Shaukat Khanum Memorial Cancer Hospital and Research Centre

Research Synopsis

R/CEN/CRO-024/v.1

Phenotype-based Model for Managing Chronic Post-treatment Pain Among Head and Neck Cancer Survivors: a Pilot Study

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I. Introduction and objectives

Chronic post-treatment pain (CPTP) represents a significant long-term complication among survivors of head and neck cancers (HNCs), with prevalence estimates of around 40 percent [1, 2]. It has a negative impact on quality of life and is closely associated with psychological morbidity, including depression and anxiety [3–5]. However, effective management of CPTP remains challenging [4, 5].

The efficacy of conventional analgesic approaches, including the World Health Organization (WHO) analgesic step-ladder, in this population remains limited [6, 7]. Prolonged opioid therapy is frequently required, yet pain relief remains suboptimal, and dependency is common [7]. This therapeutic gap indicates that current management strategies fail to address the underlying complexity of CPTP.

Recent studies suggest that CPTP among HNC survivors comprises a spectrum of distinct clinical phenotypes rather than a single homogeneous condition [8]. These phenotypes frequently parallel recognized primary pain

disorders, such as masticatory myofascial pain, cervical myofascial pain, and burning mouth syndrome, suggesting shared neurophysiological mechanisms.

Given this rationale, phenotype-guided pharmacological strategies derived from treatments for primary pain disorders may provide more effective control for HNC survivors with CPTP. The present study aims to evaluate the effectiveness and safety of a phenotype-based management plan for chronic post-treatment pain in head and neck cancer survivors.

II. Hypotheses

Primary hypothesis

H1: A phenotype-based pain management model will provide significant pain relief to participants at one month, defined as at least a 75 percent decrease from average baseline pain.

H0: A phenotype-based pain management model will provide limited pain relief to participants at one month, defined as less than a 75 percent decrease or worsening from average baseline pain.

Secondary hypothesis

H1: Discontinuation of assigned phenotype-based therapy due to adverse events by one month is 10 percent or less.

H0: Discontinuation due to adverse events is greater than 10 percent.

III. Materials and Methods

Overview

This will be an open labelled, quasi experimental trial conducted at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Pakistan. This study will recruit adult participants with CPTP following curative treatment for head and neck cancers.

Approval from the local Institutional Review Board will be obtained. All participants will have to provide a written consent for study inclusion. The study will be conducted in accordance with the Declaration of Helsinki.

Study Population and Eligibility Criteria

Following inclusion and exclusion criteria will be followed:

Inclusion criteria:

- Adults (≥18 years) with history of curative treatment for head and neck cancer
- Chronic post-treatment pain disorder, as per the criteria given in **Table 1**
- Absence of clinical and radiological evidence of recurrent disease
- Ability to provide informed consent

Exclusion criteria:

- Active disease recurrence or metastasis
- Persistent mucositis, oral infection, or hardware failure at the treatment site
- Surgical wound dehiscence
- Cognitive impairment that limits the ability to complete study questionnaires

Patient recruitment

The recruitment will start once the necessary approvals are obtained. The intention is to enroll 40 participants using a non-probability consecutive sampling technique for this pilot project. This is based on the assumption that the reduction in average pain scores following phenotype-based intervention will have a large effect size (*Cohen's d = 0.8*). Similarly, a priori sample estimation was performed using a two-tailed test with a significance level (α) of 0.05 and a statistical power (1- β) of 0.90. Furthermore, the calculation takes a 20% attrition rate into account.

Examination protocol

Participants will undergo a structured assessment process comprising three visits over a one-month period.

Visit 1: Baseline assessment (Day 0)

The first assessment will be face-to-face. During the first visit, participants will be asked about the current, worst, and least pain intensity in the last week on an 11-point numeric verbal pain rating scale, (NVPS) where 0 is indicative of "no pain" and 10 is suggestive of "worst pain imaginable." The participants will undergo a detailed history review using the *Short-version McGill pain questionnaire* and narrative interview to collect details

