PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Biological and psychosocial factors associated with the persistence of pruritus symptoms: protocol for a prospective, exploratory observational study in Germany (individual project of the Interdisciplinary SOMACROSS Research Unit [RU 5211])
AUTHORS	Schneider, Gudrun; Ständer, Sonja; Kahnert, Stefan; Pereira, Manuel; Mess, Christian; Huck, Volker; Agelopoulos, Konstantin; Frank, Gina; Schneider, Stefan W.

VERSION 1 – REVIEW

REVIEWER	Christina Schut Justus Liebig Universitat Giessen, Institute of Medical Psychology
REVIEW RETURNED	01-Apr-2022

GENERAL COMMENTS	Thank you for giving me the opportunity to review the study protocol regarding the study „Biological and psychosocial factors affecting the persistence of pruritus symptoms – protocol of project 4 of the interdisciplinary SOMACROSS research unit (RU 5211) by Schneider and coworkers. The study aims to investigate the associations between certain psychological factors and the development of pruritus in three groups (patients with AD with acute itch; patients with AD with chronic itch; patients with chronic itch without affected skin) for the time of 12 months. The big advantage of the study is that it is planned as prospective study. I think it was great to publish the protocol in ordert o give further reviewers the opportunity to look up whether changes from the protocol occurred and why. I have some minor issues which should be addressed bevor publication though: 1. Strengths and limitations: Please, be careful with statements about causality as previous studies and also the planned one are non-randomized studies and thus statements about causality cannot be made. 2. Page 5: please add citation for that AD is the most prevalent dermatologic condition. 3. Page 5: What about the role of TH17 in AD? Please consider and add citations. 4. Page 7: Please, specifiy your hypotheses. I e.g. wonder about the expected relationship between personality and the development of chronic itch. Whom do you expect to rather develop chronic itch? 5. Exclusion criteria for healthy controls: no atopic predisposition □ how will you determine this? 6. Please specify WHY the project-specific exclusion criteria will be applied. 7. What do you mean with stratify on page 8? In my understanding stratification is a method to control for confounders. 8. Why did you exactly choose these mediators and not Substance P e.g.? Please explain

	9. Do you expect correlations between the skin and blood parameters? Why do you extract both and not only the local skin parameters? 10. I do not quite understand: In your hypothesis you state that psychosocial parameters like personality should be important for the development of chronic itch, but then you do not name questionnaires to assess all these psychological variables that you regard as important. So please, beside adding specific hypotheses, also name the questionnaires and variables you will assess under predictor variables. Here, I can only find, itch-related cognitions, but also no information on which questionnaire you will use to measure these. Please add. 11. You conduct quite a lot of analyses and do not plan to control for multiple testing as far as I understand. So please add to the title of the project that this is an exploratory research project. 12. Please give a citation for the statement that an effect size of f = 1.4 represents a minimal effect size. 13. What do you plan to do in the second funding phase? Please give us an idea. Which program did you use to determine the needed sample sizes? Please add a citation here. 14. Has the study started yet? Please give details regarding the planned timeline of the study and add a figure for this.

REVIEWER	Giovanni Damiani Case Western Reserve University, Dermatology
REVIEW RETURNED	10-Apr-2022

GENERAL COMMENTS	I read with great interest this study protocol focusing on chronic pruritus with particular attention for atopic dermatitis I will point out that atopic dermatitis in the elderly sees in pruritus a major source of lack of compliance and fast therapy remains the key strategy for improving the compliance in this difficult subset [10.1111/jdv.17094]. Furthermore, COVID-19 pandemics had heavily conditioned long term compliance in dermatological patients (i.e. atopic ones) showing the need to enforce and empower the link patient-physician [10.1111/dth.13508]. Do you think that non-linear statistics may be useful to depict response clusters? In the biopsy section please specify that they will be performed in the same anatomical area to avoid inter patient differences.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Christina Schut, Justus Liebig Universitat Giessen Comments to the Author:

*Thank you for giving me the opportunity to review the study protocol regarding the study „Biological and psychosocial factors affecting the persistence of pruritus symptoms – protocol of project 4 of the interdisciplinary SOMACROSS research unit (RU 5211) by Schneider and coworkers. The study aims to investigate the associations between certain psychological factors and the development of pruritus in three groups (patients with AD with acute itch; patients with AD with chronic itch; patients with chronic itch without affected skin) for the time of 12 months. The big advantage of the study is that it is planned as prospective study. I think it was great to publish the protocol in ordert o give further reviewers the opportunity to look up whether changes from the protocol occurred and why.

Our answer:

Dear Dr Schut, thank you for this positive assessment.

