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## Development and Validation of a Product Acceptability Questionnaire for Intranasal Q-Griffithsin COVID-19 Prophylaxis (SPRAY PAL)

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3 **Development and Validation of a Product Acceptability Questionnaire for Intranasal Q-**  
4 **Griffithsin COVID-19 Prophylaxis (SPRAY PAL)**  
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41 **Running Head:** Intranasal Product Acceptability Questionnaire for COVID-19 Prophylaxis  
42 (SPRAY PAL)  
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## Abstract

**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 assessing feasibility, acceptability, and tolerability of an intranasal product designed for COVID-19 prophylaxis. Here we describe the development and psychometric validation of a product acceptability questionnaire (SPRAY PAL) for an intranasal Q-Griffithsin (Q-GRFT) drug product.

**Design:** A Phase 1 clinical trial design to test the safety, pharmacokinetics (PK), and tolerability of intranasally administered Q-GRFT for the prevention of SARS-CoV-2 infection as a prophylaxis strategy.

**Participants:** The initial product acceptability questionnaire was piloted among healthy volunteers in Phase 1a of the clinical trial (N=18) and revised for administration in Phase 1b (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. Excellent test-retest reliability and adequate convergent and divergent 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.

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3 **Trial Registration:** The trials from which this sample of participants was drawn overall survival  
4 registered at ClinicalTrials.gov, NCT05122260 and NCT05437029  
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8 **Strengths and Limitations of this Study:**  
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- 10 • We examined the reliability and validity of a novel questionnaire designed to assess  
11 acceptability, feasibility, and tolerability of a novel intranasal spray formulation.
- 12 • The questionnaire can be readily adapted and generalizable for use with other intranasal  
13 formulations.
- 14 • The study is limited by the small sample size, precluding a more sophisticated principal  
15 components analysis, and relatively short period of follow-up in which to assess retest  
16 reliability.  
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24 **Funding Statement:** The trials from which this sample of participants was drawn (PREVENT-  
25 CoV program) were funded and supported by the Department of Defense (DoD) under grant  
26 number MCDC2006-010.  
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31 **Competing Interests Statement:** The authors report no conflicts or competing interest in this  
32 work.  
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36 **Data Sharing Statement:** Study data are available upon request.  
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39 **Keywords:** product acceptability, nasal spray, psychometric validation, reliability, validity,  
40 internal consistency, COVID-19, prophylaxis, SPRAY PAL  
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## Introduction

Over the past two decades, three coronaviruses of the *Betacoronavirus* genus have emerged as serious human pathogens, with the COVID-19 pandemic causing over 645 million infections globally and over 1,088,000 deaths to date in the United States.

The virus that causes COVID-19, SARS-CoV-2, replicates efficiently in the upper respiratory tract – the nasopharynx and oropharynx (1). High viral replication in the nasopharynx in the early stages of infection, prior to symptom onset, accounts for the high transmissibility of SARS-CoV-2. Respiratory aerosols and droplets are the most frequent sources of human transmission events (2, 3). Consequently, the development of an intranasal spray that prevents the establishment of infection is an effective strategy to curb virus spread. This strategy will be synergistic to vaccine approaches and biomedical interventions, such as personal protective equipment and measures like social distancing and frequent hand washing, in eliminating the pandemic.

Due to the limited long-term durability of antibody response to vaccines, and the requirement of booster doses to maintain effective immunity to SARS-CoV-2 (4, 5), an additional level of protection of the kind likely to be offered by an intranasal spray product is critical in infection prevention. Topical delivery of drugs by the nasal route is cost-effective and eliminates or reduces potential drug-drug interactions (6, 7). Additionally, it is a convenient, easy-to-use approach, and is a widely accepted method of drug administration for a variety of patients (7, 8), especially for prolonged daily dosing periods.

As such, the PREVENT-CoV (PRE-Exposure prevention of Viral ENTRY of CoronaViruses) study was designed based on the potential utility of the intranasal drug delivery approach as a technology to prevent the establishment of upper respiratory infection. This is the first-in-human intranasal application of Q-GRFT, an oxidation-resistant variant of Griffithsin (GRFT), a lectin initially extracted from red sea algae (9, 10). The PREVENT-CoV Phase 1 clinical trial evaluated the safety, tolerability, and pharmacokinetics of the novel intranasal spray in healthy male and female volunteers, as the primary endpoint. Secondary endpoints included user perceptions, acceptability, and the impact of product use on participants' olfactory sensation, and quality of life (10).

Compliance with intranasal formulations is key to effectiveness, and this depends largely on patient preference, as seen in prior work on intranasal corticosteroid formulations (11, 12).

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3 Daily use of intranasal formulations may be impacted by product sensory attributes, such as  
4 smell and aftertaste, intranasal sensations of the product, as well as ease of product use and cost  
5 (13). Questionnaires are often used to assess these product features. However, there is no readily  
6 available instrument assessing the acceptability, feasibility, and tolerability of an intranasal  
7 formulation. This prompted the development of the product acceptability questionnaire, SPRAY  
8 PAL. Here we present the development and reliability, defined by psychometric properties, of  
9 this novel questionnaire.  
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## 19 **Methods**

### 20 *Study Design*

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22 This study consisted of 2 separate phases of a randomized, single-site trial  
23 (ClinicalTrials.gov Identifiers NCT05122260 and NCT05437029). Approval to conduct this  
24 study was granted by the University of Louisville Institutional Review Board (IRB), (Phase 1a  
25 IRB# 21.0704 and Phase 1b IRB# 22.0224). Details regarding trial design, drug product, and  
26 participant eligibility, recruitment and informed consent have been previously reported (10).  
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33 *Sample 1.* The Phase 1a study (SAMPLE 1) was performed in a double-blind fashion,  
34 with 18 participants randomly assigned 2:1 to either the study product arm or the placebo arm.  
35 After participants received either a single dose of study product or a single dose of placebo,  
36 follow-up assessments were performed at 1 hour, 6 hours, 24 hours (visit 2), and 72 hours (visit  
37 3) post-dose administration. A follow-up safety review was completed by phone approximately  
38 two weeks later (visit 4). The SPRAY PAL was administered at visits 2, 3, and 4.  
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45 *Sample 2.* The Phase 1b study (SAMPLE 2) was an open-label design conducted in 2  
46 separate groups. Group 1 participants administered the study product once daily for 7 days and  
47 were evaluated at multiple visits over the subsequent nine days. The SPRAY PAL was  
48 administered at visit 3 (midway through study product administration; study day 4), visit 4 (the  
49 final day of product administration; study day 7), and visit 6 (48 hours following the final dose;  
50 study day 9). One participant withdrew from the study due to contracting COVID-19 and  
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3 completed the SPRAY PAL at an early termination visit after having received one dose of the  
4 study product.  
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6 Group 2 participants administered the study product twice daily, approximately every 12  
7 hours, for 7 days and were evaluated over the subsequent nine days. The SPRAY PAL was  
8 administered at visit 4 (midway through study product administration; study day 5), visit 5 (the  
9 final day of product administration; study day 8), and visit 7 (48 hours following the final dose;  
10 study day 10).  
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### 16 ***Measure - Product Acceptability Questionnaire***

17 Participants evaluated product acceptability, feasibility, and tolerability. Because there  
18 was no readily available questionnaire assessing these aspects for existing intranasal  
19 formulations, questionnaire items were derived from existing, validated questionnaire items with  
20 adaptation for the current study (14). Participant experience and opinion of efficacy, sensory  
21 perceptions, spray characteristics, administration process, applicator design, and use regimen  
22 were assessed. Items are rated on 5-point Likert scales coded from one to five (most negative to  
23 most positive), with an option of “prefer not to answer” included on each item to allow  
24 participants the opportunity to opt out of a question if desired. The SPRAY PAL also included  
25 open-ended items to allow participants to comment on other characteristics of the nasal spray not  
26 assessed by the questionnaire, and to allow comment on the questionnaire items themselves. The  
27 subscale and total scale scores are calculated by summing all items in each subscale and all  
28 questionnaire (including cost) items, respectively.  
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### 41 ***Analyses***

42 *Item Revision.* Open-ended responses from participants in SAMPLE 1 were reviewed to  
43 assess for any participant comments on questionnaire item construction. SPRAY PAL items  
44 were also discussed with SAMPLE 1 participants who voluntarily provided feedback. The  
45 suggestions were incorporated, and a revised questionnaire was employed with SAMPLE 2.  
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52 *Group Comparisons and Summaries.* Demographic comparisons between SAMPLES 1  
53 and 2 were performed using independent samples t-tests and Fisher’s exact tests. Comparisons of  
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SPRAY PAL summary scores between SAMPLE 2 Group 1 and Group 2 were performed using independent samples t-tests. SPRAY PAL item responses were summarized using descriptive statistics.

*Reliability and Validity Tests.* Internal consistency was assessed using Cronbach's coefficient using responses from the first administration of the SPRAY PAL for each SAMPLE. Test-retest reliability was assessed using intraclass correlation coefficients of responses collected three times over a span of five (SAMPLE 2) to 12 (SAMPLE 1) days during study participation; at least 48 hours had elapsed between each administration of the SPRAY PAL. We assessed the Spearman correlation of each item with its own scale (with the overlapping item removed) to determine convergent validity, and each item with other scales to determine discriminant validity. All analyses were conducted using SPSS Version 27 (IBM; Armonk, NY).

## Results

*Sample Demographics.* Sample demographics are provided in Table 1. There were no significant differences in demographic characteristics across samples except that SAMPLE 2 had a significantly higher vaccination rate than SAMPLE 1 due to updates made to guidelines for booster shot administration during the data collection period.

