



## The study protocol for a multicenter observational headache registry: Brazilian Headache Registry - REBRACEF II

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### Objective

This article presents the protocol for the Brazilian Headache Registry (REBRACEF), the first national registry designed to systematically collect real-world data on patients with primary and secondary headaches at specialized centers in Brazil. The main objective is to describe the methods for patient selection, the registry infrastructure, data collection, and the standardized instruments used.

### Methodology

REBRACEF is a prospective, observational, multicenter cohort study conducted in real-world settings.

### Expected results

This protocol aims to standardize and enable the structuring of the registry, allowing its implementation in other centers across Brazil. It also ensures external feasibility by establishing a robust framework that can be replicated in other national and international healthcare institutions.

### Conclusion

The registry protocol provides a standardized framework for the collection of real-world data on patients with primary and secondary headaches, facilitating the improvement of headache management and research in Brazil.



## Introduction

The World Health Organization estimates that the three most prevalent neurologic disorders worldwide are tension-type headache, migraine, and medication overuse headache. These three disorders contribute approximately 17% of the global burden of neurologic diseases, with migraine the second most disabling disease overall (1,2).

The diagnosis and treatment of primary and secondary headaches constitute a challenge of global magnitude. There are multiple therapeutic options with proven efficacy for most patients with any of the primary headache disorders, but access to practitioners with training in Headache Medicine is limited, diagnostic accuracy is inconsistent, and the use of evidence-based treatments is suboptimal (3).

In Brazil, approximately 70% of the population has experienced some form of headache, with a prevalence of 29.5% for tension-type headache and 15.2% specifically for migraine (4). In low- and middle-income countries, the challenge of diagnosing and treating headaches is even greater, due to social, financial and clinical barriers that make access to specialized care difficult (5). These barriers lead to incorrect diagnoses and inefficient treatments, increasing the level of disability caused by the disease (6).

In this scope, the Brazilian Headache Registry (REBRACEF) was developed with the aim of collecting, storing, and analyzing information related to sociodemographic, anthropometric, clinical and lifestyle characteristics, as well as comorbidities, and treatment patterns used in patients diagnosed with primary and secondary headaches. Its fundamental purpose is to deepen the understanding of the inherent characteristics of patients with headaches who receive care at specialized centers distributed throughout the national territory in a real-life context.

Real World Evidence (RWE) studies play a crucial role in medical research, offering valuable tools for assessing the effectiveness of treatments and health management in patients robustly, beyond controlled environments (7). These studies present opportunities to analyze more diverse populations, facilitating the evaluation of comorbidities and sociodemographic characteristics with increased diversity (8). The real-world data collected from the REBRACEF are aligned with the routine of patients and participating centers, providing a comprehensive and authentic perspective.

Therefore, REBRACEF was conceived as a real-world prospective and multicenter clinical registry of patients treated in specialized centers in four regions of the country, namely:

- Headache Outpatient Clinic / Headache Center of Hospital São Lucas at the Pontifical Catholic University of Rio Grande do Sul (PUCRS) in Porto Alegre - Rio Grande do Sul.
- Santa Casa of Porto Alegre in Porto Alegre - Rio Grande do Sul.
- Regional Hospital of Barbacena Dr. José Américo – Medicine School in Barbacena (FAME) - Minas Gerais.
- Specialized Center in Hypermobility and Pain (CEHD) in Brasília – Federal District.
- Department of Physiotherapy at the Federal University of Pernambuco in Recife – Pernambuco.
- West Metropolitan Hospital Pelópidas Silveira in Recife - Pernambuco.
- Federal Fluminense University in Niterói - Rio de Janeiro.



Figure 1. Specialized centers in four regions of the country.

## Objectives

The main objective of the registry is to describe the sociodemographic, and anthropometric characteristics, treatments, medications, and comorbidities of patients with headache complaints seeking care at specialized centers in different regions of Brazil, within a real-world context. Also, the registry has other specific objectives, like:

- Analyze the frequency and intensity of headaches.
- Investigate clinical presentation and evolution.
- Investigate different headache types' personal, functional, and economic impacts on patient's daily lives, productivity, and healthcare costs.
- Examine the influence of sociodemographic variables, treatment changes, and discontinuation rates.
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- Provide a robust dataset for the analysis of potential risk factors and associations and correlations between clinical and sociodemographic characteristics.

