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# Psychological barriers to the use of opioid analgesics for treating pain in patients with advanced recurrent cancer (BAROC): protocol for a multicentre cohort study

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**Key Words:** adverse events; cancer pain; strong opioids; psychological barriers

## ABSTRACT

### Introduction

Opioid analgesics are essential for the treatment of cancer pain. However, patients are sometimes reluctant to use them because of concerns about addiction and dependence. Rapid pain relief following administration of these drugs may help to overcome the psychological barriers to opioid analgesic use. The primary objective of this study is to determine the relationship between psychological resistance to strong opioid analgesic use and speed of pain improvement in patients with advanced recurrent cancer.

### Methods and analysis

This is an ongoing, multicentre, observational study. Patients aged 20 years or older with distant metastasis or advanced recurrent cancer who are receiving strong opioid analgesics for cancer pain for the first time are eligible for participation in this study. We are investigating the relationship between psychological barriers at the start of treatment and pain relief during the first week of treatment in patients receiving strong opioids. The participants are being asked to fill out an electronic patient-reported outcome daily during the first week of treatment. The main purpose of this study is to estimate the psychological barriers to opioid use, as assessed using the Japanese version of the Barrier Questionnaire II. The sample size was determined using one-year prediction rather than using statistical methods based on the study design.

### Ethics and dissemination

The study protocol was approved by the ethics committee (approval ID B200600091) of Yokohama City University on 24 August 2020. The protocol has been reviewed by the institutional review board at the following study 3 sites. The protocol will also be reviewed at 1 sites. The results will be published in a peer-reviewed journal and will be presented at a relevant meeting.

### Trial registration number

UMIN000042443


### Strengths and limitations of the study

- This is the first multicentre observational study to evaluate psychological barriers to the use of strong opioids in Japan.
- We are studying the relationship between improvement in pain intensity and changes in psychological barriers over time.
- Adverse events related to opioid analgesic use are being assessed using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) and CTCAE v5.0-Japan Clinical Oncology Group.

- A limitation of this study is its short observation period, which leads to inability to confirm long-term variations in psychological barriers.

## INTRODUCTION

In 2017, there were 24.5 million patients with cancer worldwide, 9.6 million of whom died of cancer.[1] The number of patients with cancer increased by 33% from 2007 to 2017. In 2009, there were 775,601 patients with cancer in Japan.[2] Cancer pain is the most concerning symptom of patients with cancer, with approximately 80% of patients with advanced cancer experiencing moderate to severe pain.[3] Japanese studies have examined the number of patients with cancer requiring treatment for pain relief and the percentage of patients with cancer undergoing treatment for pain relief. When patients experiencing pain were surveyed, 32.2% described themselves as 'experiencing pain' and 'taking analgesics'. It was estimated that approximately 250,000 Japanese patients with cancer require opioid analgesic administration for pain management.

Patients with cancer often hesitate to manage their cancer pain using opioid analgesics. Their hesitation-related perceptions include concerns about addiction, gradual loss of effectiveness, and severe side effects; anxiety due to pain predicting disease progression; and the idea that physicians do not like to talk about pain.[4] The Barriers Questionnaire (BQ) quantitatively measures factors related to patients' hesitation regarding opioid use. This scale was used to evaluate 270 patients with cancer, and it was found that 37%–85% of them were concerned about addiction and believed that good patients do not complain about pain and side effects. It was also found that older individuals, those from low-income households, and those with low levels of education had higher concerns related to medical narcotics.[5] Furthermore, a relationship between the presence of barriers and pain intensity has also been reported.[6] Moreover, patients' mental anguish is positively correlated with pain, [7] and opioid analgesics may be insufficient for pain management depending on the patients' mental state.

A review investigating the barriers to cancer pain management related to healthcare professionals, patients, and systems[8] revealed that patient-related barriers included cognitive and emotional barriers and adherence to treatment. Cognitive barriers included underreporting of symptoms to doctors and misunderstandings related to painkillers. Larger barriers were associated with race, sex, and poor adherence to medication.[9] In particular, a meta-analysis showed that Asians have greater barriers to cancer pain progression, tolerance, and lethality than Westerners.[10] A survey conducted across 214 countries by the International Narcotics Control Board revealed that Japanese individuals consumed fewer medical narcotics per million people per day than those from other countries (1,192 vs. 3,027, respectively). Barriers to narcotic use included lack of training and awareness among healthcare professionals, concern regarding dependency, limited financial resources, procurement issues, cultural behaviour, fear of diversion, and international trade control and regulation. A questionnaire survey carried out by the regulatory authorities of various

countries revealed a high percentage of patients (56%) with concerns about dependency in East Asia, which includes Japan. This suggests that the higher the number of reported barriers, the lower the opioid analgesic use.[11]

A questionnaire study conducted in Japan found that 28% of patients with advanced and recurrent cancer believe that opioid analgesic use shortens their lifespan and causes addiction.[12] In a national survey of 5,000 people by Morita et al., 27%–38% participants reported that opioids shorten lifespan, while 24%–33% reported that opioids cause addiction.[13] This emphasises the need to sufficiently consider barriers when initiating treatment with opioids in Japanese patients. Despite the presence of barriers, acceptance of opioid use for pain relief is expected to improve through the practice of high-quality palliative care, pain relief following administration of narcotic medication, and improved confidence in drug safety. Consequently, we believe that pain relief immediately after drug administration is an important factor for breaking these barriers. Furthermore, we believe that patients who can confidently use opioid analgesics will take a shorter time to achieve the optimal dose and will achieve immediate pain relief. Patients' pain and mental state fluctuate daily and diurnally, and comparing findings before and after an intervention may lead to inaccurate results. A detailed assessment of the speed of pain relief requires repeated evaluation over time. To date, few reports have investigated the relationship between the presence of psychological resistance to the use of strong opioid analgesics and the speed of pain relief in patients with advanced recurrent cancer. Therefore, we designed this study to address the need for sufficient verification of the relationship between psychological barriers and the speed of pain relief.

The purpose of this study is to elucidate the relationship between psychological barriers to the use of strong opioid analgesics and the speed of pain relief in patients with advanced recurrent cancer. If it is found that cancer pain relief is difficult to achieve in patients who are hesitant to use strong opioid analgesics, this study may provide important information on how to assuage their reluctance and bring about rapid pain improvement.

## METHODS AND ANALYSIS

### Study design

This is an ongoing, multicentre, longitudinal, observational study. We are investigating the relationship between psychological barriers at the start of treatment and pain relief during the first week of treatment in patients receiving strong opioids for cancer pain. We are also evaluating the relationship between psychological barriers and adverse events associated with the use of strong opioids. Patients were not invited to collaborate during the study design; therefore, this study protocol was developed without patient and public involvement.

**Study setting, participants, and recruitment**

Recruiting is being performed at seven sites in Japan. The inclusion and exclusion criteria are shown in Box 1. The main inclusion criterion is patients aged 20 years or older with distant metastasis or advanced recurrent cancer who receive first treatment with strong opioid analgesics for cancer pain. The main exclusion criteria are patients with difficulties in providing electronic patient-reported outcome (ePRO) data and patients with neuropathic pain. Eligible patients are being invited to participate in the study by investigators at each study site. These patients are being asked to complete an ePRO daily during the first week of treatment. Observation is being discontinued if any of the following occurs: (1) death during observation, (2) the patient's condition deteriorates and the healthcare professional determines that the intervention cannot be continued; (3) the patient withdraws consent; and (4) the investigators judge that observation cannot be continued for any other reason. As a rule, standard pain relief treatments are being provided at each facility. We are neither restricting the provision of combination or supportive treatment nor specifying the post-treatment.

**Outcome measures**

Table 1 shows the timeline of enrolment and assessment. We are using the Japanese version of the Barrier Questionnaire-II (JBQ-II) [13, 14] to assess psychological barriers to opioid analgesic use and the Decision Regret Scale (DRS) [15, 16] to evaluate regret related to decision making. We are using the Patient-Reported Outcomes (PRO-) version of the Common Terminology Criteria for Adverse Events (CTCAE) [19, 20] and the CTCAE v5.0 to assess adverse events. We are evaluating pain severity using the Brief Pain Inventory (BPI)-Short Form (SF) [21-23] and Personalised Pain Goal (PPG) [25].

**Japanese version of the Barrier Questionnaire II**

To reflect practical changes in pain management, the BQ, which is a measure of psychological barriers, was revised to create the Barrier Questionnaire II (BQ-II).[14] The JBQ-II is the Japanese version of the BQ-II. It has been validated (Cronbach's $\alpha = 0.92$). [15] The JBQ-II comprises of the following five subscales: barriers related to psychological effects (distrust of symptomatic treatment), barriers related to fatalism (fateful resignation), barriers related to communication (loss of intention), barriers related to adverse effects (fear of side effects), and barriers related to disease progression (escape/defence from illness). Each item is graded on a six-point Likert scale (0–5). The subscale and total scores (overall barrier) are calculated as the mean of the scores (0–5) for the relevant items, with higher numbers indicating higher barriers.

**Patient Global Impression of Severity**

Currently, the cut-off values for classifying the presence and magnitude of psychological

barriers are unknown. In this study, we are using the Patient Global Impression of Severity (PGIS) to classify the participants' JBQ-II scores. The PGIS has not been validated to classify psychological barriers. We are grading responses to the item 'At present, how reluctant are you to use opioids for pain relief?' using following seven-point scale: 0, not at all; 1, not reluctant; 2, almost not reluctant; 3, neither; 4, slightly reluctant; 5, reluctant; and 6, extremely reluctant.

