Working Group No. 19:

Clarification of responsibility (matriculation projects, Bachelor's and Master's theses, dissertations, quality assurance projects, practice experience reports, compassionate use)

Answering the question of whether a specific research project must be approved by the competent ethics committee (EC) is based on Article 3 of the Swiss Human Research Act (HFG/HRA). This article of the Act defines, inter alia,

a. The term research (= systematic search for generalisable knowledge)
b. The term research on diseases (= research on the causes, prevention, diagnosis, treatment and epidemiology of physical and mental health problems in humans)
c. The term research on structure and function of the human body (= basic research, especially on the anatomy, physiology and genetics of the human body, as well as non disease-oriented research on interventions and effects on the human body)

If the conditions mentioned above are met and the relevant research project falls within the scope of Article 2 HRA, the research project is subject to approval by an EC (cf. Article 45 HRA). For completeness, a specific point in the legislation on human research that took effect on 1 January 2014 should be mentioned in this context: according to Article 6 letter b of the Human Research Ordinance, any project that involves taking biological material from a person or collecting health-related data from a person in order to use such biological material or health-related personal data for research purposes represents a research project subject to approval by an EC. In other words: although in this particular case and at this time there is still no specifically formulated question, it is a research project in a legal sense.

In particular, the legal definitions contained in the HRA and the associated ordinances include regulatory boundaries for all personnel involved in human medical research projects. However, acts and ordinances cannot govern matters as complex as human research in such detail as to eliminate all issues of demarcation. The following clarifications should assist uniform and legally compliant implementation in borderline areas between research subject to EC approval and research not requiring such approval.

1. Practice experience reports versus research projects subject to EC approval (Appendix 1)

Practice experience reports (PERs, also referred to as ‘Anwendungsbeobachtungen’ in Germany) are often used as marketing instruments by pharmaceutical companies. In principle, there is no reason to object to this as long as they remain within the law. However, many years of experience shows they are regularly used by pharmaceutical companies to circumvent the relatively time-consuming and costly effort involved in phase IV studies (the latter may require exercises such as post-market surveillance, evaluation of therapeutic
benefits or assessment of therapeutic strategies). To block the practice of disguised phase IV trials in the form of PERs, strict rules for the conduct of PERs were set up some time ago by the regulatory authorities. Reference should be made in this respect to the requirements for PERs, as contained in the monthly report for 3/2000 of the Intercantonal Monitoring Authority for Therapeutic Products (IKS, now Swissmedic). These requirements clearly state that the use of therapeutic products may not be (co-)determined by a clinical trial protocol, but must be based exclusively on the treatment decision of a doctor. Accordingly, only data originating from routine diagnosis or treatment may be incorporated into a PER. The attached checklist builds on the requirement profile for PERs as listed in the monthly report for 3/2000 of the IKS, and supplements it in the light of experience gained in recent years with PERs. Specifically, this means that no comparisons of different providers of therapeutic products may be made, no monitoring or auditing by the sponsor of original documents (such as medical records) is admissible, and questionnaires are only allowed if they are also part of the routine treatment.

2. Compassionate use versus research projects subject to EC approval

'Compassionate use' refers to a difficult situation in which many established methods of treatment or those with scientifically proven efficacy no longer help, and an attempt is made to achieve a cure (or at least an improvement) with a method that has not been established. In contrast to research, which is primarily concerned with the search for generalisable knowledge, compassionate use is focussed on the individual doctor-patient relationship and the most effective treatment (see "Compassionate Use - Facts and Arguments" [in German]-Fact Sheet of the Swiss Academy of Medical Sciences (SAMW, SAMS) of 29 September 2010). Other terms that have been used in association with 'compassionate use' are 'therapeutic research' and 'human experiment'. The SAMS recently submitted the guidelines "Differentiating between standard therapy and experimental therapy" for consultation. The definitive version should be adopted in the first half of 2014. These guidelines recommend that the terms 'compassionate use', 'human experiment' and 'therapeutic research' be replaced by the term 'experimental therapy'. The SAMS Fact Sheet cited above states appropriately: "However, as soon as non-established procedures are used repeatedly (i.e. systematically), all the requirements and regulations for the conduct of a research project must be complied with." This is the crucial point: at what stage can (or must) one regard procedures as repeated and therefore systematic? Until the Human Research Act took effect at Federal level on 1 January 2014, only clinical research with therapeutic products was regulated and thus subject to EC approval. For this and other reasons the 'salami tactic', practised particularly by surgeons for testing new surgical procedures, has been widespread until now (even where systematic testing of new surgical techniques was already subject to EC approval according to cantonal law prior to 1 January 2014): an initial 'compassionate use' is followed (if successful at first sight) by a second use and then by others, until eventually the results (systematically evaluated) are presented at a specialist conference and after a certain period has elapsed, the original 'compassionate use' procedures (given appropriate acceptance) have been transformed into standard treatments without prior declaration of the procedure as scientific research or approval by the responsible ethics committee. The SAMS guidelines cited above, which distinguish experimental therapies not
only from standard therapies but also from research, are silent on precisely this crucial issue. In the interests of legal certainty, particularly with regard to the legitimate expectations of researchers, a legally binding regulation is urgently needed in this regard. The working group proposes as a rough guide that conduct of the same 'compassionate use' procedure on more than five occasions would qualify it as a research project according to the Human Research Act.

