationsklausel. In: Lenk C, Duttge G, Fangerau H (eds.). Handbuch Ethik und Recht der Forschung am Menschen. Heidelberg: Springer; 2014, pp. 229–32.

If published study results are to be assessed, it is vital that the methods employed should be fully and precisely described. Only a clear description of methods enables other researchers to evaluate the strengths and weaknesses of a study and to assess the importance of the findings. As an aid to the preparation of scientific articles, a number of international groups have produced reporting guidelines. These comprise checklists of essential information to be included in reports of studies of a given type – e.g. CONSORT for randomised trials (www.consort-statement.org) or STROBE for observational studies (www.strobe-statement.org). An overview of reporting guidelines is provided by the EQUATOR Network (www.equator-network.org).

To ensure that a complete and unbiased picture can be obtained of the efficacy data for a particular treatment, it is essential to publish not only positive but also negative and inconclusive results. This helps to avoid decisions being affected by publication or dissemination bias, which occurs, for example, when – to support the approval or reimbursement process – only publications showing a treatment in a favourable light are submitted. Sources of funding, institutional ties and potential conflicts of interest are to be disclosed whenever study results are published. This allows readers to assess the validity of the results for themselves.

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CHAPTER 12

Research projects involving biological material and health-related data

Biological material (i.e. bodily substances derived from living persons, such as tissue, cells, fluids, etc.) and health-related data represent valuable resources for research. Major advances in the life sciences, as well as in informatics and computer technology, have made it possible to generate vast and steadily growing amounts of data of various kinds – genomic and other scientific data from basic and translational research, clinical data from hospital and practice settings (electronic patient records), health and lifestyle ("quantified self") data collected by individuals, commercial data from private companies (e.g. paternity or genetic compatibility tests), or behavioural data collected by (health) insurers. This rapid increase in the volume of data available creates significant opportunities for medical research. Here, biobanks and registries have a key role to play; however, problems of an ethical, legal and technical nature arise with regard not only to data quality, validity, compatibility, storage and security, but also to property rights.

12.1 Sampling of material and collection of health-related data

Because the sampling of biological material and/or the collection of health-related data[88] as part of a research project always represents an intervention compromising a person's physical and/or psychological integrity, the subjects concerned must be involved in the research project in accordance with the general rules of the HRA. However, at the time of sampling/collection, it makes sense to consider the possibility of further use of the biological material and/or data in future research projects. The persons concerned should therefore be able to give their consent not only for the specific research project, but also to further use of the material and/or data for future, as yet unspecified research projects (general consent, cf. Sect. 8.8 above).

88 Health-related personal data comprises all information concerning the health or disease of a specific or identifiable person, including genetic data (Art. 3 let. f HRA).

12.2 Further use of material and data for research purposes

Research projects in which further use is made of existing biological material and/or personal data – deriving either from a therapeutic context or from a research project – are governed by Art. 32 ff.[89] of the HRA. While such studies do not involve intervention in the physical or psychological integrity of the person concerned, there is still a risk that existing information could be misused, and they are therefore subject to the HRA.

12.3 Anonymisation and donor re-identification

The provisions of the HRA differ according to the type of research material (genetic[90] vs non genetic data) and the link to data subjects (degree of anonymisation): the greater the risk of unauthorised identification, the more stringent are the requirements concerning justification for further use and the more narrowly defined the permissible uses. The more a breach of privacy can be ruled out, the less stringent are the requirements concerning justification for further use – informed consent (*opt-in*) or absence of dissent after prior information (*opt-out*).

89 The term "further use" is to be understood in a broad sense. In Art. 24 HRO, it is defined as any handling, for research purposes, of biological material already sampled or data already collected – procuring, bringing together or collecting, registration or cataloguing, storage or inclusion in biobanks or databases, making accessible or available or transferring biological material or health-related personal data.

90 Information concerning a person's genetic material obtained by genetic testing. In Art. 3 let. a of the Federal Act of 8 October 2004 on Human Genetic Testing (HGTA), "genetic test" is defined as follows: "cytogenetic and molecular genetic tests to determine inherited characteristics of human genetic material or characteristics of human genetic material acquired during embryonic development, and all other laboratory tests whose immediate purpose is to provide such information about genetic material".

The various degrees of anonymisation are defined in the following table:

Degrees of anonymisation		
Anonymised	The data subject can only be identified with disproportionate effort. All items of information which, alone or in combination, would enable the data subject to be identified without disproportionate effort must be irreversibly masked or deleted. The more data is available for comparison, the more difficult it becomes to achieve (irreversible) anonymisation. In particular, recent technological developments such as big data increase the risk that the link to the data subject can in fact be re-established by combining anonymised information from different sources.	Art. 25 HRO [91]
Pseudonymised (coded)	Samples and data are (appropriately) coded if, from the perspective of a person lacking access to the key, they are to be described as anonymised. However, not all the identifying attributes are deleted; rather, some are replaced by a pseudonym, e.g. a sequence of letters and/or numbers. In cases where re establishing the link to the data subject is to be impossible for anyone who does not have the key, the same stringent requirements are specified as for anonymised information. In particular, no widely used pseudonyms are to be employed. In addition, the key enabling pseudonymised information to be reconnected to data subjects must be securely stored at a separate location.	Art. 26 HRO
Personally identifying (uncoded)	From the information at hand, or in combination with available information, the data subject is identified or identifiable. [93]	

