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)	Development and validation of a product acceptability questionnaire for intranasal Q-Griffithsin COVID-19 prophylaxis (SPRAY PAL)
AUTHORS	Cash, Elizabeth; Deitz, Kailyn; Potts, Kevin L.; Nabeta, Henry W.; Zahin, Maryam; Rai, Shesh N.; Dryden, Gerald W.; Palmer, Kenneth E.

VERSION 1 – REVIEW

REVIEWER	Chavda , Vivek P. LM College of Pharmacy
REVIEW RETURNED	10-Jun-2023

GENERAL COMMENTS	In my review of the manuscript "Development and Validation of a Product Acceptability Questionnaire for Intranasal Q- Griffithsin COVID-19 Prophylaxis (SPRAY PAL)" the author needs to correct the spelling and sentence forming errors, and enrich the each section with including more details about the study, in this form this manuscript not acceptable for publication, follow the below comments and solve them , it will help to enrich the content of this manuscript. Minor comments: 1. Enlist the age-related data of volunteers. 2. Keep all paragraph in justify position. 3. In result which one item? 4. Add reference at page no 5, line 9, 24, and 14 line of page 6. 5. Add reference at 38 line of the page no 7. Major comments: 1. Write an abstract. 2. Introduction is not up to the mark, refine it. Authors are requested to refers these papers in the introduction; https://doi.org/10.1016/j.drudis.2021.07.021, 10.1001/jama.2022.18485, https://doi.org/10.1038/d41591-022-00106-z, https://doi.org/10.1007/s43440-023-00463-7, https://doi.org/10.1038/s44222-022-00012-6 3. Add a detailed analysis at page no 7. 4. Author need to add the details of scores.

REVIEWER	Ruddy, Johannah Rome Foundation
REVIEW RETURNED	19-Jul-2023

GENERAL COMMENTS	Very interesting study and well designed PRO. Will be interested to see how data might change based on larger patient groups and different clinical settings. Would have liked to seen a little more ethnic diversity in the patient population as that might influence outcomes. Overall, well done and well written.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Vivek P. Chavda , LM College of Pharmacy
Comments to the Author:
In my review of the manuscript "Development and Validation of a Product Acceptability Questionnaire for Intranasal Q- Griffithsin COVID-19 Prophylaxis (SPRAY PAL)" the author needs to correct the spelling and sentence forming errors, and enrich the each section with including more details about the study, in this form this manuscript not acceptable for publication, follow the below comments and solve them , it will help to enrich the content of this manuscript.

Response: We have proofread the manuscript and ensured that there are no spelling or sentence syntax errors in the document. Please note that our manuscript is prepared using US English spelling and syntax.

Minor comments:
1. Enlist the age-related data of volunteers.

Response: Participant age ranges have been added to the Abstract. Group M and SD age was detailed in Table 1; the table has been edited to reflect the age range for both groups.

2. Keep all paragraph in justify position.

Response: The document has been revised to reflect this stylistic request.

3. In result which one item?

Response: We believe the reviewer is inquiring about the item that yielded lower reliability estimates during initial testing and was removed from the questionnaire. This is in reference to the item that asked:
"How easy or difficult would it be to carry a spray bottle like the one used in this study around with you if you needed to?"

4. Add reference at page no 5, line 9, 24, and 14 line of page 6.

Response: Citations have been added to page 5, line 9. The statement on page 5, line 24, has citations provided. Line 14 of page 6 states the objectives of the current study and does not require citation.

5. Add reference at 38 line of the page no 7.

Response: This statement is describing the questionnaire score calculation derived for summarizing questionnaire data, on which we are currently reporting, and does not require citation.

Major comments:
1. Write an abstract.

