PAIN MANAGEMENT AMONG PATIENTS WITH BONE MALIGNANCIES AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA.

BY

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DECLARATIONS

Declaration by Candidate

The candidate declares that the thesis is original and personal work and has not been presented in any other university for any award. No part of this work may be reproduced or transmitted in any form without prior permission from the author and or Moi University.

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DEDICATIONS

I dedicate this work to my siblings and my beloved parents Zepherino Tabu and Prossy Tabu.

ABSTRACT

Background: Cancer-related bone pain (CRBP) poses a substantial orthopaedic challenge in its management. Opioids remain the first treatment option for CRBP, but many Sub-Sahara patients continue to receive suboptimal pain management with analgesics. Published data are scarce on CRBP in resource-limited settings, including Kenya.

Objective: To describe the use of analgesics in the management of CRBP at MTRH and determine the proportion of patients satisfied with their pain control on analgesics.

Methods: A prospective descriptive study was conducted between March 2019 - March 2020 with 96 adult patients, consecutively sampled after obtaining consent and followed up daily for five days. Eligible patients had histo-pathologically confirmed primary tumour, osseous lesion(s) on radiographs, and cognitive capacity to rate pain on a Numerical Rating Scale. Data was collected using validated questionnaires drafted from the Brief Pain Inventory. Within the past 24 hours, self-assessed pain scores were reported on a scale of 0 (No pain) to 10 (worst Pain). Adequacy of analgesics use was assessed using the Pain Management Index (PMI). The PMI was calculated by subtracting a patient's pain intensity score from the analgesic score. A negative PMI indicated suboptimal treatment. Pain control satisfaction was evaluated as a single response question (Satisfied, Not Sure, or Dissatisfied). Descriptive statistics were used to summarise patients with moderate-severe CRBP, a negative PMI, and those satisfied with pain control. Associations were examined in multiple logistic regression models. Ethical approval was obtained.

Results: The median age was 57 (range19 to 90) years. More males (52.1%) than females (47.9%) were recruited. The commonest malignancy was Prostate cancer (25%). At baseline, 86.5% reported CRBP, with 69.8% having moderate-severe pain, 13.5% had no CRBP. Twenty-eight patients (29.2%) had pain and no analgesics; of these, 19 (19.8%) had moderate-severe Pain. On follow-up, the proportion of CRBP ranged from 83.3% to 86.5%. That of moderate to severe pain ranged from 57.3% to 62.5%. Twenty-one patients (21.9%) with pain the entire study duration received no prescribed analgesics. Opioids were prescribed to 29.2% at baseline and 15.6% on follow-up. CRBP was sub-optimally managed in 61.5% at baseline. This proportion ranged from 59.4% to 65.6% on follow-up. Multiple bone lesions (p=0.006, AOR: 0.192) and age over 60 years (p=0.013, AOR: 0.953) were significantly associated with suboptimal pain management. Overall, 70.8% were satisfied with their pain control. Patients prescribed opioids (p=0.041, AOR: 0.027) had an increased likelihood of having pain control satisfaction.

Conclusion: A high proportion of patients with bone malignancies at MTRH report CRBP. Majority of the patients receive suboptimal pain management with analgesics.

Recommendations: Efforts to include appropriate pain screening, assessment, evidence-guided treatment, and patient follow up are necessary to provide adequate CRBP management and satisfactory outcomes.

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I acknowledge the incredible support I received from my classmates for their unreserved aids. Moreso, for being the wind beneath which my wings soared. May their stars shine brighter as they walk their career paths.

A special thanks to my parents and siblings from whom I draw my academic aspirations. On this career path, may I continue to "*Aspire to Inspire before I expire"*.

Lastly, thanks to my teachers from whom I learnt the Art, I keep oath to teach the Art to those after me equally.

ABBREVIATIONS AND ACRONYMS

BPI-SF	Brief Pain Inventory Short Form
CRBP	Cancer Related Bone Pain
CT-Scan	Computed Tomography Scan
EBRT	External beam radiation therapy
IASP	International Association for the Study of Pain
IREC	Institutional Research and Ethics Committee
KNH	Kenyatta National Hospital
MRI	Magnetic Resonance Imaging
MTRH	Moi Teaching and Referral Hospital
NRS	Numerical Rating Scale
NSAID	NonSteroidal Anti-Inflammatory Drug
PMI	Pain Management Index
QoL	Quality of Life
SBRT	Stereotactic Body Radiation Therapy
SREs	Skeletal Related Events
SSA	Sub-Sahara Africa
WHO	World Health Organization

DEFINITIONS OF KEY TERMS

Pain; according to the International Association for the Study of pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

Cancer Related Bone Pain; is a multi-mechanism and complex pain coming directly from the bone due to the infiltrating tumour or indirectly resulting from the anticancer treatment.

Bone Malignancies; are tumours of the bone that destroys healthy bone tissue. They include both primary bone tumours and bone metastases.

Management; is a collaborative process that facilitates recommended treatment plans to assure that the appropriate medical care is provided to disabled, ill, or injured individuals.

CHAPTER ONE

1.0. INTRODUCTION

1.1. Background

Bone malignancies are usually associated with numerous Skeletal Related Events SREs that chiefly include bone pain, pathological fractures, spinal cord compression, and hypercalcemia. They are the most common causes of pain associated with cancer (Caraceni & Portenoy, 1999; Kane et al., 2015; Phanphaisarn et al., 2016). CRBP is prevalent in 85% of advanced Breast, Prostate, Lungs, and Kidney cancer patients (Kassamali et al., 2010; Felice et al., 2017). It poses a substantial orthopaedic challenge to its management. If not adequately managed, it would adversely reduce the patients' quality of life (Coleman, 2006; Lee & Jung, 2012; Harding et al., 2018).

With all the available treatment modalities that control CRBP, reduce tumour-induced bone remodelling and tumour growth; poorly controlled CRBP remains the chief complaint among these patients (Joaquim et al., 2015; Curtin et al., 2017; Milgrom et al., 2017). Up to 90% of patients with bone malignancies are estimated to be having varying degrees of CRBP (Milgrom et al., 2017). They often receive suboptimal pain management when it is now clear that pain is an essential determinant of cancer patients' QoL (Coleman, 2006; Kane et al., 2015; Harding et al., 2018).

CRBP is mostly moderate to severe chronic pain in severity and is not proportional to the patients' co-morbidities (Mercadante, 1997; Ripamonti et al., 2012). A complex mechanism underlies its pathophysiology (Mercadante, 1997**;** Sabino & Mantyh, 2005). In most cases, it is inadequately assessed or treated, therefore requires an interdisciplinary approach to management.

The role of analgesics remains crucial in controlling CRBP (Sabino & Mantyh, 2005; Marras & Leali, 2016). Potent Opioids are still the recommended first-line analgesics in managing moderate to severe chronic CRBP (Ripamonti et al., 2012)**.** However, the burden of suboptimal cancer pain management with analgesics is most prevalent in Africa at about 63% compared to the western countries (Greco et al., 2014; Haumann & Joosten, 2017). Mainly because of the minimal utilisation of opioids, especially in the sub-Sahara, where only less than 1% of the global morphine is consumed (Kimani et al., 2017). The low Morphine consumption has been significantly attributed to shortages of analgesics, especially opioids, under prescription, underutilisation of guidelines to misconceptions on their use (Kimani et al., 2017; Odonkor et al., 2017).

For instance, the exact proportion of patients with CRBP inadequately treated with analgesics at Kenyatta National Hospital (KNH) is unknown. Wanjuki, 2013 showed that overall, about 65% of the cancer patients at the hospital receive inadequate pain treatment. Morphine consumption was at about 10%. Muriuki, 2007 also noted that 63.3% of patients with metastatic breast cancer at KNH complained of bone pain.

This study aimed to review and describe the pharmacological approach used in managing CRBP and patients' pain treatment outcomes. So as to ascertain whether pain management is satisfactory to the patient.

1.2. Problem statement

Cancer patients on analgesics are expected to be pain-free, and analgesics provide over 80% cancer pain relief (C. Carlson, 2016), if used effectively. The lead researcher surveyed the MTRH palliative registry and noted some degree of CRBP in a sizable proportion of bone malignancy patients on prescribed analgesics. It was not clear why, despite being on painkillers, a significant number of patients continued to complain of exacerbating non-relieving pain. There was no empirical data available to indicate whether patients received appropriate analgesic prescriptions as guided by the WHO analgesics ladder. Nor could the precise number with moderate to severe pain that received optimal analgesic pain management be determined. Little was known about the use of analgesics at MTRH, particularly opioids. Under prescription or utilisation of opioids in the treatment of CRBP by the prescribing clinician would suggest why patients with moderate to severe pain received suboptimal pain management. Clinicians were also likely to have inappropriately assessed the CRBP of the patients and prescribed inappropriate analgesics. On the other hand, the under prescription could either be due to unavailability of the opioids or institutional restrictions on opioid use. Lastly, many patients were on different specific analgesics meant to control pain, but it was unknown whether patients were satisfied with their pain treatment outcomes. Published data on CRBP management and patients' treatment outcomes at MTRH is sparse. The study proposed that the use of analgesics in CRBP management be described in order to determine the proportion of patients who received satisfactory pain management and who were satisfied with pain control.

1.3. Justification

There is increasing concern that CRBP adversely reduces the quality of life of patients. Incidentally, published data on CRBP management and treatment outcomes at MTRH are scarce. The proportion of patients at MTRH who have moderate to severe CRBP is also unknown. It is thus probable that clinicians at MTRH are challenged by patients with CRBP emergencies of varying pain intensities. Baseline information on the state of CRBP will be generated from the results of this research. This data will create awareness and may assist the administration to relocate CRBP management resources.

It was equally important to assess whether patients received optimal pain management as guided by WHO cancer pain treatment guidelines in order to guarantee an improvement in CRBP management. This is beneficial because it highlights whether the regular evaluation of pain intensity in patients with bone cancer with the aid of validated assessment instruments and its proper management, as recommended in the guidelines, is routinely performed for adequate and effective pain treatment. This assessment would provide an estimated proportion of patients considered to have received pain undertreatment.

It is also crucial that treatment outcomes are satisfactory. There is a lack of published data about patients' satisfaction with cancer pain control at MTRH. Therefore, it is not possible to gauge the management and treatment outcomes of CRBP with the rest of the world at MTRH. The research, therefore, also sought to assess the pain control satisfaction of patients. For any future related research, it will act as a baseline study. Finally, comparing the results with the rest of the world will lend credibility, justify the management protocol and, if necessary, enhance it.

1.4. Research Question

How is the use of analgesics in the management of CRBP at MTRH, and what proportion of patients is satisfied with their pain control on analgesics?

1.5. Objectives

1.5.1. General objective

To describe the use of analgesics in the management of CRBP at MTRH and determine the proportion of patients satisfied with their pain control on analgesics.

1.5.2. Specific Objectives

i. To determine the proportion of patients with moderate to severe CRBP at MTRH.
ii. To describe the prescription pattern of analgesic prescribed to patients with CRBP at MTRH using the Pain Management Index.
iii. To determine the proportion of patients satisfied with their pain control on analgesics using a self-reporting pain assessment tool.