**TABLE 1. Sample Demographics**

	<b>Sample 1 (N=18)</b>	<b>Sample 2 (N=22)</b>	<b>p-value</b>
	<i>N (%)</i>	<i>N (%)</i>	
Gender			.761
Male	8 (44.0)	11 (50.0)	
Female	10 (66.0)	11 (50.0)	
Race			.111
White	6 (33.3)	14 (63.6)	

African American	0 (0.0)	1 (4.5)	
Asian	10 (55.6)	5 (22.7)	
Hispanic	0 (0)	2 (9.1)	
Mixed Race	2 (11.1)	0 (0.0)	
Fully vaccinated with booster	6 (33.3)	20 (90.9)	<.001
Average Age, years, <i>M (SD)</i>	32.6 (8.1)	35.6 (11.8)	.335
BMI, <i>M (SD)</i>	25.5 (3.8)	27.5 (7.6)	.315

*Item Revision.* After administration to participants in SAMPLE 1, who received a single nasal spray administration, internal consistency was calculated for each subscale and the total scale. Internal consistency was above the acceptable range ( $\alpha > .7$ ) for all subscales and for the total scale, excluding the Acceptability subscale, where Cronbach's  $\alpha = .514$ . Based on feedback from participants in SAMPLE 1, one Acceptability item was rephrased from inquiring about whether use of the spray would be acceptable versus not acceptable to inquiring about likelihood of use. Tolerability items were rephrased from how much the participant liked versus disliked a spray characteristic to how much each characteristic encouraged versus discouraged product use.

*Data Imputation.* In SAMPLE 2 Group 2, one participant skipped an item about comparability of the spray to the COVID vaccine on each administration of the product acceptability questionnaire. The mean score of all other items from that subscale for that participant was imputed to replace the three missing responses.

*Internal Consistency.* Internal consistency (Cronbach's  $\alpha$ ) was calculated for each subscale and for the total scale score from the initial SPRAY PAL administration for SAMPLE 2. For the Feasibility subscale,  $\alpha$  was initially .346. Reliability estimates after individual item removal indicated that one item, "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?" should be removed to improve Cronbach's  $\alpha$  to an acceptable level. This was possibly due to the item asking the participant to speculate about future use, rather than ask about current experiences, in addition to inconsistencies in ratings when compared to other items (e.g., participants who rated this item as less feasible rated other items as more feasible). After removal of the item, Cronbach's  $\alpha$  was

improved to .651 for the Acceptability subscale. Alpha was acceptable for all other subscales: .618 for the Feasibility subscale, .789 for the Tolerability subscale, and .739 for the Total Scale.

*Test-Retest Reliability.* The full SPRAY PAL was administered three times over the course of study participation for the purposes of calculating test-retest reliability. For all responses collected from participants in SAMPLE 2, intraclass coefficients were well above the acceptable threshold ( $>.7$ ) at .951 for three Acceptability Subscale scores, .888 for the Feasibility Subscale scores, .870 for the Tolerability Subscale Scores, .971 for the cost item, and .927 for the Total Scale Score.

*Convergent Validity.* No significant differences were noted in subscale scores between SAMPLE 2 Group 1 and 2, so SAMPLE 2 responses were pooled for validity and reliability tests. All but two items correlated highly with their own subscale; the item assessing likelihood of using the spray as many days as needed achieved a small correlation with the remaining items in the Feasibility subscale ( $r=.040$ ), and the item assessing whether the product ran down the back of the throat achieved a small correlation with the remaining items in the Tolerability Subscale ( $r=.134$ ). Otherwise, items demonstrated convergent validity that was within the accepted range based on a correlation with their own subscale between .2 to .7 (Table 2).

**Table 2.** Convergent and discriminant validity. Correlation coefficients on the diagonal (italicized) represent the range of correlation coefficients obtained for each item with its own subscale after removal of the overlapping item (i.e., convergent validity). All other coefficients represent divergent validity. Some negative correlations were obtained due to the varying nature of items (i.e., asking about self versus asking about friends/family).

Subscale	# Items	Acceptability	Feasibility	Tolerability
Acceptability	6	<i>.208 - .630</i>	-.303 - .132	.084 - .507
Feasibility	7	-.375 - .202	<i>.040 - .576</i>	-.252 - .311
Tolerability	9	.060 - .440	-.171 - .201	<i>.134 - .774</i>

*Discriminant Validity.* In the Accessibility subscale, the item comparing effectiveness of the spray to vaccine did not meet criterion for discriminant validity ( $r > .4$ ) from the Tolerability subscale. Similarly, in the Tolerability subscale, the item assessing likeability of the spray bottle itself did not meet the discriminant validity criterion from the Acceptability subscale. Some negative correlations were obtained due to the varying nature of items (i.e., asking about self versus asking about friends/family). Otherwise, all items correlated more highly with their own subscale score than other subscales, demonstrating good discriminant validity. The correlations between subscale scores ranged from .123 to .392, indicating adequate distinction between subscale constructs. The final SPRAY PAL is provided in Table 3.

**Table 3.** Final intranasal spray product acceptability questionnaire (SPRAY PAL).

Thank you for agreeing to complete this questionnaire. We would like to know your opinion about the nasal spray that you used as part of this study.

**Acceptability**

1. If a nasal spray like the one you used at home, provided for the study, could protect you against infection from coronavirus/COVID-19, how likely is it that you would use this nasal spray to protect against infection from coronavirus/COVID-19?
  - a. Highly unlikely
  - b. Somewhat unlikely
  - c. Neutral
  - d. Somewhat likely
  - e. Highly likely
  
2. You were asked to use the spray at home. How confident do you feel that using that amount offers sufficient protection from infection from coronavirus/COVID-19?
  - a. Not confident at all
  - b. Somewhat unconfident
  - c. Neutral
  - d. Somewhat confident
  - e. Highly confident
  
3. Future studies will determine an effective dose for the nasal spray product. Once an effective dose is determined, how confident do you feel that using this nasal spray will offer sufficient protection from *mild* complications from coronavirus/COVID-19 (e.g., symptoms similar to cold/flu)?
  - a. Not confident at all
  - b. Somewhat unconfident
  - c. Neutral
  - d. Somewhat confident
  - e. Highly confident

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4. Once an effective nasal spray dose is determined, how confident do you feel that using this nasal spray offers sufficient protection from *severe* complications from coronavirus/COVID-19 (e.g., symptoms requiring hospitalization, use of supplemental oxygen/respirator)?
    - a. Not confident at all
    - b. Somewhat unconfident
    - c. Neutral
    - d. Somewhat confident
    - e. Highly confident
  5. How do you feel the effectiveness of this nasal spray compares to that of the COVID-19 vaccines?
    - a. Quite a bit less effective
    - b. Somewhat less effective
    - c. About the same
    - d. Somewhat more effective
    - e. A great deal more effective
  6. If a nasal spray like the one that was administered at the clinic could protect you against infection from coronavirus/COVID-19, how likely would you be to recommend it to your friends/family?
    - a. Very unlikely
    - b. Somewhat unlikely
    - c. Neutral
    - d. Somewhat likely
    - e. Very likely

#### Feasibility

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Now we would like to ask you some questions about administering the spray provided in this study for take-home use. While we provided you with specific instructions on how to give the spray to yourself, we are most interested in how you actually used the spray. Please answer all of the following questions based on how you actually used the spray.

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7. How easy or difficult was it to administer the spray without missing doses?
    - a. Very difficult
    - b. Difficult
    - c. Neutral
    - d. Easy
    - e. Very easy
  8. How easy or difficult was it to administer the spray at prescribed time of day every day without missing doses?
    - a. Very difficult
    - b. Difficult
    - c. Neutral
    - d. Easy
    - e. Very easy
  9. If we find that effectiveness of the nasal spray, like the one used in this study, requires it to be used every day for as many days as needed to provide some protection from coronavirus/COVID-19, how likely would you be to use the spray as directed?
    - a. Very unlikely
    - b. Somewhat unlikely
    - c. Neutral
    - d. Somewhat likely
    - e. Very likely
  10. How easy or difficult was it to follow the instructions to administer the spray?
    - a. Very difficult

- b. Difficult
- c. Neutral
- d. Easy
- e. Very easy

11. How easy or difficult was it to insert the tip of the bottle into your nose?

- a. Very difficult
- b. Difficult
- c. Neutral
- d. Easy
- e. Very easy

12. How easy or difficult was it to spray the liquid into your nose?

- a. Very difficult
- b. Difficult
- c. Neutral
- d. Easy
- e. Very easy

13. How easy or difficult was it to handle the bottle used to deliver the liquid (or administer the spray)?

- f. Very difficult
- g. Difficult
- h. Neutral
- i. Easy
- j. Very easy

#### **Tolerability**

14. How much did the force of the nasal spray in your nose encourage or discourage your use of the product?

- a. Discouraged very much
- b. Discouraged a little
- c. Neither discouraged nor encouraged use
- d. Encouraged a little
- e. Encouraged very much

15. How much did the tip of the nasal spray bottle in your nose encourage or discourage use of the product?

- a. Discouraged very much
- b. Discouraged a little
- c. Neither discouraged nor encouraged use
- d. Encouraged a little
- e. Encouraged very much

16. How much did the scent of the nasal spray encourage or discourage you from using the product?

- a. Discouraged very much
- b. Discouraged a little
- c. Neither discouraged nor encouraged / did not notice a scent
- d. Encouraged a little
- e. Encouraged very much

17. How much did the taste/aftertaste of the nasal spray encourage or discourage your use of the product?

- a. Discouraged very much
- b. Discouraged a little
- c. Neither discouraged nor encouraged, or did not notice a taste/aftertaste
- d. Encouraged a little
- e. Encouraged very much

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18. Did the product run down the back of your throat?
- Yes, the product ran down the back of my throat and bothered me a lot
  - Yes, the product ran down the back of my throat and bothered me a little
  - Yes, the product ran down the back of my throat but did not bother me at all
  - No, the product did not run down the back of my throat
19. Overall, how much did you like or dislike using the nasal spray?
- Disliked very much
  - Disliked a little
  - Neutral
  - Liked a little
  - Liked very much
20. How would you rate your overall level of comfort or discomfort during the process of administering the spray (spraying the liquid inside your nose)?
- Very uncomfortable
  - Somewhat uncomfortable
  - Neutral
  - Somewhat comfortable
  - Very comfortable
21. How convenient was it to use the spray?
- Very inconvenient
  - Somewhat inconvenient
  - Neutral
  - Somewhat convenient
  - Very convenient
22. How much did you like or dislike the spray bottle itself?
- Disliked very much
  - Disliked a little
  - Neutral
  - Liked a little
  - Liked very much

### Cost

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23. How much would you be willing to spend on a nasal spray like the one used in this study if it provided some protection against infection from coronavirus/COVID-19?
- Less than what one spends on on an over-the-counter nasal spray (~\$10)
  - About the same as one spends on on an over-the-counter nasal spray (~\$10)
  - Twice as much as one spends on on an over-the-counter nasal spray (~\$10)
  - Three times as much
  - Four times as much or more

### Recommendations

Please help us understand what we can do to make you more likely to use this product.