## Registry Design

The REBRACEF was designed based on the STROBE (*Strengthening the Reporting of Observational Studies in Epidemiology*), a guideline from the Equator Network for observational studies (9). Additionally, the registry was designed following the Guidelines of the International Headache Society for Clinic-Based Headache Registries, 1st edition (10).

### Patients

The registry includes individuals aged 18 years or older seeking care for headache complaints at specialized centers. Participants are those who agree to take part in the study and are attending the specialized center for the first time, facilitating the mapping of the patient's journey. Patients with cognitive limitations that would hinder understanding the Informed Consent Form and completing the questionnaires are excluded.

## Statistical Analysis Plan

### Sample Size

A sample size of 385 subjects was calculated to estimate the proportion of headache occurrence with a 10% confidence interval width (with an additional 20% to account for possible losses and refusals, this number should be 482). The calculation (using the Wald method) considered a 95% confidence level and an expected headache prevalence of 50% (adapted from Borges et al. (2020)) (11). The expected occurrence percentage for the category of interest could not be obtained from the literature; therefore, we used the value of 50%, as this percentage provides maximum variability for the proportion estimator. This ensures the largest necessary sample size for the estimate (keeping the confidence level and interval width fixed). This calculation was performed using the PSS Health tool with an interface in the R environment under the command `propsize:prec_prop(p = 50/100, conf.width = 10/100, conf.level = 95/100, method = 'wald')`.

### Descriptive Analysis

Continuous variables (BMI, age) will be described using, mean and standard deviations or medians and interquartile ranges, depending on the distribution.

Categorical variables (sex, education level, comorbidities) will be presented as frequencies and percentages.

### Inferential Analysis

To compare means and medians, the statistical tests used will be the Student's t-test and the Wilcoxon-Mann-Whitney test, depending on the distribution of the data. To evaluate the impact of patient characteristics and headache types, associations will be made using chi-squares tests. To compare means and medians, the statistical analyses will employ the Student's t-test and the Wilcoxon-Mann-Whitney test, chosen based on the distribution of the data. Furthermore, correlations will be evaluated using the Spearman and Pearson tests, contingent upon the nature of the data.

Also, regression models will be used to explore how headache types affect patients' functional outcomes (e.g., productivity and healthcare costs). Multivariate logistic regression models will be used to investigate potential risk factors for more severe headache presentations or poor treatment outcomes. The models will include sociodemographic variables, comorbidities, and headache characteristics. A Mixed-Effects Model for Repeated Measures (MMRM) will be applied to assess changes over time in the variables. This analysis effectively manages the variation in data, which is crucial when dealing with real-world data that often presents a wide range of values and patterns. The use of models like MMRM (Mixed-Effects Model for Repeated Measures) offers the flexibility to capture both within-subject changes over time and between-subject differences.

### Data

Prospective data are collected through questionnaires, standardized scales, and headache diaries to assess the clinical, sociodemographic, social, and economic characteristics of patients. The registry also gathers retrospective data related to neuroimaging exams, such as computed tomography and magnetic resonance imaging of the brain. The data collection procedure is as follows: after agreeing to participate in the study and signing the consent form, the patient completes the questionnaires developed by the research team and standardized scales. Since the assessments are conducted during the patient's routine visits to the specialized center, the diagnostic questionnaires (according to ICHD-3) and medical management are answered by the specialized medical team at the center.