91 In particular, the name, address, date of birth and unique identification numbers must be masked or deleted (Art. 25 para. 2 HRO).
92 For example, in the case of information from a pathology department, the pathology number – to which almost all hospital staff have access.
93 Also if, for example, widely accessible identifiers are used for pseudonymisation.

a) Biological material and genetic data

Further use may only be made of biological material and genetic data in a *personally identifying (uncoded)* form if informed consent has been given by the person concerned, or by the legal representative or next of kin, and only for a specific research project (Art. 32 para. 1 HRA).

Likewise, further use may only be made of biological material and genetic data in a *pseudonymised (coded) form* if informed consent has been given by the person concerned, or by the legal representative or next of kin. Here, however, consent is not restricted to a specific research project, but extends to any further use of the material and data for research purposes (Art. 32 para. 2 HRA); thus, in this case, general consent is permissible.

b) Non-genetic health-related personal data

Further use may only be made of non-genetic health-related personal data in a personally identifying form for research purposes if informed consent has been given by the person concerned, or by the legal representative or next of kin (Art. 33 para. 1 HRA). Further use may only be made of non-genetic health-related personal data in a pseudonymised form for research purposes if the person concerned or the legal representative or next of kin have been informed in advance and have not dissented (Art. 33 para. 2 HRA).

c) Use in anonymised form

The use of anonymised biological material or health-related data for research purposes does not generally fall within the scope of the HRA (Art. 2 para. 2 let. b and c). However, if biological material or genetic data is to be anonymised for research purposes, an expression of wishes is required on the part of the persons concerned since, for example, it will subsequently no longer be possible for them to exercise their right to know. For this reason, further use may only be made of biological material and genetic data in an anonymised form for research purposes if the person concerned or the legal representative or next of kin have been informed in advance and have not dissented to anonymisation (Art. 32 para. 3 HRA).

The provisions of Art. 32 and Art. 33 HRA concerning further use are summarised in the following table:

		Type of research material	
		Biological material and genetic data (Art. 32 HRA)	Non-genetic health-related personal data (Art. 33 HRA)
Degree of anonymisation and purpose of research	Personally identifying (uncoded)	for a (specific) research project with consent	for research purposes with consent
	Pseudonymised (coded)	for research purposes with consent	for research purposes in the absence of dissent
	Anonymised	for research purposes in the absence of dissent	Outside the scope of the HRA

12.4 Further use of samples and data without the donor's consent

In exceptional cases, further use may also be made of biological material or health-related personal data for research purposes if the above-mentioned requirements for informed consent are not met (Art. 34 HRA). The following conditions then apply cumulatively:

- it must be impossible or disproportionately difficult to obtain consent or to provide information on the right to dissent, or this would impose an undue burden on the person concerned;
- there must be no documented refusal;[94]
- the interests of research must outweigh the interests of the person concerned in deciding on the further use of his or her biological material and data.

This clause applies exclusively for exceptional cases. The conditions are not to be over hastily or even automatically considered to be satisfied. In particular, it must not be prematurely assumed that it would be impossible or disproportionately difficult to make contact with the person concerned. Nor can it be assumed

94 For example, in the form of an advance directive, which may be deposited with the Child and Adult Protection Authority.

that any contact would cause unreasonable emotional strain.[95] Research interests do not generally outweigh self-determination interests; a specific overriding research interest is required. In cases where the person concerned merely has a right to dissent, self-determination interests may possibly be regarded as carrying less weight than in cases where consent is required.

Plans to make further use of biological material or health-related data for research purposes in cases where consent has not been obtained or information on the right to dissent has not been provided must be submitted to the responsible ethics committee for authorisation; under Art. 45 para. 1 let. b HRA, the committee has to decide whether the conditions specified for exceptional cases are met.

95 The example of renewed confrontation with a difficult situation cited in the Dispatch (BBl 2009 8123) is therefore not to be given an extensive interpretation; experience shows that, e.g. in patients with breast cancer, consciousness of the disease in subsequent years is such that, in general, the person can reasonably be asked whether she consents to further use of her samples and data for research purposes.

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CHAPTER 13

Quantitative Designs und Methoden

In quantitative medical research, data is collected and analysed using statistical methods. The data can be obtained in various ways, such as by measurement of physiological parameters (e.g. blood pressure), evaluation of characteristics (e.g. the presence of genetic variants or behaviours), or analysis of health-related events (e.g. the occurrence of a disease). The results of such investigations may be of interest in themselves – for example, the distribution of measured values or the frequencies of characteristics or health-related events – but, frequently, associations between different variables are also sought. Researchers often analyse quantitative relationships between different parameters measured (correlations, e.g. between salt intake and blood pressure) or the co-occurrence of characteristics and health-related events (associations, e.g. between genetic variants and Alzheimer's disease). If such associations are detected, the characteristics are described as *risk* or *protective factors*. Risk factors such as smoking and protective factors such as taking certain medicines are known as *exposures*; in interventional studies, the treatment is the exposure, while a health-related event – e.g. an illness, death, improvement in health status or reduction in blood pressure – is known as the *outcome*. Whether statistical associations can be interpreted as cause-effect relationships depends on the particular study design (observational or interventional study) and on additional circumstances (exclusion of confounding factors, findings from previous studies and experiments, biological plausibility, etc.). The strongest evidence for a causal relationship is provided by randomised double-blind studies based on precisely defined hypotheses.