1.6. Theoretical framework

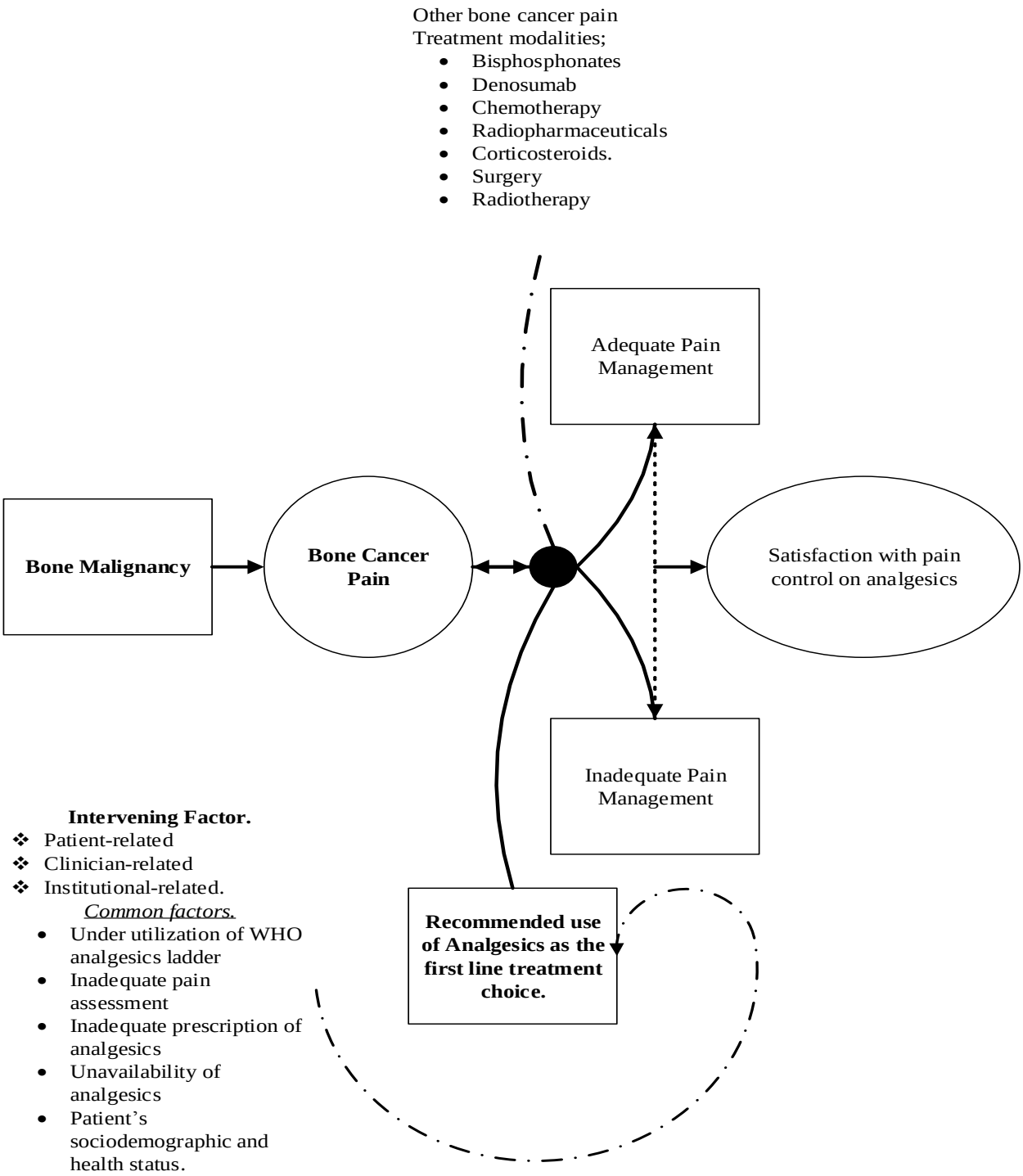

Figure 1 Showing standard CRBP treatment options.

CHAPTER TWO

2.0. LITERATURE REVIEW

2.1. Introduction

The International Association for the Study of Pain (IASP, 2017) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." In contrast, according to Kasper et al. (2015), "pain is an unpleasant sensation localised to a part of the body. Pain is often described in terms of a penetrating or tissue-destructive process (e.g., Stabbing, burning, twisting, tearing, and squeezing) or of a bodily or emotional reaction (e.g., Terrifying, nauseating, and sickening). Both definitions above preciously classify pain into two major dimensions: the physical and emotional aspects of pain. Indeed, CRBP, like any other cancer pain, is usually associated with psychosocial responses that may as well drastically affect a patient's quality of life. Cancer patients usually describe such responses as distressing and intolerable. Thus, the absolute measure of pain for clinical studies becomes a tremendous challenge that most studies only focus on the physical or sensory aspect of pain. Nevertheless, it is also crucial to note that the measure of physical pain is subjective, yet the most successful way of measuring pain intensity, given the fact that it is not proportional to the underlying pathology. Pain is only influenced by its meaning to the patient and its expected duration. "Pain is what the patient says it is" (Williamson & Hoggart, 2005).

2.2. Cancer Related Bone Pain

2.2.1. Pathophysiology of Cancer Related Bone Pain

The pain is due to increased intraosseous pressure on the endosteum, distortion of the periosteum, and nerve fibre compressions. Tumours invading and growing within the bone's medullary space activate primary afferent fibres and alter osteoblast/osteoclast balance to induce a pronounced inflammatory response. The activated osteoclasts subsequently lead to bone reabsorption and highly acidic pits formation within the bone that build up the intraosseous pressure to cause pain or compression of surrounding nerve roots or fibres. Stimulation of endosteal nerve endings destroys bone tissue and causes a release of chemical agents such as prostaglandins, bradykinin, substance P, and histamine, which distort the bone's periosteum. Subsequently, the enlarging tumour's increased stretch of the periosteum leads to pathological fractures or vertebral collapse. The growing tumour can also invade surrounding tissues to cause muscle spasms or inflammatory reactions or compress on a nerve to stimulate the expression of neuropeptides which are very sensitive to any noxious stimuli (Turabi & Plunkett, 2012; Mantyh et al., 2015; Milgrom et al., 2017).

CRBP usually involves mixed features of neuropathic and inflammatory pain pathways, which cause a state of constant hypersensitive pain (Sabino & Mantyh, 2005; Turabi & Plunkett, 2012).

2.2.2. Cancer Related Bone Pain Assessment

Appropriate assessment of pain is paramount in overall patient care, as it is the critical reason patients visit health centres. Pain is a subjective measure, and patients' self-reported assessment of their pain is the recommended standard. Although there are no single universally acceptable pain assessment tools given their limitations, numerous

validate tools have been rolled out to help standardise pain assessment in clinical practices and research. These are mostly one-dimensional tools that help health workers quantify patients' pain into a relatively objective measure. They commonly evaluate the physical dimension of pain. Some pain assessment tools include the Visual Analog Scale (VAS), Verbal Rating Scale, and Numerical Rating Scale. For this study's goal, the Numerical Rating Scale was chosen in the assessment of patients' pain intensity. That was because its reliability and validity have been tested in various pain studies. If compared to other pain scales, the tool has the highest sensitivity to pain, inclusive of CRBP (Brunelli et al., 2010). It can also provide data for statistical analysis. That made it a reliable tool for the objectives of this study.

Furthermore, many validated multidimensional pain assessment questionnaires evaluating numerous psychometric properties of pain have been constructed to provide data on both quantitative and qualitative aspects of pain. Among these is the Brief Pain Inventory. It is a validated multidimensional questionnaire with validated psychometric properties and construct validity for assessing pain intensity and pain interference of function. Its validity and reliability have also been tested in different cultural settings and languages. While testing for the BPI reliability in patients with bone metastases, Harris et al. (2006) concluded that the BPI provides excellent reliability between pain intensity and pain interference scores in patients with bone malignancies. For this reason, the BPI was adopted for the evaluation of patients' CRBP in this study.

2.2.3. Prevalence of Cancer Related Bone Pain

A geographical variation in the prevalence of CRBP exists across the globe. The variation in reported figures has been attributed to numerous ethical disparities or biases in pain prevalence and management (S. Beck, 2000; S. L. Beck & Falkson, 2001; Wyatt, 2013).

CRBP is prevalent in 85% of patients with advanced cancer of the Breast, Prostate, Lungs, and Kidney (Kassamali et al., 2010; Felice et al., 2017). This pattern varies slightly based on geographical location. For instance, in South Korea, CRBP is most prevalent in patients with liver, multiple myeloma and lung malignancies (Cho et al., 2015). If compared for individual metastatic tumours, CRBP is more prevalent in metastatic breast cancer than prostate or cervix cancers. For example, 50-90% of patients with metastatic breast cancer globally have CRBP (Wong & Pavlakis, 2011). However, the prevalence of CRBP is low in patients with metastatic cancers of the Prostate or Cervix with osseous involvement (Tsubamoto et al., 2013; Everdingen et al., 2016). Concerning primary bone tumours, CRBP is most prevalent in patients with Osteosarcoma, Chondrosarcoma, and Ewing's Sarcoma, respectively.

Approximately 60% to 90% of patients with bone malignancies experience varying severities of CRBP (Zhu et al., 2015; Milgrom et al., 2017; Vieira et al., 2019), and about 30% describe it as moderate to severe Pain (Zhu et al., 2015; Milgrom et al., 2017).

By contrast, Vieira et al. (2019) reported a comparatively higher pain proportion of patients (63.7%) with moderate to severe pain. CRBP is commonly experienced in the vertebrae, pelvis, femur, ribs, and skull (Kane et al., 2015).

2.3. Adequacy of CRBP management with analgesics

A Population-based study in Europe revealed that about 85% of patients with bone malignancies experience episodic attacks of intermittent severe pain called breakthrough pain (Davies et al., 2013). It is usually a sign of suboptimal pain management (S Mercadante & Arcuri, 1998; Milgrom et al., 2017). Numerous pain management guidelines, including the WHO analgesics ladder, have been implemented to ensure optimal pain management in all cancer patients. The WHO analgesics ladder is still the widely accepted standard guide in CRBP management, helping in clinical decision-making when choosing the appropriate analgesics (WHO, 1986).

Potent opioids remain the first choice recommended analgesics for moderate to severe CRBP (Colvin & Fallon, 2008; Kane et al., 2015; Milgrom et al., 2017; Lucchesi et al., 2017). However, opioids utilisation in the sub-Saharan remains at a minimal (Kimani et al., 2017). Studies have shown that if the WHO analgesics ladder is appropriately and effectively used, it can result in over 80% pain relief (Zech et al., 1995; WHO, 2013; Haumann & Joosten, 2017).

2.3.1. Pain management Index

The WHO analgesic ladder is very easy to administer and yet inexpensive (WHO, 2013). The Pain Management Index (PMI) is a well-validated tool regularly used to assess the adequacy of pain management with analgesics in cancer patients (Cleeland et al., 1994). The PMI employs the WHO analgesic ladder guidelines to determine whether patients are adequately treated for their pain. The tool uses scores to compare the patient's pain intensity with the most potent analgesic prescribed by a physician to manage this pain. It, therefore, indirectly assesses the utilisation of recommended adequate analgesics based on the WHO analgesics ladder.