regarding pain site(s), laterality, chronicity, frequency, quality, and duration of pain [9]. Similarly, information on psychological symptoms will be collected using Generalized Anxiety Disorder-7 (GAD-7) and Patient Health Questionnaire-9 (PHQ-9) [10, 11]. A clinical examination will be performed by an Orofacial Pain Specialist. The musculoskeletal assessment will be performed using the examination principles defined in the Diagnostic Criteria for Temporomandibular Disorders (DC-TMD). For the neurological and cervicogenic examination, other guidelines will be followed. The site of pain will be assessed across different locations in the head and neck. These included intraoral sites (tongue, buccal mucosa, alveolar process of the maxilla and mandible, and teeth), extraoral orofacial sites (temporal, masseteric, buccofacial, auricular, mandibular body, posterior auricular, submandibular, zygomatic, and infraorbital regions), cervical region (suprahyoid, infrahyoid, lateral cervical, and posterior cervical regions), and cranium (supraorbital, orbital, parietal, vertex, and occipital regions). In addition, data on the subjective presence of dry mouth (xerostomia), taste alteration (dysgeusia), and swallowing difficulties (dysphagia) will be recorded. Similarly, if the interincisal distance on maximum mouth opening is less than 20 millimetres, it will be noted as trismus (annexure A). Based on the history and clinical examination, participants will be assigned clinical phenotypes of HNC-related pain (Myofascial pain disorder, Orofacial bone pain disorder, Burning pain disorder, Neuralgia, Persistent pain disorder).

Visit 2: Interim Assessment (Week 2)

The second review will take place 2 weeks after the first visit. The subjects will be asked about the pain (intensity, location, duration, quality, and frequency), medication-related side effects, episodes of breakthrough pain and use of abortive analgesics. For medication-related side effects, a questionnaire

(**adverse events form**) will be used.

Visit 3: Final Assessment (Week 4)

The third assessment will occur after 1 month (4 weeks) of the first visit. Data collected will mirror that of the second visit, including detailed pain assessment, medication side effects, breakthrough pain frequency, and analgesic use.

Phenotype-based Pain Management Guidelines

Participants will be assigned to one or more pain phenotypes according to their clinical characteristics (**Table 2**). The phenotypes recognized in this study include myofascial pain disorder (orofacial or cervical), orofacial bone pain disorder, burning disorder (oropharyngeal or cervicofacial), neuralgia, and persistent pain disorder (cervicofacial or oropharyngeal). The complete management plan for each phenotype is outlined in **Table 3**. This is based on international guidelines and recommendations for management of primary pain disorders [12–14].

Participants identified with orofacial bone pain disorder who report a pain intensity of less than 7 out of a possible 10 on the Numeric Verbal Rating Scale (NVRS) will receive non-opioid analgesics, including acetaminophen and non-steroidal anti-inflammatory medications. In cases where the pain intensity is 7 or more, participants will be offered targeted nerve blocks. These blocks will be performed along the sensory nerves supplying the affected region to provide localized pain relief.

Participants with myofascial pain disorder will initially receive muscle relaxants, such as tizanidine (up to 8 mg per day), cyclobenzaprine (up to 30 mg per day), or amitriptyline (up to 25 mg per day). When the reported pain intensity is 7 or more out of 10, these participants will additionally undergo masticatory or cervical trigger point injections.

Those diagnosed with persistent pain disorder will be treated with either amitriptyline (up to 25 mg per day) or pregabalin (up to 600 mg per day). Participants in this group who report pain intensity of 7 or more will also be offered nerve blocks administered at sites corresponding to the involved sensory distribution. Participants with burning disorder will receive pregabalin (up to 600 mg per day), carbamazepine (up to 1200 mg per day), or clonazepam (up to 2 mg per day), and if their pain intensity meets or exceeds 7 out of 10, nerve blocks will similarly be provided to target the sensory pathways involved.

Participants classified with neuralgia will be treated with pregabalin (up to 600 mg per day) or carbamazepine (up to 1200 mg per day). Nerve blocks will be considered for those experiencing pain of 7 or more out of 10. In summary, participants with persistent pain disorder, burning disorder, or neuralgia phenotypes who present with pain intensity scores of 7 or higher will be given nerve blocks around the sensory nerves corresponding to the region of pain.

For breakthrough pain, all participants will be advised to take tramadol 50 mg capsules, with a maximum daily dose of 300 mg. To minimize adverse effects, participants receiving non-steroidal anti-inflammatory drugs will be prescribed a proton pump inhibitor, such as omeprazole (20–40 mg per day), for gastric protection. Those using tramadol will be advised to take a laxative, either lactulose (15–45 ml per day) or senna glycoside (27 mg per day), to prevent opioid-induced constipation.

Study protocol has been summarized in **Figure 1**.