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24. Would you change anything about the the bottle?
- No
  - Yes - please specify what you would change:
25. Would you change anything about the spray tip?
- No
  - Yes - please specify what you would change:
26. Would you change anything about how the product is packaged?



- a. No
- b. Yes - please specify what you would change:

27. If you have any other recommendations, please write them below.

## Discussion

Acceptability is an important consideration for the successful design and implementation of novel pharmaceutical products. Adherence to drug regimen may be greatly impacted by patient acceptance of study product and treatment regimen, including feasibility of use, tolerability of treatment and side effects, and product cost. The SPRAY PAL product acceptability questionnaire was developed to provide evidence for all these factors to better inform the development and commercialization of a novel intranasal formulation designed for COVID-19 prophylaxis. Item development was based on existing, validated questionnaires, with adjustments made based on qualitative feedback from study participants.

We observed adequate indices of internal consistency and test-retest reliability on the revised version of the SPRAY PAL. While tests of convergent and discriminant validity were generally acceptable, there were two items that fell just below conventional thresholds for each construct. This is, in part, related to the diversity of themes across items that fall under the broader theme of each subscale, such as assessments about the nature of physical spray characteristics versus impressions of efficacy. However, tests of internal consistency for the full scale did not suggest that removal of any one item would improve the overall alpha score achieved. Together with the observation of low correlations between subscales, the single full scale sum score may be the most appropriate indicator of overall product acceptability.

Because the SPRAY PAL was implemented as part of a Phase 1 clinical trial, the sample size was small, precluding the use of more sophisticated analytic procedures, such as factor analysis, for tests of item validity. Similarly, assessments of test-retest reliability were designed to fit within the existing study appointments necessary for determining safety and tolerability of the study product. As such, the retest timeframe was limited to 12 days. Retest stability over longer treatment periods will need to be addressed in future trials. The SPRAY PAL items were generated with respect to a novel intranasal COVID-19 prophylactic formulation; the generalizability of items to other applications may therefore be limited. Finally, while the

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3 SPRAY PAL was created based on a sound conceptual framework and tested using commonly  
4 utilized psychometric methods for validation and reliability assessment of a new questionnaire, it  
5 should be employed with caution until the results are confirmed among larger samples and in  
6 different clinical settings.  
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10 The SPRAY PAL was found to be psychometrically sound with adequate validity and  
11 reliability. It can be considered a credible tool for assessing patient-reported information about  
12 product acceptability, feasibility of use, tolerability of product and side effects, and cost of  
13 product for novel intranasal drug formulations. The SPRAY PAL is generalizable, and items  
14 may be readily adapted to fit modified study designs and different dosing regimens for other  
15 nasal spray product formulations as necessary.  
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26 for their support in finalizing the clinical protocol and efficiently planning the conduct of this  
27 trial and questionnaire administration. We greatly appreciate CBR International Corp., Boulder,  
28 CO for their critical input during protocol and questionnaire development.  
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#### 36 **Author Contributions**

37 EC, KP, HN, MZ, GD, SR, KP contributed to the design and conduct of the study. EC, KD, GD,  
38 and SR assisted in the development, review and editing of questionnaire items. EC carried out  
39 the analyses. All authors contributed to the interpretation of the data, critical revisions of the  
40 manuscript, and provided final approval of the manuscript.  
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# BMJ Open

## Development and Validation of a Product Acceptability Questionnaire for Intranasal Q-Griffithsin COVID-19 Prophylaxis (SPRAY PAL)

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Keywords:	COVID-19, Psychometrics, Patient Reported Outcome Measures, STATISTICS & RESEARCH METHODS

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3 **Development and Validation of a Product Acceptability Questionnaire for Intranasal Q-**  
4 **Griffithsin COVID-19 Prophylaxis (SPRAY PAL)**  
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41 **Running Head:** Intranasal Product Acceptability Questionnaire for COVID-19 Prophylaxis  
42 (SPRAY PAL)  
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## Abstract

**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,



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3 and cost of product for novel intranasal drug formulations. The SPRAY PAL is generalizable, and  
4 items may be readily adapted to assess other intranasal formulations.  
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8 **Trial Registration:** The trials from which this sample of participants was drawn overall survival  
9 registered at ClinicalTrials.gov, NCT05122260 and NCT05437029  
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### 13 **Strengths and Limitations of this Study:**

- 14 • We examined the reliability and validity of a novel questionnaire designed to assess  
15 acceptability, feasibility, and tolerability of a novel intranasal spray formulation.  
16
- 17 • The questionnaire can be readily adapted and generalizable for use with other intranasal  
18 formulations.  
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- 20 • The study is limited by the small sample size, precluding a more sophisticated principal  
21 components analysis, and relatively short period of follow-up in which to assess retest  
22 reliability.  
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29 **Keywords:** product acceptability, nasal spray, psychometric validation, reliability, validity,  
30 internal consistency, COVID-19, prophylaxis, SPRAY PAL  
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## Introduction

Over the past two decades, three coronaviruses of the *Betacoronavirus* genus have emerged as serious human pathogens, with the COVID-19 pandemic causing over 700 million infections globally (1) and over 1 million deaths to date in the United States (2).

The virus that causes COVID-19, SARS-CoV-2, replicates efficiently in the upper respiratory tract – the nasopharynx and oropharynx (3). High viral replication in the nasopharynx in the early stages of infection, prior to symptom onset, accounts for the high transmissibility of SARS-CoV-2. Respiratory aerosols and droplets are the most frequent sources of human transmission events (4, 5). Consequently, the development of an intranasal spray that prevents the establishment of infection is an effective strategy to curb virus spread. This strategy will be synergistic to vaccine approaches and biomedical interventions, such as personal protective equipment and measures like social distancing and frequent hand washing, in eliminating the pandemic.

Due to the limited long-term durability of antibody response to vaccines, and the requirement of booster doses to maintain effective immunity to SARS-CoV-2 (6, 7), an additional level of protection of the kind likely to be offered by an intranasal spray product is critical in infection prevention. Topical delivery of drugs by the nasal route is cost-effective and eliminates or reduces potential drug-drug interactions (8, 9). Additionally, it is a convenient, easy-to-use approach, and is a widely accepted method of drug administration for a variety of patients (9, 10), especially for prolonged daily dosing periods.

As such, the PREVENT-CoV (Pre-Exposure prevention of Viral ENtry of CoronaViruses) study was designed based on the potential utility of the intranasal drug delivery approach as a technology to prevent the establishment of upper respiratory infection. This is the first-in-human intranasal application of Q-GRFT, an oxidation-resistant variant of Griffithsin (GRFT), a lectin initially extracted from red sea algae (11, 12). The PREVENT-CoV Phase 1 clinical trial evaluated the safety, tolerability, and pharmacokinetics of the novel intranasal spray in healthy male and female volunteers, as the primary endpoint. Secondary endpoints included user perceptions, acceptability, and the impact of product use on participants' olfactory sensation, and quality of life (12). The Phase 1 clinical trial is ongoing to collect a final assessment of the levels of anti-drug antibodies one year after final dose administration.

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3 Compliance with intranasal formulations is key to effectiveness, and this depends largely  
4 on patient preference, as seen in prior work on intranasal corticosteroid formulations (13, 14).  
5 Daily use of intranasal formulations may be impacted by product sensory attributes, such as smell  
6 and aftertaste, intranasal sensations of the product, as well as ease of product use and cost (15).  
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8 Questionnaires are often used to assess these product features. However, there is no readily  
9 available instrument assessing the acceptability, feasibility, and tolerability of an intranasal  
10 formulation. This prompted the development of the product acceptability questionnaire, SPRAY  
11 PAL. Here we present the development and reliability, defined by psychometric properties, of this  
12 novel questionnaire.  
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## 22 **Methods**

### 23 ***Study Design***

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25 This study consisted of 2 separate phases of a randomized, single-site trial  
26 (ClinicalTrials.gov Identifiers NCT05122260 and NCT05437029). Approval to conduct this study  
27 was granted by the University of Louisville Institutional Review Board (IRB), (Phase 1a IRB#  
28 21.0704 and Phase 1b IRB# 22.0224). Details regarding trial design, drug product, and participant  
29 eligibility, recruitment and informed consent have been previously reported (12). Briefly,  
30 participants were prescreened using online questionnaires and telephone interviews to determine  
31 eligibility. Selected volunteers were invited for a screening visit at the clinical trials unit where  
32 eligibility was confirmed and written informed consent was obtained. Participants were generally  
33 healthy, aged 16-85, screened negative for SARS-CoV-2, able to attend all study visits,  
34 participating in no other concurrent drug trials, not pregnant or breastfeeding and/or were using  
35 contraception. Individuals with acute or chronic upper respiratory or pulmonary issues/illnesses,  
36 smokers, recreational drug users, and those taking intranasal medications or systemic steroids were  
37 excluded. Participants retained their right to withdraw from the study at any time for any reason.  
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50 *Sample 1.* The Phase 1a study (SAMPLE 1) was performed in a double-blind fashion, with  
51 18 participants randomly assigned 2:1 to either the study product arm or the placebo arm after  
52 stratification by race and gender. After participants received either a single dose of study product  
53 or a single dose of placebo, follow-up assessments were performed at 1 hour, 6 hours, 24 hours  
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3 (visit 2), and 72 hours (visit 3) post-dose administration. A follow-up safety review was completed  
4 by phone approximately two weeks later (visit 4). The SPRAY PAL was administered at visits 2,  
5 3, and 4.  
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10 *Sample 2.* The Phase 1b study (SAMPLE 2) was an open-label design conducted in 2  
11 separate groups stratified by race and gender. Group 1 participants administered the study product  
12 once daily for 7 days and were evaluated at multiple visits over the subsequent nine days. The  
13 SPRAY PAL was administered at visit 3 (midway through study product administration; study day  
14 4), visit 4 (the final day of product administration; study day 7), and visit 6 (48 hours following  
15 the final dose; study day 9). One participant withdrew from the study due to contracting COVID-  
16 19 and completed the SPRAY PAL at an early termination visit after having received one dose of  
17 the study product.  
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24 Group 2 participants administered the study product twice daily, approximately every 12  
25 hours, for 7 days and were evaluated over the subsequent nine days. The SPRAY PAL was  
26 administered at visit 4 (midway through study product administration; study day 5), visit 5 (the  
27 final day of product administration; study day 8), and visit 7 (48 hours following the final dose;  
28 study day 10).  
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32 A one-year follow-up assessment of anti-drug antibodies in both groups is ongoing.  
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### 36 ***Measure - Product Acceptability Questionnaire***