**Decision Regret Scale**

Regret is a negative emotion felt when one realises or imagines that one has made the wrong choice. It is a retrospective, unpleasant feeling, and people tend to focus on 'what is good' rather than 'what is bad'. It has been reported to be associated with negative emotions such as disappointment and to involve some aspect of self-blame.[16] We are evaluating regret using the DRS, which measures patient conflict regarding decision making during the treatment process.[17] A Japanese version of the DRS has been developed and validated (Cronbach's $\alpha = 0.85$).[18] It consists of five items, and the total score ranges from 0 to 100, with higher scores indicating greater regret.

**Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events**

The National Cancer Institute (NCI)-CTCAE is a standardised tool for assessing adverse events during cancer treatment. However, since grading is based on the clinician's judgement, it may not be possible to accurately evaluate the patient's condition, especially when subjective aspects are involved.[19] Basch et al. reported a discrepancy between clinicians' and the patients' assessments, indicating that clinicians underestimate CTCAE grades.[20] Therefore, the NCI has developed the PRO-CTCAE, which incorporates the concept of PRO into the CTCAE.[21] Its Japanese version has been validated.[22] In this study, we are evaluating the participants' main symptoms, such as pain, and characteristic adverse events related to opioid analgesic use, such as nausea/vomiting, constipation, drowsiness, fatigue, and thirst. We are also evaluating an additional item to measure the psychological burden of using opioid analgesics.

**Brief Pain Inventory-Short Form**

The effect of pain on daily life differs from pain intensity. It is related to the amount of pain that results in hinderance of activities such as walking, bathing, and sleeping. The BPI is a standardised scale that has been confirmed to be reliable and valid for assessing pain intensity and its effect on daily life.[23] It is a 15-item questionnaire that evaluates pain. Each item is graded on an 11-point scale, with scores ranging from 0 to 10. The Japanese version of this scale has already been validated, and its reliability and usefulness have been established (Cronbach's $\alpha = 0.80$).[24] To decrease the burden on patients related to the number of

questions to be answered, we are only using the 'worst pain in the last 24 hours' item of the BPI-SF, based on a report by Atkinson et al.[25]

**Personalised Pain Goal**

As an index of pain, the numerical rating scale (NRS) is generally used to assess the average pain over 24 hours and the degree of disability in daily life due to pain (disturbance of life) using an 11-point scale, with scores ranging from 0 (none) to 10 (the worst possible). A score of four or higher indicates moderate pain/disability, while a score of seven or higher indicates severe pain/disability.[26] From the perspective of personalised medicine for the treatment of cancer pain, it is important to involve the patient in treatment goal setting and to provide treatment with the aim of achieving those goals. In recent years, the PPG has been used as an outcome measure to determine pain-relief goals in non-Japanese patients with cancer.[27] The PPG helps patients set a personalised pain-relief goal using the following question: 'At what level would you feel comfortable with pain?' In our study, patients are being asked to use the NRS to indicate their pain treatment goals. Pain treatment is considered to be successful (achievement of the PPG) if the patient's NRS score for pain at the time of assessment is below the PPG.

**Others**

Since strong opioid use during the study period might affect the time to achieve the PPG, the following items are being investigated: (1) whether any dose of the base strong opioid was missed, (2) presence of increased opioid dosage, (3) presence of opioid switching, and (4) use of strong opioids before starting base medication with or without rescue medication.

**Sample size**

The sample size was determined to be 200 based on the number of new patients being prescribed opioids per year at the study sites, taking into account the eligibility criteria. The sample size was not calculated using statistical methods.

**Data collection and timeline**

We are using the electronic data capture (EDC) systems, Viedoc 4, and ePRO, ViedocMe (Viedoc Technologies, Sweden), to enrol the participants and collect their data. During enrolment, the investigators are inputting their personal accounts and passwords into the system. Investigators at each site are using the EDC system to input data into an electronic case report form. Patients are being administered the PROs using an ePRO application on their device (smartphone, tablet, or personal computer) at eight time points: at baseline and on days one to seven. The patients may register their phone number or email address in the EDC system and use the ePRO reminder function. The investigators are providing the patients with details about the trial. After obtaining patient consent, data regarding each patient's

psychosocial background; JBQ-II, PRO-CTCAE, and BPI-SF scores; and PPG are being collected from their electronic device. Data regarding demographics, medical history, and CTCAE v5.0-Japan Clinical Oncology Group (JCOG) score are being collected, entered into the web-based EDC system at the study site, and linked to the baseline PRO data. After starting to receive opioids, each patient is being asked to record their BPI-SF (worst pain in the last 24 hours) score daily for seven days. On the last day, each patient is being administered the JBQ-II, PGIS, DRS, and PRO-CTCAE. Each patient's CTCAE v5.0-JCOG data is being collected by an investigator at the time of their next visit (days 8–15). In addition, we are recording each patient's use of strong opioid medication prior to starting base medication and whether any dose of the strong base opioid has been missed. The study timeline is presented in Table 1.

**Data monitoring**

The data centre is located at the Department of Practical Pharmacy, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan. No personally identifiable information is being entered into the EDC system, and the participating sites are not communicating personal information to the data centre. Since this study involves data collection using an EDC system, the data is being stored on the server during the study period. After the end of the study period, the data exported from the EDC system will be stored at the data centre until the main presentation or publication. Following this, the data will be stored at the research secretariat and data centre. Monitoring is being performed to ensure that the study is conducted according to the protocol and that the data is collected accurately. Central monitoring is being performed by the data centre based on the EDC data collected. The data centre has been submitting monthly monitoring reports to the researchers, is sharing information with the researchers at all the study sites, and is striving for improvement. There is no data monitoring committee, and auditing has not been planned for this study.

**Harm**

This is a non-intervention observational study with low invasiveness. We expect no serious harm to occur. However, the contents of the questionnaire may cause mental strain to the participants. Consent may be withdrawn even while filling the questionnaire, and the participants are being sufficiently explained about the study prior to enrolment.

**Statistical analysis**

The primary outcome is the JBQ-II score at baseline. The mean JBQ-II score at baseline will be calculated for all patients, and its 95% confidence interval will be estimated. Secondary, the relationships between the total JBQ-II score and the PPG achievement period, baseline and visit 2 JBQ-II scores, changes in JBQ-II scores, and PPG achievement rate on day seven will be examined. Patients will be grouped based on their PGIS scores, and the

difference between the DRS score and PPG achievement rate between the two groups will be estimated and tested. The relationship between the JBQ-II and trends in pain scores will be investigated. In addition, the proportion of adverse events will be calculated using the PRO-CTCAE and CTCAE v5.0-JCOG for safety analysis.

## ETHICS AND DISSEMINATION

### Research ethical approval

The study is being performed in accordance with the Declaration of Helsinki; Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Japanese Ministry of Education, Science and Technology and the Ministry of Health, Labour, and Welfare; and the modified Act on the Protection of Personal Information. The protocol was approved by the ethics committee (approval ID B200600091) of Yokohama City University on 24 August 2020. The protocol version was 1.1 in November 2020. The protocol has been reviewed by the institutional review board at the following study sites: Tokyo Medical University Hospital, Yokohama Minami Kyousai Hospital, and National Cancer Center Hospital East. The protocol will also be reviewed at the Kameda General Hospital.

### Consent

Before enrolment, an investigator explains the details of the study to the patients and gives them time to think about it. All participants are being informed of their right to withdraw their consent without prejudice. The study is being conducted after obtaining written consent from all the patients.

### Trial registration

This trial has been registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000042443).

### Access to data

Investigators are only able to access the case data collected at their respective study sites. Only clinical data managers at the data centre have access to reported case data through the EDC system during the study period.

### Dissemination policy

The results of this study will be presented at conferences and published in national and international peer-reviewed medical journals.

## DISCUSSION

To date, most studies on psychological barriers to analgesia have not specifically studied the use of strong opioid analgesics. The BAROC is an exploratory study that investigates the

relationship between psychological barriers and improvement in pain. It is important to use PROs, as pain improvement contributes to health-related quality of life. Psychological barriers may be influenced by opioid switching and analgesic use before starting to regularly use strong opioid analgesics. These data are also being collected using the EDC system.

The BAROC is the first multicentre study in Japan to evaluate the relationship between psychological barriers and cancer pain. The study sites include university hospitals, specialised cancer hospitals, and community hospitals, and it is expected that the enrolled patients will have diverse demographics. One of the characteristics of this study is that eligibility is not being limited by performance status. This means that patients with poor performance status may be eligible to participate in this study. Patients being administered strong opioid analgesics often have a poor performance status, and our data will reflect actual clinical practice.

Although the use of strong opioid analgesics can be beneficial in the treatment of cancer pain, it can also cause adverse events. Nausea and drowsiness commonly occur during opioid induction. There is concern that these symptoms may lead to decreased adherence and, therefore, interruption of pain treatment. In addition, the occurrence of adverse events can cause anxiety, worry, and other psychological burdens, amplifying resistance to opioid analgesic use. In this study, data on adverse event occurrence is being collected not only from physicians, but also from the patients themselves using the PRO-CTCAE. Because adverse events and psychological barriers are closely related, precision in adverse event assessment is required. Thus, it is important to use the PRO-CTCAE in addition to the CTCAE in order to consider the relationship between psychological barriers and adverse events and to enable high-quality adverse event assessment.

This study protocol has several limitations. First, this is a hypothetical, moulded observational study. The number of subjects was not determined using statistical methods and was based on the caseload of the participating institutions. Second, because this is an observational study, we are neither specifying the explanation to be provided to the patients before initiation of strong opioid analgesic use, nor are we specifying the setting in which this explanation is to be provided; each facility is following their own protocol in this regard. Psychological barriers may fluctuate depending on the method of explanation and the environment at that time. Third, we are excluding patients with cognitive impairment or mental illness and those who cannot operate a smartphone or tablet from participation in the study. Therefore, we will not be able to enrol all the patients receiving strong opioid analgesics. Most of the excluded participants are likely to be older adults. Finally, due to the coronavirus disease-2019 pandemic, it may be difficult to recruit patients due to restrictions

on hospital functions and patients' reluctance to receive care. As a result, enrolment for this study may need to be delayed.