The prevalence of inadequate CRBP management is thought to be highest in Africa and Asia (McCaffery & Ferrell, 1995; Greco et al., 2014; Haumann & Joosten, 2017). A comparison between two studies, one done in Canada and the other in Kenya, portrayed this assertion. Study outcomes by Mitera et al. (2010) in Canada revealed that approximately 46% of patients with bone malignancies had severe pain, 58.5% were on potent opioids, while about 25.8% were reported to have had inadequately managed pain. On the other hand, a relatively similar study by Wanjuki, (2013) in Kenya revealed that overall, 85% of patients had moderate to severe pain, only 10% were on strong opioids, a majority were on non-opioids, and 65% were reported to have had inadequately managed cancer pain. Although the study does not give the exact proportions for patients with bone malignancies, the findings are evidently in agreement as with those by McCaffery and Ferrell, (1995), Greco et al. (2014) and Haumann & Joosten, (2017).

2.4. Factors associated with CRBP intensity and adequacy of pain management

Numerous barriers hinder the recommended use of analgesics in clinical practise. They have been associated with the likelihood of moderate to severe pain and suboptimal pain management. They are broadly categorised as institutional, clinician, or patient-related. They include unavailability of analgesics particularly opioids, inadequate CRBP assessment, clinician's lack of knowledge about pain management guidelines, inadequate opioids prescriptions in fear of addictions and side effects, institutional restrictions on opioids prescriptions, patient's reluctance to report their pain and poor adherence to prescribed medications among many others (Tawil & Salameh, 2018).

Even though potent opioids are recommended for moderate to severe CRBP, studies have revealed that up to 50% and as low as 20% of the clinicians prescribe opioids

analgesics for moderate to severe CRBP (Jacobsen et al., 2009). Wanjuki, (2013) estimated this percentage to be about 10% at KNH. Several patient-related characteristics, such as age, ethnicity, education level, social-economic status, disease stage, and co-morbidities, have been associated with inadequate pain management. It has been suggested that these factors play a crucial role in influencing the clinician's attitude and choice of analgesics, particularly opioids, and may thus contribute to the poor choice of painkillers for the management of the CRBP. The poor, elderly, minority and patients in an advanced stage are more likely to have inadequate pain management (Wu et al., 2013; Fujii et al., 2017). The opposite could also be true based on findings of Larue et al. (1995) and Okuyama et al. (2004).

2.5. Conventional CRBP treatment modalities

2.5.1. Analgesics

Every bone malignancy patient should have freedom from CRBP. Analgesics, therefore, need to be correctly prescribed and administered as recommended in the treatment guidelines. NSAIDs' efficacy to control CRBP is still limited (Mantyh et al., 2015), but they show better pain outcomes when used in conjunction with morphine since they have a crucial role in inflammatory pain control (Kane et al., 2015). Morphine is the most commonly prescribed strong opioid for moderate to severe CRBP. Others include methadone, hydromorphone, oxycodone, and fentanyl. There is no substantial evidence to suggest that these drugs are superior to morphine (Ripamonti et al., 2012); Marras & Leali, 2016). Morphine is well tolerated and provides a more superior analgesia level than tramadol/codeine in the management of moderate CRBP (Lucchesi et al., 2017)**.**

Morphine's peak analgesics effect lasts up to 48 to 72 hours (Aarnes & Muir, 2011). When used with other adjuvants such as anti-convulsant and anti-depressants, morphine shows superior efficacy over NSAIDs in controlling both nociceptive and neuropathic pain. That is because CRBP is a complex mixed type of pain with both nociceptive and neuropathic pain. In a randomised controlled trial, Kane et al. (2015) reported that about 75% of patients with CRBP achieve adequate pain relief with strong opioids. Likewise, Davies et al. (2011) showed high patient satisfaction levels with opioid-induced cancer pain relief.

On the contrary, morphine use is sometimes limited due to its side effects that negatively affect the patient's adherence. Common side effects include constipation, nausea/vomiting, urinary retention, pruritus, drowsiness, cognitive impairment, confusion, among many others. It is most times recommended to readjust the dosage or manage the side effects with other medications (Ripamonti et al., 2012). On the other hand, NSAIDs are well tolerated by the patients and are the most prescribed analgesics for CRBP, including moderate to severe Pain (Kane et al., 2015).

2.5.2. Radiotherapy

Convectional External Beam Radiotherapy is the cardinal treatment of choice for patients with painful bone malignancies that are associated with minimal or no neurological deficits, poor prognosis, and very short life expectancy. Radiotherapy is not of many benefits in reversing motor impairment due to spinal compression or non-radio-responsive bone tumours. However, radiotherapy is of great interest in controlling CRBP by decreasing tumour size, slowing down the malignancy growth, and preventing pathological fractures and neurological compression. That is because of radiotherapy's capability to aid ossification, diminish osteoclasts activation, and kill tumour cells (Willeumier et al., 2016; Felice et al., 2017). The EBRT is usually

prescribed as a single fraction or multiple fractions, but numerous studies have shown regardless of the model used, they are both equally efficient in controlling CRBP (Rich et al., 2018; Shuja et al., 2018). Partial to optimal pain relief within four weeks and reduced analgesics use can be achieved in 50 – 80% of patients on EBRT alone while a third will have complete pain relief. Perhaps EBRT because radiation is more effective than standard analgesics for treating neuropathic pain (Popovic et al., 2015).On average, EBRT provides pain relief for up to 19 weeks (Felice et al., 2017).

Radiotherapy is seldom associated with any serious complications. Complications of RT are usually acute and self-limiting (Westhoff et al., 2018). Recent advances of highly conformal radiotherapy modalities, such as stereotactic body radiation therapy, are said to provide more effective pain relief of up to 90% with more prolonged remission after six months and fewer side effects if compared to EBRT. One limitation of SBRT is that its safety is not well documented and is quite costly (Popovic et al., 2015; Fridley et al., 2017; Harding et al., 2018). A study conducted at a pain clinic in Portugal suggested that patients on radiotherapy are likely to receive optimal pain management with analgesics compared to those on chemotherapy (Reis-Pina et al., 2017).

2.5.3. Surgery

Historically, patients continued to have suboptimal CBRP relief, recurrent chronic pain and progressive non-reversible motor impairments, which radiotherapy alone could not adequately address. With recent significant evolutions in surgical techniques, instrumentation and better less invasive approaches, surgery has had a tremendous positive impact on improving the QoL of patients with bone malignancies (Patchell et al., 2005; Fridley et al., 2017). Surgery with adjunct radiotherapy is

currently considered the second choice in patients with persistent CRBP and complicated bone malignancies (Fridley et al., 2017).

Numerous studies have shown surgery to have an added advantage over radiotherapy in pain relief and restoring functional status. A systematic review that assessed pain relief and functional outcomes in patients who had had surgery at various sites due to bone malignancies revealed that overall over 92% and 93% of the patients had pain relief and functional restoration, respectively (Milgrom et al., 2017). These and other studies' findings might suggest that patients who get surgery are likely to receive adequate pain relief than those on chemotherapy and radiotherapy if pain outcomes were compared (Felice et al., 2017; Singh et al., 2017). Unfortunately, only less than 2% of patients with bone malignancies are offered surgery due to pain as an indication (Zaikova et al., 2011).

2.5.4. Chemotherapy and adjuvant bone target agents

The treatment of CRBP with systematic therapies generally remains unspecific because it mainly depends on the physician's understanding of these therapies' role in treating the patient's pain. This remains a significant hindrance to these therapies' optimal utilisation (von Moos et al., 2018). Although chemotherapy alone is not recommended for the management of bone CRBP, it indirectly plays a crucial role in treating the primary tumour. Study outcomes have revealed that patients on chemotherapy are more likely to receive suboptimal pain treatment with analgesics than those on radiotherapy or surgery. It can be demonstrated in a comparison of two study outcomes. Singh et al. (2017), in India revealed that 77% of patients treated with chemotherapy received suboptimal pain treatment compared to 35% on radiotherapy in a similar study in Portugal by Reis-pina et al. (2017). However, there

is no conclusive evidence to affirm this, given the studies' geographical and economic differences.

It is recommended to use chemotherapy in conjunction with adjuvant bone target agents, e.g., *bisphosphonates* or monoclonal antibodies (i.e., denosumab). Using these adjuvant therapies has proved effective in managing CRBP (Patrick et al., 2015; Milgrom et al., 2017). Using chemotherapy with adjuvant bone-targeted agents can significantly delay the progression of SREs and substantially reduce CRBP in patients with bone metastases. Patients on adjuvant bone target agents are twice less likely to develop SREs than those on chemotherapy alone. However, it is not recommended to use a mono bone target agent therapy as the first-line choice to control CRBP (Porta-Sales et al., 2017). That is because they do not directly block the pain, but slow the progression of tumour growth by causing osteoclast apoptosis and limit risk for growth of metastases in visceral tissues (Patrick et al., 2015; Milgrom et al., 2017). Nonetheless, it is suggested that patients diagnosed with bone metastases should be prescribed bisphosphonates regardless of whether they are symptomatic or not (von Moos et al., 2018).

2.6. Satisfaction with CRBP control

The concept of pain management should not only be limited to adequate pain treatment or control. It should also focus on patients' satisfaction with pain control, mainly because patients' satisfaction with pain control may be a vital indicator of analgesics effectiveness in CRBP treatment outcomes. Secondly, because a notably higher patient's satisfaction directly influences treatment adherence. The proportions of patients' satisfaction with pain control vary from as low as 44% to over 75% across diverse populations. Patient satisfaction is commonly associated with the amount of pain relief obtained by a patient (Pellino & Ward, 1998; Hanna et al., 2012). Besides

pain relief, aspects of the patient-provider interaction, pain intensity, age, beliefs and anxiety at treatment onset are predictive of satisfaction with pain control (Hirsh et al., 2005; Muller-Staub et al., 2008; Phillips et al., 2013; Baker et al., 2016); Thinh et al., 2018).

Locally, no study was found that assessed patients' satisfaction with pain control based on the extent and nature of CRBP. But other publications have linked pain control satisfaction with analgesics (J. Carlson et al., 2003)**.** Pain medications should be accessible and routine if satisfaction levels and pain management were to improve (Cleary & McNeil, 1988).

Numerous pain assessment tools usually do not evaluate patient satisfaction, and this frequently carries clinical limitations. Such limitations are characteristic of the pain rating scales. There is often a common false perception that low pain intensity scores are clinically suggestive of positive patient outcomes or satisfaction (and vice versa). Various studies have shown a paradoxical effect of high patients' pain control satisfaction in patients with high pain intensity, i.e., moderate-severe pain (Phillips et al., 2013). Therefore, it is vital to investigate the correlations of CRBP control satisfaction in patients with bone malignancies.

Satisfaction like pain is also a subjective measure which solely depends on patients' perception of the expected outcome. The patient's self-reported response is the recommend gold standard for assessing satisfaction (McDaniel & Nash, 1990; Megivern et al., 1992). The American Pain Society Patient Outcome Questionnaire was drafted to incorporate patient satisfaction in the assessed pain treatment outcomes. There is, however, no absolute objective measure of satisfaction as it can best be assessed on either a Likert scale or a numerical scale.

CHAPTER THREE

3.0. METHODOLOGY

3.1. Study Design

This descriptive, prospective, non-interventional study aimed to assess the pharmacological use of analgesics in CRBP management and pain control satisfaction in patients. The above design was selected because it gives a more accurate measure of pain management outcomes besides being quick and cost-effective. In order to minimise both investigator and patient information biases, the study employed an interview-based questionnaire and a self-administered questionnaire. At one point in time, only consented patients were enrolled, interviewed, and then followed up daily for five days to assess their pain relief and pain control satisfaction.

