1st Expert Workshop in Research Ethics followed by Public Talk by Prof. E.J. Emanuel

Dr. Isabell Verdier-Büschel, Dr. David Martin Shaw and Ina Otte work at the Institute for Biomedical Ethics of the University of Basel as research fellow, senior researcher and research assistant. They drafted this workshop report based on the contributions of the workshop participants.

Analysis of the Scientific Relevance of Research Projects by Research Ethics Committees

The Swiss Academy of Medical Sciences (SAMS) and the Institute for Biomedical Ethics (IBMB) of the University of Basel jointly organized the **1st Expert Workshop in Research Ethics** on June 21st, 2012 in Basel. The event was the result of a close scientific and administrative collaboration between these institutions; funding was provided by the SAMS.

Ten speakers from three countries (the UK, Switzerland, and the USA) shared their perspectives on essential questions arising from the definition and assessment of the scientific relevance of research projects by ethics committees. Both the workshop and the public talk were great successes, as indicated by the participation of almost 80 representatives of academia, public authorities and industry from Switzerland and abroad. The presentation of each speaker was followed by a stimulating and sometimes controversial debate with the audience.

The expert workshop was opened at 11:30 a.m. by Prof. Bernice Elger, who is the Founder and Head of the IBMB. Her introductory speech was followed by the welcome address given by Prof. Peter Meier-Abt, the President of the SAMS. The workshop was divided into a morning and an afternoon session, both of which were chaired by Prof. Elger, who also moderated the closing discussion. The public talk was introduced by Prof. Edwin Constable, Vice Rector of Research at the University of Basel and given by Prof. Ezekiel J. Emanuel, former advisor on the reform of the US health care system and Chair of the Department of Medical Ethics and Health Policy at the University of Pennsylvania.

Prof. Meier-Abt provided an overview with the title *Analysis of the Scientific Relevance of Research Projects by Research Ethics Committees*. He started by pointing out that the expertise of ethics committees is hardly sufficient for evaluating the scientific relevance of research projects, partly because only a few physicians have access to the journals and many do not regularly read scientific literature. He conceded that evaluating the scientific relevance of research is not an easy task and added that the possibly biasing influence of impact factors and peer reviews should be considered. In the eyes of the President of the SAMS, the role of ethics committees should consist in protecting patients and assisting

researchers in finding volunteers for clinical trials, whereas the assessment of scientific relevance would be best carried out by the Swiss National Science Foundation (SNSF).

In his presentation on *The Relevance Article in the Human Research Act*, Michael Gerber, an attorney and Deputy Head of the Division of Legal Affairs at the Swiss Federal Office of Public Health, provided a comprehensive overview of the existing regulations (Art. 16 of the Convention on Human Rights and Biomedicine on the protection of persons undergoing research, art. 21 of the Declaration of Helsinki, art. 6 § 3 of the GCP Directive [Good clinical practice in the conduct of clinical trials on medicinal products for human use] 2001/20/EC, and art. 10 of the Swiss ordinance on clinical trials). He also discussed the contextualization of relevance (for an individual, for communities, and for those with different values) and different perspectives (including moral, ethical, legal, commercial). Mr. Gerber stressed the challenges linked with balancing rights and freedoms, and determining social values and collective interests. He concluded that art. 5 of the new Human Research Act sets a basis for considering all the collective interests involved when revising and authorizing research projects, but this is a narrow basis which also provides a wide margin for judicial discretion. The debate then focused on the question of the acceptability of having a double standard for clinical trials and marketing studies, as the first are subject to authorization by ethics committees while the latter remain free of any prior permission procedure.