When statistical quantities are determined as the results of an analysis, three points are of particular interest: the numerical value (mean or median of a measured parameter, or relative frequency or difference in frequency of an outcome in different groups), the variability in the study population (standard deviation of measured values, quantiles of a distribution of characteristics), and the degree of uncertainty due to chance (expressed by the 95% confidence interval). When hypotheses are tested, observed effects where the 95% confidence interval does not contain the value of the null hypothesis are described as statistically significant at the 5% level.

To ensure that the conclusions drawn from a study are sound and widely applicable, the methods to be used for statistical analysis must be defined before data collection begins. The choice of statistical methods will depend on the particular research topic. If causal relationships are to be investigated (e.g. whether drug A is more effective than drug B), specific quantitative hypotheses must be formulated in the planning of the study.

Various key aspects of quantitative studies are discussed below. Each step in the implementation of a study should be clearly defined in advance in the protocol. As a general rule, the approach to be adopted (study design), as well as the measurements and the statistical analysis required, is implicit in the topic. This also means that a study design may be unsuitable for the topic in question – although this is not always immediately apparent.

13.1 Topic

The topic should be precisely formulated in concrete terms, as it is crucial for the planning of the study. It should be based on the current state of research, addressing unresolved questions. It must be clear how the planned study will increase scientific knowledge and what benefits it is intended to provide. The topic and all the hypotheses to be tested must be precisely defined in the study protocol, so that they cannot be adapted post hoc to the data obtained. It must also be apparent from the topic what study population is to be investigated over what period and in what area. In addition, it must be possible for the desired outcome to be reliably measured.

13.2 Choice of study design

The design of the study is chosen on the basis of the topic: What form would the ideal study take to answer the question raised by the topic? If similar topics have already been investigated in other studies, it must be apparent how the weak points of earlier studies are taken into account and avoided by the proposed study design. It must also be made clear what data is already available or is standardly collected in routine medical care and what will have to be additionally determined (measured).

The explanations given below concern clinical trials and observational studies – the two types which account for the majority of all studies performed in quantitative medical research.

13.3 Clinical trials

The term "clinical trials" is broadly defined to cover all studies in which human subjects are deliberately exposed to an intervention or investigation which is not individually proposed by the physician but determined by the mechanism of the study design. Apart from the classic case of drug therapy, the intervention may involve, for example, instructions for a fitness plan, additional diagnostic measures such as X-ray examinations or blood tests, or an invasive procedure (e.g. an operation). The aim of such studies is often to compare the intervention (treatment or investigation) with the existing standard treatment (standard investigation) or with a sham intervention (placebo). However, the aim may also be to compare various established interventions (comparative effectiveness research).

As a first step, it is determined which patients or persons meet the eligibility requirements for participation in the study. They are then assigned either to the intervention or to the control group. Here, systematic imbalances may arise if, for example, certain types of subject are preferentially assigned to a given group (e.g. those who are younger, more seriously ill, or university hospital patients). To eliminate such bias, randomised trials are performed.[96] However, the assignment process must be genuinely random and not amenable to influence by study staff or patients. An appropriate way of ensuring random assignment is, for example, to use computer-generated randomisation lists which are only known to the study centre.

Another important means of avoiding bias in the results of a study is *blinding*. With double-blinding, neither the researchers nor the patients know who is exposed to which intervention. This is generally only revealed after the analysis. Blinding prevents the results (i.e. assessment of the outcome) from being influenced by patients' or researchers' personal preferences. Although blinding is not feasible for every type of intervention, it should always be possible to blind the person who assesses or measures the outcome.

96 Meinert CL. Clinical trials: design, conduct, and analysis (2nd edition). New York: Oxford University Press; 2012.

Therapeutic product studies are carried out to evaluate the safety, efficacy and other properties of a medicine which is to be submitted to the drug regulatory authorities for marketing authorisation. The study procedure is formalised and is subject to the provisions of the Therapeutic Products Act (TPA). It is divided into four phases:

- In Phase I the new active substance, having been tested in animals, is used in human subjects for the first time – either in healthy volunteers or, in the case of chemotherapeutic agents of known toxicity, as an experimental treatment for patients in the absence of therapeutic alternatives. As well as examining the tolerability of the active substance in different dosages, Phase I studies provide data on pharmacokinetics (i.e. the processes which the drug undergoes in the body).
- In Phase II the drug is tested in relatively small groups of patients. Here, the focus is on identifying therapeutic and adverse effects and on determining the optimal dosage.
- In Phase III the efficacy and safety of the new substance is studied in comparison with a standard treatment or, in the absence thereof, placebo. In general, several randomised double blind trials are conducted for the registration of a therapeutic product.
- In Phase IV drugs already on the market are further investigated in observational studies. Such studies can provide valuable findings on rare adverse effects and interactions with other drugs, but they have sometimes also been used as a marketing instrument to influence physicians.

