Review 2

Application data

Project Title	Positive Emotions Program for Schizophrenia (PEPS): a randomized controlled study on improving pleasure and motivation in schizophrenia
Project title in English	Positive Emotions Program for Schizophrenia (PEPS): a randomized controlled study on improving pleasure and motivation in schizophrenia
Project number	105319_163355
Instrument	Humanities and social sciences (Division I)
Research Field	Medicine
Main Discipline	10105 Psychology
Main Applicant	Jérôme Favrod
Amount requested (CHF)	266640

Comments regarding the overall assessment

The present proposal addresses a highly relevant topic in schizophrenia research. Negative symptoms are highly relevant to social functioning and quality of life. The pragmatic clinical trial proposed by the applicants has great potential to contribute to the treatment of this very important symptom dimension.

The project creatively integrates findings from basic research on apathy/anhedonia with recent psychosocial interventions to address other dimensions of schizophrenia. The resulting intervention is novel and has great potential to impact a core symptom dimension of schizophrenia. Developing treatment for negative symptoms is considered to be of high priority by scientists, practitioners and patients.

The main applicant has an excellent track record in mental health nursing science and practical research in patients with schizophrenia. The group has all the competencies required for conducting this trial. The role of the local collaborators could be defined more clearly.

The methods proposed are fully suited to the research question under study. A pilot study has already established the feasibility of the intervention. The main new aspect of the present application is the inclusion of a treatment as usual control group, which is appropriate for a first randomized controlled trial of the intervention. The primary outcomes are highly relevant. However, I would strongly recommend to combine apathy/avolition and anhedonia/asociality into one primary outcome, because these two variables are highly correlated and consistently load on one factor. In addition to the appropriate assessment instruments proposed, I would recommend a more complete patient characterization including at least a measure of positive symptoms. Sample size calculations are appropriate and the recruitment targets can be expected to be reached by the strategies proposed.

The workplan includes a realistic schedule and milestones. The work distribution among the people working on the study remains somewhat unclear, although it can be assumed that the requested psychologist position will be required for recruitment, assessment and data analysis.

Overall, the applicants propose a small but highly relevant randomized controlled trial of a psychosocial intervention for the negative symptoms of schizophrenia. The project is entirely feasible. And I would like to add that even with limited required funds, the project has the potential to yield findings very relevant to patients with schizophrenia.

Detailed evaluation

Applicants' scientific track record and expertise

The main applicant – Jerome Favrod – has an excellent track-record in practical studies of high relevance for patients with schizophrenia. The assessment of his work is somewhat complicated by the fact that he is nursing scientist, which is still a relatively new field. However, even in comparison with psychiatrists and psychologists publishing in

the field he has developed a very consistent research agenda that is well documented by peer-reviewed publications. When compared with his peers in mental health nursing, Prof. Favrod is certainly one of the leading exponents in Switzerland, if not in Europe. His publications encompass studies on the assessment of psychological factors relevant to schizophrenic symptoms. The findings from these studies are then used in controlled trials of psychosocial interventions such as the one proposed here.

Alexandra Nguyen's background in training engineering is important to the proposed project. This competency is documented in a monography and several co-authored articles. Prof. Nguyen does not list any peer-reviewed articles as a first or last author. However, again it has to be kept in mind that nursing science is a relatively new field and requirements for publication are just beginning to develop.

Iannis McCluskey is president of the Swiss Romand network of peer practicioners in psychiatry. He does not have a scientific background in terms of publications. The assessment of his role cannot follow a classical route. Peer participation in mental health treatment and science is considered of increasing importance. The way that this participation should be implemented is still a matter of debate, but participating in the development and conduct of a trial as a co-applicant seems to be an appropriate way. Incorporation of the peer perspective is a strength of the proposal in my view.

Philippe Golay contributes to the project as a methods expert. He has published several peer-reviewed articles that clearly demonstrate his methods competence. However, none of the publications is related to clinical trial methodology. Nevertheless, his statistical expertise can certainly be applied to the present project.

Charles Bonsack has an excellent record regarding research relevant to community psychiatry and schizophrenia. He has successfully conducted to interventional studies that were funded by the SNF. Although the journals selected for publications might not be among the highest ranking in psychiatry, they are influential in the field of community psychiatry.