3.2. Study Site

The study was conducted at the Moi Teaching and Referral Hospital in Eldoret Town in western Kenya's Uasin Gishu County for one year. It is situated 300 km northwest of the capital city of Kenya, Nairobi. MTRH has a bed capacity of 1000, and after Kenyatta National Hospital, it is the second-largest national referral hospital. Its catchment is mainly in Kenya's western part and surrounding counties. It also receives a few patients from Uganda's eastern region and other neighbouring counties. For this study, MTRH was an appropriate site primarily because; MTRH has an average outpatient of 210,000 per year, roughly 600 outpatients per day. It also has a cumulative 35,000 inpatients per year. At least 600 cases of cancer are diagnosed at MTRH annually, and approximately five outpatients with bone malignancies are reviewed weekly. In western Kenya, MTRH serves as the most prominent cancer treatment centre. The study was conducted in the wards, outpatients' clinics.

3.3. Study Population

The study population included hospital-based adult cancer patients diagnosed with bone malignancies reviewed at MTRH.

3.3.1. Case Definition for Cancer Related Bone Pain

A case was an adult cancer patient with a histo-pathologically confirmed tumour and an osseous lesion(s) on a radiograph. CRBP was defined as pain or discomfort localised in the region of the osseous lesion. The pain was either caused as a direct result of the malignant bone lesion or the administered anticancer therapy, that is, radiotherapy, chemotherapy, or surgery used to treat these bone malignancies. It included physical (neuropathic or somatic pain), i.e., pain caused by either compression, infiltration, or inflammation of the affected bone, surrounding soft tissues, or nerves. However, it excluded pain due to emotions or psychological factors, i.e., depression, stress, anxiety, etc., that may also be associated with this disease. A patient could describe it as a discomfort in the affected bone(s) or as a dull/throbbing pain that increases in intensity with time or with the tumour's growth and may or may not limit their daily activities. A patient was said not to have CRBP if they had bone pain due to a noncancerous osseous lesion. That is to say, TB, traumatic injuries, or as a complication from co-morbidities or co-infections.

3.3.2. Inclusion criteria

An eligible patient was a consenting adult who;

- Had a histo-pathologically confirmed primary malignancy
- Had a radio-graphically (preferably MRI or CT-Scan) confirmed osseous lesion
- Had a cognitive capacity to rate their pain on a Numerical Rating Scale

3.3.3. Exclusion Criteria

A patient was excluded if they declined to consent and or;

- The patient had Non-cancer-related bone pain.
- A patient who could not be contacted on follow up. That is via phone, SMS, or any other selected communication platform.

3.4. Sample Size Determination

The study was a census because it was challenging to determine the estimated number of patients with bone malignancies reviewed at MTRH. A primary survey conducted at the palliative clinic estimated that approximately five bone tumour patients were seen weekly. There were 284 patients screened for study eligibility. In the final analysis, only 96 patients were included, as shown in figure two.

3.5. Sampling procedure

Preliminary screening for eligible study participants was done. It involved reviewing patients' files at the various study entry points. Those patients thought eligible were then approached by the researcher, who explained the study proceedings to them and obtained written informed consent from those fitting the inclusion-exclusion criteria.

Only consented patients willing to participate in the study were then sampled using a non-probabilistic consecutive sampling technique until the minimum required sample size was obtained. Outpatients were selected after their appointed clinic review, while inpatients after the ward review.

A baseline assessment of patients' prescribed analgesics and pain was done at recruitment. Subsequent daily follow up assessments for five days evaluating pain relief and satisfaction with pain control were done thereafter.

3.6. Data Collection Methods

3.6.1. Questionnaire and Validation

Data collection involved administering two types of questionnaires: an interview-based questionnaire *(appendix 3a)* and a self-administered questionnaire *(appendix 3b)*. The interview-based questionnaire was designed with information compiled from various sources and previous studies. This questionnaire had a section on a patient's socio-demographic and another on their medical history. It explored the bone malignancies pattern and some of the most reported factors associated with inadequate cancer pain management. Information regarding bone malignancies pattern was collected on the type of primary cancer, site of bone tumour and related visceral metastases, current cancer-specific treatment modalities, current analgesics medications, etc. A current cancer-specific treatment modality was considered as one prescribed and administered no more than three months ago. Data concerning patients' performance status was also collected using the Eastern Cooperative Oncology Group (ECOG) functional status tool.

The questionnaire was administered only by the researcher who record the patients' responses to minimise information biases. It was done because almost more than half of the data for this questionnaire was sourced from the patients' treatment hospital files. In doing so, the researchers believed that would minimise errors caused by entering incorrect data, especially when dealing with patients who are not well acquainted with their medical history. Therefore, data, especially about the patients' medical history, was collected from the patient's treatment file.

On the other hand, the assessment of a patient's CRBP and pain control satisfaction on analgesics involved administering a self-administered questionnaire *(appendix 3b)*.

This questionnaire was drafted using questions from the Brief Pain Inventory Short Form BPI-SF and the American Pain Society Patient Outcome Questionnaires for this study's objectives. These were selected as the best tools for assessing patients' pain and satisfaction because they are simple and easy to administer. Most importantly, they are well-validated tools to evaluate cancer pain, including CRBP. For these reasons, they were adopted in this study. The questionnaires have been used in numerous cancer studies globally, including Kenya. For example, in a pain study conducted at KNH quoted above Wanjuki, (2013). For patients who could not understand English, a translator was used. A Swahili version of the self-administered questionnaire was also available.

3.6.1.1. General Baseline Assessment

A general baseline assessment was done at the time of recruitment. The researcher documented data on patients' primary cancer diagnosis, metastatic sites, and medical history of specific anticancer treatments (i.e., chemotherapy, radiotherapy, and surgery) prescribed and administered within three months of pre-study recruitment.

Baseline pain assessment included Brief Pain Inventory (BPI) ratings on a 0 to 10 scale, pain duration in months, and average pain intensity scores. CRBP intensity was categorised into mild (0 - 3), moderate (4 – 6), and severe (7 – 10) for statistical analyses. Furthermore, currently prescribed analgesic medications and adjuvants were also recorded before noting the analgesics scores and calculating the baseline Pain Management Indexes. The time spent with each patient was approximately 25 to 30 minutes.

3.6.1.2. Follow up Assessment of Satisfaction with Pain Control

Upon enrollment, the consented patient and their caretakers were instructed on how to fill the follow-up questionnaire *(appendix 3c)***.** This questionnaire assessed a patient's daily average pain intensity score in 24 hours, pain relief, pain control satisfaction, and any modifications made in the analgesics prescribed. For inpatients, these modifications in analgesics as per treatment sheet were noted by the researcher. Patients were given five leaflets of this questionnaire in a sealed envelope and were encouraged to fill each independent of the other.

An individual additional written consent was obtained from outpatients on whether to be contacted via phone for follow up on data documentation and progress status. Those who agreed were contacted on day two and day five of follow up to check progress and document their responses to the research questions. Each telephone conversation lasted, on average 15mins. Patients also returned the questionnaires on the following review for record-keeping and recorded data concordance.

Study participation ended primarily if a patient; i) completed the follow-up period, ii) was lost to follow-up, iii) had not started the prescribed medications within 48 hours of recruitment, iv) died and v) in the even that an inpatient was discharged or outpatient admitted before completion of follow up period.

3.6.2. Pilot study

A pilot study to test the data collecting tools was conducted at Alexandria Cancer Centre for two weeks. Two staff clinicians and at least ten patients (10.4%) were selected at convenience based on research ethical principles to participate in the pilot study. To ensure content and culture validity, the researcher during this period sought feedback on whether the questionnaires were user friendly, missing information or

contained misinterpreted questions that would have led to information errors. Items that did not address the research objectives were omitted from the questionnaire.

Thus items 8, 10 and 11 in the self-administered questionnaire *(appendix 3b)* in the previously submitted proposal were excluded. They seemed not to be easily understood by the patients and were not suitable at the baseline assessment. Furthermore, expert opinions also found no statistical significance or reasons for assessing satisfaction and pain relief before administering the treatment under investigation.

3.7. Data Management:

3.7.1. Variables

The dependent variables were; moderate to severe CRBP, pain control satisfaction and adequacy of pain management.

The primary independent were; i) socio-demographics, i.e. age, sex, occupation and level of education, ii) medical history, i.e. tumour type, number of bone lesions, ECOG, anticancer treatment modalities and presence of pathological fractures or spinal cord compression.

3.7.2. Measures

3.7.2.1. Pain Intensity

Patients ranked CRBP intensity on a Numerical Rating Scale (NRS), which ranks pain on a scale of zero to ten with zero-rated as "No pain" and ten as "worst pain imaginable". The assessment excluded Pain due to emotions or psychological factors, i.e. depression, stress, anxiety, etc., even though it is also equally important when evaluating pain in cancer patients. The pain intensity scores were categorised as illustrated in the clinical manual *(appendix 2)* on use of the NRS based on the severity of pain as shown in the table below;

Table 1 Showing categorised pain intensities.

0 = *No Pain*	**1 – 3 = *Mild pain***	**4 – 6 = *Moderate Pain***	**7 – 10 = *Severe Pain***

3.7.2.2. Average Pain Severity score:

The average pain severity score of any given patient was calculated by adding the pain intensity scores of items 3, 4, 5 and 6 on the self-administered questionnaire *(appendix 3b)*. The total score was then divided by four to obtain an average severity score out of ten that was then used to grade the patient's pain intensity, as illustrated in table-1 above.

3.7.2.3. Analgesics Scores:

Patients' analgesics were categorised into two categories, i.e. Prescribed Analgesics and Self Medicated Analgesics. In this context, Prescribed Analgesics were those legally prescribed by a medical practitioner while Self Medicated Analgesics were those obtained by a patient without a medical practitioner's prescription. The analgesics score for each patient was calculated based on the prescribed analgesics' potency using the analgesic quantification algorithm as stated; (0: No analgesics, 1: Non-Opioid Analgesics, 2: Weak Opioid Analgesics, 3: Strong Opioid Analgesics). In cases where the patient was on multiple analgesics of varying potencies, the most potent analgesic as by the WHO analgesics ladder was then used for this calculation.

3.7.2.4. Adequacy of Analgesics use and Pain Management Index

Adequacy of analgesics use for CRBP treatment was defined and determined by the Pain Management Index PMI *(appendix 4)*. The Pain Management Index (PMI) for each patient was calculated by subtracting the categorised Pain Intensity Score from

the Analgesic Score. The Pain Management Index ranges from -3 to 3. A Negative score was suggestive of potentially inadequate pain management by the prescriber while a positive score or zero was considered as the acceptable recommended treatment for CRBP.

3.7.2.5. Overall Satisfaction with Pain Control

Patients' satisfaction with pain control on analgesics was evaluated as a single response question (Satisfied, Not Sure or Dissatisfied) on follow up. No prior specific period on a given bone cancer treatment or episodes of contact with the patient was considered in this evaluation. Satisfaction was evaluated longitudinally on each day of follow up. After follow-up, a patient's overall satisfaction level was regarded as a single response with the most correspondence. That is three or more of the similar single response. In case a patient had equivocal responses, their response was then regarded as "Not Sure". That is two similar responses for two separate single responses.