The BAROC study may provide important information that may help to reduce psychological barriers to cancer pain relief in patients who are reluctant to use strong opioid analgesics. Clarifying the relationship between the achievement of pain relief goals and psychological barriers at the time of introduction of strong opioid analgesics will provide basic data for future interventional studies and contribute to improving the quality of cancer pain treatment.

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**Contributors**
TT contributed to trial conception and is the principal investigator.
TT, TF, TK, AK, and HH contributed to the study design.
TF, TK, and TY contributed to data management. TK and TY planned the data analysis.
Data analysis and interpretation will be conducted by TT, TF, TK, and TY.
TT, AM, KA, TS, TI, and JK acquired the data.
All authors have read and approved the final manuscript and meet the criteria for authorship as established by the International Committee of Medical Journals Editors.

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**Competing interests**
None declared.

**Patient and public involvement**
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**Box 1: Eligibility criteria**

**Inclusion criteria**

1. Patients diagnosed with remote metastasis or advanced recurrent cancer by a doctor
2. First treatment with strong opioid analgesics for cancer pain
3. Patients who are 20 years or older
4. Highest intensity of pain in the last 24 hours of NRS 4 or higher
5. Patients providing written consent for participating in the study

**Exclusion criteria**

1. Patients who have difficulty in providing ePRO data (e.g. those who do not have a smartphone or cannot use a tablet)
2. Patients with cognitive impairments that would hinder PRO administration
3. Patients with mental illnesses that would hinder PRO administration
4. Patients whose main mechanism of pain is neuropathic
5. Other factors that the attending physician deems inappropriate

ePRO, electronic version of the Patient-Reported Outcomes Questionnaire; NRS, numerical rating scale; PRO, Patient-Reported Outcomes Questionnaire.

**Table 1: Study timeline**

| Day | Visit 1<br>0 (baseline) | Time after initiating opioid therapy<br>1 | <br>2 | <br>3 | <br>4 | <br>5 | <br>6 | <br>7 | Visit 2<br>8–15 |
|---|---|---|---|---|---|---|---|---|---|
| **Patient reported outcomes :** | | | | | | | | | |
| Psychosocial background | ● | | | | | | | | |
| JBQ-II | ● | | | | | | | ● | |
| PGIS | | | | | | | | ● | |
| DRS | | | | | | | | ● | |
| PRO-CTCAE | ● | | | | | | | ● | |
| BPI-SF (strongest pain in the last 24 hours) | ● | ● | ● | ● | ● | ● | ● | ● | |
| PPG | ● | | | | | | | | |
| Use of strong opioids before starting base medication with or without rescue medication (outpatients) | | ● | | | | | | | |
| Whether any dose of the base strong opioid was missed (outpatients) | | | | | | | | ● | |
| **Clinician reported outcomes:** | | | | | | | | | |
| Demographics and medical history | ● | | | | | | | | |
| CTCAE v5.0-JCOG | ● | | | | | | | | ● |
| Presence of increased opioid dosage | | | | | | | | | ● |
| Presence of opioid switching | | | | | | | | | ● |
| Use of strong opioids before starting base medication with or without rescue medication (inpatients) | | | | | | | | | ● |
| Whether any dose of the base strong opioid was missed (inpatients) | | | | | | | | | ● |

BPI-SF, Brief Pain Inventory-Short Form; CTCAE, Common Terminology Criteria for Adverse Events; DRS, Decision Regret Scale; JBQ-II, Japanese version of the Barrier Questionnaire II; JCOG, Japan Clinical Oncology Group; PGIS, Patient Global Impression of Severity; PPG, Personalised Pain

Goal; PRO, Patient Reported Outcome

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# Psychological barriers to the use of opioid analgesics for treating pain in patients with advanced recurrent cancer (BAROC): protocol for a multicentre cohort study

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| | |

# Psychological barriers to the use of opioid analgesics for treating pain in patients with advanced recurrent cancer (BAROC): protocol for a multicentre cohort study

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## ABSTRACT

### Introduction

Opioid analgesics are essential for treating cancer pain. However, patients are sometimes reluctant to use them because of concerns about addiction and dependence. Rapid pain relief following opioid administration may help overcome the psychological barriers to opioid analgesic use. This study aims to determine the relationship between psychological resistance to strong opioid analgesic use and pain amelioration speed in patients with advanced recurrent cancer.

### Methods and analysis

This ongoing, multicentre, observational study enrols patients aged 20 years or older with distant metastasis or advanced recurrent cancer receiving strong opioid analgesics for cancer pain for the first time. We are investigating the relationship between psychological barriers at the start of treatment and pain relief during the first week of treatment in these patients. The primary outcome is the Japanese version of the Barriers Questionnaire-II score at baseline. The secondary outcomes are the relationships between psychological barriers to strong opioid analgesic use and changes in pain over time. The participants are asked to fill out an electronic patient-reported outcome daily during the first week of treatment. The sample size was determined based on the number of patients in the year prior to study commencement who used

strong opioid analgesics, met the eligibility criteria, and could be expected to consent to participate in the study.

## Ethics and dissemination

The study protocol was approved by the ethics committee (approval ID B200600091) of Yokohama City University on 24 August 2020. The protocol has been reviewed by the institutional review boards at the four participating study sites. The results will be published in a peer-reviewed journal and will be presented at a relevant meeting.

## Trial registration number

UMIN000042443

## Strengths and limitations of the study

- This is the first multicentre observational study to evaluate psychological barriers to the use of strong opioids in Japan.
- An understanding of Japanese version of the Barriers Questionnaire-II scores before and after opioid initiation may be useful for educating healthcare providers to reduce psychological barriers.
- Adverse events related to opioid analgesic use are assessed using the Patient-Reported

Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) and CTCAE v5.0-Japan Clinical Oncology Group.

- A limitation of this study is its short observation period, which leads to an inability to confirm long-term variations in psychological barriers.

## INTRODUCTION

In 2017, there were 24.5 million incident cancer cases worldwide, 9.6 million of whom died of cancer. [1] The incidence of cancer increased by 33% from 2007 to 2017. In 2009, there were 775,601 patients with cancer in Japan. [2] Cancer pain is the most concerning symptom of patients with cancer, with approximately 80% of patients with advanced cancer experiencing moderate to severe pain. [3] Japanese studies have examined the percentage of patients with cancer requiring and undergoing treatment for pain relief. In a survey, 60% of patients with cancer had pain, with 20% having moderate to severe pain. [4] Based on the prevalence of cancer in Japan, it is estimated that approximately 155,000 Japanese patients have moderate to severe pain and require opioid analgesics.

Patients with cancer often hesitate to manage their cancer pain using opioid analgesics. Their hesitation-related perceptions include concerns about addiction, gradual loss of effectiveness, severe side effects, anxiety due to pain predicting disease progression, and the idea that physicians are reluctant to talk about pain. [5] The Barriers Questionnaire (BQ) quantitatively measures factors related to patients' hesitation regarding opioid use. This scale was used to evaluate 270 patients with cancer, and it was found that 37%–85% of them were concerned about addiction and believed that good patients do not complain about pain and side effects. Additionally, older individuals, those from low-income households, and those with low levels

of education had higher concerns related to medical narcotics. [6] Furthermore, a relationship between the presence of barriers and pain intensity has also been reported. [7] Moreover, patients' mental anguish is positively correlated with pain, [8] and opioid analgesics may be insufficient for pain management depending on the patients' mental state.

A review investigating the barriers to cancer pain management related to healthcare professionals, patients, and systems [9] revealed that patient-related barriers included cognitive and emotional barriers and treatment adherence. Cognitive barriers included underreporting of symptoms to doctors and painkiller-related misunderstandings. Large barriers were associated with race, sex, and poor medication adherence. [10] In particular, a meta-analysis showed that Asians have greater barriers to cancer pain progression, tolerance, and lethality than Westerners. [11] A survey conducted across 214 countries by the International Narcotics Control Board revealed that Japanese individuals consumed fewer medical narcotics per million people per day than those from other countries (1,192 vs 3,027, respectively). Barriers to narcotic use included lack of training and awareness among healthcare professionals, concern regarding dependency, limited financial resources, procurement issues, cultural behaviour, fear of diversion, and international trade control and regulation. [12] Using a questionnaire, regulatory authorities of various countries found a high percentage of patients (56%) with concerns about dependency in East Asia, which includes Japan. This suggests that the higher the number of reported barriers, the lower the opioid analgesic use. [12]

A Japanese questionnaire study found that 28% of patients with advanced and recurrent cancer believe that opioid analgesic use shortens their lifespan and causes addiction. [13] A national survey of 5,000 people revealed that 27%–38% of participants reported that opioids shorten lifespan, while 24%–33% reported that opioids cause addiction. [14] This emphasises the need to thoroughly consider barriers when initiating treatment with opioids in Japanese patients. Despite barriers, acceptance of opioid use for pain relief is expected to improve through the practice of high-quality palliative care, pain relief following administration of narcotic medication, and improved confidence in drug safety. [14] Consequently, we believe that pain relief immediately after drug administration is important for breaking these barriers and that patients who confidently use opioid analgesics will quickly achieve the optimal dose and experience immediate pain relief. Patients' pain and mental state fluctuate daily and diurnally, and comparing pre- and post-intervention findings may lead to inaccurate results. [8] A detailed assessment of the speed of pain relief requires repeated evaluation over time.