37 Participants evaluated product acceptability, feasibility, and tolerability. Because there was  
38 no readily available questionnaire assessing these aspects for existing intranasal formulations,  
39 questionnaire items were derived from existing, validated questionnaire items with adaptation for  
40 the current study (16). Participant experience and opinion of efficacy, sensory perceptions, spray  
41 characteristics, administration process, applicator design, and use regimen were assessed. Items  
42 are rated on 5-point Likert scales coded from one to five (most negative to most positive), with an  
43 option of “prefer not to answer” included on each item to allow participants the opportunity to opt  
44 out of a question if desired. The SPRAY PAL also included open-ended items to allow participants  
45 to comment on other characteristics of the nasal spray not assessed by the questionnaire, and to  
46 allow comment on the questionnaire items themselves. The subscale and total scale scores are  
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3 calculated by summing all items in each subscale and all questionnaire (including cost) items,  
4 respectively.  
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### 8 *Analyses*

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10 Responses were collected from participants on paper forms and were double-entered into  
11 a REDCap database hosted at the University of Louisville (17, 18). Entries were compared and,  
12 when mismatches occurred, data accuracy was confirmed against paper records. In SAMPLE 2  
13 Group 2, one participant skipped an item about the comparability of the spray to the COVID  
14 vaccine on each administration of the product acceptability questionnaire. The mean score of all  
15 other items from that subscale for that participant was imputed to replace the three missing  
16 responses. Otherwise, all SPRAY PAL items were answered completely. Item responses for all  
17 participants were summarized using descriptive statistics.  
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27 *Item Revision.* Open-ended responses from participants in SAMPLE 1 were reviewed to  
28 assess for any participant comments on questionnaire item construction. SPRAY PAL items were  
29 also discussed with SAMPLE 1 participants who voluntarily provided feedback. The suggestions  
30 were incorporated, and a revised questionnaire was employed with SAMPLE 2.  
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37 *Group Comparisons.* Statistical comparisons of demographic data between SAMPLES 1  
38 and 2 were performed using independent samples t-tests and Fisher's exact tests. SPRAY PAL  
39 summary scores between SAMPLE 2 Group 1 and Group 2 were compared using independent  
40 samples t-tests.  
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50 *Reliability and Validity Tests.* Internal consistency was assessed using Cronbach's coefficient  
51 based on responses from the first administration of the SPRAY PAL for each SAMPLE. Test-retest  
52 reliability was assessed by calculating the intraclass correlation coefficients of responses  
53 collected three times over a span of five (SAMPLE 2) to 12 (SAMPLE 1) days during study  
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participation; at least 48 hours had elapsed between each administration of the SPRAY PAL. We assessed the Spearman correlation of each item with its own scale (with the overlapping item removed) to determine convergent validity, and the Spearman correlation of each item with other scales to assess discriminant validity. All analyses were conducted using SPSS Version 27 with alpha set at .05 (IBM; Armonk, NY).

*Patient and Public Involvement.* None.

## Results

*Sample Demographics.* Sample demographics are provided in Table 1. There were no significant differences in demographic characteristics across samples except that SAMPLE 2 had a significantly higher vaccination rate than SAMPLE 1 due to updates made to guidelines for booster shot administration during the data collection period.

**TABLE 1. Sample Demographics**

	<b>Sample 1 (N=18)</b>	<b>Sample 2 (N=22)</b>	<b>p-value</b>
	<i>N (%)</i>	<i>N (%)</i>	
Gender			.761
Male	8 (44.0)	11 (50.0)	
Female	10 (66.0)	11 (50.0)	
Race			.111
White	6 (33.3)	14 (63.6)	
African American	0 (0.0)	1 (4.5)	
Asian	10 (55.6)	5 (22.7)	
Hispanic	0 (0)	2 (9.1)	
Mixed Race	2 (11.1)	0 (0.0)	
Fully vaccinated with booster	6 (33.3)	20 (90.9)	<.001
Average Age, years, <i>M (SD, range)</i>	32.6 (8.1, 25-55)	35.6 (11.8, 24-59)	.335
BMI, <i>M (SD)</i>	25.5 (3.8)	27.5 (7.6)	.315

*Item Revision.* After administration to participants in SAMPLE 1, who received a single nasal spray administration, internal consistency was calculated for each subscale and the total

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3 scale. Internal consistency was above the acceptable range ( $\alpha > .7$ ) for all subscales and for the  
4 total scale, excluding the Acceptability subscale, where Cronbach's  $\alpha = .514$ . Based on  
5 feedback from participants in SAMPLE 1, one Acceptability item was rephrased from inquiring  
6 about whether use of the spray would be acceptable versus not acceptable to inquiring about  
7 likelihood of use. Tolerability items were rephrased from how much the participant liked versus  
8 disliked a spray characteristic to how much each characteristic encouraged versus discouraged  
9 product use.

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17 *Internal Consistency.* Internal consistency (Cronbach's  $\alpha$ ) was calculated for each  
18 subscale and for the total scale score from the initial SPRAY PAL administration for SAMPLE 2.  
19 For the Feasibility subscale,  $\alpha$  was initially .346. Reliability estimates after individual item  
20 removal indicated that one item, "How easy or difficult would it be to carry a spray bottle like the  
21 one used in this study around with you if you needed to?" should be removed to improve  
22 Cronbach's  $\alpha$  to an acceptable level. This was possibly due to the item asking the participant  
23 to speculate about future use, rather than ask about current experiences, in addition to  
24 inconsistencies in ratings when compared to other items (e.g., participants who rated this item as  
25 less feasible rated other items as more feasible). After removal of the item, Cronbach's  $\alpha$  was  
26 improved to .651 for the Acceptability subscale.  $\alpha$  was acceptable for all other subscales: .618  
27 for the Feasibility subscale, .789 for the Tolerability subscale, and .739 for the Total Scale.

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38 *Test-Retest Reliability.* The full SPRAY PAL was administered three times over the course  
39 of study participation for the purposes of calculating test-retest reliability. For all responses  
40 collected from participants in SAMPLE 2, intraclass coefficients were well above the acceptable  
41 threshold ( $> .7$ ) at .951 for three Acceptability Subscale scores, .888 for the Feasibility Subscale  
42 scores, .870 for the Tolerability Subscale Scores, .971 for the cost item, and .927 for the Total  
43 Scale Score.

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50 *Convergent Validity.* No significant differences were noted in subscale scores between  
51 SAMPLE 2 Group 1 and 2, so SAMPLE 2 responses were pooled for validity and reliability tests.  
52 All but two items correlated highly with their own subscale; the item assessing likelihood of using  
53 the spray as many days as needed achieved a small correlation with the remaining items in the  
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Feasibility subscale ( $r=.040$ ), and the item assessing whether the product ran down the back of the throat achieved a small correlation with the remaining items in the Tolerability Subscale ( $r=.134$ ). Otherwise, items demonstrated convergent validity that was within the accepted range based on a correlation with their own subscale between .2 to .7 (Table 2).

**Table 2.** Convergent and discriminant validity. Correlation coefficients on the diagonal (italicized) represent the range of correlation coefficients obtained for each item with its own subscale after removal of the overlapping item (i.e., convergent validity). All other coefficients represent divergent validity. Some negative correlations were obtained due to the varying nature of items (i.e., asking about self versus asking about friends/family).

Subscale	# Items	Acceptability	Feasibility	Tolerability
Acceptability	6	<i>.208 - .630</i>	-.303 - .132	.084 - .507
Feasibility	7	-.375 - .202	<i>.040 - .576</i>	-.252 - .311
Tolerability	9	.060 - .440	-.171 - .201	<i>.134 - .774</i>

*Discriminant Validity.* In the Accessibility subscale, the item comparing effectiveness of the spray to vaccine did not meet criterion for discriminant validity ( $r>.4$ ) from the Tolerability subscale. Similarly, in the Tolerability subscale, the item assessing likeability of the spray bottle itself did not meet the discriminant validity criterion from the Acceptability subscale. Some negative correlations were obtained due to the varying nature of items (i.e., asking about self versus asking about friends/family). Otherwise, all items correlated more highly with their own subscale score than other subscales, demonstrating good discriminant validity. The correlations between subscale scores ranged from .123 to .392, indicating adequate distinction between subscale constructs. The final SPRAY PAL is provided in supplemental materials.