I have some minor issues which should be addressed bevor publication though:

1. Strengths and limitations: Please, be careful with statements about causality as previous studies and also the planned one are non-randomized studies and thus statements about causality cannot be made.

Our answer:

We tried to eliminate all statements about causality and to describe only associations.

2. Page 5: please add citation for that AD is the most prevalent dermatologic condition.

Our answer:

We added citation 8:.

Bieber T. Atopic dermatitis. N Engl J Med. 2008:358(14):1483-94.

3. Page 5: What about the role of TH17 in AD? Please consider and add citations.

Our answer:

According to this citation from the paper below, IL-17 does not seem to play a major role in AD.

"Failure of clinical trials for investigating the efficacy of anti-IL-12/23 p40 in AD has suggested that IL-17 expressed in skin lesions should not be the main player but a bystander responding to barrier dysfunction."

Sugaya M. The Role of Th17-Related Cytokines in Atopic Dermatitis. Int J Mol Sci. 2020 Feb 15;21(4):1314. doi: 10.3390/ijms21041314. PMID: 32075269; PMCID: PMC7072946.

4. Page 7: Please, specifiy your hypotheses. I e.g. wonder about the expected relationship between personality and the development of chronic itch. Whom do you expect to rather develop chronic itch?

Our answer:

We regret, but as this is an exploratory study in which we want to detect associations (as you also remarked in your comment 1 and 11, we cannot further specify this hypothesis. A confirmatory analysis of the exploratory results of this first funding period will be subject of the second funding period.

5. Exclusion criteria for healthy controls: no atopic predisposition how will you determine this?

Our answer:

Atopic predisposition will be assessed by a board certified dermatologist using the Erlanger Atopy Score (EAS). The EAS assesses atopic diathesis in 6 domains: family history of atopy, self history of atopy, atopic minimal manifestations, atopic stigmata, laboratory values and dermographism. Scores can range from 0 to 42, while a score of 10 or higher indicates that an atopic predisposition is likely.

(Uter W, Schwanitz HJ, Pfahlberg A, Gefeller O. Atopic signs and symptoms: assessing the 'atopy score' concept. Dermatology 2001; 202: 4-8.)

6. Please specify WHY the project-specific exclusion criteria will be applied.

Our answer:

We included chronic pain conditions including fibromyalgia, as well as intake of analgesics as exclusion criteria, since these conditions and drugs may affect functional assessments of quantitative sensory testing and alloknesis/allodynia.

Additionally we included certain topical and systemic agents (namely systemic steroids, systemic immunosuppressants and topical steroids) as exclusion criteria, as these drugs may affect the expression of relevant markers/genes in the skin, and make difficult the interpretation of findings obtained from skin biopsies.

Allergy to local anesthetics is also an exclusion criterion, since local anesthesia is needed in order to perform the skin biopsies.

We inserted this paragraph on page 7 as third paragraph.

7. What do you mean with stratify on page 8? In my understanding stratification is a method to control for confounders.

Our answer:

We changed the sentence to:

„We will divide the patients at 12 months into a PSS group (0-1 points change on the pruritus NRS) and a non-PSS group (decrease of ≥ 2 pruritus NRS points).”

8. Why did you exactly choose these mediators and not Substance P e.g.? Please explain

Our answer:

We agree with the reviewer that Substance P (SP) is an important mediator in pruritus. Our primary selection of mediators was based on their involvement in neuroanatomy (e.g., NGF, SEMA3A, ARTN) and their pro-inflammatory properties and involvement upstream (e.g., IL-1beta) or downstream (e.g., IL-6) of the SP pathway. However, this selection is not limited to these markers and we will also consider other markers such as SP as the study progresses

9. Do you expect correlations between the skin and blood parameters? Why do you extract both and not only the local skin parameters?

Our answer:

We indeed expect skin and blood parameter correlations. To identify psychosocial as well as biological factors affecting the persistence of pruritus symptoms, we hope for a patient-group specific correlation pattern of both, systemic and local inflammatory / pruritogenic parameters

10. I do not quite understand: In your hypothesis you state that psychosocial parameters like personality should be important for the development of chronic itch, but then you do not name questionnaires to assess all these psychological variables that you regard as important. So please, beside adding specific hypotheses, also name the questionnaires and variables you will assess under predictor variables. Here, I can only find, itch-related cognitions, but also no information on which questionnaire you will use to measure these. Please add.

