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# The Swiss Etiological Study of Adjustment and Mental Health (SESAM)

## Anatomy of Failure of a Research Project

**I would like to present a research project that illustrates some of the problems that can arise with a complex, longitudinal, interdisciplinary study that involves human subjects, especially the difficulties that can be encountered with research involving neonates, children, genetics, and the ethics review of such projects.**

In recognition of the increasing problem that mental health represents around the world, the main objective of SESAM – Swiss Etiological Study of Adjustment and Mental Health – was to understand the development and interactions of mental health and illness with a particular focus on emotion, cognition and behavior and genetic, biological and social factors. In order to study the complex causal chains of genetic, environmental, psychological, social, and biological risk factors implicated in mental health issues, the project design was large-scale, longitudinal and interdisciplinary. The project was led by a team of psychologists and was made possible by the successful submission of the project in response to a call issued by the Swiss National Science Foundation for the establishment of new NCCRs – National Centre of Competence in Research. NCCRs promote long-term research projects in areas of vital strategic importance. Each NCCR is under the directorship of a leading house around which Swiss-wide research groups and networks are created. The SESAM national network comprised 6 investigational sites, with Basel being the leading house. The NCCR SESAM was approved by the Federal Council in March 2005.

### Ambitious Research Program

The ambitious research program planned to integrate epidemiological and experimental methods from psychology, sociology, psychobiology and molecular genetics, including the examination of genotype and gene-environment interactions. The time scale

of SESAM was that the longitudinal interdisciplinary research should start during pregnancy, and follow 3000 newborn subjects and their families up until the age of twenty. SESAM took into consideration that the age of onset of mental disorders, especially anxiety and impulse-control disorders often falls into childhood, and therefore focused research on the early period of life.

### Unique in the Swiss Context, but Comparable on an International Level

SESAM was in many respects unique in the Swiss context although comparable work has been undertaken in the UK, US and other European countries. The expected benefits ascribed to the project by its creators was not only the laudable aim of avoiding the harms of mental health problems for individuals, but also to reduce Swiss health care costs, and more controversially, to increase the competitiveness of the Swiss economy by reducing losses in the work place due to mental illness.

The critical and central SESAM core study was detailed in the protocol as being based on recruiting at the start of the first tranche 3000 pregnant women in their 10–12th week of gestation, and the to involve the parents, the grandparents and the neonate until the infants reached two years of age. The multidisciplinary portfolio of research methodologies included face-to-face interviews, questionnaires, taking biological samples (blood, urine, saliva), and collecting observational data.

include an ethics review, the first step for the project was logically to prepare a submission to the appropriate research ethics committee. Indeed a sensible approach to such an ambi-

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tious project would have been to submit to the ethics committee a protocol of a feasibility study in order to discover any ethical concerns that could hinder the research program. However this did not happen. More than a year later, in summer 2006, the responsible Ethics Committee of Basel Town and Country – the EKBB – received a number of prestudies, mainly to evaluate questionnaires and also to assay the genetic investigations, although the core study had not yet been submitted. The EKBB declined to evaluate these prestudies before the approval of the main core study, based on the argument that the involvement of subjects in these side studies would be worthless if the core study should later not be authorised for any reason, a position in line with the CIOMS guideline [1] that states that the ethical justification of biomedical research involving human subjects is the prospect of discovering new ways of benefiting people's health (carried out of course in a justifiable manner). Eventually, the SESAM Core Study was submitted to the EKBB on October 31st 2006.

### The Main Ethical Issues

The revision of the very bulky study protocol was extremely challenging for

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Because the approval of the project grant by the Federal Council did not

the EKBB. One of the main questions was from where they should draw guidance for their evaluation of the many strands of the SESAM research that included not only clinical methods, but also methods from psychology, genetics and the social sciences, bearing especially in mind the vulnerable nature of the core group of research participants being pregnant women, foetus, neonates and infants, and the special issues that a longitudinal genetic research study will involve especially when conducted on population that are not able to give informed consent for themselves (the neonates).

A particular question that arises with research on neonates and children is to what research activities should the legal representative (usually the parents) be allowed to agree on behalf of

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## One standard for allowing research to be conducted on neonates and children is that the research is likely to be of direct benefit for the neonates

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the neonate? Should they have “carte blanche”? One standard for allowing research to be conducted on neonates and children is that the research is likely to be of direct benefit for the neonates, a situation that would not however have applied to SESAM. Exceptions can be made if the research has the aim of contributing benefits to persons in the same age category or afflicted with the same disease or disorder, or having the same condition, and if the research entails only minimal risk and minimal burden for the individual concerned [2].