## Discussion



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3 Acceptability is an important consideration for the successful design and implementation  
4 of novel pharmaceutical products. Adherence to drug regimen may be greatly impacted by patient  
5 acceptance of study product and treatment regimen, including feasibility of use, tolerability of  
6 treatment and side effects, and product cost. The SPRAY PAL product acceptability questionnaire  
7 was developed to provide evidence for all these factors to better inform the development and  
8 commercialization of a novel intranasal formulation designed for COVID-19 prophylaxis. Item  
9 development was based on existing, validated questionnaires, with adjustments made based on  
10 qualitative feedback from study participants.  
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12 We observed adequate indices of internal consistency and test-retest reliability on the  
13 revised version of the SPRAY PAL. While tests of convergent and discriminant validity were  
14 generally acceptable, there were two items that fell just below conventional thresholds for each  
15 construct. This is, in part, related to the diversity of themes across items that fall under the broader  
16 theme of each subscale, such as assessments about the nature of physical spray characteristics  
17 versus impressions of efficacy. However, tests of internal consistency for the full scale did not  
18 suggest that removal of any one item would improve the overall alpha score achieved. Together  
19 with the observation of low correlations between subscales, the single full scale sum score may be  
20 the most appropriate indicator of overall product acceptability.  
21

22 Because the SPRAY PAL was implemented as part of a Phase 1 clinical trial, the sample  
23 size was small, precluding the use of more sophisticated analytic procedures, such as factor  
24 analysis, for tests of item validity. Similarly, assessments of test-retest reliability were designed to  
25 fit within the existing study appointments necessary for determining safety and tolerability of the  
26 study product. As such, the retest timeframe was limited to 12 days. Retest stability over longer  
27 treatment periods will need to be addressed in future trials. The SPRAY PAL items were generated  
28 with respect to a novel intranasal COVID-19 prophylactic formulation; the generalizability of  
29 items to other applications may therefore be limited. Finally, while the SPRAY PAL was created  
30 based on a sound conceptual framework and tested using commonly utilized psychometric  
31 methods for validation and reliability assessment of a new questionnaire, it should be employed  
32 with caution until the results are confirmed among larger samples and in different clinical settings.  
33

34 The SPRAY PAL was found to be psychometrically sound with adequate validity and  
35 reliability. It can be considered a credible tool for assessing patient-reported information about  
36 product acceptability, feasibility of use, tolerability of product and side effects, and cost of product  
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3 for novel intranasal drug formulations. The SPRAY PAL is generalizable, and items may be  
4 readily adapted to fit modified study designs and different dosing regimens for other nasal spray  
5 product formulations as necessary.  
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## Contributorship Statement

EC, KP, HN, MZ, GD, SR, KP contributed to the design and conduct of the study. EC, KD, GD, and SR assisted in the development, review and editing of questionnaire items. EC carried out the analyses. All authors contributed to the interpretation of the data, critical revisions of the manuscript, and provided final approval of the manuscript.

## Competing Interests

The authors report no conflicts or competing interest in this work.

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## Data Sharing Statement

The results reported herein utilize data that was collected as part of a Phase 1 clinical trial. These data will be made available as part of the data sharing plan that accompanies the report of the larger Phase 1 results. Thus, the data is not shared for the current manuscript.

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**SPRAY PAL Intranasal Product Acceptability Questionnaire**

Participant ID \_\_\_\_\_

Date \_\_\_\_\_

Thank you for agreeing to complete this questionnaire. We would like to know your opinion about the nasal spray that you used as part of this study.

**Acceptability**

1. If a nasal spray like the one you used at home, provided for the study, could protect you against infection from coronavirus/COVID-19, how likely is it that you would use this nasal spray to protect against infection from coronavirus/COVID-19?
  - a. Highly unlikely
  - b. Somewhat unlikely
  - c. Neutral
  - d. Somewhat likely
  - e. Highly likely
  - f. Prefer not to answer
2. You were asked to use the spray at home. How confident do you feel that using that amount offers sufficient protection from infection from coronavirus/COVID-19?
  - a. Not confident at all
  - b. Somewhat unconfident
  - c. Neutral
  - d. Somewhat confident
  - e. Highly confident
  - f. Prefer not to answer
3. Future studies will determine an effective dose for the nasal spray product. Once an effective dose is determined, how confident do you feel that using this nasal spray will offer sufficient protection from *mild* complications from coronavirus/COVID-19 (e.g., symptoms similar to cold/flu)?
  - a. Not confident at all
  - b. Somewhat unconfident
  - c. Neutral
  - d. Somewhat confident
  - e. Highly confident
  - f. Prefer not to answer
4. Once an effective nasal spray dose is determined, how confident do you feel that using this nasal spray offers sufficient protection from *severe* complications from coronavirus/COVID-19 (e.g., symptoms requiring hospitalization, use of supplemental oxygen/respirator)?
  - a. Not confident at all
  - b. Somewhat unconfident
  - c. Neutral
  - d. Somewhat confident
  - e. Highly confident
  - f. Prefer not to answer

**SPRAY PAL Intranasal Product Acceptability Questionnaire**

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3 5. How do you feel the effectiveness of this nasal spray compares to that of the COVID-19 vaccines?  
4 a. Quite a bit less effective  
5 b. Somewhat less effective  
6 c. About the same  
7 d. Somewhat more effective  
8 e. A great deal more effective  
9 f. Prefer not to answer  
10  
11  
12 6. If a nasal spray like the one that was administered at the clinic could protect you against infection from  
13 coronavirus/COVID-19, would likely would you be to recommend it to your friends/family?  
14 a. Very unlikely  
15 b. Somewhat unlikely  
16 c. Neutral  
17 d. Somewhat likely  
18 e. Very likely  
19 f. Prefer not to answer  
20  
21

**Feasibility**

22  
23 Now we would like to ask you some questions about administering the spray provided in this study for take-  
24 home use. While we provided you with specific instructions on how to give the spray to yourself, we are most  
25 interested in how you actually used the spray. Please answer all of the following questions based on how you  
26 actually used the spray.  
27

- 28  
29 7. How easy or difficult was it to administer the spray without missing doses?  
30 a. Very difficult  
31 b. Difficult  
32 c. Neutral  
33 d. Easy  
34 e. Very easy  
35 f. Prefer not to answer  
36  
37  
38 8. How easy or difficult was it to administer the spray at prescribed time of day every day without missing  
39 doses?  
40 a. Very difficult  
41 b. Difficult  
42 c. Neutral  
43 d. Easy  
44 e. Very easy  
45 f. Prefer not to answer  
46  
47  
48 9. If we find that effectiveness of the nasal spray, like the one used in this study, requires it to be used  
49 every day for as many days as needed to provide some protection from coronavirus/COVID-19, how  
50 likely would you be to use the spray as directed?  
51 a. Very unlikely  
52 b. Somewhat unlikely  
53 c. Neutral  
54 d. Somewhat likely  
55 e. Very likely  
56 f. Prefer not to answer  
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**SPRAY PAL Intranasal Product Acceptability Questionnaire**

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3 10. How easy or difficult would it be to carry a spray bottle like the one used in this study around with you if  
4 you needed to?  
5 a. Very difficult  
6 b. Difficult  
7 c. Neutral  
8 d. Easy  
9 e. Very easy  
10 f. Prefer not to answer  
11  
12  
13 11. How easy or difficult was it to follow the instructions to administer the spray?  
14 a. Very difficult  
15 b. Difficult  
16 c. Neutral  
17 d. Easy  
18 e. Very easy  
19 f. Prefer not to answer  
20  
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22 12. How easy or difficult was it to insert the tip of the bottle into your nose?  
23 a. Very difficult  
24 b. Difficult  
25 c. Neutral  
26 d. Easy  
27 e. Very easy  
28 f. Prefer not to answer  
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31 13. How easy or difficult was it to spray the liquid into your nose?  
32 a. Very difficult  
33 b. Difficult  
34 c. Neutral  
35 d. Easy  
36 e. Very easy  
37 f. Prefer not to answer  
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39  
40 14. How easy or difficult was it to handle the bottle used to deliver the liquid (or administer the spray)?  
41 a. Very difficult  
42 b. Difficult  
43 c. Neutral  
44 d. Easy  
45 e. Very easy  
46 f. Prefer not to answer  
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**SPRAY PAL Intranasal Product Acceptability Questionnaire****Tolerability**

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4 15. How much did the force of the nasal spray in your nose encourage or discourage your use of the  
5 product?  
6 a. Discouraged very much  
7 b. Discouraged a little  
8 c. Neither discouraged nor encouraged use  
9 d. Encouraged a little  
10 e. Encouraged very much  
11 f. Prefer not to answer  
12  
13
- 14 16. How much did the tip of the nasal spray bottle in your nose encourage or discourage use of the product?  
15 a. Discouraged very much  
16 b. Discouraged a little  
17 c. Neither discouraged nor encouraged use  
18 d. Encouraged a little  
19 e. Encouraged very much  
20 f. Prefer not to answer  
21  
22
- 23 17. How much did the scent of the nasal spray encourage or discourage you from using the product?  
24 a. Discouraged very much  
25 b. Discouraged a little  
26 c. Neither discouraged nor encouraged / did not notice a scent  
27 d. Encouraged a little  
28 e. Encouraged very much  
29 f. Prefer not to answer  
30  
31
- 32 18. How much did the taste/aftertaste of the nasal spray encourage or discourage your use of the product?  
33 a. Discouraged very much  
34 b. Discouraged a little  
35 c. Neither discouraged nor encouraged, or did not notice a taste/aftertaste  
36 d. Encouraged a little  
37 e. Encouraged very much  
38 f. Prefer not to answer  
39  
40
- 41 19. Did the product run down the back of your throat?  
42 a. Yes, the product ran down the back of my throat and bothered me a lot  
43 b. Yes, the product ran down the back of my throat and bothered me a little  
44 c. Yes, the product ran down the back of my throat but did not bother me at all  
45 d. No, the product did not run down the back of my throat  
46 e. Prefer not to answer  
47  
48
- 49 20. Overall, how much did you like or dislike using the nasal spray?  
50 a. Disliked very much  
51 b. Disliked a little  
52 c. Neutral  
53 d. Liked a little  
54 e. Liked very much  
55 f. Prefer not to answer  
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**SPRAY PAL Intranasal Product Acceptability Questionnaire**

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3 21. How would you rate your overall level of comfort or discomfort during the process of administering the  
4 spray (spraying the liquid inside your nose)?  
5 a. Very uncomfortable  
6 b. Somewhat uncomfortable  
7 c. Neutral  
8 d. Somewhat comfortable  
9 e. Very comfortable  
10 f. Prefer not to answer  
11  
12  
13 22. How convenient was it to use the spray?  
14 a. Very inconvenient  
15 b. Somewhat inconvenient  
16 c. Neutral  
17 d. Somewhat convenient  
18 e. Very convenient  
19 f. Prefer not to answer  
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21  
22 23. How much did you like or dislike the spray bottle itself?  
23 a. Disliked very much  
24 b. Disliked a little  
25 c. Neutral  
26 d. Liked a little  
27 e. Liked very much  
28 f. Prefer not to answer  
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**Cost**

- 31  
32 24. How much would you be willing to spend on a nasal spray like the one used in this study if it provided  
33 some protection against infection from coronavirus/COVID-19?  
34 a. Less than what one spends on on an over-the-counter nasal spray (~\$10)  
35 b. About the same as one spends on on an over-the-counter nasal spray (~\$10)  
36 c. Twice as much as one spends on on an over-the-counter nasal spray (~\$10)  
37 d. Three times as much  
38 e. Four times as much or more  
39 f. Prefer not to answer  
40  
41

**Recommendations**

42 Please help us understand what we can do to make you more likely to use this product.  
43  
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- 45 25. Would you change anything about the the bottle?  
46 a. No  
47 b. Yes - please specify what you would change:  
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**SPRAY PAL Intranasal Product Acceptability Questionnaire**

1  
2 26. Would you change anything about the spray tip?