Several studies have shown a positive correlation between psychological barriers and pain level, possibly due to inadequate analgesic use. [7 15] Furthermore, psychological barriers were lower when analgesics appropriate for the level of pain were used than when inadequate analgesics were used. However, the use of strong opioid analgesics has not been specifically studied. [16-18] A study conducted at six medical centres in three countries that regulate the use of strong opioid analgesics examined psychological barriers in patients who had been using strong opioid

analgesics for more than 72 hours and showed that patients who had been using strong opioid analgesics for a short period reported higher barrier scores than those who had been using them for a long time. [19] Therefore, it is important for future cancer pain treatment to identify changes in psychological barriers during and after initiation of use of strong opioid analgesics. However, these are cross-sectional studies, and, to date, only a few studies have investigated the relationship between psychological resistance to strong opioid analgesic use upon initiation and the speed of pain relief immediately after initiation in patients with advanced recurrent cancer. Therefore, we designed this study to address the need for sufficient verification of the relationship between psychological barriers and the speed of pain relief.

This study aimed to elucidate the relationship between psychological barriers to strong opioid analgesics use and the speed of pain relief in patients with advanced recurrent cancer. If it is found that cancer pain relief is difficult to achieve in patients hesitant to use strong opioid analgesics, this study may provide important information on how to assuage their reluctance and enable rapid pain improvement.

## METHODS AND ANALYSIS

### Study design

This is an ongoing, multicentre, longitudinal, observational study. We are investigating the relationship between psychological barriers at the start of treatment and pain relief during the

first week of treatment in patients receiving strong opioids for cancer pain. We are also evaluating the relationship between psychological barriers and adverse events associated with the use of strong opioids.

## Patient and public involvement

Patients were not invited to collaborate during the study design; therefore, this study protocol was developed without patient and public involvement. The enrolment was started in August 2020, and planned to close in October 2021.

## Study setting, participants, and recruitment

Recruiting is being performed at five sites in Japan. The inclusion and exclusion criteria are shown in Box 1. The main inclusion criterion is patients aged 20 years or older with distant metastasis or advanced recurrent cancer who receive first treatment with strong opioid analgesics for cancer pain. The main exclusion criteria are patients with difficulties in providing electronic patient-reported outcome (ePRO) data and patients with neuropathic pain. Eligible patients are being invited to participate in the study by investigators at each study site. These patients are being asked to complete an ePRO daily during the first week of treatment. Observation is being discontinued if any of the following occurs: (1) death during observation, (2) the patient's condition deteriorates and the healthcare professional determines that the intervention cannot be continued; (3) the patient withdraws consent; and (4) the investigators

judge that observation cannot be continued for any other reason. As a rule, standard pain relief treatments are being provided at each facility. We are neither restricting the provision of combination or supportive treatment nor specifying the post-treatment.

**Box 1: Eligibility criteria**

| |
|---|
| Inclusion criteria<br><br>1. Patients diagnosed with remote metastasis or advanced recurrent cancer by a doctor.<br><br>2. First treatment with strong opioid analgesics for cancer pain.<br><br>3. Patients who are 20 years or older.<br><br>4. Highest intensity of pain in the last 24 hours of an NRS score of 4 or higher.<br><br>5. Patients providing written consent for participating in the study. |
| Exclusion criteria<br><br>1. Patients who have difficulty in providing ePRO data (e.g. those who do not have a smartphone or cannot use a tablet).<br><br>2. Patients with cognitive impairments that would hinder PRO administration.<br><br>3. Patients with mental illnesses that would hinder PRO administration.<br><br>4. Patients whose main mechanism of pain is neuropathic.<br><br>5. Other factors that the attending physician deems inappropriate. |
| ePRO, electronic version of the Patient-Reported Outcomes Questionnaire; NRS, numerical rating scale; PRO, Patient-Reported Outcomes Questionnaire |

## Outcome measures

Table 1 shows the timeline of enrolment and assessment. We are using the JBQ-II [20] to assess

psychological barriers to opioid analgesic use and the Decision Regret Scale (DRS) [21] to evaluate regret related to decision making. We are using the PRO version of the CTCAE [22] and the CTCAE v5.0 to assess adverse events. We are evaluating pain severity using the Brief Pain Inventory (BPI)-Short Form (SF) [23] and PPG. [24]

**Table 1: Study timeline**

| Day | Visit 1 | Time after initiating opioid therapy | | | | | | | Visit 2 |
|---|---|---|---|---|---|---|---|---|---|
| | 0 (baseline) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8–15 |
| **Patient reported outcomes :** | | | | | | | | | |
| Psychosocial background | ● | | | | | | | | |
| JBQ-II | ● | | | | | | | ● | |
| PGIS | | | | | | | | ● | |
| DRS | | | | | | | | ● | |
| PRO-CTCAE | ● | | | | | | | ● | |
| BPI-SF (strongest pain in the last 24 hours) | ● | ● | ● | ● | ● | ● | ● | ● | |
| PPG | ● | | | | | | | | |
| Use of strong opioids before starting base medication with or without rescue medication (outpatients) | | ● | | | | | | | |
| Whether any dose of the base strong opioid was missed (outpatients) | | | | | | | | ● | |
| **Clinician reported outcomes:** | | | | | | | | | |
| Demographics and medical history | ● | | | | | | | | |
| CTCAE v5.0-JCOG | ● | | | | | | | | ● |
| Presence of increased opioid dosage | | | | | | | | | ● |
| Presence of opioid switching | | | | | | | | | ● |
| Use of strong opioids before starting base medication with or without rescue medication (inpatients) | | | | | | | | | ● |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Whether any dose of the base strong opioid was missed (inpatients) | | | | | | | | | • |

BPI-SF, Brief Pain Inventory-Short Form; CTCAE, Common Terminology Criteria for Adverse Events; DRS, Decision Regret Scale; JBQ-II, Japanese version of the Barriers Questionnaire II; JCOG, Japan Clinical Oncology Group; PGIS, Patient Global Impression of Severity; PPG, Personalized Pain Goal; PRO, Patient Reported Outcome

**Japanese version of the Barriers Questionnaire II**

To reflect practical changes in pain management, the BQ, a measure of psychological barriers, was revised to create the Barriers Questionnaire II (BQ-II). [17] The JBQ-II is the Japanese version of the BQ-II. It has been validated (Cronbach's $\alpha = 0.92$). [20] The JBQ-II comprises the following five subscales: barriers related to psychological effects (distrust of symptomatic treatment), barriers related to fatalism (fateful resignation), barriers related to communication (loss of intention), barriers related to adverse effects (fear of side effects), and barriers related to disease progression (escape/defence from illness). Each item is graded on a six-point Likert scale (0–5). The subscale and total scores (overall barrier) are calculated as the mean of the scores (0–5) for the relevant items, with higher numbers indicating higher barriers.

**Patient Global Impression of Severity**

Currently, the cut-off values for classifying the presence and magnitude of psychological barriers are unknown. We are using the Patient Global Impression of Severity (PGIS) to classify the participants' JBQ-II scores. The PGIS has not been validated to classify psychological

barriers. We are grading responses to the item 'At present, how reluctant are you to use opioids for pain relief?' using the following seven-point scale: 0, not at all; 1, not reluctant; 2, almost not reluctant; 3, neither; 4, slightly reluctant; 5, reluctant; and 6, extremely reluctant.

**Decision Regret Scale**

Regret is a negative emotion experienced when one realises or imagines that one has made the wrong choice. It is a retrospective, unpleasant feeling, and people tend to focus on 'what is good' rather than 'what is bad'. It has been reported to be associated with negative emotions, such as disappointment, and involve some aspect of self-blame. [25] We are evaluating regret using the DRS, which measures patient conflict regarding decision making during the treatment process. [26] A Japanese version of the DRS has been developed and validated (Cronbach's $\alpha = 0.85$). [21] It consists of five items. The total score ranges from 0 to 100, with higher scores indicating greater regret.

**Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events**

The National Cancer Institute (NCI)-CTCAE is a standardised tool for assessing adverse events during cancer treatment. However, since grading is based on the clinician's judgement, it may not be possible to accurately evaluate the patient's condition, especially when subjective aspects are involved. [27] Basch et al. reported a discrepancy between clinicians' and the patients'

assessments, indicating that clinicians underestimate CTCAE grades. [28] Therefore, the NCI developed the PRO-CTCAE, which incorporates the concept of PRO into the CTCAE. [29] Its Japanese version has been validated. [22] In this study, we are evaluating the participants' main symptoms, such as pain, and characteristic adverse events related to opioid analgesic use, such as nausea/vomiting, constipation, drowsiness, fatigue, and thirst. We are also evaluating an additional item to measure the psychological burden of using opioid analgesics.

**Brief Pain Inventory-Short Form**

The effect of pain on daily life differs from pain intensity. It is related to the amount of pain that hinders activities such as walking, bathing, and sleeping. The BPI is a standardised scale that has been confirmed to be reliable and valid for assessing pain intensity and its effect on daily life. [30] It is a 15-item questionnaire that evaluates pain. Each item is graded on an 11-point scale, with scores ranging from 0 to 10. The Japanese version of this scale has already been validated, and its reliability and usefulness have been established (Cronbach's $\alpha = 0.80$). [23] To decrease the burden on patients related to the number of questions to be answered, we are only using the 'worst pain in the last 24 hours' item of the BPI-SF, based on a report by Atkinson et al. [31]

**Personalized Pain Goal**

The numerical rating scale (NRS) is generally used as an index of the average pain over 24

hours and the degree of pain-related disability in daily life (disturbance of life). It is an 11-point scale, with scores ranging from 0 (none) to 10 (the worst possible). A score of ≥ 4 indicates moderate pain/disability, while a score of ≥ 7 indicates severe pain/disability. [32] From the perspective of personalized medicine for the treatment of cancer pain, it is important to involve the patient in treatment goal setting and provide treatment with the aim of achieving those goals. The PPG has recently been used as an outcome measure to determine pain-relief goals in non-Japanese patients with cancer. [33] The PPG helps patients set a personalized pain-relief goal using the following question: 'At what level would you feel comfortable with pain? [24]'. In our study, patients are being asked to use the NRS to indicate their pain treatment goals. Pain treatment is considered to be successful (achievement of the PPG) if the patient's NRS score for pain at the time of assessment is below the PPG.