### Rapid Spread of DNA Material

This question of the ethical and legal scope of a parent's role in permitting a child to become a research subject is particularly critical in genetic research and remains controversial [3].

One problem is how to define the risk involved in genetic research, with no consensus existing on the level of risk and burden that is involved in birth cohort studies involving genetic research [4]. The nature of genetic research and

the data that can be produced or incidentally disclosed can lead to particular risks and burdens: genetic analysis in pediatric research can identify presymptomatic conditions, susceptibility to a specific condition, or carrier status (e.g. sickle anaemia), with the nature of genetic information collected in research being that it reveals both individual and familial information. Genetic material is also particular as it remains unique from the moment of birth as a permanent identifier throughout an individual's life. The problematic scenario of the rapid spread of DNA material and data should also be born in mind in evaluating a project such as SESAM in the contemporary research climate of rapid throughput whole genome analysis, with the fast and open data sharing widely practiced in the spirit of the Bermuda Principles and the Fort Lauderdale Agreement [5]. This means that if parents donate their child's DNA for use in research, the genomic analysis can enter the public domain and be identified at some time in the future back to the child.

In the light of these considerations, could the SESAM research be classified as having a minimal level of risk and burden? One response to such concerns is the argument that although the work of collecting storing and analyse DNA and phenotypic data can take place in real time, genomic data should not be made more generally available until the affected children are able to give their informed consent [6]. Therefore parents should not be free to make DNA samples or genomic data available on any kind of open biobank until such time as the children are fully able to take this decision for themselves [7]. Objections to this position have been raised however based on the argument that this will slow the progress of research [8,9].

A further complication for a study such as SESAM is the question of the applicability and suitability of research ethics codes and norms developed primarily for application in medical fields for use in psychology and related social science research. This is a contentious and much debated question.

### Public Response to SESAM

The Swiss system of direct democracy allows for both opposition and to support for biotechnologies to be given voice and become transparent. Public votes have taken place on genetically modified food stuffs, and the use of stem cells of human embryos for research purposes. The SESAM project came to the attention of the general public and the media, leading to a public debate on various issues raised by the project, and with motions being tabled in the local and national parliament. At the centre of the debate were objections to using healthy children for research from which they would not directly benefit, especially because the declared aims of SESAM as published on their website included economic aims. The opposition culminated in the collection of over 12 000 signatures requesting the EKBB to reject the study proposal. The EKBB received these requests but was not available for comment or discussion. It remains unclear to what extent these various groups of opposition contributed to the unhappy fate of the SESAM project. According to the view of the SESAM leadership, this influence was rather marginal – but we will never know.

### The EKBB Opinion

Following a thorough workup of the SESAM Study – a hearing with five independent experts – repeated discussions and written reviews, the EKBB finally conferred the “nihil obstat” to the SESAM study on July 25th 2007 with several caveats, the most important of which will now be outlined:

1. Veto of genetic investigations in newborns: the EKBB reached the conclusion that the genetic testing of psychic risk factors in newborns was ethically not acceptable as it did not comply with the requirement that an intervention should carry only a minimal burden (as required in the draft Swiss Federal Law on Scientific Research in Humans that was current at that time). The disclosure of genetic risk factors to a young person might engender serious psychological burdens that cannot be classified as being a minimum risk. The EKBB further argued that the

study participants would most probably obtain no personal benefit from the genetic investigations, and that research in the field of sensitive psychic risk factors might burden these children in their later life. Therefore SESAM would not comply with the requirements of the European Bioethics Convention. Approval was granted however given to genetic testing in competent adults.

2. The EKBB did not object to epigenetic investigations in both adults and newborns, and the collection of epigenetic material including saliva from the newborns for later analysis to identify interaction with the environment that may occur in the course of the project. The privacy of the DNA samples was however to be secured (although full anonymity of the samples and the data was neither feasible nor desirable).
3. The EKBB was also concerned that steps be taken to ensure that should in the course of the research mental health problems be observed in

any participant, the commitment of the psychologists involved must be assured that they would act in line with the responsibilities of their professional ethos.

4. Furthermore the EKBB had concerns about the vulnerability of the pregnant women, and possible mental ill-health in their offspring. The EKBB requested that a parallel accompanying independent study be made with the aim of monitoring SESAM, and identifying any negative impacts resulting from participation in the project.
5. The EKBB also requested that plans to charge a fee for proving participants with information on personal findings in the study be dropped.

