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Statistical Analysis Plan (SAP)

VALIDATION OF THE QUESTIONNAIRE OF OLFACTORY DISORDERS (QOD) FOR BRAZILIAN PORTUGUESE LANGUAGE

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1. BACKGROUND

Chronic smell disorders have a significant impact on quality of life [1]. Anxiety and eating disorders, exposure to food or environmental risks, social isolation, relationship problems are well known complications of smell loss. In 2005, Frasnelli et al. developed the first questionnaire that relates olfactory dysfunctions with the impact on patients' daily life, called: “Questionnaire of Olfactory Disorders (QOD)” [1]. The QOD was used in some clinical publications[2–5] and validated for English in 2019 by Langstaff et al. [6]. However, the questionnaire has not yet been translated and validated into Brazilian Portuguese.

2. OBJECTIVES

2.1. General objectives

Our main goal is to validate the Portuguese version of the Questionnaire of Olfactory Disorders (QOD) based on the original English version.

2.2. Specific objectives

- Compare the quality-of-life (QOL) scores of patients with olfactory alteration of different etiologies (post-viral, nasosinusal diseases, others)

- To describe the impact of olfactory alteration on the QOL of patients with long COVID.

3. METHODOLOGY

3.1. Study design

We will conduct an observational and cross-sectional study with a specific methodology for the validation of foreign language questionnaires (Specificities to be described in later sections) based on the guideline proposed by Beaton et al [7].

3.2. Setting

Data collection will be performed in a multicenter setting, in two different states of Brazil:

1. Post-COVID-19 Center (CPC), located at Octávio Mangabeira Hospital (HEOM), Salvador-Bahia. A multiprofessional center specialized in rehabilitation of long COVID conditions.
2. Private Olfact Clinic, located at Londrina-Paraná. A center of excellence in treatment of nasal diseases and the first clinic specialized in olfactory disorders in Brazil.

3.3. Study population

Adult patients (>18 years) complaining of quantitative or qualitative smell alteration assisted in the medical centers mentioned above.

For long COVID cases, we will define time of symptom onset greater than one month, with a positive diagnostic test (Swab RT-PCR, rapid tests and others) presented during the first medical consult.

For other etiology, non-COVID post-infectious, traumatic, idiopathic and chronic rhinosinusitis were considered.

3.4. Baseline characteristics

Table 1 displays all variables grouped by category available for this study. Outcome data are described in “QOD data”. The remaining categories contain data on important steps for questionnaire validation, potential confounding factors or outcome modifiers.

Data category	Data item
Socio-demographic and clinical info	Age
	Sex
	Educational level
	Smell alteration etiology
	Smoking habits
	Parosmia
	Phantosmia
Objective olfactory measurement	Upsite Score
	Classification of olfactory loss
QOD data*	QOD – Sincerity statements score
	QOD – Life quality statements score
	QOD – Parosmia statements score
	QOD - Q1- Q29 individual statements
	QOD – annoying VAS
	QOD – frequency VAS
	QOD – professional VAS
	QOD – free time VAS
	QOD – private life VAS
General Quality of Life data	WHOQOL – physical health
	WHOQOL – psychological health
	WHOQOL – social relationships
	WHOQOL – environmental health
	WHOQOL – total mean score
Test-retest	Test-retest*

** All QOD variables are reapplied in test-retest validation step*

3.5. Selection criteria

The eligible study population will be individuals aged equal or above 18 years in Brazil that present olfactory alteration that signed the Free and Informed Consent Form (ICF).

We will exclude:

1. *Incomplete questionnaire;*
2. *Olfactory loss not documented in objective testing;*
3. *Age > 65 years;*
4. *Multiple etiology olfactory loss*
5. *Cognitive deficit;*
6. *Pregnancy.*

3.6. QOD description

The QDO is a self-report questionnaire focused on understanding the impact of olfactory alteration on QoL. The last version of the QDO comprises 29 statements with 3 domains: 19 statements about QoL (LQ); 6 statements about sincerity (S); 4 statements referring to parosmia (P). In addition, 5 sentences must be answered using a visual analog scale (VASs) with scores ranging from 0 to 10. The scoring form for each domain follows specific summation rules, with inversion of specific questions and different weights for each domain, following the instruction guidelines.

The QOD was previously validated for other languages, such as Korean, Chinese, Greek [2,3,8].

3.7. Cross-cultural translation and validation protocol

The cross-cultural validation process comprises four stages: translation and cultural adaptation, back-translation, pilot test and validation, according to the validation guideline provided by Beaton et al.[7]An authorization for the translation process, the current version of the QoD and scoring instructions were requested for the instrument's original creators (Johannes Frasnelli and Thomas Hummel). The original English version of the questionnaire (QOD) and a written consent for validation were obtained.