- 3 a. No  
4 b. Yes - please specify what you would change:  
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11 27. Would you change anything about how the product is packaged?

- 12 a. No  
13 b. Yes - please specify what you would change:  
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21 28. If you have any other recommendations, please write them below.  
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29 **Thank you very much for responding to this survey!**  
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# BMJ Open

## Development and validation of a product acceptability questionnaire for intranasal Q-Griffithsin COVID-19 prophylaxis (SPRAY PAL)

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3 **Development and validation of a product acceptability questionnaire for intranasal Q-**  
4 **Griffithsin COVID-19 prophylaxis (SPRAY PAL)**  
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## Abstract

**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,

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3 and cost of product for novel intranasal drug formulations. The SPRAY PAL is generalizable, and  
4 items may be readily adapted to assess other intranasal formulations.  
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8 **Trial registration:** The trials from which this sample of participants was drawn are registered at  
9 ClinicalTrials.gov, NCT05122260 and NCT05437029.  
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### 13 **Strengths and limitations of this study**

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- 15 • We examined the reliability and validity of a novel questionnaire designed to assess  
16 acceptability, feasibility, and tolerability of a novel intranasal spray formulation.  
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- 18 • The questionnaire can be readily adapted and generalizable for use with other intranasal  
19 formulations.  
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- 21 • The study is limited by the small sample size, precluding a more sophisticated principal  
22 components analysis, and relatively short period of follow-up in which to assess retest  
23 reliability.  
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29 **Keywords:** product acceptability, nasal spray, psychometric validation, reliability, validity,  
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## Introduction

Over the past two decades, three coronaviruses of the *Betacoronavirus* genus have emerged as serious human pathogens, with the coronavirus disease of 2019 (COVID-19) pandemic causing over 700 million infections globally (1) and over 1 million deaths to date in the United States (2).

The virus that causes COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), replicates efficiently in the upper respiratory tract – the nasopharynx and oropharynx (3). High viral replication in the nasopharynx in the early stages of infection, prior to symptom onset, accounts for the high transmissibility of SARS-CoV-2. Respiratory aerosols and droplets are the most frequent sources of human transmission events (4, 5). Consequently, the development of an intranasal spray that prevents the establishment of infection is an effective strategy to curb virus spread. This strategy will be synergistic to vaccine approaches and biomedical interventions, such as personal protective equipment and measures like social distancing and frequent hand washing, in eliminating the pandemic.

Due to the limited long-term durability of antibody response to vaccines, and the requirement of booster doses to maintain effective immunity to SARS-CoV-2 (6, 7), an additional level of protection of the kind likely to be offered by an intranasal spray product is critical in infection prevention. Topical delivery of drugs by the nasal route is cost-effective and eliminates or reduces potential drug-drug interactions (8, 9). Additionally, it is a convenient, easy-to-use approach, and is a widely accepted method of drug administration for a variety of patients (9, 10), especially for prolonged daily dosing periods.

As such, the PREVENT-CoV (Pre-Exposure prevention of Viral ENTRY of CoronaViruses) study was designed based on the potential utility of the intranasal drug delivery approach as a technology to prevent the establishment of upper respiratory infection. This is the first-in-human intranasal application of Q-GRFT, an oxidation-resistant variant of Griffithsin (GRFT), a lectin initially extracted from red sea algae (11, 12). The PREVENT-CoV Phase 1 clinical trial evaluated the safety, tolerability, and pharmacokinetics of the novel intranasal spray in healthy male and female volunteers, as the primary endpoint. Secondary endpoints included user perceptions, acceptability, and the impact of product use on participants' olfactory sensation, and quality of life (12). The Phase 1 clinical trial is ongoing to collect a final assessment of the levels of anti-drug antibodies one year after final dose administration.

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3 Compliance with intranasal formulations is key to effectiveness, and this depends largely  
4 on patient preference, as seen in prior work on intranasal corticosteroid formulations (13, 14).  
5 Daily use of intranasal formulations may be impacted by product sensory attributes, such as smell  
6 and aftertaste, intranasal sensations of the product, as well as ease of product use and cost (15).  
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8 Questionnaires are often used to assess these product features. However, there is no readily  
9 available instrument assessing the acceptability, feasibility, and tolerability of an intranasal  
10 formulation. This prompted the development of the product acceptability questionnaire, SPRAY  
11 PAL. Here our objective is to report on the development and reliability, defined by psychometric  
12 properties, of a novel questionnaire measuring key components of key intranasal product features.  
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## 22 **Methods**

### 23 *Study design*

24 This study consisted of 2 separate phases of a randomized, single-site trial (ClinicalTrials.gov  
25 identifiers NCT05122260 and NCT05437029). Approval to conduct this study was granted by the  
26 University of Louisville Institutional Review Board (IRB), Phase 1a IRB# 21.0704 and Phase 1b  
27 IRB# 22.0224. Details regarding trial design, drug product, and participant eligibility, recruitment  
28 and informed consent have been previously reported (12). Briefly, participants were prescreened  
29 using online questionnaires and telephone interviews to determine eligibility. Selected volunteers  
30 were invited for a screening visit at the clinical trials unit where eligibility was confirmed and  
31 written informed consent was obtained. Participants were generally healthy, aged 16-85, screened  
32 negative for SARS-CoV-2, able to attend all study visits, participating in no other concurrent drug  
33 trials, not pregnant or breastfeeding and/or were using contraception. Individuals with acute or  
34 chronic upper respiratory or pulmonary issues/illnesses, smokers, recreational drug users, and  
35 those taking intranasal medications or systemic steroids were excluded. Participants retained their  
36 right to withdraw from the study at any time for any reason.  
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48 The Phase 1a study (SAMPLE 1) was performed in a double-blind fashion, with 18  
49 participants randomly assigned 2:1 to either the study product arm or the placebo arm after  
50 stratification by race and gender. After participants received either a single dose of study product  
51 or a single dose of placebo, follow-up assessments were performed at 1 hour, 6 hours, 24 hours  
52 (visit 2), and 72 hours (visit 3) post-dose administration. A follow-up safety review was completed  
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3 by phone approximately two weeks later (visit 4). The SPRAY PAL was administered at visits 2,  
4 3, and 4.  
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6 The Phase 1b study (SAMPLE 2) was an open-label design conducted in 2 separate groups  
7 stratified by race and gender. Group 1 participants administered the study product once daily for  
8 7 days and were evaluated at multiple visits over the subsequent nine days. The SPRAY PAL was  
9 administered at visit 3 (midway through study product administration; study day 4), visit 4 (the  
10 final day of product administration; study day 7), and visit 6 (48 hours following the final dose;  
11 study day 9). One participant withdrew from the study due to contracting COVID-19 and  
12 completed the SPRAY PAL at an early termination visit after having received one dose of the  
13 study product.  
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20 Group 2 participants administered the study product twice daily, approximately every 12  
21 hours, for 7 days and were evaluated over the subsequent nine days. The SPRAY PAL was  
22 administered at visit 4 (midway through study product administration; study day 5), visit 5 (the  
23 final day of product administration; study day 8), and visit 7 (48 hours following the final dose;  
24 study day 10).  
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29 A one-year follow-up assessment of anti-drug antibodies in both groups is ongoing.  
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### 32 ***Measure - product acceptability questionnaire*** 33

34 Participants evaluated product acceptability, feasibility, and tolerability. Because there was no  
35 readily available questionnaire assessing these aspects for existing intranasal formulations,  
36 questionnaire items were derived from existing, validated questionnaire items with adaptation for  
37 the current study (16). Participant experience and opinion of efficacy, sensory perceptions, spray  
38 characteristics, administration process, applicator design, and use regimen were assessed. Items  
39 are rated on 5-point Likert scales coded from one to five (most negative to most positive), with an  
40 option of “prefer not to answer” included on each item to allow participants the opportunity to opt  
41 out of a question if desired. The SPRAY PAL also included open-ended items to allow participants  
42 to comment on other characteristics of the nasal spray not assessed by the questionnaire, and to  
43 allow comment on the questionnaire items themselves. The subscale and total scale scores are  
44 calculated by summing all items in each subscale and all questionnaire (including cost) items,  
45 respectively.  
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### *Analyses*

Responses were collected from participants on paper forms and were double-entered into a REDCap database hosted at the University of Louisville (17, 18). Entries were compared and, when mismatches occurred, data accuracy was confirmed against paper records. In SAMPLE 2 Group 2, one participant skipped an item about the comparability of the spray to the COVID vaccine on each administration of the product acceptability questionnaire. The mean score of all other items from that subscale for that participant was imputed to replace the three missing responses. Otherwise, all SPRAY PAL items were answered completely. Item responses for all participants were summarized using descriptive statistics.