Prof. Andre Perruchoud, President of the Basel Ethics Committee (EKBB) and editor of Swiss Medical Weekly, explored the *Assessment of Relevance by Ethics Committees.* He first commented on the dilemmas faced by ethics committees and their background, role, and competence. After having recalled the four principles of Beauchamp and Childress (respect for autonomy, nonmaleficence, beneficence and justice), he described the case of a study aiming at determining the causes of Chlamydia trachomatis, which is a sexually transmitted disease in Canton Basel-Stadt. Its causation is linked with sexual behavior, alcohol consumption and drug abuse. As the protocol required the recruitment of participants aged between 15 and 35, the question arose whether the parents of minors should be involved. The role of the ethics committee is to evaluate the research project, make suggestions for modifications and, in the end, approve the project. When assessing the relevance of the study, the ethics committee must take into account the added value of the project, its scientific quality, the correct choice of probands or patients, a favorable risk-benefit ratio, peer review and respect for participants. The dilemma, according to Prof. Perruchoud, consists in the fact that while study participants are often *being informed*, in reality they *are not informed*, so the ultimate aim is being ignored. Also, uncertainties remain regarding the assessment of the value of the research project (visibility, futility, predictability), its scientific quality (is it up to the ethics committees to redesign the project? How to assess whether there is any competition? What about competence?), and also the risk-benefit ratio. In order to alleviate the tasks of ethics committees, the President of the EKBB suggests that they should be assisted by a scientific secretariat, thus enabling them to concentrate on essential tasks such as evaluating the risk/benefit balance of the submitted project. He further suggested adopting a pragmatic approach: a “science-friendly” attitude with more direct contact, rapid evaluation (4 weeks or less), a focus on real problems, follow-up, and audits, while at the same time bearing in mind that resources (probands and patients) are limited. As a solution to the described case he suggests that it has to be ensured that young persons who have the capacity to consent should participate without the involvement of their parents. Prof. Meier-Abt then asked who should be in charge of reviewing ethics committees and pointed out that while the university`s Faculty of Medicine is officially responsible for research, the practical problem remains “copinage” (cronyism).

Prof. E.J. Emanuel dedicated his presentation to the question of what scientifically relevant research is about. He thinks that we currently have too little data on this subject. For example, he suggested that it would be useful to have evidence on the value that is added by the work of ethics committees. In his eyes, research is a preliminary requirement for regulation, especially given that it is difficult to change existing regulation ("the moment where you make a requirement you'd better be prepared to live with it forever"). Prof. Emanuel then moved on to a case study which deals with the problem of producing a rare enzyme. Among 72 research participants (24 Caucasians, 24 Africans, 24 Asians), only 1 had a problem in producing it. This person was an Aka Pygmy. In the framework of the study, an anthropologist went to meet this Pygmy, gave him a toothbrush and had him spit in a cup. When evaluating the harms and benefits to the community of this research project, everyone would agree that buccal brushing is harmless. As to the benefits for the individual research participant, he or she gets a toothbrush, while the community of this particular research participant obtained financing for the completion of the floor of their school and the hiring of a teacher. According to Prof. Emanuel, scientific relevance is a mixture of socially valuable and scientifically valid criteria. Scientific relevance means that it should advance scientific knowledge. In order to be ethical, the research must produce reliable and valid data that can be interpreted. In contrast, invalid research includes underpowered studies, studies with biased endpoints, biased instruments, biased statistical tests and studies that cannot enroll sufficient subjects.

Prof. Emanuel questioned the meaning of the term "social value". In his opinion, clinical research must lead to improvements in health or advancement in generalizable knowledge. Overall, this means that clinical research must advance scientific knowledge. Adding the adjective "scientific" to "relevance" is an error in his eyes, as the example of embryonic stem cell research shows: whereas it is scientifically precious, social values may go against it. According to Prof. Emanuel, research lacks social value if the studies are non-generalizable, if they are a repetition of well-established research ("me-too" studies), or if the data is not published or made available to others. He suggested that there should be a low threshold for fulfilling the social value criterion if a researcher is going to devote time and energy to research, insofar as the latter bears minimal risk and will produce valid and reliable (even negative) data. *A contrario*, this means that in order to assume more research risk one needs to more justify the social value of it. To conclude, Prof. Emanuel underlined that a research project advances scientific knowledge if the data it produces are valid, reliable, disseminated and new.