Response: An abstract is provided on page 2 of the manuscript. It is reproduced here for ease of reference:

Objectives: Patient experiences are critical when determining the acceptability of novel interventional pharmaceuticals. Here we report the development and validation of a product acceptability questionnaire (SPRAY PAL) assessing feasibility, acceptability, and tolerability of an intranasal Q-Griffithsin (Q-GRFT) drug product designed for COVID-19 prophylaxis.
Design: SPRAY PAL validation was undertaken as part of an ongoing Phase 1 clinical trial designed to test the safety, pharmacokinetics (PK), and tolerability of intranasally administered Q-GRFT for the prevention of SARS-CoV-2 infection.
Setting: The Phase 1 clinical trial took place at a University Outpatient Clinical Trials Unit from November 2021 until August 2023.
Participants: The initial SPRAY PAL questionnaire was piloted among healthy volunteers ages 25 to 55 in Phase 1a of the clinical trial (N=18) and revised for administration in Phase 1b for participants ages 24 to 59 (N=22).
Results: Spearman correlations tested convergent and discriminant validity. Internal consistency was assessed using Cronbach's alpha, and test-retest reliability was assessed using intraclass correlation coefficients of responses collected from three repeated questionnaire administrations. The initial version demonstrated excellent internal consistency. The revised version demonstrated very good internal consistency after removal of one item (alpha=.739). Excellent test-retest reliability (intraclass coefficient=.927) and adequate convergent (r's=.208-.774) and discriminant (r's=.123-.392) validity were achieved. Subscales adequately distinguished between the constructs of acceptability, feasibility, and tolerability.
Conclusions: The SPRAY PAL product acceptability questionnaire is a valid and reliable patient-reported outcomes measure that can be considered a credible tool for assessing patient-reported information about product acceptability, feasibility of use, tolerability of product and side effects, and cost of product for novel intranasal drug formulations. The SPRAY PAL is generalizable, and items may be readily adapted to assess other intranasal formulations.

2. Introduction is not up to the mark, refine it. Authors are requested to refers these papers in the introduction; https://doi.org/10.1016/j.drudis.2021.07.021, https://doi.org/10.1001/jama.2022.18485, https://doi.org/10.1038/d41591-022-00106-z, https://doi.org/10.1007/s43440-023-00463-7, https://doi.org/10.1038/s44222-022-00012-6

Response: We wish to clarify that the Phase 1 trial described herein is not testing a COVID-19 nasal vaccine, but rather a prophylactic formulation. Similarly, this submission reports the validation and reliability testing of a patient acceptability questionnaire (the SPRAY PAL), not the results of the Phase 1 trial itself, which will be reported in a separate, forthcoming report. As such, we believe the reviewer's requested citations focused on nasal vaccine development and trials fall outside the scope of the scientific background necessary to understand the focus of the current manuscript. In addition, we wish to exercise caution and closely follow established COPE Council publication guidelines (https://doi.org/10.24318/cope.2019.3.1) that recommend avoiding reviewer self-citation. Finally, as the Nature News article titled "Intranasal COVID-19 Vaccine Fails to Induce Mucosal Immunity" is not a peer-reviewed source. Thus, we have opted not to include these citations here. We are confident

that the introduction to this manuscript is poised to provide the necessary information for reader comprehension of our stated aims and hypotheses.

3. Add a detailed analysis at page no 7.

Response: Details regarding the statistical models employed to conduct group comparisons, including descriptive statistics (e.g., mean, standard deviation), independent samples t-tests, and Fisher's exact tests, are provided in the Analyses section. Statistical methods necessary to assess reliability and validity of the SPRAY PAL instrument, including Cronbach's alpha coefficient, intraclass correlation coefficients, and Spearman correlation, are also described in the Analyses section. We have reorganized and added additional statements to make this section a bit clearer and more detailed.

4. Author need to add the details of scores.

Response: We feel that the most appropriate place to report the obtained scores on the SPRAY PAL will be in the forthcoming manuscript reporting the results of the Phase 1 clinical trial. As our final round of data collection is ongoing, this manuscript is forthcoming.

Reviewer: 2
Dr. Johannah Ruddy, Rome Foundation
Comments to the Author:
Very interesting study and well designed PRO. Will be interested to see how data might change based on larger patient groups and different clinical settings. Would have liked to seen a little more ethnic diversity in the patient population as that might influence outcomes. Overall, well done and well written.