3.8. Data analysis

Stored data was verified, cleaned, coded and entered into SPSS (Statistical Package for Social Science) for analysis. Univariate analysis was used to get the general description of the data concerned with patient's demographics, medical history, pain scores, analgesics use and pain control satisfaction levels. Descriptive statistics for categorical variables, i.e. gender, occupation, etc., were described as frequencies and percentages. The continuous variables like pain, age, etc., were described as means, medians, standard deviation, and ranges. The Descriptive statistics were then presented appropriately in graphs, tables, and charts.

Chi-square test and the Fishers Exact t-test were used to check for associations between categorical variables. In contrast, the Mann-Whitney test was used to compare differences in the means of continuous variables. A bivariate analysis was used to determine factors associated with moderate to severe pain, inadequate pain management, and satisfaction with pain control. Variables that had *p*-values < 0.05 were then entered into multivariate analysis.

Multiple logistic regression models were used to identify variables independently associated with the presence of moderate-severe pain, satisfaction with pain control and inadequate pain management. Odds ratios, 95% confidence intervals, and ***p***-values were computed for each variable. A ***p***-value of less than 0.05 was considered statistically significant in explaining the presence of the dependent factor investigated.

3.9. Ethics Consideration

All procedures performed in this study involving humans were per the ethical standards. The study first sought approval from the Institutional Research and Ethics Committee of Moi University, MTRH Chief Executive Officer and Oncology Unit In-Charge. The study approval number was 0003262, and ethical clearances were received *(see appendices 5 and 6)*. Informed written consent *(appendix 1)* was obtained from each patient enrolled in the study. The study objectives were fully explained to participants in a language they fully understood. All information collected was treated with confidentiality. No harm of any nature was imposed on the patients. There was equity in providing health care to all patients, whether enrolled in the study or not. No rewards were provided to any subject who consented and enrolled in the study. The patient had the autonomy to exit the study at whatever point they wanted during the interview or follow up without prejudice or bias of assessing health care. There were not any conflicts of interest in this study research if any

known to the researcher. The study did not receive any external funding. The study was the researcher's work and not plagiarised. No fabrication or falsification of the results was done during the compilation of this research report. The disposal of the collected patients' particulars will be done by shredding as per IREC guidelines.

The collected data was locked in a secure locker that was only accessible to the investigator. Electronic data was stored in a password-protected laptop. To further ensure and guarantee patients' confidentiality and privacy, all patients' identifications on reported data were de-identified. Study findings will be published in a selected journal, and a copy of the thesis book will be submitted to the Moi University School of Medicine Library for public access.

3.10. Study Implications

The study findings will potentially provide a basis to aid the hospital administration in reevaluating its cancer care services, especially the utilisation of the recommended cancer pain management guidelines and patients' satisfaction policy. Subsequently, this will help increase and maximise the number of cancer patients receiving adequate pain management at MTRH. It will also tremendously have a considerable impact on patients' quality of life. Lastly, the study findings will be significantly important in influencing the procurement of unavailable CRBP treatment modalities at MTRH.

3.11. Study flow chart:

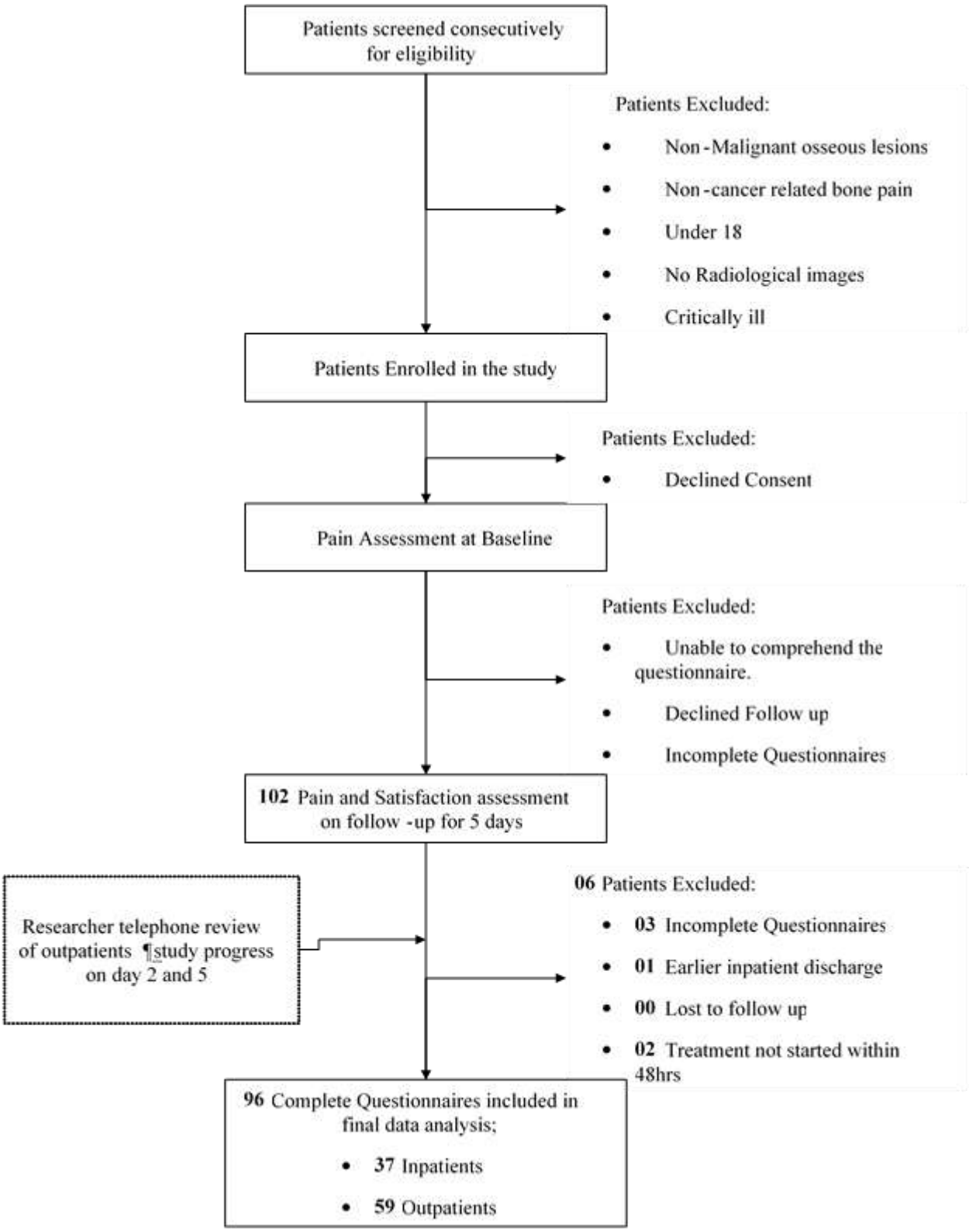

Figure 2 Summarizing the study's flow of procedures

CHAPTER THREE

4.0. RESULTS

4.1. Introduction

The study was conducted between March 2019 and March 2020. Of the 102 patients enrolled and followed, only 96 were included in the final statistical analysis, as illustrated in the flow chart in *figure 2* above.

4.2. Patients Baseline Characteristics

Table 2 :Patients' socio-demographics.

Variable	*Category where* N=96	*Frequency (n)*	*Percentage (%)*
Age	Median (IQR)	57 (44, 69.5)	-
Sex	Male	50	52.1
	Female	46	47.9
Occupation	Farmer/ Self-employed	41	42.7
	Unemployed/student/ Retired	35	36.5
	Public /private sector	12	12.5
	Casual laborer	8	8.3
Education	No Formal Education	38	39.6
	Primary	32	33.3
	Secondary	13	13.5
	College	13	13.5

4.2.1. Patients' baseline socio-demographics

The study population's socio-demographic data are summarised in *table 2* above. The median age was 57 (range19 to 90) years. More males 50 (52.1%) than females 46 (47.9%) were recruited. Most patients attained a primary education level (33.3%) or no formal education (39.6%). A majority of the patients (42.7%) were farmers/ Self-employed.

Table 3 : Patients' medical history

Variable	*Category where N=96*	*Frequency (n)*	*Percentage (%)*
Tumour type	Primary	33	34.4
	Secondary	63	65.6
Bone lesions	Solitary	45	46.9
	Multiple	51	53.1
ECOG	0 – 2	65	67.7
	3 – 4	31	32.3
Pathological fracture	Absent	61	63.5
	Present	35	36.5
Spinal cord compression	Absent	76	79.2
	Present	20	20.8
Treatment modalities	Chemotherapy alone	61	63.5
	Symptomatic	17	17.7
	Surgery ± Chemo	14	14.6
	Radio ± Chemo	4	4.2

ECOG *Eastern Cooperative Oncology Group functional status*

4.2.2. Patients' baseline medical history

The study population's medical history data are summarised in *table 3* above. Most patients, 63 (65.6%), had metastatic bone tumours. Cancers of; Prostate (38.1%), Breast (34.4%), and Gastrointestinal tumours (14.3%) were the commonest metastatic bone tumours. Others included thyroid, lymphoma, and malignant melanoma. Multiple myeloma (66.7%) and Osteosarcoma (27.3%) were the commonest primary bone tumours. Others included Giant cell carcinoma and lymphoma.

Bone lesions frequented the spine, followed by the femur and pelvis, and more patients had multiple bone lesions (53.1%). Sixty-five patients (67.7%) had an Eastern Cooperative Oncology Group (ECOG) functional status of 0-2. Regarding Skeletal

Related Events SREs, 35 (36.5%) patients had pathological fractures while 20 (20.8%) patients had spinal cord compression.

Seventy-four percent (74%) underwent chemotherapy with or without any other treatment with 61 (63.5%) patients on chemotherapy alone. Radiotherapy was offered to 4 (4.2%) patients, and 14 (14.6%) patients underwent surgery with or without chemotherapy.

4.3. Cancer Related Bone Pain:

According to the BPI pain severity scores, 83 (86.5%) patients reported pain at the baseline assessment. With 67 (69.8%) patients having moderate to severe pain, 29 (30.2%) had mild to no pain. CRBP was most prevalent in patients with cancer of Breast and Multiple myeloma, followed by Prostate cancer.

Table 4 : Baseline pain intensity assessment

Variable	*Category where N=96*	*Frequency (n)*	*Percentage (%)*
Pain intensity	No pain	13	13.5
	Mild pain	16	16.7
	Moderate pain	50	52.1
	Severe pain	17	17.7

The follow-up pain assessment was comparatively in range of the baseline evaluation. The proportion of CRBP ranged from 83.3% to 86.5%. That of moderate to severe pain ranged from 57.3% to 62.5%.

4.3.1. Factors associated with moderate to severe CRBP

In the baseline bivariate analysis listed in (tables 5), there was an association between moderate to severe pain and age, ECOG, pathological fracture, spinal compressions and treatment modalities ($p<0.05$).