3.8. Validation steps

3.8.1. Cultural Translation

The original English version is translated into Portuguese by two independent Brazilian-native Portuguese translators: a specialist in otorhinolaryngology (content translation) and a non-specialist translator (cultural translation). For each translation, an individual version translated from English to Portuguese (Vp^1 and Vp^2) is created. A third translator, non-specialist and independent of the research, is called to unite the 2 versions and produce the combined translated version (Vp^c).

A general evaluation committee is created, comprising: the main investigators, an otolaryngologist specialist, a psychologist and two laymen. After the final version (Vp^c) passed committee´s approval, the back-translation step is initialized.

3.8.2. Back-translation

The Vp^c is translated into English for the "back-translation" step. Two independent translators (specialist and layman), whose native language is English, retrogradely translate the Vp^c into the original language (Retranslated English Version – Vi^r). The committee compared Vi^r to the original version made available by Frasnelli and Hummel[1]. Small semantic changes are made and, after acceptance by the Brazilian translators, the pre-pilot version of the questionnaire in Brazilian Portuguese is completed (Vp^{pp}).

3.8.3. Pilot test

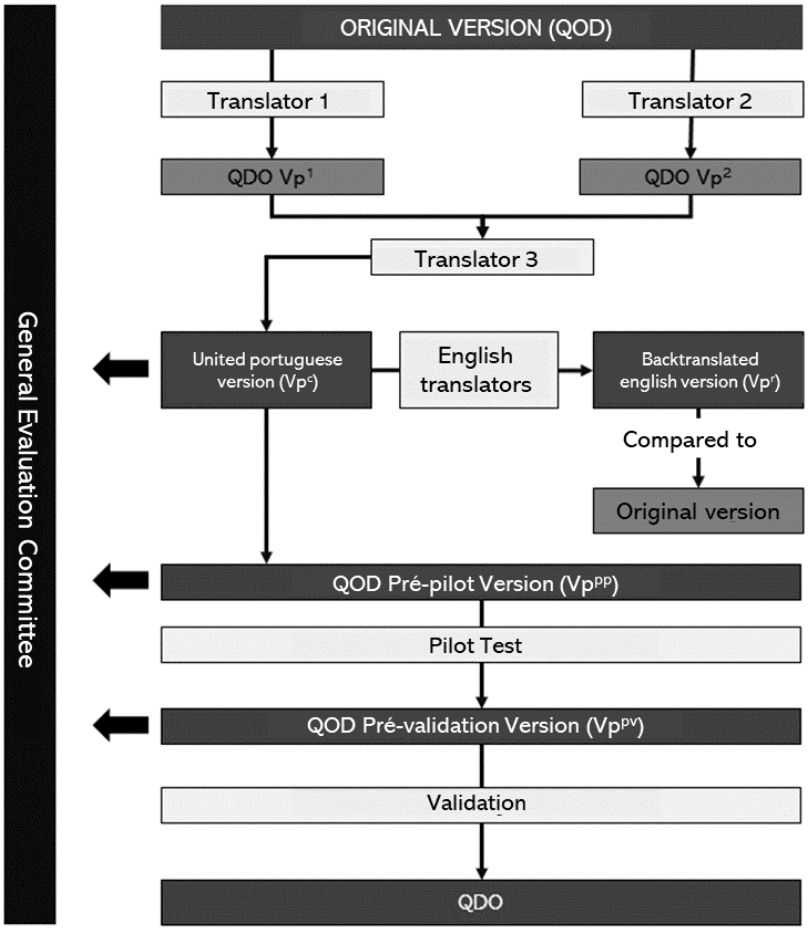
In the pilot test step, the QDO Vp^{pp} underwent a general understanding test in 30 individuals. In each application, the understanding of the assertions individually, the degree of relevance and possible suggestions about the construct are questioned. With the data collection, the pre-pilot version of the questionnaire are re-evaluated by the committee and released for the validation test (Vp^{pv}).

3.8.4. Validation step

The current validation step consists of guaranteeing a reliable, consistent instrument with good content validity. Content validity is demonstrated by correlation with already validated questionnaires with similar content of the target construct's. Considering that the QDO consists of measuring the impact on "quality of life" caused by "olfactory disorders", specific questionnaires will be applied to objectively measure olfactory function (University of Pennsylvania Smell Identification Test - UPSIT) and general QoL (World Health Organization QoL questionnaire - WHOQOL) during the validation stage. Specific details on statistical methods can be found in section "4. Statistical analysis"

Figure 1 summarizes the stages of cross-cultural translation and validation guidelines.