Diagnostic studies are also to be classified as clinical studies (trials) if the use of a diagnostic procedure is specified by the study protocol. Studies which merely analyse the results of routine diagnostic investigations are, however, observational. Interventional diagnostic studies pursue two types of goals. Firstly, they assess to what extent the results of a diagnostic test make it possible to distinguish between subjects with and without a disease, and then evaluate how the results affect the clinical outcome. Widely discussed examples in this category are studies concerning screening for breast or prostate cancer. Diagnostic studies of the second type seek to evaluate the agreement between two different procedures. In these studies, both procedures are applied to the same subjects – e.g. a conventional computerized tomography (CT) scan versus a CT scan with a reduced radiation dose. Here, too, bias can be avoided with the aid of blinding, i.e. the person assessing one procedure must be blinded to the results of the other.

In a special type of study known as *cluster-randomised trials*[97] not individuals but whole sets of subjects are allocated to the intervention or control group. A more recent development of this type of study is the *stepped wedge trial design*,[98] where a new treatment or investigation is rolled out sequentially to clusters over a number of time periods. Studies of this kind are frequently used to investigate the influence of organisational changes (e.g. implementation of guidelines) in practices, hospitals or local care delivery structures. Randomisation is carried out, not at the individual level, but for example at the practice, hospital or community level. Here, however, there is a risk that the results of the study may be biased by between-cluster variation in factors associated with the outcome (e.g. age distribution or socioeconomic status) – for example, if the intervention is applied predominantly in clusters with a more favourable risk profile. These points need to be taken into consideration not only in study planning and the estimation of study size, but also in the statistical analysis.

97 Donner A, Klar N. Design and analysis of cluster randomization trials in health research. New York: Oxford University Press; 2000.

98 Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. BMC Med Res Methodol. 2006; 6: 54.

13.4 Observational studies

In contrast to clinical trials, observational studies do not involve any interventions determined by researchers – rather, the interventions are undertaken as part of routine medical care. Studies of this kind are designed merely to document what has occurred. The goal of observational studies may be to investigate the association between an exposure and an outcome, usually when a cause-effect relationship is suspected. Another common goal is to examine the incidence and course of understudied diseases.

The quality of an observational study is largely dependent on the appropriate collection of all the information required for the study goal. Guaranteeing this generally entails considerable efforts, e.g. in the form of audits. The description of the study must specify the quality assurance measures required for this purpose and indicate how the necessary efforts can be realised.

The main study designs differ primarily with regard to whether information is collected at one or several time points, and whether the selection criteria for subjects are defined on the basis of the exposure or the outcome.

13.5 Cohort studies

In cohort studies, groups of people are monitored over time. The selection criteria are primarily defined on the basis of exposure. The aim is to determine whether – over specified periods – an exposed group develops a given outcome more or less frequently than an unexposed group. Cohort studies are particularly suitable when different consequences of an exposure are to be investigated. For example, a cohort study can be used to quantify the risks for smokers and non smokers of contracting various types of cancer. This type of study design is well-suited for frequent outcomes or rare exposures. If the exposure can also arise and be recorded in the course of the study, the exposure status of cohort members may change over time; this can be taken into account in the analyses.

13.6 Case-control studies

In case-control studies, participants are selected on the basis of whether a given outcome has or has not occurred. Previous exposure status in cases is determined retrospectively and compared with that of controls. Case-control studies are particularly suitable for investigating new conditions of unknown etiology, for simultaneously analysing a number of different exposures in relation to a given outcome, or for studying rare outcomes.

13.7 Cross-sectional studies

In cross-sectional studies, data on all variables is collected at the same time. This means that the study can be performed within a short period. But because there is only one time point, in subjects with the suspected exposure and the associated outcome it cannot always be determined whether the former actually preceded the latter. If an association is detected, a cause-effect relationship can only be established by conducting a more elaborate case-control or cohort study, or (ideally) a randomised controlled study. Frequently, however, the goal of cross-sectional studies is not to explore a causal relationship, but to provide a quantitative description of the prevalence of certain phenomena, health problems, etc. In such cases, it is important that the study should enable representative conclusions to be drawn for the population concerned.

13.8 Avoiding biased or invalid results in observational studies

Detailed and careful study planning is essential not only for scientific reasons. It is pointless – and indeed unethical – to impose additional burdens on patients and persons in routine medical care if the results will be invalidated by the choice of study design, inadequate sample size or inappropriate measurement methods. The risks of generating biased or invalid results differ depending on the type of study design. In each case, attention needs to be paid to specific potential sources of error.