**Others**

Since strong opioid use during the study period might affect the time to PPG achievement, the following items are being investigated: (1) whether any dose of the base strong opioid was missed, (2) presence of increased opioid dosage, (3) presence of opioid switching, and (4) use of strong opioids before starting base medication with or without rescue medication.

**Sample size**

Since this is an observational study conducted to form a hypothesis rather than a confirmatory

study conducted to test it, [34] the sample size is focus on feasibility and is based on the number of patients receiving strong opioid analgesics at the main medical institution. At Yokohama City University Medical Center, 378 patients started receiving strong opioid analgesics in 2019 (total oral and injection, excluding local use). Among them, 60% met the eligibility criteria, and 60% of them were assumed to be able to express consent, which leads us to estimate that 136 people could enrol into this study within 1 year. In addition, it is expected that 10–40 patients will be enrolled annually at Tokyo Medical University Hospital, National Cancer Centre Hospital East, Yokohama-Minami Kyosai Hospital, and Kameda General Hospital. Based on these estimates, we set the sample size target at 200.

**Data collection and timeline**

We are using the electronic data capture (EDC) systems Viedoc 4 and ViedocMe (Viedoc Technologies, Sweden) and ePRO, to enrol the participants and collect their data. During enrolment, the investigators input their personal accounts and passwords into the system. Investigators at each site use the EDC system to input data into an electronic case report form. Patients are being administered the PROs using an ePRO application on their device (smartphone, tablet, or personal computer) at eight time points: at baseline and on days one to seven. The patients may register their phone number or e-mail address in the EDC system and use the ePRO reminder function. The investigators are providing the patients with details about

the trial. After obtaining patient consent, data regarding each patient's psychosocial background; JBQ-II, PRO-CTCAE, and BPI-SF scores; and PPG are collected from their electronic device. Data regarding demographics, medical history, and CTCAE v5.0-JCOG score are collected, entered into the web-based EDC system at the study site, and linked to the baseline PRO data. After starting to receive opioids, each patient is asked to record their BPI-SF (worst pain in the last 24 hours) score daily for 7 days. On the last day, each patient is administered the JBQ-II, PGIS, DRS, and PRO-CTCAE. Each patient's CTCAE v5.0-JCOG data is collected by an investigator at the time of their next visit (days 8–15). In addition, we are recording each patient's use of strong opioid medication prior to starting base medication and whether any dose of the strong base opioid has been missed. The study timeline is presented in Table 1.

**Data monitoring**

The data centre is located at the Department of Practical Pharmacy, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan. No personally identifiable information is being entered into the EDC system, and the participating sites are not communicating personal information to the data centre. Since this study involves data collection using an EDC system, the data is stored on the server during the study period. After the end of the study period, the data exported from the EDC system will be stored at the data centre until

presentation or publication. Following this, the data will be stored at the research secretariat and data centre. Monitoring is being performed to ensure that the study is conducted according to the protocol and that the data is collected accurately. Central monitoring is being performed by the data centre based on the EDC data collected. The data centre has been submitting monthly monitoring reports to the researchers, is sharing information with the researchers at all the study sites, and is striving for improvement. There is no data monitoring committee, and auditing has not been planned for this study.

**Harm**

This is a non-intervention observational study with low invasiveness. We expect no serious harm to occur. However, the questionnaire contents may cause mental strain to the participants. Consent may be withdrawn even while filling the questionnaire, and the study is explained in detail to the participants prior to enrolment.

**Statistical analysis**

The primary outcome is the Japanese version of the Barriers Questionnaire-II (JBQ-II) score at baseline. The secondary outcomes are the relationships between the total JBQ-II score and the time to Personalized Pain Goal (PPG) achievement, JBQ-II scores at baseline and at the second visit, changes in JBQ-II scores, and PPG achievement rate on day 7. In addition, the proportion of adverse events will be calculated using the Patient-Reported Outcomes (PRO)- Common

Terminology Criteria for Adverse Events (CTCAE) and CTCAE v5.0- Japan Clinical Oncology Group (JCOG) for safety analysis. The mean JBQ-II score at baseline will be calculated for all patients, and its 95% confidence interval will be estimated. The relationships between the total JBQ-II score and the PPG achievement period, JBQ-II scores at baseline and at the second visit, changes in JBQ-II scores, and PPG achievement rate on day seven will be examined. Patients will be grouped based on their PGIS scores, and the difference between the DRS score and PPG achievement rate between the two groups will be estimated and tested. The relationship between the JBQ-II and trends in pain scores will be investigated. In addition, the proportion of adverse events will be calculated using the PRO-CTCAE and CTCAE v5.0-JCOG for safety analysis.

## ETHICS AND DISSEMINATION

### Research ethical approval

The study is being performed in accordance with the Declaration of Helsinki; Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Japanese Ministry of Education, Science and Technology and the Ministry of Health, Labour, and Welfare; and the modified Act on the Protection of Personal Information. The protocol was approved by the ethics committee (approval ID B200600091) of Yokohama City University on 24 August 2020. The protocol version was 1.1 in November 2020. The protocol has been reviewed by the institutional review board at the following study sites: Tokyo Medical

University Hospital, Yokohama Minami Kyousai Hospital, National Cancer Center Hospital East, and Kameda General Hospital.

## Consent

Before enrolment, an investigator explains the details of the study to the patients and gives them time to think about it. All participants are informed of their right to withdraw their consent without prejudice. The study will be conducted after obtaining written consent from all the patients.

## Trial registration

This trial has been registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000042443).

## Access to data

Investigators can only access the case data collected at their respective study sites. Only clinical data managers at the data centre have access to reported case data through the EDC system during the study period.

## Dissemination policy

The results of this study will be presented at conferences and published in national and international peer-reviewed medical journals.

## DISCUSSION

To date, most studies on psychological barriers to analgesia have not specifically studied the use of strong opioid analgesics. The BAROC is an exploratory study investigating the relationship between psychological barriers and improvement in pain. It is important to use PROs, as pain improvement contributes to health-related quality of life. [35-38] Psychological barriers may be influenced by opioid switching and analgesic use before the commencement of regular strong opioid analgesics use. [17 35 39] These data are also being collected using the EDC system.

The BAROC is the first multicentre study in Japan to evaluate the relationship between psychological barriers and cancer pain. The study sites include university hospitals, specialised cancer hospitals, and community hospitals, and it is expected that the enrolled patients will have diverse demographics. One of the characteristics of this study is that eligibility is not limited by performance status. This means that patients with a poor performance status may be eligible to participate in this study. Patients on strong opioid analgesics often have a poor performance status, and our data will reflect actual clinical practice.

Although the use of strong opioid analgesics can be beneficial in treating cancer pain, it can also cause adverse events. Nausea and drowsiness commonly occur during opioid induction. There is concern that these symptoms may lead to decreased adherence and, therefore, interruption of pain treatment. In addition, the occurrence of adverse events can cause anxiety, worry, and other psychological burdens, amplifying resistance to opioid analgesic use. In this study, data on adverse event occurrence is being collected not only from physicians but also from the patients themselves using the PRO-CTCAE. Because adverse events and psychological barriers are closely related, precision in adverse event assessment is required. Thus, it is important to use the PRO-CTCAE in addition to the CTCAE to consider the relationship between psychological barriers and adverse events and enable high-quality adverse event assessment.

Von Roenn et al. used case scenarios to survey 897 physicians from the Eastern Cooperative Oncology Group about the prevalence of pain in cancer patients and physicians' perceptions of managing pain. Although the case scenarios described patients with moderate to severe pain, 51% of physicians reported that they would prescribe ‘weak’ opioids. [40] However, for cancer patients with moderate pain, low doses of morphine can result in a significantly greater reduction in pain intensity than weaker opioids with similarly good tolerability and early effects. [41] Therefore, it is important to remove barriers to introducing strong opioids at an early stage and achieve rapid pain relief.

This study protocol has several limitations. First, this is an exploratory hypothesis-generating observational study. The number of participants was not determined using statistical methods and was based on the caseload of the participating institutions. Second, because this is an observational study, we are neither specifying the explanation to be provided to the patients before initiation of strong opioid analgesic use nor are we specifying the setting in which this explanation is to be provided; each facility is following its protocol in this regard. Psychological barriers may fluctuate depending on the method of explanation and the environment at that time. There are situations in which treatment must be started despite significant barriers, as not using opioid analgesics even when the pain becomes severe can significantly reduce quality of life. This study was conducted in a population that has already started treatment. Therefore, the results from this study cannot be applied to populations in whom strong opioid analgesics have not yet been considered. Third, we exclude patients with cognitive impairment or mental illness and those who cannot operate a smartphone or tablet from this study. Therefore, we will not be able to enrol all patients receiving strong opioid analgesics. Most of the excluded participants are likely to be older adults. Finally, due to the coronavirus disease-2019 pandemic, it may be difficult to recruit patients due to restrictions on hospital functions and patients' reluctance to receive care. As a result, enrolment for this study may need to be delayed.

The BAROC study may provide important information that may help reduce psychological barriers to cancer pain relief in patients who are reluctant to use strong opioid analgesics.