Table 5 :Bivariate analysis for the associations between pain intensity and patients' baseline characteristics

		Pain Intensity (n)		
Variable	*Category*	*No/Mild*	*Moderate/severe*	*p-value*
Sex	Male	17	33	0.399[c]
	Female	12	34	
Age	Median (IQR)	46(26,62)	59(49,70)	0.025[m]
Occupation	Farmer/ Self-employed	13	28	0.867[f]
	Unemployed/student/Retired	9	26	
	Public /private sector	4	8	
	Casual labourer	3	5	
Education	None	7	31	0.105[f]
	Primary	13	19	
	Secondary	3	10	
	College/University	6	7	
Tumour type	Primary	10	23	0.988 [c]
	Secondary	19	44	
Bone lesions	Solitary	18	27	0.050 [c]
	Multiple	11	40	
ECOG	0-2	25	40	0.011 [c]
	3-4	4	27	
Pathological fracture	Absent	27	34	<0.001[c]
	Present	2	33	
Spinal cord compression	Absent	28	48	0.006[c]
	Present	1	19	
Treatment Modalities	Chemotherapy	18	43	0.004f
	Symptomatic	1	16	
	Surgery ± Chemo	9	5	
	Radiotherapy ± Chemo	1	3	
Prescribed Analgesics	None	15	19	0.088[c]
	NSAID	8	26	
	Opioid	6	22	

[c] Chi-Square; [f] Fishers Exact Test; [m] Mann Whitney U test; [(n)] number of patients
Moderate to severe pain was categorised as an Average Pain Severity Score of ≥ 4.

In the confirmatory multiple logistic regression *(table 6)*, having a pathological fracture (*p*: 0.030, AOR: 12.285, Cl: 1.268-119.019) was associated with an increased likelihood of experiencing moderate to severe pain.

Table 6:Multivariate logistics analysis showing factors associated with moderate-severe pain

Variable	*Categories*	*AOR*	*p-value*	*95% CI*
Age	Covariate	1.032	0.063	0.998 - 1.067
ECOG	0-2			
	3-4	3.697	0.077	0.866 - 15.770
Pathological Fracture	Absent			
	Present	12.285	0.030*	1.268 - 119.019
Spinal cord compression	Absent			
	Present	1.621	0.757	0.076 - 34.411

AOR Adjusted Odds Ratio; Cl Confidence Interval

4.4. Prescription pattern of prescribed analgesics

A sum of 62 (64.6%) patients were prescribed analgesics at baseline. Non-opioids were prescribed to 34 (35.4%) patients, while opioids were given to 28 (29.2%) patients. During follow-up, 20 (20.87%) patients were prescribed analgesics. Of those prescribed analgesics, 15 patients received opioids.

At baseline, 28 (29.2%) patients with pain were prescribed no analgesics. Of these, 19 (19.8%) patients reported moderate to severe pain *(table 7)*.

On follow up, 21 (21.9%) patients with pain for the entire study duration received no prescribed analgesics. Of these, 16 (16.7%) patients had moderate to severe pain for the entire duration.

Table 7 :How analgesics were prescribed for different pain intensities at baseline

Pain Intensity	*Prescribed analgesic*		*where N=96*		*n (%)*
	None	NSAID	Weak Opioid	Strong Opioid	Total
None (0)	6 (6.3)	5 (5.2)	1 (1.0)	1 (1.0)	13 (13.5)
Mild (1 – 3)	9 (9.4)	3 (3.1)	1 (1.0)	3 (3.1)	16 (16.6)
Moderate (4 – 6)	17 (17.7)	22 (22.9)	1 (1.0)	10 (10.5)	50 (52.1)
Severe (7 – 10)	2 (2.1)	4 (4.2)	5 (5.2)	6 (6.3)	17 (17.8)
Total	34 (35.4)	34 (35.4)	8 (8.3)	20 (20.9)	96 (100)

[n] number of patients *[%] percentage of patient of the whole population N*

4.4.1. Self-prescribed analgesics

Nineteen (19.8%) patients with pain, all of whom were outpatients on follow up obtained self-prescribed analgesics. Paracetamol, followed by local herbs and ibuprofen, were the most frequented self-prescribed analgesics. *Table 8* below shows the types of self-prescribed analgesics obtained by patients and the number of patients who received each analgesic.

Table 8 :Most frequented self-prescribed analgesics

Self-Prescribed Analgesics	*Frequency, n*	*Percentage**
Paracetamol	12	12.5
Ibuprofen	5	5.21
Local Herbs	5	5.21
Pain Gel	5	5.21
Diclofenac	3	3.13
Aceclofenac	2	2.08
Tramadol	1	1.04

**Percentage of the total sample (n=96); many patients were on more than one pain medication.*

4.4.2: Adequacy of analgesics use

A negative PMI is suggestive of probable inadequate analgesics use based on WHO guidelines. At baseline, 59 (61.5%) patients received suboptimal pain management with analgesics. The proportion of patients with a negative PMI ranged from 59.4% to 65.6% at follow up.

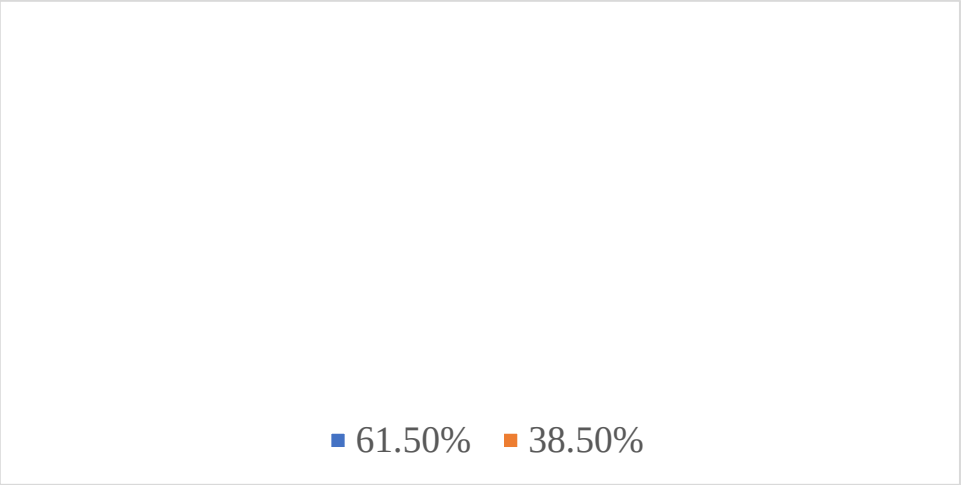

Figure 3: Baseline assessment of the adequacy of pain management

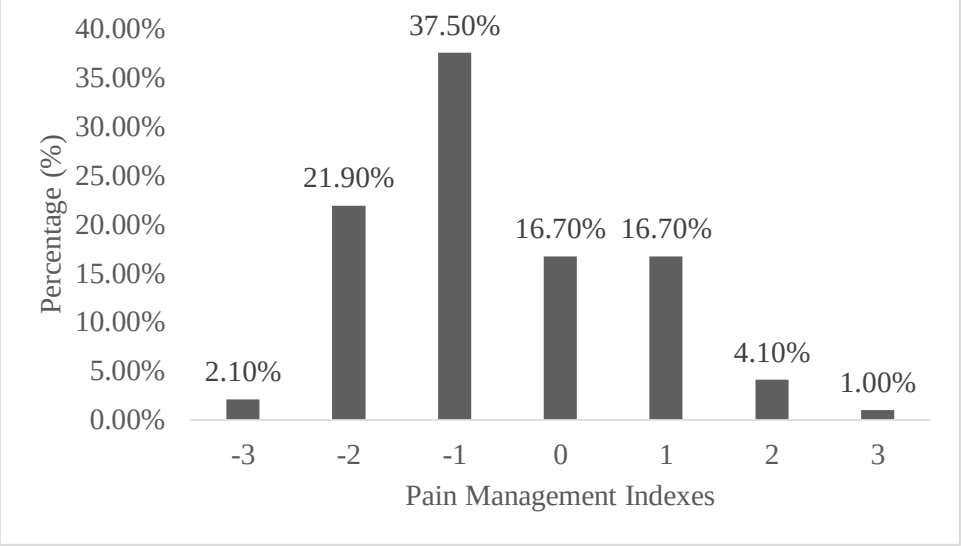

Figure 4 :Distribution of the different Pain Management Indexes at baseline

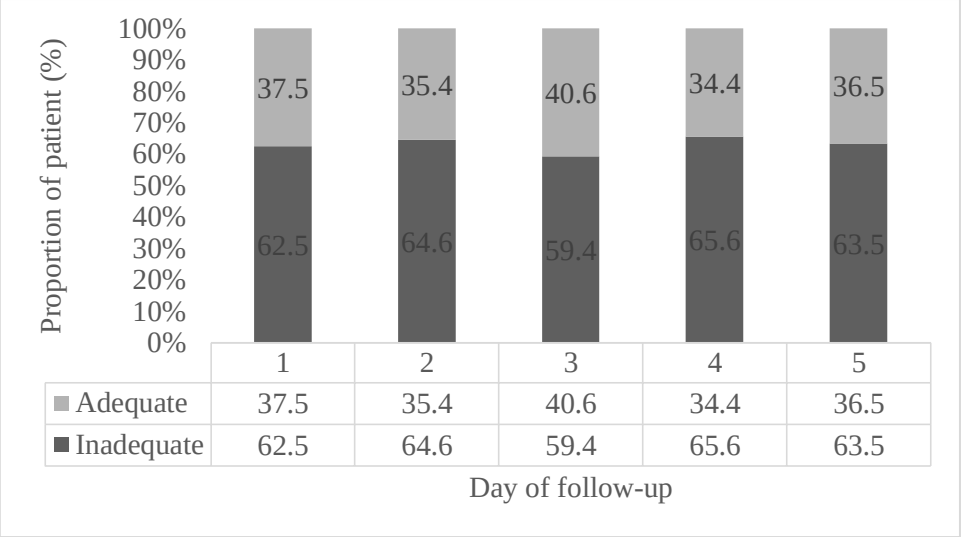

Figure 5 Follow up assessment of the adequacy of pain management

4.4.3. Factors associated with adequacy of analgesics use.

In a baseline bivariate analysis *(table 9)*, adequacy of analgesics use was significantly associated with; age, bone lesions, ECOG, pathological fracture and spine compression ($p<0.05$).