For all study designs, particular consideration should be given to the choice of the *study population and control groups*. The inclusion and exclusion criteria must be clearly defined in the protocol before the start of the study. The exposed and unexposed groups should as far as possible be well matched in every respect except the exposure. Not everyone who is eligible to be included in a study will actually be willing or able to participate. Persons who meet the inclusion criteria but do not accept the invitation to participate are known as *non-participants*. In addition, especially in cohort studies, participants may drop out in the course of the study or become untraceable – a phenomenon known as loss to follow-up. If non-participation or loss to follow-up are associated with the exposure and the outcome, the results may be systematically distorted (*participation bias and attrition bias*). If non-participants differ from participants but this difference is independent of exposure and outcome, only the generalisability of the results is affected.

To avoid biased results in case-control studies, exposure status must be equally well (retrospectively) determined in both groups. The results obtained are often unreliable if exposure is ascertained solely on the basis of what is reported by cases and controls (*recall bias*). In addition, if a case-control study is to generate valid results, the exposure must not be highly rare.

If certain characteristics are associated with both the exposure and the outcome, an association detected may not reflect the true causal relationships (e.g. a spurious relationship between coffee consumption and cardiovascular disorders may be postulated if both of these are associated with smoking, but the latter is not observed); this is known as *confounding*. In such cases, the strength of the association between exposure and outcome can be over- or underestimated. Randomised studies offer the advantage that confounding factors are evenly distributed among the intervention and control groups. In observational studies, possible confounders can be taken into account in the statistical analysis so that causal relationships are then correctly quantified. However, this requires confounders to be identified as such in the study planning and appropriately observed during the study.

The absence of *blinding* can lead to problems not only in clinical trials but also in observational studies. Therefore, in a cohort study, for example, the person assessing whether the outcome has occurred should not know whether the participant in question was exposed or not; otherwise, the assessment could be influenced (observer bias). The results could also be biased (consciously or unconsciously) if the data is assessed by statisticians with specific expectations.

In addition, it is important that the information available should be of the same quality for all study groups. In a case-control study, for example, if detailed medical records are available for the cases but only self-reported information for controls, then it is not possible for the data to be compared. Similar problems arise if exposure is determined on the basis of subjects' recollections: those who are seriously ill will reflect in more depth on possible risks to which they have been exposed in the past than healthy subjects in the control group (*recall bias*).

As repeatedly emphasised above, it needs to be ensured at the planning stage that information will be fully and appropriately collected in the course of the study. The chosen measurement method must be sufficiently sensitive to detect material changes and sufficiently specific to measure what is relevant for the study. Measurement data must be reproducible, and equipment and methods calibrated and validated. In addition, study personnel must be appropriately instructed and capable of operating the equipment.

13.9 Statistical analysis

Both for clinical trials and for observational studies, it must be defined in the protocol what analyses are to be performed in order to answer the fundamental question, and what statistical methods are to be used. It must also be specified in advance how missing measurements or outcome data are to be dealt with in the analysis, as well as known confounders and other foreseeable problems.

The proposed sample size is also to be defined and justified in the study protocol. As a general rule, smaller numbers of participants are required for studies with a numerical outcome variable (e.g. change in blood pressure, or a pain score determined using a validated questionnaire) than for studies where the outcome is a clinical condition which may or may not occur (e.g. death, recurrent myocardial infarction, rehospitalisation, recurrent fracture).

In general, two types of argument can be used to justify the choice of sample size. Firstly, it can be defined in advance what difference between groups is to be regarded as clinically relevant. The sample size is then selected so that there is a specified likelihood of observing a significant difference if it actually exists. This likelihood (also known as the *statistical power* of the study) should be at least 80%.

With the second type of argument, rather than postulating a specific difference, it is specified how precise the expected result should be (i.e. the width of the 95% confidence interval for the variable of interest in the main analysis). The desired precision must be discussed in the context of the results of other studies and possible decision criteria. This approach is primarily adopted for studies where the aim is to determine the frequency of certain phenomena.

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CHAPTER 14

Qualitative designs and methods

Qualitative social research – for all the diversity of methods, approaches and schools in existence – is concerned with the social production of meaning and reality.

The starting point is the everyday practice and everyday knowledge of the subjects under investigation. By pursuing an interpretative, semantic approach to social reality, qualitative research – in a methodologically controlled and systematic fashion – generates knowledge of social reality which goes beyond mere everyday knowledge.

Far from being homogeneous, the field of qualitative research takes a wide variety of forms. A useful distinction between qualitative and reconstructive approaches is expressed by Kruse as follows: "Everyone who conducts reconstructive research employs qualitative methods. But not everyone who *employs qualitative methods* conducts reconstructive research."[99]

Qualitative research involves detailed descriptive analysis of meaningful social reality. Here, interest is focused on the perspectives of research subjects and everyday events. In contrast, reconstructive approaches explore the foundations of social interaction, seeking to reconstruct the *meaning behind the meaning*. Here, the emphasis is placed not on what is expressed by research subjects, but on how and why the social production of reality takes place.[100] Underlying such approaches are reconstructionist assumptions about reality which are ascribed to the "interpretative paradigm". Important sociological applications include ethnomethodology (Garfinkel), symbolic interactionism (Blumer, Mead), social phenomenology (Schütz, Berger, Luckmann) and sociology of knowledge (Mannheim).