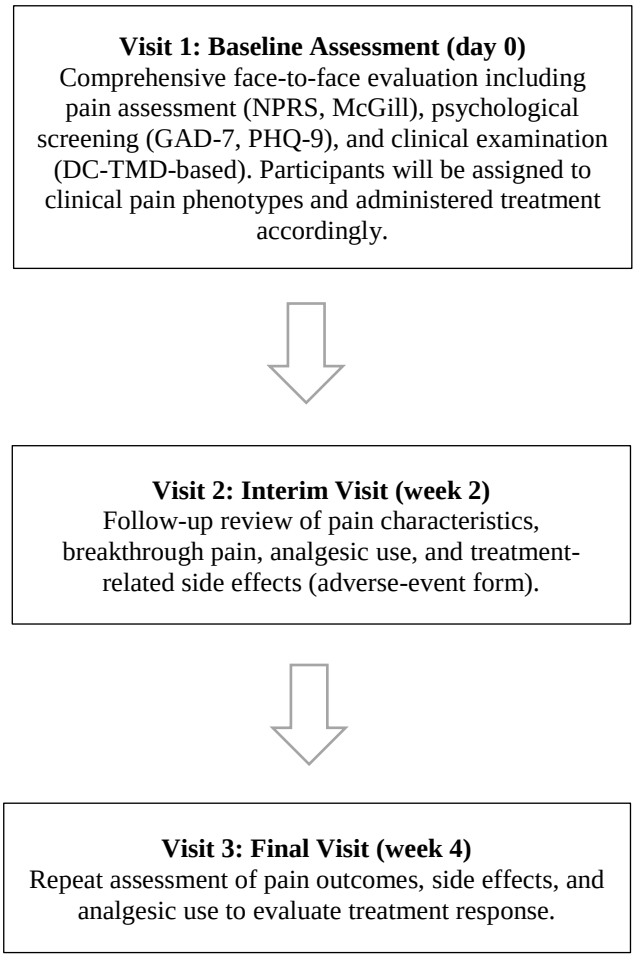


Figure 1: Overview of study visits and assessments conducted at baseline, week 2, and week 4.

Data collection and analysis

Medical charts will be reviewed to extract data regarding participant demographics, medical history, cancer characteristics, prior anti-cancer therapies, and information about the recurrence or metastasis of the

disease. Data analysis will be performed using SPSS version 29.0 or the latest software (SPSS Inc., Chicago, IL, USA). Descriptive statistics will be computed for each variable. A paired t-test will be used for the analysis between independent and dependent variables. A p-value of < 0.05 will be considered statistically significant. Paired Cohen's d will be calculated using the mean and standard deviation to determine the effect size.

Resource requirement

It will be the responsibility of the investigator or their designee to obtain informed consent from each individual participating in this study. Participants will be approached in the waiting area or the clinic rooms. Data will be recorded using the study questionnaire (Appendix A and B). All of the recorded data will be transformed into SPSS software and analysed, as explained previously.

Data Privacy and Confidentiality

To ensure the confidentiality of subject information, each subject enrolled will be assigned a unique serial number. Likewise, all of the questionnaires will be kept in a secure and locked cabinet. The electronic files will be kept on a password-protected computer in a secure, locked office. Only the study personal will have access to data. The information will only be shared between the researchers. The investigator will maintain all study records following completion or termination of this study in accordance with institutional policy.

Risks and Compensation

The participants will receive medications based on the clinical presentation of their symptoms. These pharmacological interventions will be based on international guidelines and standards. These medications are routinely used (and approved by relevant authorities) for the management of primary and secondary pain disorders. The risks associated with the use of various medications, along with their corresponding incidence rates, are presented in Table **4**. If a participant experiences any adverse drug reaction, it will be managed at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, in accordance with policy or predefined mechanisms. If any participant decides to withdraw from the study at any point, he or she will be allowed to do so, and it will not interfere with their management and care. Similarly, participants will not receive any special favors or compensation for participating in this investigation.

Table 1: Diagnostic criteria for chronic post-treatment pain associated with head and neck cancer (HNC).

A. Any pain limited to the head, face, and neck region persisting or recurring for >3 months and fulfilling criteria B-D.

B. All the following:

    a. History of radical treatment (chemotherapy, surgery, or radiotherapy) for HNC;

    b. Imaging or pathological evidence of complete disease remission; and

    c. Clinical or imaging evidence of post-treatment changes in the underlying tissue[1]

C. Onset of pain[2] within 6 months of completion of the treatment

D. Pain may be associated with somatosensory signs and symptoms

E. Not better accounted for another ICOP or ICHD-3 diagnosis

[1] No signs of hardware failure, regional necrosis, or infection.