Table 9 :Bivariate analysis for factors associated with adequacy of analgesics use

Variable	Category	*Adequacy of analgesics use (n)* *Inadequate (-ve PMI)*	*Adequate (+ve PMI)*	*P-value*
Sex	Male	33	17	0.340[c]
	Female	26	20	
Age	Median (IQR)	60(50, 70)	46(36, 61)	0.011[m]
Occupation	Farmer/ Self-employed	27	14	0.192[f]
	Unemployed/student/Retired	22	13	
	Public /private sector	8	4	
	Casual labourer	2	6	
Education	None	28	10	0.198[f]
	Primary	16	16	
	Secondary	8	5	
	College/University	7	6	
Tumour type	Primary	16	17	0.059 [c]
	Secondary	43	20	
Bone lesions	Solitary	20	25	0.001 [c]
	Multiple	39	12	
ECOG	0-2	34	31	0.008 [c]
	3-4	25	6	
Pathological	Absent	32	29	0.017 [c]
fracture	Present	27	8	
Spinal cord	Absent	42	34	0.015[c]
compression	Present	17	3	
Treatment	Chemotherapy	38	23	-
Modalities	Symptomatic	15	2	
	Surgery ± Chemo	2	12	
	Radiotherapy ± Chemo	4	0	

[c] Chi-Square; [f] Fishers Exact Test; [m] Mann Whitney U test; [(n)] number of patients

A confirmatory multiple logistic regression analysis *(table 10)* revealed that age over (60 years) (*p*: 0.013, AOR: 0.953, Cl: 0.917-0.989) and multiple bones (*p*: 0.006, AOR: 0.192, Cl: 0.059-0.615) were associated with an increased likelihood of having suboptimal CRBP management with analgesics

Table 10 :Multivariate logistics analysis for factors associated with adequacy of analgesics use

Variable	*Categories*	*AOR*	*p-value*	*95% CI*
Age	Covariate	0.953	0.013	0.917 - 0.989
Bone Lesions	Solitary			
	Multiple	0.192	0.006	0.059 - 0.615
ECOG grp	0-2			
	3-4	0.282	0.073	0.070 - 1.126
Pat Fracture	Absent			
	Present	0.703	0.589	0.196 - 2.517

AOR Adjusted Odds Ratio; Cl Confidence Interval

4.4.4. Modifications in prescribed analgesics

Of the 59 patients at baseline who received inadequate treatment with analgesics (negative PMI);

- On day one, 55 (93.2%) patients still had a negative PM1, 4 (7.3%) of them had modifications done in their prescribed pain medications. One (1.8%) patient obtained self-prescribed analgesics while 3 (5.5%) patients had these alternations done by a reviewing clinician.
- On day two, 54 (91.5%) patients still had a negative PM1, 3 (5.6%) of them had modifications done in their prescribed pain medications. One (1.9%) patient obtained self-prescribed analgesics while 2 (3.7%) patients had these alternations done by a reviewing clinician.
- On day three, 48 (81.4%) patients still had a negative PM1, 4 (8.3%) of them had modifications done in their prescribed pain medications. Three (6.3%) patients obtained self-prescribed analgesics while 1 (2.0%) patient had these alternations done by a reviewing clinician.

- On day four, 49 (83.1%) patients still had a negative PM1, but only 5 (10.2%) of them had modifications done in their prescribed pain medications. All of them obtained self-prescribed analgesics. A clinician did no alternations.
- On the fifth day, 48 (81.4%) patients still had a negative PM1, but only 9 (18.8%) of them had modifications done in their pain medications. Seven (14.6%) patients obtained self-prescribed analgesics while 2 (4.2%) patients had these alternations done by a reviewing clinician.

4.5. Pain control satisfaction

Overall, 68 (70.8%) patients were satisfied with their pain control on analgesics, 14 (14.6%) were dissatisfied, and 14 (14.6%) not sure. Generally, pain control satisfaction slightly improved with pain relief *(figure 7)*. The proportion of satisfied patients ranged from 57.3% to 70.8%. The highest level of satisfaction was observed on day 3 *(table 14)*.

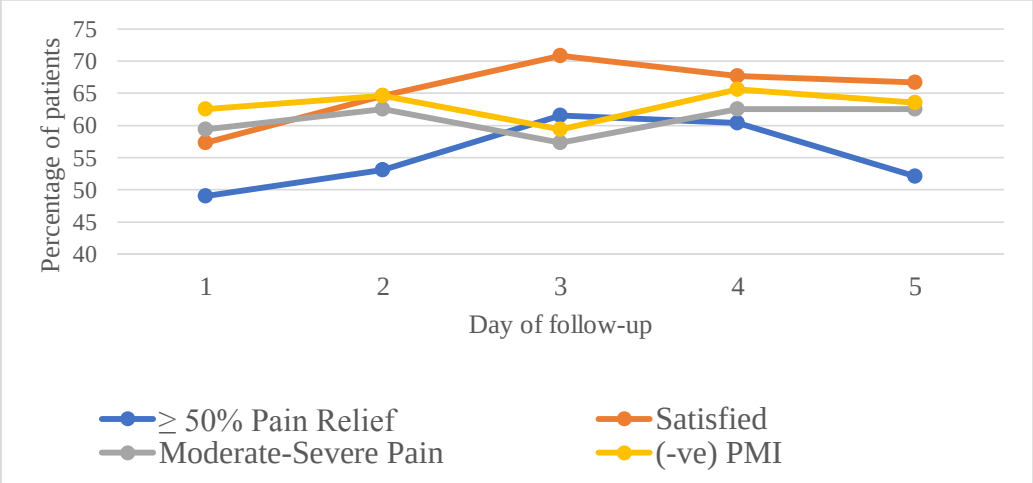

Figure 6:Showing a summarised trend of pain assessment on follow up

Table 11 Bivariate analysis for factors associated with pain control satisfaction

		Satisfaction level; (n)		
Variable	Category	Satisfied	Not satisfied	p-value
Sex	Male	31	19	0.047[c]
	Female	37	9	
Age	Median (IQR)	56.5(36.5,65)	65.5(50.5,70)	0.022[m]
Occupation	Farmer/ Self-employed	31	10	0.485[f]
	Unemployed/student/Retired	22	13	
	Public /private sector	8	4	
	Casual labourer	7	1	
Education	None	24	14	0.670[f]
	Primary	24	8	
	Secondary	10	3	
	College/University	10	3	
Tumour type	Primary	30	3	0.002 [c]
	Secondary	38	25	
Bone lesions	Solitary	38	7	0.006 [c]
	Multiple	30	21	
ECOG	0-2	50	15	0.057 [c]
	3-4	18	13	
Pathological fracture	Absent	49	12	0.007 [c]
	Present	19	16	
Spine compression	Absent	59	17	0.004[c]
	Present	9	11	
Pain Intensity	Mild/No pain	29	0	-
	Moderate/Severe	39	28	
Treatment Modalities	Chemotherapy	44	17	-
	Symptomatic	7	10	
	Surgery ± Chemo	14	0	
	Radiotherapy ± Chemo	3	1	
Prescribed Analgesics	None	18	16	0.007[c]
	NSAID	25	9	
	Opioid	25	3	
PMI	Inadequate	31	28	-
	Adequate	37	0	

[c] Chi-Square; [f] Fishers Exact Test; [m] Mann Whitney U test; [(n)] number of patients

A confirmatory multiple logistic regression analysis *(table12)* revealed that type of prescribed analgesics ($p < 0.05$) was significantly associated with pain control satisfaction. Patients prescribed opioids (p=0.041, AOR: 0.027) had an increased likelihood of having pain control satisfaction.

Table 12 : Multivariate logistics analysis for factors associated with pain control satisfaction

Variable	*Categories*	*AOR*	*p-value*	*95% CI*
Sex	Male	1		
	Female	0.338	0.301	0.043 - 2.639
Age	Covariate	1.052	0.205	0.972 - 1.137
Tumour type	Primary	1		
	Secondary	65.533	0.011	2.558 - 1678.496
Bone Lesions	Solitary	1		
	Multiple	4.431	0.130	0.646 - 30.373
Pathological Fracture	Absent	1		
	Present	12.197	0.156	0.386 - 384.924
Spinal cord Compression	Absent	1		
	Present	5.913	0.329	0.166 - 209.994
Analgesic Type	None	1		
	NSAID	0.587	0.628	0.068 - 5.043
	Opioid	0.027	0.041	0.000 - 0.858

AOR Adjusted Odds Ratio; Cl Confidence Interval

4.6. Follow up summary

Table 13 :A summarised trend of satisfaction and pain assessment on follow up

Variable	*Category n (%)*	*Day 1*	*Day2*	*Day3*	*Day4*	*Day5*
Pain severity	No/Mild pain	39(40.6)	36(37.9)	41(42.7)	36(37.5)	36(37.5)
	Moderate/severe pain	57(59.4)	60(62.5)	55(57.3)	60(62.5)	60(62.5)
Pain relief	<50%	49(51.0)	45(46.9)	37(38.5)	38(39.6)	46(47.9)
	≥50%	47(49.0)	51(53.1)	59(61.5)	58(60.4)	50(52.1)
PMI	Inadequate	60(62.5)	62(64.6)	57(59.4)	63(65.6)	61(63.5)
	Adequate	36(37.5)	34(35.4)	39(40.6)	33(34.4)	35(36.5)
Satisfaction with pain Control	Dissatisfied	23(24.0)	15(15.6)	11(11.5)	16(16.7)	16(16.7)
	Satisfied	55(57.3)	62(64.6)	68(70.8)	65(67.7)	64(66.7)
	Not sure	18(18.8)	19(19.8)	17(17.7)	15(15.6)	16(16.7)
Adherence	Poor	15(15.6)	15(15.6)	12(12.5)	11(11.5)	12(12.5)
	Fair	11(11.5)	8(8.3)	14(14.6)	12(12.5)	10(10.4)
	Good	70(72.9)	73(76.0)	70(72.9)	73(76.0)	74(77.1)
Modification	No	89(92.7)	82(85.4)	82(85.4)	85(88.5)	84(87.5)
	Yes	7(7.3)	14(14.6)	14(14.6)	11(11.5)	12(12.5)

[n] number of patients, [(%)] percentage of patients

A notable change in parameters is seen on day 3; the mean pain score and relief were 3.9 and 54.9% respectively. Fifty-five (57.3%) patients reported moderate to severe pain, while 59 (61.5%) patients had 50% or more pain relief. About 59.4% were classified as receiving inadequate analgesics. Patients satisfied with their pain control were 70.8%, and those adherent to treatment were 72.9%.

CHAPTER FIVE

5.0. DISCUSSION

5.1. Introduction

This chapter covers the discussions of the research findings as per the stated specific objectives.

5.2. Proportion of Cancer Related Bone pain

Cancer of the Prostate formed a quarter of the sample size, which elucidates why our study population was predominantly male. CRBP was most prevalent in patients with cancer of the Breast and Multiple myeloma, followed by Cancer of the Prostate. This finding did not differ significantly from other studies' findings (Wong & Pavlakis, 2011; Everdingen et al., 2016; Vieira et al., 2019). However, the distribution differed slightly from that reported by Cho et al. (2015),who showed CRBP to be most prevalent in patients with liver, multiple myeloma and lung malignancies. But this could be mainly because of differences in geographical locations.

A notably high proportion of patients (83.3% to 86.5%) experienced CRBP. Despite scarce publications on CRBP, the high proportion reported in this study was in range and comparable to that found in patients with bone malignancies elsewhere. In these publications, the said comparable CRBP prevalence ranged from 60% to 90% (Zhu et al., 2015; Milgrom et al., 2017; Vieira et al., 2019). A relatively similar study, Vieira et al. (2019), reported a comparatively higher pain proportion of 91.6% in patients with bone malignancies but relatively the same proportion of 63.7% of moderate to severe pain comparable to our study. The comparatively higher proportion of pain in Vieira et al. (2019) can be explained based on findings of other studies that have reported numerous ethical disparities or biases in pain prevalence and management (S. Beck, 2000; S. L. Beck & Falkson, 2001; Wyatt, 2013). One significant finding

reported was that underrated or underreported pain is more prevalent in Africans, especially men. They are said to be reluctant to report pain even when experiencing it. It was also noted that the proportion of patients experiencing moderate-severe pain (57.3% to 69.8%) in this study was slightly higher compared to other recent publications (Turabi & Plunkett, 2012; Zhu et al., 2015; Milgrom et al., 2017). That could possibly be because suboptimal pain management with analgesics is more prevalent in African countries (Greco et al., 2014; Haumann & Joosten, 2017) where utilisation of Opioids is minimal. Also, those developed countries have better resources for CRBP management (McCaffery & Ferrell, 1995).