14.1 Methodology

The conception of reality as a product of social interaction has consequences for qualitative methods of data collection and analysis.

A key methodological element is the principle of openness. Vis-à-vis the object of investigation, researchers should, as far as possible, be open-minded as to the results. This means that they should not have recourse to prior knowledge, and should explore and become aware of pre existing assumptions and background-knowledge concepts (research attitude).

99 Kruse J. Qualitative Interviewforschung. Ein integrativer Ansatz. Weinheim und Basel: Beltz Juventa; 2014, p. 24.
100 Ibid. pp. 24 ff.

Research is understood as communication and interaction with the research subjects or the research field.

Data collection is also governed by the principle of openness and, as far as possible, is guided by questions which are relevant from the research subjects' perspective (i.e. relevance is defined by the subjects).

a) Sampling

The question of case selection is of similar (central) importance for qualitative research as sampling for standardised (quantitative) research, since it exerts a substantial influence on the quality of the data and the applicability of the results. In qualitative research, case selection must also take into account the heterogeneity of the research field. The goal, however, is not *statistical representativity*, but *qualitative representation* – either at the level of the subject or of social institutions.[101]

To reflect the heterogeneity of the research field, two strategies can be pursued. Firstly, the sample can be defined in advance, with cases being considered on the basis of various (theoretically grounded) characteristics. Here, in accordance with the principle of maximum structural variation, the widest possible range of types is defined so as to provide a basis for subsequent recruitment, with classical categories including gender, age, educational level, etc.

The second strategy for obtaining a contrasting sample is known as *theoretical sampling*. Here, fundamentally, case selection is geared to the successive elaboration of theory, although at the beginning of data collection researchers also have recourse to existing conceptual/theoretical assumptions about the research field. In seeking and selecting potential interviewees, different categories will be relevant depending on the specific topic (e.g. gender, age, occupation, duration of disease, etc.). In the analytical process, other important characteristics are continuously fed into the selection of cases; in other words, after an interview has been conducted, efforts are made to recruit new interviewees whose characteristics contrast minimally or maximally with those of the previous interviewee(s). This method ensures that the heterogeneity of the research field is reflected as fully as possible. The criterion for completion of the data collection process is *theoretical saturation* – i.e. the point at which, in spite of maximally contrasting cases, no further new theoretical insights can be generated. To achieve this goal, appropriate recruitment strategies are also required.

101 Ibid. pp. 241 ff.

b) Recruitment

Rather than being a fixed unit, the field of investigation is conceptually determined by the knowledge-generation interests of research and the questions guiding research. Where can communication/interactions be observed and data be collected which could illuminate the research topic? Recruitment strategies and access to the field thus illustrate the context-dependency of qualitative data.

14.2 Forms of data collection

In qualitative and especially in reconstructive research projects, data collection follows as closely as possible the topics and questions which are important for the research subjects (relevance defined by the subjects). This orientation is essentially grounded in the epistemological foundations of qualitative research and is thus of methodological importance. In principle, a distinction can be made between data collection by means of observation and interviews.

a) Observation

As a data collection method, observation may be *participant or non-participant* and *overt* or *covert*. The choice depends essentially on the object of research. Observation is appropriate in cases where (sufficiently comprehensive) verbal statements cannot be obtained, or if data is to be collected on the behaviour of persons or groups. Here, emphasis is placed on the direct observation of human action, encompassing not only linguistic utterances but also social characteristics such as customs, dress, non-verbal reactions, etc. Careful observation of behaviour patterns and relationship structures permits a deep insight into everyday events and values embedded in a social context. In participant observation, the particular challenge lies in striking a balance between involvement and detachment: without becoming involved one can scarcely observe all the significant aspects of the situation, but without remaining detached one cannot reflect on one's observations from a social scientific perspective.[102]

102 Przyborski A, Wohlrab-Sahr M. Qualitative Sozialforschung. Ein Arbeitsbuch. Munich: Oldenbourg; 2008, p. 60.

Observation records provide a basis for the preparation of detailed reports after returning from the field. The latter generally involve a chronological account of the data collected. During fieldwork, the time and place should therefore be recorded in the first column. The phenomenon observed is then described in the next column. Contextual information, and methodological and theoretical reflections, can be recorded in separate columns. These different headings help to prevent observations being subjected to premature theorisation.[103] Written records of observations represent the first step in the process of analytical selection, with researchers' impressions being conceptualised and verbalised. Writing is thus an act of "reconstructive preservation".[104] Notes should be made promptly, but not generally in the presence of research subjects, so that their interactions are influenced as little as possible.

b) Interviews

Interviews can take various forms, differing with regard to the extent to which the dialogue is structured or open. Depending on the research interest, different types of interview are suitable for data collection. In general, both the data collection instruments (interview guide) and the questions formulated should permit the greatest possible openness. In other words, the primary goal is to elicit information while avoiding the impression that subjects are being quizzed or even interrogated. If a thematic focus is defined by the interviewers for practical reasons, the subjects should still be able – within this framework – to express themselves as freely and without interruption as possible, or to act in an unconstrained manner within the observational setting. Open "stimulus questions" used in interviews should generate a narrative-type response which is topic specific but self-sustaining. This fundamentally open type of interview makes it possible to identify attitudes, needs and the patterns of interpretation and meaning which underlie decision making.