3. Matriculation projects, Bachelor's and Master's theses and dissertations versus research projects subject to EC approval (Appendix 2)

a. Matriculation projects, Bachelor's and Master's theses

The 'Master's Thesis Handbook' of the Faculty of Medicine at the University of Zurich states: "Novel scientific findings are not required in the Master's thesis. It is more important that students learn (under guidance) how to conduct a project independently using scientific thinking and methodology and to document it in a report." This statement applies all the more to Bachelor's theses and matriculation projects. Although such work need not generate new scientific data or generalisable scientific knowledge, the latter is still permitted. This means that matriculation projects, Bachelor's theses and Master's theses may be classified as research projects subject to EC approval in individual cases - even though they may not be properly regarded as scientific research.

b. Dissertations

The situation is different with dissertations. The message of the Federal Act on Research Involving Human Beings (HRA) states: "Scientific theses associated with qualifications such as Master's theses and dissertations are only treated as research for the purposes of the present draft if their scope is greater than the acquisition of particular data, and knowledge is gained that is generalisable for the 'scientific community' (BBl 2009 8093). This statement is incorrect with respect to dissertations. Authors of dissertations must always demonstrate that they are able to "generate new evidence with independent scientific research achievements in the human or natural sciences" (§ 3 of the Doctorate Ordinance of the Medical Faculty of the University of Zurich). It follows that dissertations are normally classified as research projects subject to EC approval, provided that they are subject to Article 2 of the HRA.

4. Quality assurance projects versus research projects subject to EC approval (Appendix 3)

From its establishment until its dissolution on 31 December 2013, the Swiss Federal Expert Commission on professional secrecy in medical research supported and established the concept that quality assurance projects (also referred to as quality controls or quality control studies) be subsumed without exception under the term "research". The HRA defines research more narrowly than this: there are many quality assurance projects that cannot be...
regarded as research within the meaning of the HRA. One example that could be mentioned is the systematic collection of statistics and verification of the hygiene practices of hospital staff. However, the crux of the matter is that many quality assurance projects and real research projects overlap in many ways, so that it is extremely difficult to define demarcation criteria that allow one to assign projects unambiguously to one category or the other. The attached checklist is therefore primarily intended as a kind of catalogue of indicators or a decision aid for the relevant ethics committees.

In any case, a useful principle may be the observation that in quality assurance projects, *service providers* are the main focus (e.g. hospitals), whereas with research projects it is the *service recipients* (patients and trial participants) who are the focus. Due to the increasingly close integration of aspects of quality assurance with specific elements of research, a general rule of thumb is to designate a project as subject to EC approval in doubtful cases.

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Members of Working Group no. 19:

Niklaus Herzog, Lic. iur. et theol, KEK Zurich (Executive); Dr. med. Gabriela Senti, CTC USZ; Dr. sc. nat. Eva Brombacher, CTC USZ; Prof. Dr. med. Christian Seiler, University Hospital Bern; Dr. sc. nat. Janine Dünner, Zurich

[KEK: Cantonal Ethics Committee; CTC: Clinical Trial Certificate; USZ: University Hospital Zurich]
Appendix 1: Practical experience report (PER)

- The data to be included in a PER are exclusively data that are collected independently of the PER as part of regular medical practice and/or routine treatment.

- There should be no interference with the ordinary course of treatment, i.e. no additional diagnostic or monitoring procedures are performed. The use of questionnaires is only allowed if they are a part of routine treatment.

- The use of the therapeutic product as well as the visit intervals are not determined or co-determined by a trial protocol, but are solely the result of routine treatment decisions by the doctor. The patient receives the medication and dosage that he needs according to the independent treatment decision of the doctor.

- The therapeutic product is applied according to authorised prescribing information or product information (indication / intended purpose, dosage etc.).

- If a doctor has insufficient experience with the use of a recently authorised therapeutic product, treatment with this product cannot be regarded as routine. In this case, completion of a PER is not permitted.