[2] Localized to the area of treatment or region directly related to the procedure (for example, at the site of the graft harvesting or the site of biopsy or line insertion).

Table 2: Phenotypes of chronic post-treatment pain (CPTP) associated with head and neck cancers (HNC), adapted from the International Classification of Orofacial Pain, first edition (ICOP), and the International Classification of Headache Disorders, third edition (ICHD-3). Cases are assumed to fulfil the general diagnostic criteria for CPTP associated with HNC, as outlined in **Table 1**.

Phenotype‡	Location	Pain characteristics	Temporal pattern or duration	Modifying factors	Associated sensory signs or symptoms
Orofacial Bone Pain	Orofacial bones (mandible, maxilla, nasal, or zygoma) or temporomandibular joint (TMJ)	Dull, aching, nagging, or sharp	Intermittent or constant; episodes ≥30 minutes, once or more/day	Exacerbated by jaw opening (assisted/unassisted), lateral or protrusive movements, or pressure on TMJ or bone(s)	Paresthesia, dysesthesia, allodynia, hyperesthesia, numbness, hypoalgesia, or hypoesthesia may be present
Myofascial Pain Disorder (orofacial or cervical)	Masticatory or cervical muscles	Dull, aching, nagging, or sharp	Intermittent or constant; episodes ≥30 minutes, once or more/day	Exacerbated by functional or parafunctional jaw or cervical movements, or muscle palpation	
Neuralgia	Distribution of trigeminal, glossopharyngeal, vagus or cervical nerves (no radiation beyond nerve distribution)	Severe, electric shock-like, shooting, stabbing, or sharp; may include continuous dull ache, soreness, nagging, throbbing or sharp pain between episodes	Paroxysms lasting seconds to 2 minutes, occurring once or multiple times per day	May be precipitated by innocuous stimuli within affected nerve distribution	
Persistent Pain Disorder (oral or cervicofacial)	Oral cavity, face or neck; poorly localized, deep or superficial; not confined to nerve or muscle distributions	Dull, aching, throbbing or nagging	Typically constant with variable intensity; daily ≥2 hours	Not specified	
Burning Disorder (oral or cervicofacial)	Intraoral, facial, or cervical regions along trigeminal, glossopharyngeal or cervical nerve distributions	Burning, usually superficial in oral mucosa or skin; no paroxysms	Typically constant; may be intermittent >2 hours/day with variable intensity	May be spontaneous or precipitated by innocuous stimuli	

‡Some phenotypes may overlap, and multiple phenotypes may exist concurrently.

Table 3: Summary of guidelines for Phenotype-based Management Plan.

Medications / Phenotypes	Myofascial Pain Phenotype	Orofacial Bone Pain Phenotype	Neuralgia Pain Phenotype	Burning Pain Phenotype	Persistent Pain Phenotype
Acetaminophen	X	X			
Non-steroidal anti-inflammatory drugs	X	X			X
Amitriptyline	X				X
Pregabalin			X	X	X
Carbamazepine			X	X	
Muscle relaxants (Tizanidine or cyclobenzaprine)	X				
Clonazepam				X	
Trigger point injections (NVPS: ≥7 out of 10)	X				
Nerve blocks (NVPS: ≥7 out of 10)		X	X	X	X

Table 4: Common side effects associated with pharmacological interventions

Medications	Side effects
Acetaminophen	Erythema of skin, skin blister, skin rash, hearing loss
Non-steroidal anti-inflammatory drugs	Upset stomach or stomach pain, Constipation or diarrhoea, gas or heartburn, nausea and vomiting, dizziness, stuffy or runny nose, sore throat, change in taste, rash
Codeine	Nausea, vomiting, constipation, lightheadedness, dizziness, drowsiness, or sweating
Tramadol	Nausea, vomiting, constipation, lightheadedness, dizziness, drowsiness, or headache
Morphine	Nausea, vomiting, constipation, lightheadedness, dizziness, drowsiness, or sweating
Amitriptyline	Drowsiness, dizziness, dry mouth, blurred vision, constipation, weight gain, or urinary hesitancy
Pregabalin	Dizziness, sleepiness, fluid retention, blurred vision, dry mouth, weight gain, difficulty concentrating
Carbamazepine	Nausea, vomiting, dizziness, drowsiness, constipation, dry mouth, or unsteadiness
Tizanidine	Dry mouth, drowsiness, dizziness, lightheadedness, constipation, weakness, and tiredness
Cyclobenzaprine	Drowsiness, dizziness, dry mouth, constipation, or tiredness
Clonazepam	Drowsiness, gait disturbance, dizziness, depression, fatigue, problems with memory
Trigger point injections (lignocaine 2%)	Local pain, bruising or swelling; lightheadedness, dizziness, vasovagal reaction, temporary local numbness or weakness, local infection
Nerve blocks (lignocaine 2% and/or bupivacaine 0.5%)	Local pain, bruising or swelling; lightheadedness, dizziness, vasovagal reaction, temporary numbness, weakness or paresthesia in distribution of blocked nerve; local infection