Clarifying the relationship between the achievement of pain relief goals and psychological barriers at the time of introduction of strong opioid analgesics will provide basic data for future interventional studies, encourage education of healthcare providers for reducing psychological barriers in advance to enable rapid pain amelioration, and contribute to improving the quality of cancer pain treatment.

## Acknowledgements

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## Contributors

TT contributed to trial conception and is the principal investigator.

TT, TF, TK, AK, and HH contributed to the study design.

TF, TK, and TY contributed to data management. TK and TY planned the data analysis.

Data analysis and interpretation will be conducted by TT, TF, TK, and TY.

TT, AM, KA, TS, TI, and JK acquired the data.

All authors have read and approved the final manuscript and meet the criteria for authorship as established by the International Committee of Medical Journals Editors.

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## Competing interests

None declared.

## Patient consent for publication

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## Provenance and peer review

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## Open access



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STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 3-5 |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported Page 6-8 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses Page 8,9 |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper Page 9,10 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 10,11 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 11<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls N/A<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants N/A |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed N/A<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 11,12 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 13-17 |
| Bias | 9 | Describe any efforts to address potential sources of bias N/A |
| Study size | 10 | Explain how the study size was arrived at Page 17,18 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why N/A |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding Page 13 |
| | | (*b*) Describe any methods used to examine subgroups and interactions N/A |
| | | (*c*) Explain how missing data were addressed N/A |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed N/A<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed N/A<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy N/A |
| | | (*e*) Describe any sensitivity analyses N/A |

Continued on next page

| | | |
|---|---|---|
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed N/A |
| | | (b) Give reasons for non-participation at each stage N/A |
| | | (c) Consider use of a flow diagram N/A |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders N/A |
| | | (b) Indicate number of participants with missing data for each variable of interest N/A |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) N/A |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time N/A |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure N/A |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures N/A |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included N/A |
| | | (*b*) Report category boundaries when continuous variables were categorized N/A |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses N/A |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives N/A |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 25 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence N/A |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results N/A |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 27 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Psychological barriers to the use of opioid analgesics for treating pain in patients with advanced recurrent cancer (BAROC): protocol for a multicentre cohort study

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|---|---|
| Heading</b>: | |
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| | |

# Psychological barriers to the use of opioid analgesics for treating pain in patients with advanced recurrent cancer (BAROC): protocol for a multicentre cohort study

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## ABSTRACT

### Introduction

Opioid analgesics are essential for treating cancer pain. However, patients are sometimes reluctant to use them because of concerns about addiction and dependence. Rapid pain relief following opioid administration may help overcome the psychological barriers to opioid analgesic use. This study aims to determine the relationship between psychological resistance to strong opioid analgesic use and pain amelioration speed in patients with advanced recurrent cancer.

### Methods and analysis

This ongoing, multicentre, observational study enrols patients aged 20 years or older with distant metastasis or advanced recurrent cancer receiving strong opioid analgesics for cancer pain for the first time. All participants, both inpatient and outpatient, were recruited from five Japanese hospitals. We are investigating the relationship between psychological barriers at the start of treatment and pain relief during the first week of treatment in these patients. The primary outcome is the Japanese version of the Barriers Questionnaire-II score at baseline. The secondary outcomes are the relationships between psychological barriers to strong opioid analgesic use and changes in pain over time. The participants are asked to fill out an electronic patient-reported outcome daily during the first week of treatment. The sample size was

determined based on the number of patients in the year prior to study commencement who used strong opioid analgesics, met the eligibility criteria, and could be expected to consent to participate in the study.

## Ethics and dissemination

The study protocol was approved by the ethics committee (approval ID B200600091) of Yokohama City University on 24 August 2020. The protocol has been reviewed by the institutional review boards at the four participating study sites. The results will be published in a peer-reviewed journal and will be presented at a relevant meeting.

## Trial registration number

UMIN000042443

## Strengths and limitations of the study

- This is the first multicentre observational study to evaluate psychological barriers to the use of strong opioids in Japan.
- Adverse events related to opioid analgesic use are assessed using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) and CTCAE v5.0-Japan Clinical Oncology Group.

- A limitation of this study is its short observation period, which leads to an inability to confirm long-term variations in psychological barriers.

## INTRODUCTION

In 2017, there were 24.5 million incident cancer cases worldwide, and 9.6 million of people who died of cancer. [1] The incidence of cancer increased by 33% from 2007 to 2017. In 2009, there were 775,601 patients with cancer in Japan. [2] Cancer pain is the most concerning symptom of patients with cancer, with approximately 80% of patients with advanced cancer experiencing moderate to severe pain. [3] Japanese studies have examined the percentage of patients with cancer requiring and undergoing treatment for pain relief. [4] In a survey, 60% of patients with cancer had pain, with 20% having moderate to severe pain. [5] Based on the prevalence of cancer in Japan, it is estimated that approximately 155,000 Japanese patients have moderate to severe pain and require opioid analgesics.

Patients with cancer often hesitate to manage their cancer pain using opioid analgesics. Their hesitation-related perceptions include concerns about addiction, gradual loss of effectiveness, severe side effects, anxiety due to pain predicting disease progression, and the idea that physicians are reluctant to talk about pain. [6] The Barriers Questionnaire (BQ) quantitatively measures factors related to patients' hesitation regarding opioid use. This scale was used to evaluate 270 patients with cancer, and it was found that 37%–85% of them were concerned about addiction and believed that good patients do not complain about pain and side effects. Additionally, older individuals, those from low-income households, and those with low levels

of education had higher concerns related to medical narcotics. [7] Furthermore, a relationship between the presence of barriers and pain intensity has also been reported. [8] Moreover, patients' mental anguish is positively correlated with pain, [9] and opioid analgesics may be insufficient for pain management depending on the patients' mental state.

A review investigating the barriers to cancer pain management related to healthcare professionals, patients, and systems [10] revealed that patient-related barriers included cognitive and emotional barriers and treatment adherence. Cognitive barriers included underreporting of symptoms to doctors and painkiller-related misunderstandings. Large barriers were associated with race, sex, and poor medication adherence. [11] In particular, a meta-analysis showed that Asians have greater barriers to cancer pain progression, tolerance, and lethality than Westerners. [12] A survey conducted across 214 countries by the International Narcotics Control Board revealed that Japanese individuals consumed fewer medical narcotics per million people per day than those from other countries (1,192 vs 3,027, respectively). Barriers to narcotic use included lack of training and awareness among healthcare professionals, concern regarding dependency, limited financial resources, procurement issues, cultural behaviour, fear of diversion, and international trade control and regulation. [13] Using a questionnaire, regulatory authorities of various countries found a high percentage of patients (56%) with concerns about dependency in East Asia, which includes Japan. This suggests that the higher the number of reported barriers, the lower the opioid analgesic use. [13]

A Japanese questionnaire study found that 28% of patients with advanced and recurrent cancer believe that opioid analgesic use shortens their lifespan and causes addiction. [14] A national survey of 5,000 people revealed that 27%–38% of participants reported that opioids shorten lifespan, while 24%–33% reported that opioids cause addiction. [15] This emphasises the need to thoroughly consider barriers when initiating treatment with opioids in Japanese patients. Despite barriers, acceptance of opioid use for pain relief is expected to improve through the practice of high-quality palliative care, pain relief following administration of narcotic medication, and improved confidence in drug safety. [15] Consequently, we believe that pain relief immediately after drug administration is important for breaking these barriers and that patients who confidently use opioid analgesics will quickly achieve the optimal dose and experience immediate pain relief. Patients' pain and mental state fluctuate daily and diurnally, and comparing pre- and post-intervention findings may lead to inaccurate results. [9] A detailed assessment of the speed of pain relief requires repeated evaluation over time.

Several studies have shown a positive correlation between psychological barriers and pain level, possibly due to inadequate analgesic use. [8, 16] Furthermore, psychological barriers were lower when analgesics appropriate for the level of pain were used than when inadequate analgesics were used. However, the use of strong opioid analgesics has not been specifically studied. [17-19] A study conducted at six medical centres in three countries that regulate the use of strong opioid analgesics examined psychological barriers in patients who had been using

strong opioid analgesics for more than 72 hours and showed that patients who had been using strong opioid analgesics for a short period reported higher barrier scores than those who had been using them for a long time. [20] Therefore, it is important for future cancer pain treatment to identify changes in psychological barriers during and after initiation of use of strong opioid analgesics. However, these are cross-sectional studies, and, to date, only a few studies have investigated the relationship between psychological resistance to strong opioid analgesic use upon initiation and the speed of pain relief immediately after initiation in patients with advanced recurrent cancer. Therefore, we designed this study to address the need for sufficient verification of the relationship between psychological barriers and the speed of pain relief.

This study aimed to elucidate the relationship between psychological barriers to strong opioid analgesics use and the speed of pain relief in patients with advanced recurrent cancer. If it is found that cancer pain relief is difficult to achieve in patients hesitant to use strong opioid analgesics, this study may provide important information on how to assuage their reluctance and enable rapid pain improvement.

## METHODS AND ANALYSIS

### Study design

This is an ongoing, multicentre, longitudinal, observational study. We are investigating the relationship between psychological barriers at the start of treatment and pain relief during the

first week of treatment in patients receiving strong opioids for cancer pain. We are also evaluating the relationship between psychological barriers and adverse events associated with the use of strong opioids.

## Patient and public involvement

Patients were not invited to collaborate during the study design; therefore, this study protocol was developed without patient and public involvement. The enrolment was started in August 2020, and planned to close in October 2021.