#### **The Progress of SESAM – Failure to Recruit Study Participants**

The recruitment of the pregnant women was then free to commence, and started in October 2007. As indicated, the initial aim was to collect 3000 future mothers, with at least

200 to 300 being recruited in the first half year. However after six months, the number of recruited study par-

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ticipants amounted to no more than 17 subjects, approximately 5% of the expected amount. Due to this situation, the SESAM Directorate decided on March 13th 2008 to cancel the core study.

#### **Post Mortem**

The dramatic failure in recruiting study participants requires an analysis of the causes with the hope of avoiding a similar misfortunes in future projects. The SESAM leadership, but equally the Swiss National Science Foundation and the lead Uni-



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versity which had supported SESAM both with funds and goodwill, were challenged to reflect on events. Also the EKBB were called upon to question whether errors had been made in their review of the study, errors which might have been foreseen and possibly avoided. As the president at that time of the EKBB, I was especially affected by these reflections. The following statements are based on personal perceptions, references in the media, and hints from subjects directly involved in the study proceedings. I will consider the main causes of the lack of readiness to participate in the SESAM study from the view of the potential study participants, with the following comments corresponding to the causes most often given for refusing participa-

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tion as far as can be deduced from the fragmentary information available.

**1. Reluctance of the mother to engage the unborn child in a twenty-year study, affecting very personal and sensitive spheres**

A group of women were questioned by the local media on their reasons for declining participation. The majority

gave the answer “they did not know what the child would feel once he or she became aware that he or she was in an observational study, and therefore different from other kids,” and that they did not feel entitled to make this decision for their unborn child. Such comments show the difficulty in making a free decision to participate or not in a clinical study, particularly when a pregnant woman had to decide for her unborn child.

It underlines the importance of an open information approach towards the prospective study participant.

**2. Reluctance to morally commit family members to participate in a study over a time span of 20 years that would involve the collection of personal and very sensitive data.**

Several potential candidates declined the participation because they refused to embed further family members in the study that would involve some very private questions. This problem might have been corrected if it had been identified in a pilot study. The hesitant attitude was probably enhanced by the fact that family members implicated would include those not related by blood. There was certainly also a fear that the confidentiality of the data could not be assured, with all the consequences that might then follow.

**3. Exorbitant demands of the study structure**

Some of the pregnant women felt they would be overwhelmed by the workload engendered by study participa-

tion. Apparently the more educated women, with an already fully booked agenda, declined mainly for this reason. The main problem was obviously the huge number of questionnaires – 109 for the mother, 85 for the father and 15 for the grandparents over the first two years. Some of the questionnaires had more than fifty questions. In addition, there were still several interviews planned, and various observational studies of the child. This would have been indeed a remarkable workload. The question arises whether the methodology required so many questionnaires that also repeated some questions for reasons of validations of the results, an argument that was difficult to communicate to the study participants.

**4. Practical issues of the study design and recruitment strategy**

The necessary understanding of the questionnaires presupposed a solid linguistic knowledge. The questionnaires were available only in the German and French language.

The recruitment of the pregnant women was planned to take place only in the state run obstetric outpatient clinic located in the University Hospitals. The state-run obstetric outpatient clinics are used mostly by the migrant population, a group of pregnant women that are often not well placed to understanding the nuances of the study information and therefore not able to grant an informed consent. According to information in the local media, only 20% of women to be found at the place of recruitment

would have fulfilled the linguistic requirements. The women who would have had the necessary language skills to enter the study are usually accompanied in their pregnancy by a private obstetrician. When they finally enter a hospital for delivery of their child, the deadline for registration in the SESAM study would have long since passed. Thus without the involvement of obstetricians in their private practise, reaching the planned 3000 women in the narrow recruitment window of 12th to 14th week of gestation was scarcely feasible, and the failure of the project was inevitable.

### Final Conclusion

It would most probably have been of advantage to design and start the project by conducting a pilot study with modest financial exposure, and enlarge it after collecting the necessary experiences. That is probably the most important lesson we can learn from this unfortunate story. Such an ambitious

and complex undertaking is highly exposed to experience difficulties in the elaboration of the study design, and it is vital to secure the support of society. This discussion of some of the aspects of the study is not intended to attribute responsibility for the problems, but has aimed at reflecting on what can be learnt from the shortcomings that are almost inevitable in a study of this magnitude.

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