c) Narrative interviews

The narrative interview format was introduced by Schütze.[105] Of all the various types of interview, it allows informants the greatest freedom. The aim is to elicit a spontaneous narrative, not prepared in advance. This type of interview is suitable in cases where an account is to be given of processes and events which people have experienced themselves. Narration – it is assumed – most closely reflects the cognitive processing of experience; an existing state or situation is thus rendered plausible and explained. Narrative interviews are often used for biograph-

103 Ibid., p. 66.

104 Bergmann J. Flüchtigkeit und methodische Fixierung sozialer Wirklichkeit: Aufzeichnungen als Daten der interpretativen Soziologie. In: Bonss W, Hartmann H (eds.). Entzauberte Wissenschaft: Zur Relativität und Geltung soziologischer Forschung. Soziale Welt, Sonderband 3. Göttingen: Schwarz; 1985, pp. 299–320.

105 For example: Schütze F. Biographieforschung und narratives Interview. Neue Praxis. 1983; 3: 283–93.

ical research topics, but they are not to be equated with the biographical interview. Narrative interviews are generally conducted without an interview guide. The main component is a spontaneous narration, prompted by an introductory (open stimulus) question. During this part of the interview, the informant enjoys absolute freedom to speak in monologue. At the end of the autobiographical account, the interviewer will ask questions which merely seek clarification ("immanent" questions) and further ("exmanent") questions, addressing new subjects. Here, a guide may be used if appropriate. The interview concludes with a final assessment. Ideally, narrative passages should also be accommodated within other, more structured formats, such as the guided interview.

d) Guided interviews

In more controlled formats, the interview is structured with the aid of a guide. Narrative elements can also be combined with this type of interview if a guide is prepared but an open stimulus is retained. The questions prepared in advance are only introduced towards the end of the interview, when the narrative flow is exhausted. For the interview guide, questions are compiled using specific methods and are generally divided into thematic blocks. Depending how and to what extent the interview is structured, the blocks can be hierarchical or on the same level. In the latter case, possible aspects to be covered are merely listed for guidance, but answers to these questions are not actively sought by the interviewer. Ideally, within each thematic block, space should be left for the subject to speak freely, and the flow should merely be supported by open questions which provide encouragement, remaining within the narrated situation (so called sustaining questions, e.g. "Can you tell me some more about that?"). At the end of narrative sequences, information can be actively elicited on points which are important for the research project (exmanent questions, going beyond the interview situation, such as "What is best/most difficult for you?"). In general, with the subjects' consent, interviews are digitally recorded and – depending on the method of analysis – partly or fully transcribed in more or less detail (i.e. with or without phonetic features).

106 Cf. Rosenthal G. Erlebte und erzählte Lebensgeschichte: Gestalt und Struktur biographischer Selbstbeschreibungen. Frankfurt a. M.: Campus; 1995

e) Expert interviews

Expert status is ascribed to an individual by researchers. Experts are considered to represent the practices, perspectives and knowledge systems of a particular group. They thus have knowledge relating to their specific professional or occupational activities. Expert interviews are designed to make this knowledge accessible to researchers. Here, a distinction is made between "contextual knowledge" and "operational knowledge".[107] The former encompasses the complex system of bodies of knowledge relating to the activities of a group of persons. The latter consists of knowledge relating to the occupational processes of interest – including, for example, specific skills developed by an occupational group as a result of relations with a group of patients frequently extending over many years. Operational knowledge, which often comprises routine practice, customs and occupational traditions, is considered to be highly action-guiding. Expert interviews can also be used to obtain relevant, objective and valuable contextual knowledge. In addition, they can serve to reconstruct implicit knowledge in the form of routine behaviour and patterns of interpretation which influence decision-making in everyday occupational practice.

f) Group discussions / focus groups

In group discussions, attention is paid to the organisation of the discussion and to particularly important passages, with the goal being to trace the construction of collective views. Here, as a rule, individual positions are less relevant than the attitudes collectively generated through social interaction – on the basis of Mannheim's concept of the "conjunctive experiential space".[108] Groups can be defined in different ways. In the literature, a distinction is made between *natural* and *artificial* groups: the latter are formed purely for the purposes of data collection. In addition, depending on the research interest, artificial groups can be of homogeneous or (deliberately) heterogeneous composition. The aim of this type of data collection is to reconstruct the logic of the discussion and the argumentation deployed; epistemologically, it is based on Mannheim's sociology of knowledge.

107 Bogner A, Littig B, Menz W (eds.). Das Experteninterview: Theorie, Methode, Anwendung. Wiesbaden: Verlag für Sozialwissenschaften; 2005.