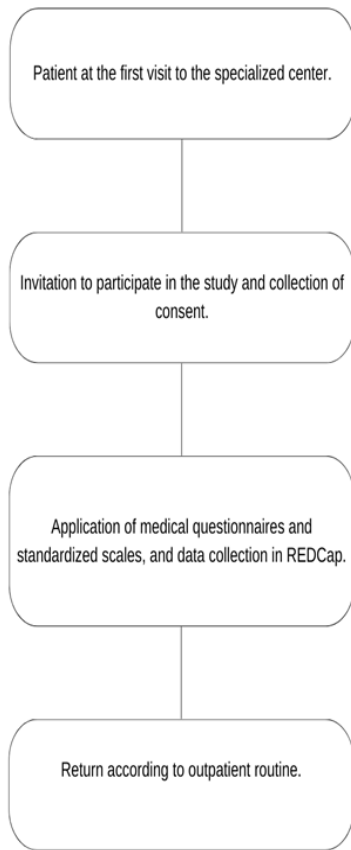


Figure 2. Data collection procedures

### Diagnosis

To substantiate the diagnostic assessment, the International Classification of Headache Disorders, 3rd edition (ICHD-3) was employed—a widely acknowledged and utilized classification system renowned for categorizing and delineating diverse headache types and associated disorders (12). As published by the International Headache Society (IHS), the ICHD-3 provides meticulous diagnostic criteria for distinct headache varieties. The classification is grounded in precise clinical criteria, encompassing parameters such as duration, frequency, pain characteristics, associated symptoms, and potential underlying etiologies. The International Classification of Headache Disorders (ICHD-3) is used by the attending physicians at each specialized center participating in the registry for the clinical diagnosis of primary and secondary headaches.

## Assessment Instruments

### Questionnaire

The standard questionnaire developed by the research team consists of questions related to patient identification, anthropometric, clinical, sociodemographic characteristics, comorbidities, and lifestyle habits. Additionally, questions regarding headache characteristics such as intensity, frequency, medications, and treatments are also included in the questionnaire.

### Women's Questionnaire

Migraine is more prevalent in women, especially during reproductive age, and it exhibits different symptomatology and response to treatment compared to men (5,13). Sex hormones, menstrual cycle, and pregnancy play significant roles in the pathophysiology of the disease, contributing to the observed differences between genders. Despite being one of the most debilitating conditions globally, it remains an invisible illness, particularly for women who are disproportionately affected (14).

Due to this, REBRACEF has a specific questionnaire for individuals of the female gender, designed to comprehensively address the specificities and peculiarities of these patients. The questionnaire includes questions related to menstruation, contraceptive methods, pregnancies, and hormonal replacement therapy, seeking a better understanding of the patient with headaches as a whole.

### Migraine Disability Assessment (MIDAS)

The MIDAS scale is a sensitive questionnaire for screening disability due to headaches, consisting of 5 questions divided into 3 domains: work/school, household chores, and non-work-related events (family, social, and leisure). The scores range from 0 to 27 and are classified as Grade I (scores 0 to 5, representing no or minimal disability), Grade II (6 to 10, mild disability), Grade III (11 to 20, moderate disability), and Grade IV (21 or higher, severe disability) (10).

MIDAS is widely used for assessing patients with headache complaints and is capable of demonstrating various degrees of disability, allowing for disease tracking and monitoring. Moreover, it is an easily understandable and concise scale. Additionally, it has been translated and adapted for Brazilian patients (15).



### *Patient Health Questionnaire-9 (PHQ-9)*

Depressive symptoms are highly prevalent in the population with headaches, contributing to a lower response to treatment. To assess the presence of depressive symptoms, the PHQ-9 (Patient Health Questionnaire-9) was selected by the Registry team (16).

It is a self-administered questionnaire for screening patients with depressive symptoms and validated for individuals with migraine. Each item in the instrument is related to a symptom, with scores ranging from 0 (not at all) to 3 (nearly every day). The total score ranges from 0 to 27 points, with the following classifications: minimal depression (0 to 4), mild depression (5 to 9), moderate depression (10 to 14), moderately severe depression (15 to 19), and severe depression (20 to 27) (17).

The questionnaire is used to assess the presence and severity of depressive symptoms. It is easy and quick to administer, facilitating better communication between the doctor and patient. Moreover, it is validated for Brazilian patients in the context of primary health care showing good discriminative validity and recommended for migraine patients by the International Headache Society (18,19).

### *Generalized Anxiety Disorder-7 (GAD-7)*

Considering psychiatric comorbidities, anxiety is considered the most relevant comorbidity among patients with headaches, influencing clinical outcomes, treatment response, and symptomatology (20). Moreover, the presence of psychiatric comorbidities can contribute to an increase in the frequency and intensity of episodes (21).

The GAD-7 (Generalized Anxiety Disorder-7) is used in REBRACEF to assess anxiety and is validated for patients with headaches (22). It consists of seven items with scores ranging from 0 (not at all) to 3 (nearly every day), with a final score ranging from 0 to 21. The severity of the condition is classified based on the score: no anxiety symptoms (0 to 4), mild anxiety (5 to 9), moderate anxiety (10 to 14), and severe anxiety (15 to 21) (23).