Our answer:

We apologize. In our manuscript we omitted the details of the psychosocial variables and questionnaires beecause these are common for all projects of the Research Unit and have been reported in detail in the following publication in BMJ Open:

Löwe B, Andresen V; Van den Bergh O; Huber TB, von dem Knesebeck O, Lohse AW, Nestoriuc Y, Schneider G, Schneider SW, Schramm C, Ständer S, Vettorazzi E, Zapf A, Shedden-Mora M, Toussaint A. Persistent SOMAtic Symptoms ACROSS Diseases - From Risk Factors to Modification: Scientific Framework and Overarching Protocol of the Interdisciplinary SOMACROSS Research Unit (RU 5211). BMJ Open 2022;12: e057596. doi:10.1136/ bmjopen-2021-057596

However, we forgot to explain this in our manuscript. Therefore we inserted the following paragraph on page 9.

“Sociodemographic and psychosocial variables:

In order to assure comparability of the projects within the Research unit, this study employs the same questionnaires to assess sociodemographic and psychosocial variables as the other projects of the Research Unit Somacross- the so–called “core set of instruments”. These have been listed and described in detail in table 2 of the publication of Löwe et al. [6] in this journal. The „core set” of instruments assesses socipodemographic and psychosocial factors, cognitive-perceptual and emotional mechanisms and behavioral factors by well-established and validated self-assessment questionnaires. For details please consult Löwe et al. [6] in this journal.”

Because the study is exploratory and many of these instruments have not been administered to patients with chronic pruritus before, we cannot state more explicit hypotheses, only expect associations, which we intend to confirm in a second funding phase.

The mention of itch-related cognitions was an error and we deleted it from the manuscript.

11. You conduct quite a lot of analyses and do not plan to control for multiple testing as far as I understand. So please add to the title of the project that this is an exploratory research project.
Our answer:
We added „exploratory“ to the title and abstract.

12. Please give a citation for the statement that an effect size of f = 1.4 represents a minimal effect size.
Our answer:
Based on our preliminary data, we specifically calculated a minimal effect size of f = 1.4 for our observed parameters, leading to the stated group size. The abovementioned sample size estimations are based on accepted standard principles of power calculations. For this, we added reference 33: Schmidt SAJ, Lo S, Hollestein LM. Research Techniques Made Simple: Sample Size Estimation and Power Calculation. J Invest Dermatol. 2018 Aug;138(8):1678-1682. doi: 10.1016/j.jid.2018.06.165. PMID: 30032783.

13. What do you plan to do in the second funding phase? Please give us an idea.
Our answer:
On page 13, in the first paragraph „Impact and contribution to overall project objectives", we already explained that …..
….„In this first exploratory phase of the project, we expect to identify biomedical and psychosocial factors associated with the persistence of pruritus, thus generating a predictive model that we intend to replicate and validate for other skin diseases during a planned second funding phase. “
We now added:
„The data generated in the first funding phase are relevant for our objectives and will allow us to generate hypotheses on the mechanisms of pruritus, which will be tested during the second funding phase.“ (page 12, last paragraph)

Which program did you use to determine the needed sample sizes? Please add a citation here.
Our answer:
We added reference 33:
Schmidt SAJ, Lo S, Hollestein LM. Research Techniques Made Simple: Sample Size Estimation and Power Calculation. J Invest Dermatol. 2018 Aug;138(8):1678-1682. doi: 10.1016/j.jid.2018.06.165. PMID: 30032783.

14. Has the study started yet? Please give details regarding the planned timeline of the study and add a figure for this.
Our answer:
We inserted a paragraph and figure 5 on page 12, third paragraph.
„Current status and timeline of the study:
Patient recruitment started in October 2021 and the first patients have been included. We expect to complete the study within 4 years. The work schedule and milestones are reported in Figure 5.
-Figure 5 approx. here-

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Reviewer 2
Dr. Giovanni Damiani, Case Western Reserve University Comments to the Author:
I read with great interest this study protocol focusing on chronic pruritus with particular attention for atopic dermatitis
I will point out that atopic dermatitis in the elderly sees in pruritus a major source of lack of compliance and fast therapy remains the key strategy for improving the compliance in this difficult subset [10.1111/jdv.17094].

Furthermore, COVID-19 pandemics had heavily conditioned long term compliance in dermatological patients (i.e. atopic ones) showing the need to enforce and empower the link patient-physician [10.1111/dth.13508].
Do you think that non-linear statistics may be useful to depict response clusters?
Our answer:
Thank you very much for your comment. We have not thought about this yet but will take your hint into consideration for our further statistical analysis.

In the biopsy section please specify that they will be performed in the same anatomical area to avoid inter patient differences.
Our answer:
We inserted the following sentence:
The biopsies at month 12 will be performed in the same anatomical area to avoid inter patient differences (page 9, first paragraph)

VERSION 2 – REVIEW

REVIEWER	Giovanni Damiani Case Western Reserve University, Dermatology
REVIEW RETURNED	15-May-2022

GENERAL COMMENTS	Authors had included all my suggestion in the reviewed paper