## Study setting, participants, and recruitment

Recruiting is being performed at five sites in Japan. The inclusion and exclusion criteria are shown in Box 1. The main inclusion criterion is patients aged 20 years or older with distant metastasis or advanced recurrent cancer who receive first treatment with strong opioid analgesics for cancer pain. The main exclusion criteria are patients with difficulties in providing electronic patient-reported outcome (ePRO) data and patients with neuropathic pain. Eligible patients are being invited to participate in the study by investigators at each study site. These patients are being asked to complete an ePRO daily during the first week of treatment. Observation is being discontinued if any of the following occurs: (1) death during observation, (2) the patient's condition deteriorates and the healthcare professional determines that the intervention cannot be continued; (3) the patient withdraws consent; and (4) the investigators

judge that observation cannot be continued for any other reason. As a rule, standard pain relief treatments are being provided at each facility. We are neither restricting the provision of combination or supportive treatment nor specifying the post-treatment.

**Box 1: Eligibility criteria**

| |
|---|
| Inclusion criteria<br><br>1. Patients diagnosed with remote metastasis or advanced recurrent cancer by a doctor.<br><br>2. First treatment with strong opioid analgesics for cancer pain.<br><br>3. Patients who are 20 years or older.<br><br>4. Highest intensity of pain in the last 24 hours of an NRS score of 4 or higher.<br><br>5. Patients providing written consent for participating in the study. |
| Exclusion criteria<br><br>1. Patients who have difficulty in providing ePRO data (e.g. those who do not have a smartphone or cannot use a tablet).<br><br>2. Patients with cognitive impairments that would hinder PRO administration.<br><br>3. Patients with mental illnesses that would hinder PRO administration.<br><br>4. Patients whose main mechanism of pain is neuropathic.<br><br>5. Other factors that the attending physician deems inappropriate. |
| ePRO, electronic version of the Patient-Reported Outcomes Questionnaire; NRS, numerical rating scale; PRO, Patient-Reported Outcomes Questionnaire |

## Outcome measures

Table 1 shows the timeline of enrolment and assessment. We are using the JBQ-II [21] to assess

psychological barriers to opioid analgesic use and the Decision Regret Scale (DRS) [22] to evaluate regret related to decision making. We are using the PRO version of the CTCAE [23] and the CTCAE v5.0 to assess adverse events. We are evaluating pain severity using the Brief Pain Inventory (BPI)-Short Form (SF) [24] and PPG. [25]

**Table 1: Study timeline**

| Day | Visit 1 | Time after initiating opioid therapy | | | | | | | Visit 2 |
|---|---|---|---|---|---|---|---|---|---|
| | 0 (baseline) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8–15 |
| **Patient reported outcomes :** | | | | | | | | | |
| Psychosocial background | ● | | | | | | | | |
| JBQ-II | ● | | | | | | | ● | |
| PGIS | | | | | | | | ● | |
| DRS | | | | | | | | ● | |
| PRO-CTCAE | ● | | | | | | | ● | |
| BPI-SF (strongest pain in the last 24 hours) | ● | ● | ● | ● | ● | ● | ● | ● | |
| PPG | ● | | | | | | | | |
| Use of strong opioids before starting base medication with or without rescue medication (outpatients) | | ● | | | | | | | |
| Whether any dose of the base strong opioid was missed (outpatients) | | | | | | | | ● | |
| **Clinician reported outcomes:** | | | | | | | | | |
| Demographics and medical history | ● | | | | | | | | |
| CTCAE v5.0-JCOG | ● | | | | | | | | ● |
| Presence of increased opioid dosage | | | | | | | | | ● |
| Presence of opioid switching | | | | | | | | | ● |
| Use of strong opioids before starting base medication with or without rescue medication (inpatients) | | | | | | | | | ● |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Whether any dose of the base strong opioid was missed (inpatients) | | | | | | | | | • |

BPI-SF, Brief Pain Inventory-Short Form; CTCAE, Common Terminology Criteria for Adverse Events; DRS, Decision Regret Scale; JBQ-II, Japanese version of the Barriers Questionnaire II; JCOG, Japan Clinical Oncology Group; PGIS, Patient Global Impression of Severity; PPG, Personalized Pain Goal; PRO, Patient Reported Outcome

**Japanese version of the Barriers Questionnaire II**

To reflect practical changes in pain management, the BQ, a measure of psychological barriers, was revised to create the Barriers Questionnaire II (BQ-II). [18] The JBQ-II is the Japanese version of the BQ-II. It has been validated (Cronbach's $\alpha = 0.92$). [21] The JBQ-II comprises the following five subscales: barriers related to psychological effects (distrust of symptomatic treatment), barriers related to fatalism (fateful resignation), barriers related to communication (loss of intention), barriers related to adverse effects (fear of side effects), and barriers related to disease progression (escape/defence from illness). Each item is graded on a six-point Likert scale (0–5). The subscale and total scores (overall barrier) are calculated as the mean of the scores (0–5) for the relevant items, with higher numbers indicating higher barriers.

**Patient Global Impression of Severity**

Currently, the cut-off values for classifying the presence and magnitude of psychological barriers are unknown. We are using the Patient Global Impression of Severity (PGIS) to classify the participants' JBQ-II scores. The PGIS has not been validated to classify psychological

barriers. We are grading responses to the item 'At present, how reluctant are you to use opioids for pain relief?' using the following seven-point scale: 0, not at all; 1, not reluctant; 2, almost not reluctant; 3, neither; 4, slightly reluctant; 5, reluctant; and 6, extremely reluctant.

**Decision Regret Scale**

Regret is a negative emotion experienced when one realises or imagines that one has made the wrong choice. It is a retrospective, unpleasant feeling, and people tend to focus on 'what is good' rather than 'what is bad'. It has been reported to be associated with negative emotions, such as disappointment, and involve some aspect of self-blame. [26] We are evaluating regret using the DRS, which measures patient conflict regarding decision making during the treatment process. [27] A Japanese version of the DRS has been developed and validated (Cronbach's $\alpha = 0.85$). [22] It consists of five items. The total score ranges from 0 to 100, with higher scores indicating greater regret.

**Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events**

The National Cancer Institute (NCI)-CTCAE is a standardised tool for assessing adverse events during cancer treatment. However, since grading is based on the clinician's judgement, it may not be possible to accurately evaluate the patient's condition, especially when subjective aspects are involved. [28] Basch et al. reported a discrepancy between clinicians' and the patients'

assessments, indicating that clinicians underestimate CTCAE grades. [29] Therefore, the NCI developed the PRO-CTCAE, which incorporates the concept of PRO into the CTCAE. [30] Its Japanese version has been validated. [23] In this study, we are evaluating the participants' main symptoms, such as pain, and characteristic adverse events related to opioid analgesic use, such as nausea/vomiting, constipation, drowsiness, fatigue, and thirst. We are also evaluating an additional item to measure the psychological burden of using opioid analgesics.

**Brief Pain Inventory-Short Form**

The effect of pain on daily life differs from pain intensity. It is related to the amount of pain that hinders activities such as walking, bathing, and sleeping. The BPI is a standardised scale that has been confirmed to be reliable and valid for assessing pain intensity and its effect on daily life. [31] It is a 15-item questionnaire that evaluates pain. Each item is graded on an 11-point scale, with scores ranging from 0 to 10. The Japanese version of this scale has already been validated, and its reliability and usefulness have been established (Cronbach's $\alpha = 0.80$). [24] To decrease the burden on patients related to the number of questions to be answered, we are only using the 'worst pain in the last 24 hours' item of the BPI-SF, based on a report by Atkinson et al.[32]

**Personalized Pain Goal**

The numerical rating scale (NRS) is generally used as an index of the average pain over 24

hours and the degree of pain-related disability in daily life (disturbance of life). It is an 11-point scale, with scores ranging from 0 (none) to 10 (the worst possible). A score of ≥ 4 indicates moderate pain/disability, while a score of ≥ 7 indicates severe pain/disability. [33] From the perspective of personalized medicine for the treatment of cancer pain, it is important to involve the patient in treatment goal setting and provide treatment with the aim of achieving those goals. The PPG has recently been used as an outcome measure to determine pain-relief goals in non-Japanese patients with cancer. [34] The PPG helps patients set a personalized pain-relief goal using the following question: 'At what level would you feel comfortable with pain? [25]'. In our study, patients are being asked to use the NRS to indicate their pain treatment goals. Pain treatment is considered to be successful (achievement of the PPG) if the patient's NRS score for pain at the time of assessment is below the PPG.

**Others**

Since strong opioid use during the study period might affect the time to PPG achievement, the following items are being investigated: (1) whether any dose of the base strong opioid was missed, (2) presence of increased opioid dosage, (3) presence of opioid switching, and (4) use of strong opioids before starting base medication with or without rescue medication.

**Sample size**

Since this is an observational study conducted to form a hypothesis rather than a confirmatory

study conducted to test it, [35] the sample size is focus on feasibility and is based on the number of patients receiving strong opioid analgesics at the main medical institution. At Yokohama City University Medical Center, 378 patients started receiving strong opioid analgesics in 2019 (total oral and injection, excluding local use). Among them, 60% met the eligibility criteria, and 60% of them were assumed to be able to express consent, which leads us to estimate that 136 people could enrol into this study within 1 year. In addition, it is expected that 10–40 patients will be enrolled annually at Tokyo Medical University Hospital, National Cancer Centre Hospital East, Yokohama-Minami Kyosai Hospital, and Kameda General Hospital. Based on these estimates, we set the sample size target at 200.