Figure 1 – Flowchart of the steps performed for cross-cultural translation of the QDO.



3.9. Olfactory function test

Among many objective tests for assessing olfactory function, the University of Pennsylvania Smell Identification Test (UPSIT) is a top-used questionnaire. The test consists of applying 4 cards, with 10 odors each, to the patient, who must scrape a specific area of the questionnaire and smell the exhaled odor. After that, four alternatives of daily life odors will be presented (i.e. Banana, grass, coffee, mint) and the answer to each questionnaire is documented. The UPSIT score consists of a simple sum of correct answers. The diagnosis of normosmia, hyposmia (mild to severe) and anosmia is calculated based on predefined tables, previously validated for Brazilians, which are stratified by sex, age and UPSIT score [9].

3.10. Health-related QoL

The WHOQOL-BREF is a well-known QoL questionnaire developed by the World Health Organization that contains 26 items divided in four different domains: physical health (7 items), psychological health (6 items), social relationships (3 items), and environmental health (8 items) [10]. Each individual statement should be answered in a 1 to 5 Likert-type ordinal scale. The scores are transformed to a 0–100-scale for proportional comparison. Considering QoL as a multidimensional and subjective concept, several areas of daily life are considered, such as: mobility, pain, sleep, positive and negative thoughts, social support, financial resources, and others.

3.11. Outcome

The outcomes of interest will be: (i) QDO Scores (ii) general QoL questionnaires and objective measurement of smell scores.

3.12. Sample size calculation

The sample size calculation of this study was performed based on the expected correlation coefficient for the primary outcome: $N = [(Z\alpha + Z\beta) \div C]^2 + 3$, where "N" is the estimated number of patients needed, "Zα" the deviation from the normal distribution for "α", "Zβ" the normalized deviation from the normal distribution for β. The value of C is obtained by the equation: $C = 0.5 \times \ln[(1 + r)/(1 – r)]$, where "r" is the correlation coefficient established as expected.

The parameters used were: r of 0.3 (imagining a weak correlation), two-tailed α of 0.05, and a β of 0.20 (80% statistical power). The expression result demonstrates an N of 85 patients for the instrument validation step. Assuming a 10% loss to follow-up of patients, 94 adult patients were estimated for recruitment.

3.13. Ethics approval

The study was approved by the ethics committees of the "*Universidade do Estado da Bah*ia" (UNEB; protocol nº 38281720.2.0000.0057) and "*Hospital Santo Antônio*" (OSID; protocol nº. 33366030.5.0000.0047), in Salvador-Ba, and by the ethics

committee of the State University of Londrina, under number 48238421.9.0000.5231.

4. Statistical analysis

4.1. Analysis procedure

Initially, a descriptive analysis of the questionnaire's qualitative variables and scores will be performed. Qualitative results will be described through absolute (n) and relative (%) frequency. Quantitative results will be described as mean (± standard deviation) or median (interquartile range), according to normality. Smell loss etiology will be properly described within the results. Normality will be tested by analyzing numerical and graphical parameters (histogram analysis). For the frequency description of the QOD statements, “I totally agree” and “I partially agree” will be considered as positive answers.

For the internal consistency of the construct, Cronbach's Alpha[11] will be used for each QOD domain, as well as for the individual questionnaire statements. Values of Cronbach's α coefficient above 0.7 will be considered sufficient.

The reliability will be assessed using the Split-half and “test/retest” analysis. In first medical contact, the patient will be interviewed by an examiner, where the Portuguese version of QOD, UPSIT and WHOQOL-BREF will be applied (QOD-Score 01). Without any intervention, the adult will be invited to a second clinic visit to answer the same questionnaire and perform an olfactory evaluation(QOD-Score 2). Patients unable to return within 6 months were considered as loss to follow-up.

The Kruskal-Wallis test will be used to assess the QOD scores between the UPSITE classifications (normosmia, hyposmia and anosmia).

The convergent validity of the questionnaire will be performed through Pearson's correlation analysis, using the QDO domains and WHO-QoL and UPSIT scores.

Data will be independently analyzed according to the collection center (Ba/Pr) or all observations will be unified in a single analysis, according to the collected sample size. Heterogeneity tests may be performed to help define the best method. The established significance level was 5% for all tests.

4.2. Missing data:

Missing data will not be included in the main outcome analysis. There will be no statistical forms of dealing with missing data (imputation). Follow-up loss will be described on the flowchart according to STROBE guidelines.

4.3. Statistical Software:

SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp will be used for analysis.

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