### *Item revision*

Open-ended responses from participants in SAMPLE 1 were reviewed to assess for any participant comments on questionnaire item construction. SPRAY PAL items were also discussed with SAMPLE 1 participants who voluntarily provided feedback. The suggestions were incorporated, and a revised questionnaire was employed with SAMPLE 2.

### *Group comparisons*

Statistical comparisons of demographic data between SAMPLES 1 and 2 were performed using independent samples t-tests and Fisher's exact tests. SPRAY PAL summary scores between SAMPLE 2 Group 1 and Group 2 were compared using independent samples t-tests.

### *Reliability and validity tests*

Internal consistency was assessed using Cronbach's coefficient based on responses from the first administration of the SPRAY PAL for each SAMPLE. Test-retest reliability was assessed by calculating the intraclass correlation coefficients of responses collected three times over a span of five (SAMPLE 2) to 12 (SAMPLE 1) days during study participation; at least 48 hours had elapsed between each administration of the SPRAY PAL. We assessed the Spearman correlation of each

item with its own scale (with the overlapping item removed) to determine convergent validity, and the Spearman correlation of each item with other scales to assess discriminant validity. All analyses were conducted using SPSS Version 27 with alpha set at .05 (IBM; Armonk, NY).

### *Patient and public involvement*

None.

## **Results**

### *Sample demographics*

Sample demographics are provided in Table 1. There were no significant differences in demographic characteristics across samples except that SAMPLE 2 had a significantly higher vaccination rate than SAMPLE 1 due to updates made to guidelines for booster shot administration during the data collection period.

**Table 1.** Sample demographics and baseline characteristics

	<b>Sample 1 (N=18)</b>	<b>Sample 2 (N=22)</b>	<b>Total (N=40)</b>	<b>p- value</b>
	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>	
Gender				.761
Male	8 (44.0)	11 (50.0)	19 (47.5)	
Female	10 (66.0)	11 (50.0)	21 (52.5)	
Race				.111
White	6 (33.3)	14 (63.6)	20 (50.0)	
African American	0 (0.0)	1 (4.5)	1 (2.5)	
Asian	10 (55.6)	5 (22.7)	15 (37.5)	
Hispanic	0 (0)	2 (9.1)	2 (5.9)	
Mixed Race	2 (11.1)	0 (0.0)	2 (5.0)	
Fully vaccinated with booster	6 (33.3)	20 (90.9)	26 (65.0)	<.001
Age, years, <i>M (SD, range)</i>	32.6 (8.1, 25-55)	35.6 (11.8, 23-59)	34.3 (30.5, 23-59)	.335
BMI, <i>M (SD)</i>	25.5 (3.8)	27.5 (7.6)	26.6 (6.2)	.315

### *Item revision*

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3 After administration to participants in SAMPLE 1, who received a single nasal spray  
4 administration, internal consistency was calculated for each subscale and the total scale. Internal  
5 consistency was above the acceptable range ( $\alpha > .7$ ) for all subscales and for the total scale,  
6 excluding the Acceptability subscale, where Cronbach's  $\alpha = .514$ . Based on feedback from  
7 participants in SAMPLE 1, one Acceptability item was rephrased from inquiring about whether  
8 use of the spray would be acceptable versus not acceptable to inquiring about likelihood of use.  
9 Tolerability items were rephrased from how much the participant liked versus disliked a spray  
10 characteristic to how much each characteristic encouraged versus discouraged product use.  
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### 19 ***Internal consistency***

20 Internal consistency (Cronbach's  $\alpha$ ) was calculated for each subscale and for the total scale  
21 score from the initial SPRAY PAL administration for SAMPLE 2. For the Feasibility subscale,  
22  $\alpha$  was initially .346. Reliability estimates after individual item removal suggested removal of  
23 one item which improved Cronbach's  $\alpha$  to .651 for the Acceptability subscale.  $\alpha$  was  
24 acceptable for all other subscales: .618 for the Feasibility subscale, .789 for the Tolerability  
25 subscale, and .739 for the Total Scale.  
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### 32 ***Test-retest reliability***

33 The full SPRAY PAL was administered three times over the course of study participation for the  
34 purposes of calculating test-retest reliability. For all responses collected from participants in  
35 SAMPLE 2, intraclass coefficients were well above the acceptable threshold ( $> .7$ ) at .951 for three  
36 Acceptability Subscale scores, .888 for the Feasibility Subscale scores, .870 for the Tolerability  
37 Subscale Scores, .971 for the cost item, and .927 for the Total Scale Score.  
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### 45 ***Convergent validity***

46 No significant differences were noted in subscale scores between SAMPLE 2 Group 1 and 2, so  
47 SAMPLE 2 responses were pooled for validity and reliability tests. All but two items correlated  
48 highly with their own subscale; the item assessing likelihood of using the spray as many days as  
49 needed achieved a small correlation with the remaining items in the Feasibility subscale ( $r = .040$ ),  
50 and the item assessing whether the product ran down the back of the throat achieved a small  
51 correlation with the remaining items in the Tolerability Subscale ( $r = .134$ ). Otherwise, items  
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demonstrated convergent validity that was within the accepted range based on a correlation with their own subscale between .2 to .7 (Table 2).

**Table 2.** Convergent and discriminant validity. Correlation coefficients on the diagonal (italicized) represent the range of correlation coefficients obtained for each item with its own subscale after removal of the overlapping item (i.e., convergent validity). All other coefficients represent divergent validity. Some negative correlations were obtained due to the varying nature of items (i.e., asking about self versus asking about friends/family).

Subscale	# Items	Acceptability	Feasibility	Tolerability
Acceptability	6	<i>.208 - .630</i>	-.303 - .132	.084 - .507
Feasibility	7	-.375 - .202	<i>.040 - .576</i>	-.252 - .311
Tolerability	9	.060 - .440	-.171 - .201	<i>.134 - .774</i>

### ***Discriminant validity***

In the Accessibility subscale, the item comparing effectiveness of the spray to vaccine did not meet criterion for discriminant validity ( $r > .4$ ) from the Tolerability subscale. Similarly, in the Tolerability subscale, the item assessing likeability of the spray bottle itself did not meet the discriminant validity criterion from the Acceptability subscale. Some negative correlations were obtained due to the varying nature of items (i.e., asking about self versus asking about friends/family). Otherwise, all items correlated more highly with their own subscale score than other subscales, demonstrating good discriminant validity. The correlations between subscale scores ranged from .123 to .392, indicating adequate distinction between subscale constructs. The final SPRAY PAL is provided in the Supplemental Material.

### **Discussion**

Acceptability is an important consideration for the successful design and implementation of novel pharmaceutical products. Adherence to drug regimen may be greatly impacted by patient



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3 acceptance of study product and treatment regimen, including feasibility of use, tolerability of  
4 treatment and side effects, and product cost. Our objective was to develop the SPRAY PAL  
5 product acceptability questionnaire to provide evidence for all these factors in efforts to better  
6 inform the development and commercialization of a novel intranasal formulation designed for  
7 COVID-19 prophylaxis. Item development was based on existing, validated questionnaires, with  
8 adjustments made based on qualitative feedback from study participants.  
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13 Initial tests of internal consistency indicated that one item, “How easy or difficult would it  
14 be to carry a spray bottle like the one used in this study around with you if you needed to?” should  
15 be removed to improve Cronbach’s alpha to an acceptable level. This was possibly due to the item  
16 asking the participant to speculate about future use, rather than ask about current experiences, in  
17 addition to inconsistencies in ratings when compared to other items (e.g., participants who rated  
18 this item as less feasible rated other items as more feasible). After this item was removed, we  
19 observed adequate indices of internal consistency as well as test-retest reliability on the revised  
20 version of the SPRAY PAL.  
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27 While tests of convergent and discriminant validity were generally acceptable, there were  
28 two items that fell just below conventional thresholds for each construct. This is, in part, related to  
29 the diversity of themes across items that fall under the broader theme of each subscale, such as  
30 assessments about the nature of physical spray characteristics versus impressions of efficacy, and  
31 inquiring about administration for one's self versus others. However, tests of internal consistency  
32 for the full scale did not suggest that removal of any one item would improve the overall alpha  
33 score achieved. Together with the observation of low correlations between subscales, the single  
34 full scale sum score may be the most appropriate indicator of overall product acceptability.  
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41 Because the SPRAY PAL was implemented as part of a Phase 1 clinical trial, the sample  
42 size was small, precluding the use of more sophisticated analytic procedures, such as factor  
43 analysis, for tests of item validity. Confirmation of item validity should be further tested in a larger,  
44 and more diverse, sample of patients. Similarly, assessments of test-retest reliability were designed  
45 to fit within the existing study appointments necessary for determining safety and tolerability of  
46 the study product. As such, the retest timeframe was limited to 12 days. Retest stability over longer  
47 treatment periods will need to be addressed in future trials. The SPRAY PAL items were generated  
48 with respect to a novel intranasal COVID-19 prophylactic formulation; the generalizability of  
49 items to other applications may therefore be limited. Finally, while the SPRAY PAL was created  
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3 based on a sound conceptual framework and tested using commonly utilized psychometric  
4 methods for validation and reliability assessment of a new questionnaire, it should be employed  
5 with caution until the results are confirmed among larger samples and in different clinical settings.  
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## 10 **Conclusions**

11 Compliance with intranasal formulations can be impacted by product administration schedules,  
12 sensory attributes, ease of use, and cost. The lack of a readily available instrument to assess these  
13 features in an intranasal formulation has challenged accurate assessment of patient perception.  
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15 This prompted the development of the SPRAY PAL among a small sample of patients  
16 participating in a phase 1 clinical trial. The SPRAY PAL product acceptability questionnaire was  
17 found to be psychometrically sound with adequate validity and reliability, though further  
18 psychometric validation steps should be performed. It can be considered a credible tool for  
19 assessing patient-reported information about product acceptability, feasibility of use, tolerability  
20 of product and side effects, and cost of product for novel intranasal drug formulations. The  
21 SPRAY PAL is generalizable, and items may be readily adapted to fit modified study designs  
22 and different dosing regimens for other nasal spray product formulations as necessary.  
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37 their support in finalizing the clinical protocol and efficiently planning the conduct of this trial and  
38 questionnaire administration. We greatly appreciate CBR International Corp., Boulder, CO for  
39 their critical input during protocol and questionnaire development.  
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## 45 **Contributors**

46 EC, KEP, HN, MZ, GD, SR, KP contributed to the design and conduct of the study. EC, KD, GD,  
47 and SR assisted in the development, review and editing of questionnaire items. EC carried out the  
48 analyses. All authors contributed to the interpretation of the data, critical revisions of the  
49 manuscript, and provided final approval of the manuscript.  
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### **Competing interests**

The authors report no conflicts or competing interest in this work.