- No comparisons may be made between therapeutic products from different vendors. The PER may not be designed in such a way that the physician provides comparative data / results, either in general or for a particular indication.

- The data may only be reported in anonymised or encrypted form in the PER (for the legal definitions of the terms "anonymised" and "encrypted", see Article 3 of the Human Research Act).

- Monitoring or auditing by the sponsor (e.g. pharmaceutical company), i.e. inspection of the original documents (e.g. medical history) is not allowed.

- No additional costs may be charged to the patient / health insurance fund.

- If free samples are provided, this must be done in accordance with Article 32 of the Therapeutic Products Act and/or Articles 2 and 10 of the Advertising of Medicinal Products Ordinance (see www.admin.ch).

- The PER (data collection form and other documents) should contain no advertising items for the therapeutic product.
Appendix 2: Matriculation projects, Bachelor’s and Master’s theses versus research subject to EC approval (including dissertations)

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<thead>
<tr>
<th>Matriculation projects, Bachelor’s and Master’s theses</th>
<th>Research (including dissertations)</th>
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<tbody>
<tr>
<td>Aim</td>
<td>Evidence of independent scientific thinking and methodology</td>
</tr>
<tr>
<td>Duration</td>
<td>Normally a few weeks or months</td>
</tr>
<tr>
<td>Publication</td>
<td>Publication only occurs in exceptional cases, especially if this results in a further gain in scientific knowledge (although this is not mandatory).</td>
</tr>
<tr>
<td>Legal basis</td>
<td>Federal Matriculation Accreditation Ordinance, MAV; university statutes and associated examination regulations</td>
</tr>
<tr>
<td>Risk for participants in trials</td>
<td>Normally little or no risk</td>
</tr>
</tbody>
</table>

* If an assessment is required by the Ethics Committee due to intention to publish or for institutional reasons, the EC may issue a declaration of absence of health hazards. This is not a decree or approval and does not involve comprehensive scientific assessment. Basis: HRA Article 51, para 2:

You (ethics committees) may give the researchers advice, especially on ethical issues and on requests for an opinion on research proposals not subject to this Act, especially on those carried out abroad.
## Appendix 3: Quality assurance projects versus research

<table>
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<th>Quality assurance projects</th>
<th>Research</th>
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| **Aim**               | • Review of existing operations in order to optimise and increase efficiency  
                        | • The immediate and primary aim should be improvement of the institution  
                        | • Implementing project results as rapidly as possible  
                        | • Generally object-related (e.g. hospital)                          | • Systematic search for generalisable knowledge about diseases as well as the structure and function of the human body  
                        |                                                                 | • Targeted gain in knowledge: object-independent                      |
| **Initiation:**       | By the institution as such (management)                          | By individuals (researchers) within the institution and/or sponsors (companies) external to the institution |
| **Subject of investigation** | Service provider (e.g. hospital)                                | Service receiver (patient / trial participant)                           |
| **Sequence**          | Continual adaptation of the protocol often planned at the start of the project |
| **Scope of consent of the person involved in the project** | As a rule, only consent to use of data                           | As a rule, consent to involvement of the whole person in the research project (including use of data) |
| **Risk for participants** | No risk or risk no greater than in routine                      | Minimal to high, depending on the project                                 |
| **Participation**     | Participants are often required to participate on moral grounds (e.g. vaccination of hospital staff) or for reasons related to employment law (e.g. hygiene control) | Voluntary nature of participation in the project is a precondition        |
| **Publication**       | Usually not envisaged; however, results may turn out to be of such medical or public interest after the event that a decision is made to publish. | Whenever possible in a recognized scientific journal                      |
| **Examples**          | • Number of patients with a certain diagnosis / recording certain diagnoses on a particular date  
                        | • Recording the number of new cases e.g. wound infection after a certain operation  
                        | • Recording complications                                                | • Analysis or comparison of the efficacy of certain methods (retrospective or prospective)  
                        |                                                                 | • Analysis of new diseases e.g. wound infection after a certain operation |

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Clarification of responsibility

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|                                                                                   | • **Period until revision of implant is required** | • **Patient survey on QoL during treatment**  
|                                                                                   |                                                  | • **Safety of an implant**  
|                                                                                   |                                                  | • **Analysis of complications** |
| **Applicable legislation**                                                      | Privacy legislation, Health Insurance Act [KVG] | Human Research Act, Therapeutic Products Act and associated execution ordinances |
| **EC approval**                                                                 | No, but that does not mean that an external review of the projects is ruled out; declaration of absence of health hazards is possible for intended publications | Yes, if the project is subject to Article 2 of the Human Research Act |