The applicants have considerable experience in developing psychosocial interventions for people with schizophrenia and have successfully conducted several clinical trials for their assessment, which were in part funded by the SNF. In particular, the studies employing metacognitive training and motivational intervention for cannabis abuse are comparable in their scope and trial structure to the present study. Thus, I have no doubt that the applicants have the competencies required for conducting this trial. In addition, the interdisciplinary approach including nurses, psychiatrists, peer practitioners and psychologists will also benefit the conduct of the trial. Also, the direct participation of peers in the development of the intervention can be expect to increase its relevance to patients and will also increase its acceptance by the patient community.

A minor critical comment regards the role of the local collaborators, which did not become entirely clear to me. Prof. Do plans to do anhedonia-related EEG assessment and explore blood biomarkers of depression. I assume that this add-on research will be conducted out of separate funds by Prof. Do's department. It would be important to state this more clearly, because if SNF funds would be used for this, a much more detailed argumentation would be needed. Regarding the collaboration with Prof. Regnier I see two different topics - an EEG pilot study on anticipation, decision-making and risk taking and a study related to health management. I am not sure how these topics are linked or whether two different research questions will be pursued.

Scientific relevance, originality and topicality

The negative symptoms of schizophrenia remain one of the biggest challenges in psychiatric treatment today. They have a massive impact on all patient relevant outcome parameters, but pharmacological and psychosocial treatment approaches remain limited as correctly outlined by the applicants. Thus, it is a very timely proposal to target one important dimension of negative symptoms – apathy and anhedonia – with a pragmatic psychosocial intervention.

The proposed intervention draws on current research that has clearly shown that patients with schizophrenia have difficulties in anticipating future events and that this dysfunction is associated with apathy and anhedonia. Thus, the intervention is limited to a very specific target construct in contrast to more complex interventions such as cognitive behavior therapy. In my view this has the advantage of yielding information whether this specific target construct is relevant for clinical effects.

The other important characteristic of the trial to point out is its pragmatic approach, which features a short intervention in a group setting. Importantly, training requirements for facilitators are limited. This is highly relevant, because currently there is a large disparity between evidence-based psychosocial interventions for schizophrenia and their delivery into clinical practice. One major reason is the lack of highly trained specialists, thus pragmatic

interventions like the one presented here could help to bridge the gap between evidence and implementation.

The structure of the program draws on the metacognitive training for delusions developed by Steffen Moritz. The applicants also participated in a major French speaking trial of this intervention. The basic structure in terms of facilitation, group setting and sessions is quite similar. However, in my view this does not affect the originality of the proposal as a completely new target construct and symptom is addressed. Another original aspect is the incorporation of aspects of training engineering in the development of the intervention. This has approach has already been used for interventions addressing cognitive dysfunction in patients with schizophrenia, but has to my knowledge never been applied to negative symptoms.

Regarding the timeliness of the study it has to be emphasized that the interest in negative symptoms has massively increased over the last decade. This increase has been driven by a 2006 NIMH consensus statement and new developments in related psychological and neuroscientific research. Unfortunately, this increase in publications has not lead to an equal increase in evidence based therapeutics. Thus, the proposed projects is particularly timely by using the massive increase in basic research to develop a pragmatic intervention.

A critical comment regards the structure of the review of the applicants' research. The first section includes a lot of research by other authors, which renders it somewhat difficult to disentangle the applicants' contribution. In my view it would have been more straightforward to integrate the symptom based approach to negative symptoms with the review of prior interventions studied by other groups.

Overall, given the considerable treatment resistance of negative symptoms so far, some doubts can be raised whether a short intervention as proposed here will really have a fundamental and sustained effect. However, the applicants put forward a convincing argument why it is worth trying this approach. Their approach is novel and addresses a highly relevant topic in an original fashion.

Broader impact (forms part of the assessment of scientific relevance, originality and topica

For this proposal there is a strong overlap between scientific and clinical impact. Thus, the clinical relevance has already been addressed to some extent in the previous section.