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### **Data availability statement**

The results reported herein utilize data that was collected as part of a Phase 1 clinical trial. These data will be made available as part of the data sharing plan that accompanies the report of the larger Phase 1 results. Thus, the data is not shared for the current manuscript.

### **Patient consent for publication**

Not applicable.

### **Ethics approval**

Approval to conduct this study was granted by the University of Louisville Institutional Review Board (IRB), Phase 1a IRB# 21.0704 and Phase 1b IRB# 22.0224.

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**SPRAY PAL Intranasal Product Acceptability Questionnaire**

Participant ID \_\_\_\_\_

Date \_\_\_\_\_

Thank you for agreeing to complete this questionnaire. We would like to know your opinion about the nasal spray that you used as part of this study.

**Acceptability**

1. If a nasal spray like the one you used at home, provided for the study, could protect you against infection from coronavirus/COVID-19, how likely is it that you would use this nasal spray to protect against infection from coronavirus/COVID-19?
  - a. Highly unlikely
  - b. Somewhat unlikely
  - c. Neutral
  - d. Somewhat likely
  - e. Highly likely
  - f. Prefer not to answer
2. You were asked to use the spray at home. How confident do you feel that using that amount offers sufficient protection from infection from coronavirus/COVID-19?
  - a. Not confident at all
  - b. Somewhat unconfident
  - c. Neutral
  - d. Somewhat confident
  - e. Highly confident
  - f. Prefer not to answer
3. Future studies will determine an effective dose for the nasal spray product. Once an effective dose is determined, how confident do you feel that using this nasal spray will offer sufficient protection from *mild* complications from coronavirus/COVID-19 (e.g., symptoms similar to cold/flu)?
  - a. Not confident at all
  - b. Somewhat unconfident
  - c. Neutral
  - d. Somewhat confident
  - e. Highly confident
  - f. Prefer not to answer
4. Once an effective nasal spray dose is determined, how confident do you feel that using this nasal spray offers sufficient protection from *severe* complications from coronavirus/COVID-19 (e.g., symptoms requiring hospitalization, use of supplemental oxygen/respirator)?
  - a. Not confident at all
  - b. Somewhat unconfident
  - c. Neutral
  - d. Somewhat confident
  - e. Highly confident
  - f. Prefer not to answer

**SPRAY PAL Intranasal Product Acceptability Questionnaire**

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3 5. How do you feel the effectiveness of this nasal spray compares to that of the COVID-19 vaccines?  
4 a. Quite a bit less effective  
5 b. Somewhat less effective  
6 c. About the same  
7 d. Somewhat more effective  
8 e. A great deal more effective  
9 f. Prefer not to answer  
10  
11  
12 6. If a nasal spray like the one that was administered at the clinic could protect you against infection from  
13 coronavirus/COVID-19, would likely would you be to recommend it to your friends/family?  
14 a. Very unlikely  
15 b. Somewhat unlikely  
16 c. Neutral  
17 d. Somewhat likely  
18 e. Very likely  
19 f. Prefer not to answer  
20  
21

**Feasibility**

22  
23 Now we would like to ask you some questions about administering the spray provided in this study for take-  
24 home use. While we provided you with specific instructions on how to give the spray to yourself, we are most  
25 interested in how you actually used the spray. Please answer all of the following questions based on how you  
26 actually used the spray.  
27

- 28  
29 7. How easy or difficult was it to administer the spray without missing doses?  
30 a. Very difficult  
31 b. Difficult  
32 c. Neutral  
33 d. Easy  
34 e. Very easy  
35 f. Prefer not to answer  
36  
37  
38 8. How easy or difficult was it to administer the spray at prescribed time of day every day without missing  
39 doses?  
40 a. Very difficult  
41 b. Difficult  
42 c. Neutral  
43 d. Easy  
44 e. Very easy  
45 f. Prefer not to answer  
46  
47  
48 9. If we find that effectiveness of the nasal spray, like the one used in this study, requires it to be used  
49 every day for as many days as needed to provide some protection from coronavirus/COVID-19, how  
50 likely would you be to use the spray as directed?  
51 a. Very unlikely  
52 b. Somewhat unlikely  
53 c. Neutral  
54 d. Somewhat likely  
55 e. Very likely  
56 f. Prefer not to answer  
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**SPRAY PAL Intranasal Product Acceptability Questionnaire**

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3 10. How easy or difficult would it be to carry a spray bottle like the one used in this study around with you if  
4 you needed to?  
5 a. Very difficult  
6 b. Difficult  
7 c. Neutral  
8 d. Easy  
9 e. Very easy  
10 f. Prefer not to answer  
11  
12  
13 11. How easy or difficult was it to follow the instructions to administer the spray?  
14 a. Very difficult  
15 b. Difficult  
16 c. Neutral  
17 d. Easy  
18 e. Very easy  
19 f. Prefer not to answer  
20  
21  
22 12. How easy or difficult was it to insert the tip of the bottle into your nose?  
23 a. Very difficult  
24 b. Difficult  
25 c. Neutral  
26 d. Easy  
27 e. Very easy  
28 f. Prefer not to answer  
29  
30  
31 13. How easy or difficult was it to spray the liquid into your nose?  
32 a. Very difficult  
33 b. Difficult  
34 c. Neutral  
35 d. Easy  
36 e. Very easy  
37 f. Prefer not to answer  
38  
39  
40 14. How easy or difficult was it to handle the bottle used to deliver the liquid (or administer the spray)?  
41 a. Very difficult  
42 b. Difficult  
43 c. Neutral  
44 d. Easy  
45 e. Very easy  
46 f. Prefer not to answer  
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**SPRAY PAL Intranasal Product Acceptability Questionnaire****Tolerability**

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15. How much did the force of the nasal spray in your nose encourage or discourage your use of the product?
- Discouraged very much
  - Discouraged a little
  - Neither discouraged nor encouraged use
  - Encouraged a little
  - Encouraged very much
  - Prefer not to answer
16. How much did the tip of the nasal spray bottle in your nose encourage or discourage use of the product?
- Discouraged very much
  - Discouraged a little
  - Neither discouraged nor encouraged use
  - Encouraged a little
  - Encouraged very much
  - Prefer not to answer
17. How much did the scent of the nasal spray encourage or discourage you from using the product?
- Discouraged very much
  - Discouraged a little
  - Neither discouraged nor encouraged / did not notice a scent
  - Encouraged a little
  - Encouraged very much
  - Prefer not to answer
18. How much did the taste/aftertaste of the nasal spray encourage or discourage your use of the product?
- Discouraged very much
  - Discouraged a little
  - Neither discouraged nor encouraged, or did not notice a taste/aftertaste
  - Encouraged a little
  - Encouraged very much
  - Prefer not to answer
19. Did the product run down the back of your throat?
- Yes, the product ran down the back of my throat and bothered me a lot
  - Yes, the product ran down the back of my throat and bothered me a little
  - Yes, the product ran down the back of my throat but did not bother me at all
  - No, the product did not run down the back of my throat
  - Prefer not to answer
20. Overall, how much did you like or dislike using the nasal spray?
- Disliked very much
  - Disliked a little
  - Neutral
  - Liked a little
  - Liked very much
  - Prefer not to answer



**SPRAY PAL Intranasal Product Acceptability Questionnaire**

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3 21. How would you rate your overall level of comfort or discomfort during the process of administering the  
4 spray (spraying the liquid inside your nose)?  
5 a. Very uncomfortable  
6 b. Somewhat uncomfortable  
7 c. Neutral  
8 d. Somewhat comfortable  
9 e. Very comfortable  
10 f. Prefer not to answer  
11  
12  
13 22. How convenient was it to use the spray?  
14 a. Very inconvenient  
15 b. Somewhat inconvenient  
16 c. Neutral  
17 d. Somewhat convenient  
18 e. Very convenient  
19 f. Prefer not to answer  
20  
21  
22 23. How much did you like or dislike the spray bottle itself?  
23 a. Disliked very much  
24 b. Disliked a little  
25 c. Neutral  
26 d. Liked a little  
27 e. Liked very much  
28 f. Prefer not to answer  
29  
30

**Cost**

- 31  
32 24. How much would you be willing to spend on a nasal spray like the one used in this study if it provided  
33 some protection against infection from coronavirus/COVID-19?  
34 a. Less than what one spends on on an over-the-counter nasal spray (~\$10)  
35 b. About the same as one spends on on an over-the-counter nasal spray (~\$10)  
36 c. Twice as much as one spends on on an over-the-counter nasal spray (~\$10)  
37 d. Three times as much  
38 e. Four times as much or more  
39 f. Prefer not to answer  
40  
41

**Recommendations**

42 Please help us understand what we can do to make you more likely to use this product.  
43  
44

- 45 25. Would you change anything about the the bottle?  
46 a. No  
47 b. Yes - please specify what you would change:  
48  
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**SPRAY PAL Intranasal Product Acceptability Questionnaire**

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2 26. Would you change anything about the spray tip?

- 3 a. No  
4 b. Yes - please specify what you would change:  
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11 27. Would you change anything about how the product is packaged?

- 12 a. No  
13 b. Yes - please specify what you would change:  
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21 28. If you have any other recommendations, please write them below.  
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29 **Thank you very much for responding to this survey!**  
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