108 Bohnsack R. Rekonstruktive Sozialforschung: Einführung in qualitative Methoden. Opladen: Leske Budrich; 2003.

14.3 Methodological specifics

a) Baseline and subsequent data collection

If a situation changes over time, a longitudinal study design may be appropriate. This is of particular relevance in the case of chronic diseases, where changes occur over the course of care and treatment processes as the therapeutic regimen is increasingly intensified. It may therefore be advisable to collect data before, during and after care episodes. In qualitative evaluation research, this is already explicitly specified in the study design.

b) Triangulation and mixed methods research

Triangulation refers to the combination of different methods of data collection. When certain topics are studied, a variety of methodological approaches may be used in order to increase the knowledge generated. In some cases, validation of data is also cited as a reason for combining different methods. In *mixed methods research*, qualitative and quantitative elements are combined in different phases and with different weights being attached to each approach. Such designs call for a broad knowledge of both the quantitative and the qualitative paradigm, with respect not only to methods but also to the theoretical/methodological foundations.[109]

14.4 Data analysis

Qualitative data analysis is not a uniform field. Essentially, two different approaches can be distinguished – categorising and sequential analysis.

a) Categorising analysis

In *categorising* or *coding analysis*, textual material is broken down into individual words or short passages, which are then assigned substantive codes. Techniques of this kind include *theoretical coding* (in accordance with grounded theory) and *content analysis* (developed by Mayring). In content analysis, textual material is systematically analysed, with progressive application of category systems previously developed from the material in a theory-guided manner. Here, three forms of analysis can be distinguished – summary, explication and structuring. In *summary*, "the object of the analysis is to reduce the material in such a way that the essential contents remain, in order to create through abstraction a comprehensive overview of the base material which is nevertheless still an image of it." *Explication* seeks "to provide additional material ... with a view to increasing understanding, explaining, interpreting the particular passage of text." The aim

109 Kelle U, Erzberger C. Qualitative und quantitative Methoden – kein Gegensatz. In: Flick U, von Kardorff E, Steinke I (eds.). Qualitative Forschung. Ein Handbuch. Reinbek: Rowohlt; 2000, pp. 299–309.

of *structuring* is "to filter out particular aspects of the material, to give a cross-section through the material ... or to assess the material according to certain criteria."[110] Various aspects of content analysis have been criticised by exponents of reconstructive approaches – the pronounced schematisation and formulation of the individual steps, as well as the fact that the approach is guided by the ideal of standardised methodology. The categories are theoretically grounded in advance, and the focus tends to be on the surface content rather than on possible deeper layers. Content analysis is not a hermeneutical approach; paraphrase tends to reduce analysis to a summary of the manifest content.

Theoretical coding using grounded theory codes is, however, also suitable for reconstructive research. Here, codes and categories developed from the material document as succinctly as possible the manifest/substantive or latent level of meaning. Grounded theory aims to reconstruct the relationships between categories. Asking "What is connected to *what* and *in what way*?", it ultimately seeks to develop a theory which is grounded in the data. Of fundamental importance for grounded theory analysis are the iterative/cyclical reasoning process and the principle of constant comparison of the data collected. The following basic analytical operations are distinguished: open, axial and selective coding. In *open coding*, the first codes and concepts are generated. This stage, carried out sequentially and intensively, represents the first step towards theorisation. In *axial coding*, categories and subcategories are developed with the aim of defining a core category. Only when this category has been elaborated does *selective coding* begin. This process may involve recoding, with concepts being analysed in relation to the core category. These concepts are finally integrated into a theory.

110 Mayring P. Qualitative content analysis: theoretical foundation, basic procedures and software solution. Klagenfurt, 2014: 64.

This open and, at the same time, systematic approach, involving repeated analysis of the empirical material, permits deeper insights into sometimes unexpected connections. The data analysis must therefore be based on a verbatim transcription of recorded interviews or on a description of observations which is as detailed as possible.[111] Fundamental to this analytical approach is the iteration of inductive, deductive and abductive reasoning. In a circular process, theoretical considerations and propositions are developed, verified using additional material and, if necessary, modified. Throughout the process of data collection and analysis, memos are written to facilitate the formulation of theoretical ideas.

Various software products are available to support categorising data analysis (e.g. MAXQDA, f4analyse or ATLAS.ti).

b) Sequential analysis

Methods of this type include objective hermeneutics, hermeneutic sociology of knowledge and conversation analysis. Sequential analysis focuses on how an interview unfolds, considering its sequential structure to be essential in relation to the process of social construction of reality and meaning. Social reality is understood as a reality of progression; at different points in the sequence, different possibilities are opened up. Which of these are realised is an expression of individuals' selectivity in their action. The passages chosen by researchers for detailed analysis make it possible to infer action-guiding patterns of selection. The aim of objective hermeneutics, for example, is to reconstruct the "case structure" and formulate case structure hypotheses.

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Przyborski A, Wohlrab-Sahr M. Qualitative Sozialforschung. Ein Arbeitsbuch. Munich: Oldenbourg; 2008.

111 The transcripts are anonymised so as to contain no information which would allow the interviewee to be identified. The anonymisation procedures are explained in a separate key. Thus, names are replaced by a description, e.g. "[name of the person supported]", and places by a numbered series, e.g. "[place 1]", "[place 2]", etc. Occupational details form a relevant analytical category providing essential contextual information. They cannot, therefore, reasonably be anonymised.

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