Dr. David Shaw, Lecturer in Ethics and Chair of the Research Ethics Committee (REC) at the College of Medical, Veterinary and Life Sciences at the University of Glasgow, discussed the relevance criterion under the title *The Relevance of Relevance in UK Ethics Review*. From his own experience as a member of a National Health Service REC, he revealed that investigators are told that if they do not attend a meeting of the committee, there might be a delay in the processing of their research project because researchers who attend can often answer all the questions that the committee might have. He quoted art. 4.2. of the SAMS Manual on human research, according to which a study must have sociological value. This criterion excludes studies "that cannot provide any generalizable knowledge, studies that do not investigate any relevant question, that are already covered by available confirmed data, or studies for which publication is not envisaged". In the UK, new GAfREC Guidelines (Governance Arrangements for NHS Research Ethics Committees) were issued in 2011. Whereas it follows from article 5.4.2 (a) that "A REC need not reconsider the quality of the science, as this is the responsibility of the sponsor and will have been subject to review by one or more experts in the field (known as 'peer review')", article 1.2.2. states that "Researchers must satisfy a research ethics committee that the research they propose will

be ethical and worthwhile. The committee has to be assured that any anticipated risks, burdens or intrusions will be minimized for the people taking part in the research and are justified by the expected benefits for the participants or for science and society." Dr. Shaw thus assumed that relevance is relevant. He offered the following reasons for this: irrelevant research squanders valuable resources (1), it harms participants (2) and corrupts the evidence base (3). He explained why RECs in the UK are sometimes willing to accept technically irrelevant low-risk studies under specific circumstances, such as underpowered "pilot" studies, repeated research in different subgroups, studies generating new, but not relevant knowledge, and small student projects; frequently, such research is of educational value for the students conducting it, and is relevant in this sense. He underlined that design drawbacks are always communicated to researchers. In particular, he recommended that the fact that a study is carried out in order to gain a qualification should always be stated. As to irrelevant studies, two types are to be distinguished: on the one hand, similar studies that have been done before or where the answer is already known; and on the other hand, badly designed studies such as a the study that aimed at getting pregnant women in poor areas to stop smoking by offering them a financial incentive (20 Swiss Francs per week); the study used an endpoint that did not establish the efficacy of the study; had the REC approved it, public policy would have been based on poor evidence. In conclusion, Dr. Shaw stated that according to the UK Guidelines scientific relevance is both relevant and irrelevant. However, as irrelevant studies are unethical, scientific relevance is extremely important. As a matter of fact, RECs cannot ensure that research is ethical without assessing relevance. However, what constitutes relevance may need more careful consideration.

Prof. Dr. med. Beat Müller, Head of the Medical University Clinic at the Cantonal Hospital of Aarau described the point of view of researchers regarding *Ethics Committees and Scientific Relevance*, from the perspective and experiences of a "clinical researcher". According to Prof. Müller, physicians and medicine per se does not cure but merely postpones imminent death. Among other questions, he asked: why medical doctors should do research and that they should question if "current medical practice" is ethically correct, quoting the example of the mis- and over-use of antibiotics in humans for RTIs (respiratory tract infections). Using clinical signs and symptoms, we cannot distinguish viral from bacterial respiratory tract infections. As a consequence, many doctors treat RTIs with antibiotics, despite a viral origin in 75% of the cases. The problem with this is that antibiotic resistance emerges and causes morbidity and mortality. Prof. Müller also observed that medical doctors decide about practice in hospitals every day without anybody controlling them in a systematic way. Only when doing research is their activity subject to be monitored as a "control group" with a study protocol being reviewed by ethics committees. He further pointed out that health business is big business and that it can be questioned whether medicine is indeed an ethical and scientific business. In conclusion, Prof. Müller stated that there is a need for ethical regulation. However, scientific censorship and administrative hurdles must be rejected and minimized, respectively in order to keep investigator-initiated research possible also in future. Latter research never has the budgets of pharmaceutical companies.

Prof. Urs Frey of the Research Council of the Swiss National Science Foundation (SNSF) and Dr. Ayşim Yılmaz, Head of the Division of Biology and Medicine of the SNSF, presented the methods according to which the SNSF assesses relevance by commenting on the principles of project funding, the scientific evaluation criteria, scientific relevance and broader impact, and "scientificness" ("Wissenschaftlichkeit").