Similar to the PHQ-9, the GAD-7 scale is also recommended by the International Headache Society. It is a quick and short scale that helps the medical team determine the presence and severity of anxiety symptoms, aiding in diagnosis and treatment monitoring. It has shown good evidence of reliability and validity for Brazilian samples (24).

### *Athens Insomnia Scale*

Patients with headaches often face greater difficulty in initiating and maintaining sleep, experience excessive fatigue, daytime sleepiness, and a reduced amount of

sleep, necessitating an evaluation of sleep quality (25). The physiological mechanisms of this association are not fully clear; however, studies have hypothesized that neurotransmitters such as serotonin and melatonin may be involved in the sleep-migraine relationship (26).

To assess aspects related to sleep, the Registry uses the Athens Insomnia Scale, a self-administered instrument consisting of eight items that allows the evaluation of the presence of insomnia, with questions related to sleep quality, such as duration and awakenings. Scores from 0 to 5 indicate the absence of insomnia; 6 to 9, mild insomnia; 10 to 15, moderate insomnia; and 16 to 24, severe insomnia (27).

### *The World Health Organization Quality of Life-8 (WHOqol-8)*

To assess the quality of life of the patients in the registry, the WHOqol-8 (The World Health Organization Quality of Life-8) scale was chosen. This scale, validated for the Brazilian population, consists of eight items that assess overall quality of life, ability to perform daily activities, satisfaction with health, personal relationships, self-esteem, energy, living conditions, and financial resources (28).

Using a Likert scale, each question is rated from 0 to 5, so the total score can range from 0 to 32, where a higher score corresponds to a perception of better quality of life. This evaluation tool was developed by the World Health Organization (WHO) and has been used in population studies on headaches (29,30).

### *Pain Catastrophizing Scale*

Pain catastrophizing is a cognitive response to pain evaluated from three dimensions: magnification, rumination and helplessness. Patients with migraine and pain catastrophizing tend to experience more frequent and prolonged pain attacks, heightened pain sensitivity, and a diminished response to treatment (31). Reduction of pain catastrophizing, particularly its helplessness dimension, has been pointed as a predictor factor both for headache frequency and medication intake (32).

Therefore, the Brazilian Headache Registry sought to assess the presence of pain catastrophizing in the study's patients. To achieve this, the Pain Catastrophizing Scale (PCS) is employed, consisting of 13 statements related to pain, where individuals evaluate the intensity degree of thoughts and feelings related to pain on a 5-point Likert scale ranging from 0 to 4. A higher score on the scale indicates a greater tendency to catastrophize pain. The scale shows a satisfactory level of internal consistency, with Cronbach's alphas varying from 0.86 to 0.93 among magnification, rumination and helplessness subscales (33).



### Allodynia Symptom Checklist (ASC-12)

For the same reason, the Registry team also chose to assess the presence of allodynia among patients with headaches. Allodynia is characterized by perceiving non-nociceptive stimuli as painful, which can influence the intensity and progression of headaches (34).

This instrument allows the evaluation of the presence and severity of allodynia, consisting of 12 questions about sensitivity to pain regarding non-painful stimuli. Each item is answered on a 5-point Likert scale (0 = never, 0 = rarely, 1 = less than half the time, 2 = half the time or more). Scores range from 0 to 24, and a score of  $\geq 3$  was used as the cutoff point for the presence of allodynia (35).

### Work Productivity and Activity Impairment Questionnaire (WPAI)

Migraine is more prevalent around the age of 40, an economically active age and a peak period of productivity, often accompanied by higher stress levels (36). The presence of headache leads to higher levels of absenteeism and presenteeism, significantly impacting the professional and economic lives of patients (37).

Considering this, REBRACEF has added to its assessment instruments a questionnaire regarding productivity at work. The Work Productivity and Activity Impairment Questionnaire (WPAI) consists of 6 questions related to absenteeism, presenteeism, productivity loss, and activity impairment (38). This questionnaire is validated for the Brazilian population and has been used in other studies involving migraine patients (39).