In addition, it seems important to mention that negative symptoms are not only considered by the scientific community to have a high priority for treatment development. Practitioners treating patients with schizophrenia also consistently attribute high priority to this symptom dimension. Equally, the patient's themselves consider negative symptoms to have high relevance as they are closely related to the recovery process.

To put the problem in a broader perspective it has to be mentioned that schizophrenia is consistently among the top 10 causes for disability worldwide. Schizophrenia is also a leading driver of healthcare costs in Switzerland. The biggest effect is on lost productivity, because patients develop the illness in early adulthood and it then affects their whole work trajectory. It has also major impact on family and social life as well as quality of life. Negative symptoms are among the strongest predictors for work and social functioning. Thus, even a small reduction achieved by the proposed intervention proposed here could have enormous impact for the individual patient and the society. I have to add that this argument has surprisingly not been made by the applicants, but should nevertheless be considered.

If this randomized controlled trial yields a positive result, the intervention could be quite rapidly implemented in clinical practice. As the authors emphasizes the required resources and training are less extensive than for more complex interventions. Furthermore, the applicants have already made their training material publicly available.

Suitability of methods and feasibility

The feasibility of the intervention has already been tested in a pilot study, which is summarized in the proposal and currently under revision at Schizophrenia Research. In my view it would have been helpful to provide the unpublished manuscript. Overall, the pilot study makes a convincing case that the intervention is feasible and can be carried out in the way foreseen by the authors. It is difficult to interpret the patients' improvement, because there was no control group. However, the authors correctly state that this is the rationale for the trial proposed here.

Overall, the study design is well suited to the research question. It is feasible to complete the schedule and milestones in the proposed time. I will now review the research plan in some more detail as follows.

Regarding the hypotheses the applicants select two primary outcomes from the Scale for the Assessment of Negative Symptoms, which is a standard rating instrument for negative symptoms. Psychometric properties of the French version have been well established. Thus, the SANS is a fully suited for assessing the study's primary outcomes. I do not fully understand the rationale for selecting two primary outcomes apathy-avolition and anhedonia-asociality. These two subscales are highly correlated and it has been consistently shown that they load on the same factor, which can be called apathy/anhedonia or motivation/pleasure. Thus, I would highly recommend to combine these two subscales into a factor score. This reduction to one primary outcome variable would have the advantage of increasing the study's power.

The proposed sample size is reasonable and the sample size calculation is performed correctly. In my view the main factor likely to change the effect size from the pilot study is the fact that in the trial proposed here the main test is between groups, while in the pilot study it was within groups. However, the applicants have already reduced the expected effect size and there will also be an increase in power, if they decide to follow the suggestion on primary outcomes above. The settings for recruitment are appropriate and I do not expect any problems with the proposed recruitment strategy. Ethical aspects are adequately considered. The procedures for randomization and assuring independence of raters are appropriate.

The applicants have selected treatment as usual as a control group. There is currently some discussion in the community, whether an active control group is more appropriate when testing psychosocial interventions. If there is a positive result compared to treatment as usual, it might not be clear whether the specific intervention was effective or just the higher treatment intensity and group exposure. However, I agree with the applicants that at this stage and for this study treatment as usual is an appropriate control condition. First of all, the improvement over treatment as usual has to be shown. Second, the treatment as usual as conducted here is already an enriched condition with group exposure. Third, negative symptoms tend to be more stable than other symptom dimension, which would render an effect over treatment as usual even more relevant.

The assessment instruments proposed by the applicants are appropriate. However, I would suggest to aim at a more complete characterization of the patients. In particular, I want to mention the important distinction between primary negative symptoms directly related to the schizophrenic illness and secondary negative symptoms caused by depression, positive symptoms, side effects and social deprivation. Thus, I would highly recommend to include an assessment of positive symptoms and possibly also extrapyramidal side effects (e.g. Angus-Simpson-Scale).

Regarding the workplan my only critical comment regards the distribution of work among the people working on the project, which did not become entirely clear to me. The applicants look for funding for a 100% psychologist position, but there is no full description of his/her responsibilities in the text. I assume that he/she will be responsible for recruitment, assessment and data analysis. Also, it did not become fully clear how the facilitators are recruited, peer facilitators are mentioned and I assume that nurses will play an important role.