The closing discussion was moderated by Prof. Elger. Referring to Prof. Rütsche and the expertise that he had provided with regard to the drafting of the new Swiss Federal act on research on human beings, she pointed out that if the term "relevance" in article 5 was to be

understood as “scientific relevance”, then it would be redundant because art. 10 § 1 b) already refers to “scientific quality”. She highlighted another problem linked to the fact that it is not always possible to evaluate social value in the present, as the true relevance of a study can often be judged only in the future. Finally, she reminded that it is important to recognize and value sufficiently the time and effort individual members of ethics committees spend during these activities. Prof. Emanuel added that ethics committees should not use the relevance criterion in a too restrictive way and should not be too worried about negative results.

The general conclusion of the workshop was that relevance is relevant but we need to be tolerant towards new ideas.

The public talk given by Prof. Emanuel was entitled *Research on Research Ethics and the Assessment of Risk* and was introduced by Prof. Edwin Constable, the Vice Rector of Research at University of Basel. Prof. Emanuel, started by presenting the following case: the research participant is a 46 year old post-menopausal mentally disabled woman with LCIS (lobular carcinoma in situ). Caregivers from her “home” take her to participate in a phase III clinical trial even though she is mentally ill. The IRB refuses and doctors want to know why this is not ethical. Prof. Emanuel then traced the history of consent back to 1767 when the first recorded mention of it occurs in the British lawsuit Slater v. Baker & Stapleton. He recalled the episode when Osler condemned Sanarelli for practicing medical research without obtaining prior consent in 1898 and the decision of Walter Reed in 1901 that research ethics were required. He highlighted that the Jesse Lazear case and the Nuremberg Nazi experience have led to responses such as the drafting of the Helsinki Declaration, the creation of CIOMS (the Council for International Organizations of Medical Sciences), the drafting of the Belmont Report, and observed that all of these are examples of rules that “were born in a scandal”. They are guidelines that do not provide a systematic ethical framework. They are frequently incomplete and sometimes even contradict one another. According to Prof. Emanuel, there are eight ethical requirements that have to be met to make a clinical study ethical: collaborative partnership, social value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for human subjects. Even though these requirements are universal, they need to be adapted to local health, economic and technological circumstances. For example, consent can be expressed in different manners: by a nod, during a meal, by shaking hands etc. The most important requirement in the eyes of Prof. Emanuel is a favorable risk-benefit ratio, yet this may be the least well elucidated one. He suggests a four step evaluation. First, risks must be identified, assessed and minimized. These must include physical risks (death), psychological risks (depression and anxiety), social risks (discrimination) and economic risks (job loss). We have to assess them, not invent them. Second, potential benefits to individual participants need to be enhanced (not optimized). Is there an assessment of the psychological impact of participation in clinical trials? Third, the potential benefits to the individual have to outweigh the risks to the individual. Fourth and finally, if the third requirement is not met, then the risk has to be evaluated against social value. From the experience of Prof. Emanuel, IRBs typically fail to clearly identify and quantify the magnitude of risk as they rely on intuitions. They too often assume that what is familiar, reversible, and over which we have control is less risky. But the context also matters. For example, in October 2001, just one month after the 9/11 terrorist attacks, a US poll showed that 48% of the population thought that flying was dangerous whereas 44 % thought that driving was dangerous and 8% had no opinion. Another difficulty consists in evaluating the magnitude of harms. Prof. Emanuel and colleagues developed seven criteria :

1. negligible harm (bruise/cut)
2. small (common cold)
3. moderate (bone fracture)
4. significant (knee instability: ski accident)
5. major (rheumatoid arthritis)
6. severe (paraplegia)
7. catastrophic (death or persistent vegetative state)

According to Prof. Emanuel, we need more data on the risks of daily life in different countries. What really varies among contexts are the risks of daily life and the likelihood of experiencing risks. He believes that researchers expose people to risk just like sports coaches. He stressed the need to assess the risks of research procedures such as glocuse tolerance tests, , lumbar punctures, bronchoscopy, and skin biopsy.

In conclusion, Prof. Emanuel stated that current ethical guidance for research is limited. The least studied but most important requirement is the risk-benefit ratio. Rather than gut reactions, he proposes the systematic evaluation of risk; gathering data on the risk frontier is an easy way to identify the risk of research.

A discussion with the audience followed. The event ended at 6 p.m.