### Headache Diary

The headache diary of REBRACEF was developed to analyze the frequency and intensity of headache attacks in participating patients. The diary includes a legend: "C" - medical appointment, "X" - mild attack (does not interfere with work or other activities), "XX" - moderate attack (interferes but does not prevent work or other activities), "XXX" - severe attack (prevents work or other activities), and "O" - analgesic use. Other global registry studies also use the headache diary. In REBRACEF, patients receive the diary in printed form instead of online, aiming to ensure that patients without daily internet access can still fill it out (40).

## Infrastructure

### Data Collection

The Research Electronic Data Capture (REDCap) electronic system is the method used to collect and store clinical and demographic data, as well as the clinical trajectory of research participants during the follow-up period. The

REDCap platform was chosen because it is a web-based database that provides tools for identifying sensitive data and limiting access levels, in compliance with the Brazilian General Data Protection Law (LGPD). Additionally, it offers various features to ensure the security and privacy of collected data, such as data encryption, user authentication, access control, data auditing, automated daily backups, and anonymization and pseudonymization of data (41).

Furthermore, the platform provides an alert and messaging system that allows researchers to configure automatic notifications and communications with other researchers. For instance, if a patient scores above the threshold on a risk scale, such as the PHQ-9, REDCap sends an alert message or email to the pre-selected researchers, optimizing the attention of the medical and research team towards the patient. This was introduced in REBRACEF, as well as an alert in case of adverse events.

To integrate data into the REDCap platform, a license was obtained, and user accounts were created. With this step completed, researchers structured the questionnaires, building the Case Report Form (CRF) based on previously selected and validated scales. In this process, the research team implemented mechanisms on the platform to predefine types and formats of data, mitigating potential errors in data entry. With the data collection instruments in place, a testing phase was conducted to assess the effectiveness of the data collection process. Subsequently, the project transitioned from the development phase to production, ensuring the quality of the obtained data.

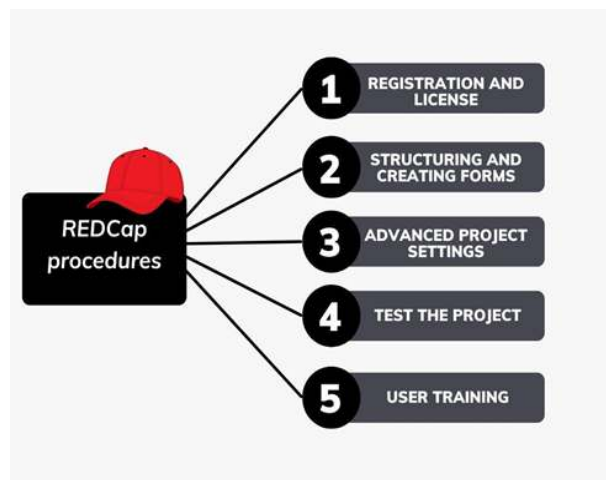


Figura 3. REDCap procedures

## Research Group

### Scientific Committee

The scientific committee of REBRACEF consists of neurologists, headache specialists, physiotherapists, and



researchers with extensive experience in epidemiology and statistics. The scientific committee plays a key role in training various participating centers, instructing them on data collection procedures using the REDCap platform, and conducting training sessions aimed at expanding understanding and competence in using this tool. Additionally, the committee is responsible for ethical and regulatory aspects related to the research, overseeing the release and access to data, as well as the submission of research projects. The scientific committee regulates and evaluates the use of Registry data, authorizing its use in scientific publications. Furthermore, in order to maintain a quality standard in data collection using REDCap, the scientific committee has developed a Standard Operating Protocol to assist researchers in understanding and automating data collection processes.

#### *Research line*

In this context, a research line in epidemiology and data science in headaches was developed at the Pontifical Catholic University of Rio Grande do Sul, standing out as pioneering in Brazil. This line is composed of researchers with experience in various fields, including neurologists, headache specialists, physiotherapists, as well as experts in statistics and data science. Developed in conjunction with the Brazilian Registry, this research line aims to equip researchers in epidemiology and headache data science, contributing to a deeper and broader understanding of this health condition based on real data collected from specialized centers across the country.