Response: We appreciate the complementary review. We agree that greater diversity in this small sample would have been beneficial. We are making efforts to attain greater diversity in upcoming trials as product development advances to the next stages.

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We thank the editor and reviewers for their comments and the time and attention paid to reviewing our manuscript. The suggestions have strengthened the resubmission, and we hope that we have adequately responded to the stated concerns.

VERSION 2 – REVIEW

REVIEWER	Chavda , Vivek P. LM College of Pharmacy
REVIEW RETURNED	20-Aug-2023

GENERAL COMMENTS	In my review of the manuscript "Development and Validation of a Product Acceptability Questionnaire for Intranasal Q-Griffithsin COVID-19 Prophylaxis (SPRAY PAL)" the author needs to correct the spelling and sentence forming errors, and enrich each section by including more details about the study, in this form this manuscript not acceptable for publication. The writing only describes a data, but it lacks the flow and a reason for that

	sentence. follow the below comments and solve them, it will help to enrich the content of this manuscript. Minor comments: 1. Objective statement is not up to the mark. 2. Only write 5 to 6 keywords. 3. Add full form of COVID-19 and SARS-CoV-2 before starting abbreviations. 4. Table 1 is not properly written. 5. Add headings to the sections 6. There are a lot of grammar errors and sentence formation errors. Improvise it. Major comments: 1. Improve the conclusion. 2. Add proper objective statement. 3. An author should refer below articles for further modifications. https://doi.org/10.1016/j.lansea.2022.100036 https://doi.org/10.1016/j.drudis.2021.07.021 https://doi.org/10.3389/fpubh.2023.1161881 https://doi.org/10.3389/fpubh.2023.1161881 https://doi.org/10.1007/s43440-023-00463-7

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Vivek P. Chavda , LM College of Pharmacy

Comments to the Author:

In my review of the manuscript "Development and Validation of a Product Acceptability Questionnaire for Intranasal Q-Griffithsin COVID-19 Prophylaxis (SPRAY PAL)" the author needs to correct the spelling and sentence forming errors, and enrich each section by including more details about the study, in this form this manuscript not acceptable for publication. The writing only describes a data, but it lacks the flow and a reason for that sentence. follow the below comments and solve them, it will help to enrich the content of this manuscript.

Minor comments:

1. Objective statement is not up to the mark.

Response: Our objective statement has been edited for clarity and detail added.

2. Only write 5 to 6 keywords.

Response: We have narrowed our keywords to now include only the six most relevant to the objectives of the article.

3. Add full form of COVID-19 and SARS-CoV-2 before starting abbreviations.

Response: This edit has been made.

4. Table 1 is not properly written.

Response: We have added additional detail to the Table 1 title and data.

5. Add headings to the sections

Response: We have included headings and italicized subheadings throughout the manuscript in accordance with journal guidelines.

6. There are a lot of grammar errors and sentence formation errors. Improvise it.

Response: We have carefully edited this manuscript to ensure accuracy of grammar and spelling, and feel confident that there are no errors.

Major comments:

1. Improve the conclusion.

Response: We have added further detail throughout the discussion and have included additional statements to strengthen the conclusions made in the manuscript.

2. Add proper objective statement.

Response: See response to #1 in minor comments above.

3. An author should refer below articles for further modifications.

https://doi.org/10.1016/j.lansea.2022.100036

https://doi.org/10.1016/j.drudis.2021.07.021

https://doi.org/10.3389/fpubh.2023.1161881

https://doi.org/10.3389/fpubh.2023.1161881

https://doi.org/10.1007/s43440-023-00463-7

Response: We have reviewed the suggested articles and, where appropriate, have used the information to inform modifications of our manuscript, including edits to table 1 and subheadings.

We appreciate the continued time and attention on the part of the editorial team and reviewer. We hope that we have sufficiently strengthened the revised manuscript.