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ANNEXURE A: Phenotype-based Model for Managing Chronic Post-treatment Pain Among Head and Neck Cancer Survivors

Gender: Male | Female **Age:** **Cancer type:** **Cancer stage:** I | II | III | IV

Primary cancer site: **Medical history:** **Allergies:**

First visit (Day 1):

Current pain intensity: **Worst pain intensity:** **Least pain intensity:**

Pain locations:
Tongue | Buccal mucosa | Alveolar (maxilla) | Alveolar (mandible) | Dental (upper) | Dental (lower) | Temporal | Masseter | Infrahyoid Suprahyoid | Buccofacial | Mandible | Posterior mandibular | Auricular | Posterior auricular | Submandibular | Zygomatic | Infraorbital Supraorbital | Orbital | Lateral cervical | Posterior cervical | Parietal | Vertex | Occipital | Other _____ **No. of pain sites:**

Laterality: Unilateral | Bilateral **Frequency:** Intermittent | Constant **Tightness**: Yes | No

Pain quality: Sharp | Pressing | Electric | Burning | Throbbing | Stinging | Dull ache | Other _____

Pain aggravating factors: **Pain alleviating factors:** **Xerostomia:** Yes | No

Dysphagia: Yes | No **Dysgeusia:** Yes | No **Trismus (<20 mm):** Yes | No

Pain phenotype: Myofascial (orofacial) | Myofascial (cervical) | Orofacial bone pain | Persistent pain (cervicofacial) | Neuralgia Persistent pain (oropharyngeal) | Burning disorder (cervicofacial) | Burning disorder (oropharyngeal) | Unknown

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Medications prescribed:

Name	Dose	Frequency

Trigger point injections: Yes | No

Medication	Site	Laterality	Volume (ml)

Nerve blocks: Yes | No

Medication	Nerve	Laterality	Volume (ml)

Second visit (Day ___):

Current pain intensity: **Worst pain intensity:** **Least pain intensity:**

Pain locations:

Tongue | Buccal mucosa | Alveolar (maxilla) | Alveolar (mandible) | Dental (upper) | Dental (lower) | Temporal | Masseter | Infrahyoid

Suprahyoid | Buccofacial | Mandible | Posterior mandibular | Auricular | Posterior auricular | Submandibular | Zygomatic | Infraorbital

Supraorbital | Orbital | Lateral cervical | Posterior cervical | Parietal | Vertex | Occipital | Other _____ **No. of pain sites:**

Laterality: Unilateral | Bilateral **Frequency:** Intermittent | Constant **Tightness**: Yes | No

Pain quality: Sharp | Pressing | Electric | Burning | Throbbing | Stinging | Dull ache | Other _____

Use of break through drugs: Yes | No **If yes, number used:** _____

Current medications:

Name	Dose	Frequency

- **Third visit (Day ___)**

Current pain intensity: **Worst pain intensity:** **Least pain intensity:**

Pain locations:

Tongue | Buccal mucosa | Alveolar (maxilla) | Alveolar (mandible) | Dental (upper) | Dental (lower) | Temporal | Masseter | Infrahyoid

Suprahyoid | Buccofacial | Mandible | Posterior mandibular | Auricular | Posterior auricular | Submandibular | Zygomatic | Infraorbital

Supraorbital | Orbital | Lateral cervical | Posterior cervical | Parietal | Vertex | Occipital | Other _____ **No. of pain sites:**

Laterality: Unilateral | Bilateral **Frequency:** Intermittent | Constant **Tightness**: Yes | No

Pain quality: Sharp | Pressing | Electric | Burning | Throbbing | Stinging | Dull ache | Other _____

Use of break through drugs: Yes | No **If yes, number used:** _____

Current analgesics:

Name	Dose	Frequency