#### *Funding for the registry*

The Brazilian Headache Society plays a fundamental role as a supporter and sponsor of REBRACEF, dedicating itself to the dissemination of scientific knowledge and specialized clinical practice in the diagnosis and treatment of headaches in Brazilian patients. Made up of neurologists and headache specialists, the society adopts a multi-professional vision and makes solid commitments to social and intellectual responsibility in relation to headache studies in Brazil.

#### *Ethical Aspects*

To protect the rights and autonomy of the participants and patients involved in the study, the ethical and legal commitment is formalized through an Informed Consent Form (42). This document presents to the patient all the possible risks and benefits of their participation in the Registry, demonstrating that the medical and research team provides all necessary support to the patient. Similarly, Registry researchers sign a data usage commitment form, attesting to the team's responsibility for the anonymity and security of all collected data. Additionally, a Good Clinical Practice course is undertaken by the entire research team at the specialized centers, aiming to improve attention and

care in the evaluation. The study received ethical approval from the Research Ethics Committee of the coordinating center (CAEE: 76369523.3.1001.5336, Opinion Number: 6.769.169) in accordance with Resolution No. 466/2012 of the National Health Council, which regulates research involving human subjects in Brazil. The centers included in the registry must obtain ethical approval from their respective Research Ethics Committees before start the data collection.

## Discussion

Longitudinal and real-world data studies are of great importance for medical research, as they allow for a more comprehensive patient monitoring and access to variables outside of a controlled environment (43). This type of approach is crucial for better understanding the progression of chronic diseases, such as migraine, in settings that are more representative of clinical practice, which in turn significantly contributes to the formulation of more effective therapeutic strategies and the improvement of healthcare (44).

This type of study has been widely used in patients with headaches. It highlights gaps in healthcare services and provides a greater diversity of patients due to less stringent exclusion criteria, including patients with comorbidities and medication use, which are common among headache patients (45).

In Europe and North America, registry studies involving patients with headaches are responsible for generating valuable data and information regarding various clinical and social characteristics of these patients. For example, the study "The headache registry of the German Migraine and Headache Society (DMKG)" (46) included 1351 German patients, where a large portion of the patients had a diagnosis of episodic migraine, with up to 7 days of medication per month. Researchers collected data related to the disease using the MIDAS scale (Migraine Disability Assessment), and 64% of the sample scored with severe dysfunction due to migraine. The same scale is also used in REBRACEF as it is validated for Brazilian patients (15).

The MIDAS scale was also used in the Italian registry. The Italian Migraine Registry (I-GRAINE) is a longitudinal, prospective, and multicenter study that included 231 patients with migraine in Italy. In the 12 centers analyzed in the first report, it was noted that patients in specialized centers are predominantly women, making up more than 80% of the sample, affected by episodic and chronic migraine, with comorbid conditions and severe migraine-related disability. Additionally, it was shown that patients rarely consult headache specialists, instead seeking multiple consultations with other specialties and undergoing unnecessary tests within the Italian healthcare system (47).



The study My Migraine Voice (48), which evaluated over 11,000 patients, as well as REBRACEF, also used the Work Productivity and Activity Impairment - General Health Questionnaire (WPAI-GH) (38) to assess the burden of headache on patients' professional and productive lives, with results showing approximately 48% of patients experiencing "presenteeism".

Population-based longitudinal studies such as the American Migraine Prevalence and Prevention (AMPP) (49) and the Chronic Migraine Epidemiology and Outcomes Study (CaMEO) (50) have provided important information on prevalence data and disability associated with episodic and chronic migraine. The American Migraine Prevalence and Prevention (AMPP) was a longitudinal study conducted between 2004 and 2009 that provided data on sociodemographic profile, economic impact, disability, comorbidities, and prognostic factors. Conducted between 2012 and 2013, the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study expanded on the findings of the AMPP by enlarging the sample of patients with chronic migraine and assessing the impact of the condition on quarterly periods rather than annually. The study was innovative in including the evaluation of impact from the perspective of family members, and it also identified the obstacles faced by migraine patients in accessing healthcare (50).

## Conclusion

In line with this, the Brazilian Headache Registry was designed as a longitudinal, multicenter study aimed at being present in four regions of the country, seeking to understand how sociocultural, economic, and clinical differences can impact the frequency and intensity of headaches, as well as treatment response.

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