**Data collection and timeline**

We are using the electronic data capture (EDC) systems Viedoc 4 and ViedocMe (Viedoc Technologies, Sweden) and ePRO, to enrol the participants and collect their data. During enrolment, the investigators input their personal accounts and passwords into the system. Investigators at each site use the EDC system to input data into an electronic case report form. Patients are being administered the PROs using an ePRO application on their device (smartphone, tablet, or personal computer) at eight time points: at baseline and on days one to seven. The patients may register their phone number or e-mail address in the EDC system and use the ePRO reminder function. The investigators are providing the patients with details about

the trial. After obtaining patient consent, data regarding each patient's psychosocial background; JBQ-II, PRO-CTCAE, and BPI-SF scores; and PPG are collected from their electronic device. Data regarding demographics, medical history, and CTCAE v5.0-JCOG score are collected, entered into the web-based EDC system at the study site, and linked to the baseline PRO data. After starting to receive opioids, each patient is asked to record their BPI-SF (worst pain in the last 24 hours) score daily for 7 days. On the last day, each patient is administered the JBQ-II, PGIS, DRS, and PRO-CTCAE. Each patient's CTCAE v5.0-JCOG data is collected by an investigator at the time of their next visit (days 8–15). In addition, we are recording each patient's use of strong opioid medication prior to starting base medication and whether any dose of the strong base opioid has been missed. The study timeline is presented in Table 1.

**Data monitoring**

The data centre is located at the Department of Practical Pharmacy, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan. No personally identifiable information is being entered into the EDC system, and the participating sites are not communicating personal information to the data centre. Since this study involves data collection using an EDC system, the data is stored on the server during the study period. After the end of the study period, the data exported from the EDC system will be stored at the data centre until

presentation or publication. Following this, the data will be stored at the research secretariat and data centre. Monitoring is being performed to ensure that the study is conducted according to the protocol and that the data is collected accurately. Central monitoring is being performed by the data centre based on the EDC data collected. The data centre has been submitting monthly monitoring reports to the researchers, is sharing information with the researchers at all the study sites, and is striving for improvement. There is no data monitoring committee, and auditing has not been planned for this study.

**Harm**

This is a non-intervention observational study with low invasiveness. We expect no serious harm to occur. However, the questionnaire contents may cause mental strain to the participants. Consent may be withdrawn even while filling the questionnaire, and the study is explained in detail to the participants prior to enrolment.

**Statistical analysis**

The primary outcome is the Japanese version of the Barriers Questionnaire-II (JBQ-II) score at baseline. The secondary outcomes are the relationships between the total JBQ-II score and the time to Personalized Pain Goal (PPG) achievement, JBQ-II scores at baseline and at the second visit, changes in JBQ-II scores, and PPG achievement rate through Day 7. In addition, the proportion of adverse events will be calculated using the Patient-Reported Outcomes (PRO)-

Common Terminology Criteria for Adverse Events (CTCAE) and CTCAE v5.0- Japan Clinical Oncology Group (JCOG) for safety analysis. The mean JBQ-II score at baseline will be calculated for all patients, and its 95% confidence interval will be estimated. The relationships between the total JBQ-II score and the PPG achievement period, JBQ-II scores at baseline and at the second visit, changes in JBQ-II scores, and PPG achievement rate through Day 7 will be examined. Patients will be grouped based on their PGIS scores, and the difference between the DRS score and PPG achievement rate between the two groups will be estimated and tested. The relationship between the JBQ-II and trends in pain scores will be investigated. In addition, the proportion of adverse events will be calculated using the PRO-CTCAE and CTCAE v5.0-JCOG for safety analysis.

## ETHICS AND DISSEMINATION

### Research ethical approval

The study is being performed in accordance with the Declaration of Helsinki; Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Japanese Ministry of Education, Science and Technology and the Ministry of Health, Labour, and Welfare; and the modified Act on the Protection of Personal Information. The protocol was approved by the ethics committee (approval ID B200600091) of Yokohama City University on 24 August 2020. The protocol version was 1.1 in November 2020. The protocol has been

reviewed and approved by the institutional review board at the following study sites: Tokyo Medical University Hospital, Yokohama Minami Kyousai Hospital, National Cancer Center Hospital East, and Kameda General Hospital.

## Consent

Before enrolment, an investigator explains the details of the study to the patients and gives them time to think about it. All participants are informed of their right to withdraw their consent without prejudice. The study will be conducted after obtaining written consent from all the patients.

## Trial registration

This trial has been registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000042443).

## Access to data

Investigators can only access the case data collected at their respective study sites. Only clinical data managers at the data centre have access to reported case data through the EDC system during the study period.

## Dissemination policy

The results of this study will be presented at conferences and published in national and international peer-reviewed medical journals.

## DISCUSSION

To date, most studies on psychological barriers to analgesia have not specifically studied the use of strong opioid analgesics. The BAROC is an exploratory study investigating the relationship between psychological barriers and improvement in pain. It is important to use PROs, as pain improvement contributes to health-related quality of life. [36-39] Psychological barriers may be influenced by opioid switching and analgesic use before the commencement of regular strong opioid analgesics use. [18, 36, 40] These data are also being collected using the EDC system.

The BAROC is the first multicentre study in Japan to evaluate the relationship between psychological barriers and cancer pain. The study sites include university hospitals, specialised cancer hospitals, and community hospitals, and it is expected that the enrolled patients will have diverse demographics. One of the characteristics of this study is that eligibility is not limited by performance status. This means that patients with a poor performance status may be eligible to participate in this study. Patients on strong opioid analgesics often have a poor performance status, and our data will reflect actual clinical practice.

Although the use of strong opioid analgesics can be beneficial in treating cancer pain, it can also cause adverse events. Nausea and drowsiness commonly occur during opioid induction. There is concern that these symptoms may lead to decreased adherence and, therefore, interruption of pain treatment. In addition, the occurrence of adverse events can cause anxiety, worry, and other psychological burdens, amplifying resistance to opioid analgesic use. In this study, data on adverse event occurrence is being collected not only from physicians but also from the patients themselves using the PRO-CTCAE. Because adverse events and psychological barriers are closely related, precision in adverse event assessment is required. Thus, it is important to use the PRO-CTCAE in addition to the CTCAE to consider the relationship between psychological barriers and adverse events and enable high-quality adverse event assessment.

Von Roenn et al. used case scenarios to survey 897 physicians from the Eastern Cooperative Oncology Group about the prevalence of pain in cancer patients and physicians' perceptions of managing pain. Although the case scenarios described patients with moderate to severe pain, 51% of physicians reported that they would prescribe ‘weak’ opioids. [41] However, for cancer patients with moderate pain, low doses of morphine can result in a significantly greater reduction in pain intensity than weaker opioids with similarly good tolerability and early effects. [42] Therefore, it is important to remove barriers to introducing strong opioids at an early stage and achieve rapid pain relief.

This study protocol has several limitations. First, this is an exploratory hypothesis-generating observational study. The number of participants was not determined using statistical methods and was based on the caseload of the participating institutions. Second, because this is an observational study, we are neither specifying the explanation to be provided to the patients before initiation of strong opioid analgesic use nor are we specifying the setting in which this explanation is to be provided; each facility is following its protocol in this regard. Psychological barriers may fluctuate depending on the method of explanation and the environment at that time. There are situations in which treatment must be started despite significant barriers, as not using opioid analgesics even when the pain becomes severe can significantly reduce quality of life. This study was conducted in a population that has already started treatment. Therefore, the results from this study cannot be applied to populations in whom strong opioid analgesics have not yet been considered. Third, we exclude patients with cognitive impairment or mental illness and those who cannot operate a smartphone or tablet from this study. Therefore, we will not be able to enrol all patients receiving strong opioid analgesics. Most of the excluded participants are likely to be older adults. Finally, due to the coronavirus disease-2019 pandemic, it may be difficult to recruit patients due to restrictions on hospital functions and patients' reluctance to receive care. As a result, enrolment for this study may need to be delayed.

The BAROC study may provide important information that may help reduce psychological barriers to cancer pain relief in patients who are reluctant to use strong opioid analgesics.

Clarifying the relationship between the achievement of pain relief goals and psychological barriers at the time of introduction of strong opioid analgesics will provide basic data for future interventional studies, encourage education of healthcare providers for reducing psychological barriers in advance to enable rapid pain amelioration, and contribute to improving the quality of cancer pain treatment.

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## Contributors

TTs contributed to the study conception and is the principal investigator.

TTs, TF, TK, AK, and HHak participated in the design of the study.

TF, TK, and TY played a primary role in designing the data management approach.

TK and TY played a primary role in designing statistical analysis.

Data analysis and interpretation will be conducted by TTs, TF, TK, and TY.

TTs, RY, KK, AM, KA, TS, HM, TI, TM, HO, JK, TTa, HHam and YO have carried out recruitment and collected the data.

All authors have read and approved the final manuscript and meet the criteria for authorship as established by the International Committee of Medical Journals Editors.

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## Competing interests

None declared.

## Patient consent for publication

Not required.

## Provenance and peer review

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## Open access



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STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 3-5 |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported Page 6-8 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses Page 8,9 |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper Page 9,10 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 10,11 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 11<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls N/A<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants N/A |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed N/A<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 11,12 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 13-17 |
| Bias | 9 | Describe any efforts to address potential sources of bias N/A |
| Study size | 10 | Explain how the study size was arrived at Page 17,18 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why N/A |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding Page 13 |
| | | (*b*) Describe any methods used to examine subgroups and interactions N/A |
| | | (*c*) Explain how missing data were addressed N/A |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed N/A<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed N/A<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy N/A |
| | | (*e*) Describe any sensitivity analyses N/A |

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| | | |
|---|---|---|
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed N/A |
| | | (b) Give reasons for non-participation at each stage N/A |
| | | (c) Consider use of a flow diagram N/A |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders N/A |
| | | (b) Indicate number of participants with missing data for each variable of interest N/A |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) N/A |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time N/A |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure N/A |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures N/A |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included N/A |
| | | (*b*) Report category boundaries when continuous variables were categorized N/A |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses N/A |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives N/A |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 25 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence N/A |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results N/A |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 27 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.