Having a pathological fracture (AOR 12.285, P: 0.030, CI: 1.268-119.019) was associated with moderate-severe pain. Literature has shown that bone malignancies usually present with numerous Skeletal Related Events such as pathological fractures and hypercalcemia (Coleman, 2006; Phanphaisarn et al., 2016). That could explain the association of moderate-severe CRBP with the presence of a pathological fracture in this study. One could also argue that the wide confidence interval suggests a lack of precision to provide conclusive evidence to support the association. Whichever the case, pain is a subjective measure that is often unrelated to the underlying factors but rather is mainly influenced by its meaning to the patient. That emphasises the importance of appropriately and individually assessing the patient's pain regardless of their underlying factors.

There was no significant change in the proportions of reported CRBP on follow-up. That may be related to the relatively brief follow up period. The mean pain scores ranged from 3.9 to 4.12 and were generally skewed to moderate pain. The proportion of moderate to severe pain was at its lowest at 57.3% on day 3. This notable reduction in the proportion of moderate to severe pain on day 3 could have been due to the

modifications done in the patients' medications in the preceding two days. More clinician-based treatment modifications or alternations in types of prescribed analgesics and fewer self-prescriptions happened on those days.

All in all, this finding emphasises the need to review patients' analgesics on follow up routinely and re-adjust prescribed analgesics accordingly to their pain intensity. The less observed clinician-based modifications in prescribed analgesics on follow up could also have contributed to the suboptimal management of patients' pain. The observation is consistent with (Tawil & Salameh, 2018). That could also explain why patients' pain on follow up was generally skewed to moderate pain.

5.3. Prescription pattern of analgesic and adequacy of analgesics use

Opioids particularly morphine remain the treatment option for moderate to severe CRBP. This study noted lower opioids prescription (15.6% to 29.2%) at MTRH given higher proportions of reported moderate to severe CRBP. In comparison, opioids prescription was in range with study findings of 37.5% of Wanjuki, (2013) at KNH. However, it was in contrast to Mitera et al. (2010) findings that found 58.5% of patients with CRBP on opioids.

A substantial number of patients, 19.8% notably outpatient obtained self-prescribed analgesics. This proportion was relatively lower than 34% that reported by Wanjuki, (2013) at KNH. However, in both studies, most patients obtained NSAIDs, particularly paracetamol. Notably, a majority of patients who got self-prescribed analgesics also had a negative PMI.

The under-prescription of opioids in this study could significantly contribute to why many patients, 59.4% to 65.6%, received inadequate pain management or less than

adequate analgesics. It was comparative to range the (4 to 68%) reported in a systemic review by Greco et al. (2014) for studies published after 2008.

Study results of Greco et al. (2014) and Haumann & Joosten, (2017) provided some evidence to support the high proportion of inadequate pain management in this study. They suggested that inadequate cancer pain management was more prevalent in developing countries compared to the developed ones.

As a significant finding in this study, the underutilization of opioids could be outlined as one of the barriers to adequate CRBP management at MTRH. In agreement, S. Beck, (2000), Kimani et al. (2017) and Haumann & Joosten, (2017) have also proposed the underutilization of opioids generally in African countries as a reason for inadequate cancer pain management. Recent publications also recommend low dose morphine because it is well tolerated and provides a better adequate analgesia level than tramadol/codeine for the management of moderate CRBP (Lucchesi et al., 2017).

It is recommended that all patients on cancer pain treatment are routinely followed up and have their pain medications altered or readjusted appropriately relative to their pain intensity. In this study outpatients barely had such clinician-based treatment modifications. This could have postulated why the 19 outpatients with inadequate pain sought self-medicated analgesics. And it could have portrayed an urge of trying to attain adequate pain control by these patients.

Patients with multiple bone lesions (p=0.006, AOR: 0.192) or aged over 60 years (p=0.013, AOR: 0.953) had an increased likelihood of receiving suboptimal pain management. The finding was in agreement with most cancer studies showing an association between PMI with age and patients' morbidities (Singh et al., 2017; Fujii et al., 2017). In contrast, other studies have also correspondingly shown younger

patients and those without much morbidities, i.e. healthier patients, to be more likely to receive inadequate pain management (Larue et al., 1995; Okuyama et al., 2004). The fact that the study population was mainly elderly patients could have contributed to our study's reported associations. The disparities in study results emphasise that CRBP ought to be assessed appropriately and effectively managed regardless of the age or underlying morbidity even when they have the least pain scores.

5.4. Pain control Satisfaction

Satisfaction with pain control varied slightly on each day of follow up. One of the outstanding vital findings was that most patients (70.8%) were satisfied with pain control despite high proportions of reported unrelieved moderate-severe pain and inadequate pain management. The researchers also noted that satisfaction relatively increased with mean pain relief and as the number of patients with pain relief of ≥ 50% increased. Further review of the literature provided some evidence to support these findings. Some previous studies have also reported this absurdity of high proportions of satisfied patients with unrelieved moderate to severe pain (Phillips et al., 2013; Thinh et al., 2018). It is attributed to the fact that different patients have varying expectations and perceptions of pain relief when on a given treatment (Pellino & Ward, 1998; Hanna et al., 2012). Also, given that pain relief is predictive of improved satisfaction Hirsh et al. (2005), could explain the noted improvement in patients' satisfaction as the number of patients with pain relief ≥ 50% increased.

On the other hand, other studies have shown a negative correlation between satisfaction and pain intensity (Pellino & Ward, 1998). Others have also reported correlation with age (Baker et al., 2016) and patient's psych-emotional state (Muller-Staub et al., 2008). On the contrary, our study found an association between pain control satisfaction and the most potent prescribed analgesics. Patients prescribed

opioids were more likely to be satisfied with their pain control. Although the researchers did not explore the relationship between satisfaction and pain relief, they can hypothesize that patients on morphine were more likely to achieve a more reasonable amount of pain relief than their counterparts. This argument can be supported by Davies et al. (2011), study findings in their multicenter research, which revealed that (76%) of cancer patients were satisfied with opioid-induced pain relief despite 60% reporting severe pain. To further back up this postulation, a previous study by (J. Carlson et al., 2003) had also shown that satisfaction as a measure of pain management outcome is influenced by the effectiveness of pain medications and is somewhat independent of pain intensity and communication. However, this remains a subject of further investigation.

5.5. Study limitations

Several limitations to PMI as a tool for accessing adequacy of pain management with analgesics exist. The tool does not consider aspects like adherence to the prescribed analgesics, drug dosages, administration of the prescribed medicines, and administration route. It also does not reveal the impact of the non-pharmacological CRBP therapies nor reflect patients' satisfaction with pain control. This study explored patients' adherence to the administered analgesics and patients' satisfaction with pain control to overcome some of these limitations. Lastly, the study also excluded patients who had not started the prescribed analgesics within 48 hours.

CHAPTER SIX

6.0. CONCLUSIONS AND RECOMMENDATIONS

6.1. Conclusions

The present study established that a high proportion of bone malignancy patients at MTRH reported CRBP. And a notable percentage of these survive with moderate to severe pain. Patients with pathological fractures were more likely to have moderate to severe pain. This suggests that clinicians at MTRH are challenged by patients with CRBP of varying pain intensities.

A majority of patients received suboptimal pain management with analgesics. Multiple bone lesions and age over 60 years were significantly associated with suboptimal pain management. The study also demonstrated that opioids prescriptions in CRBP management were relatively low.

Overall, 70.8% were satisfied with their analgesics pain control. Patients prescribed opioids had an increased likelihood of having pain control satisfaction. However, it was not fully understood why many patients showed satisfaction with pain control despite the relatively high percentages of reported moderate to severe pain. There was a noticeable increase in satisfaction levels with an increase in pain relief which postulates a relationship between satisfaction and pain relief. This suggests an in-depth study.

6.2. Recommendations

Cancer pain control is a quality of healthcare matter. The present study recommends that;

Efforts to implement appropriate pain screening with reliable pain scales that include in-depth assessments of the pain's symptoms, characteristics, and impact on life quality should be made. Clinicians should appropriately screen and independently assess individual patients' CRBP regardless of their underlying comorbidities.

Approved evidence-guided organizational standards of operation must be adopted and practised up to globally acceptable cancer pain treatment guidelines so as to provide adequate CRBP management and satisfactory outcomes. In the same regard, barriers to effective CRBP management at MTRH should be thoroughly studied. The study recommends an increase in opioids prescription in CRBP management.

Organizational health policies that sustenance and ensure ready accessibility of analgesics, particularly opioids, should be implemented. So as patients can quickly and cheaply assess the best potent analgesics for their CRBP management.

Lastly, the absurdity of high proportions of satisfied patients despite significant levels unrelieved moderated to severe pain and or inadequate pain management requires further exploration at multicenter level with long term longitudinal assessments.

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APPENDICES

Appendix 1: Informed consent form

Form Serial Number: ☐☐☐☐☐☐☐☐☐

Title: Pain Management among patients with bone malignancies at Moi Teaching and Referral Hospital.

Researcher: Kaggwa Andrew of P.O.BOX 2048, Kampala, Uganda.

This Informed Consent Form has two parts:

Information Sheet (to share information about the study with you)

Certificate of Consent (for signatures if you choose to participate)

You will be given a copy of the signed Informed Consent Form

Part I: Information Sheet

Introduction:

You are being asked to take part in a research study. This information is provided to tell you about the study. Please read this form carefully. You will be given a chance to ask questions. If you decide to be in the study, you will be given a copy of this consent form for your records.

Taking part in this research study is voluntary. You may choose not to take part in the study. You could still receive other treatments. Saying no will not affect your rights to health care or services. You are also free to withdraw from this study at any time. If you choose to quit after data collection, you can request that the information provided by you be destroyed under supervision and thus not used in the research

study. You will be notified if new information becomes available about the risks or benefits of this research. Then you can decide if you want to stay in the study.

You have been selected as a possible participant because you were previously diagnosed with cancer that involves or has spread to your bone(s). You probably have (or have not) developed pain in those affected bones due to this diagnosis.

Purpose of Study:

This study seeks to determine the proportions of different cancer rated bone pain intensity levels and whether the management of cancer-related bone pain in patients with bone malignancies at MTRH is as per the WHO pain management guidelines?

Ultimately, this research will be presented as part of the principal investigator's university thesis and or may be published as part of an article in a preferred journal of medicine.

Procedure:

The study has two data collecting questionnaires that is an interview-based questionnaire and a self-administered questionnaire. The investigator will interview you and record your responses in the interview-based questionnaire. He/she will also look through your treatment file to retrieve any information deemed necessary about your medical history. You will be voluntarily requested to provide any information regarding your bone malignancy and associated medical history.

After that, you will be given a second self-administered questionnaire where you will be asked to assess and score your bone pain. At all times, the investigator will encourage you to personally and voluntarily fill this questionnaire. However, your immediate care-taker will be allowed to assist you in case you ask to be helped.

Risks:

There are no reasonably foreseeable (or expected) risks that will come to you due to your involvement in this study. There may be unknown risks.

Benefits:

You may personally not receive any direct benefits or any reimbursements for being a part of this study.

However, possible benefit(s) to the society as a result of your participation will be; this study will provide evidence-based information on the prevalence of inadequately managed cancer-related bone pain at MTRH. The findings of this study will potentially help to maximize the number of cancer patients receiving adequate pain management at MTRH.

Confidentiality:

The records of this study will be kept strictly confidential. Research records will be held in a locked file, and all electronic information will be coded and secured using a password-protected file. We will not include any information in any report we may publish that would make it possible to identify you.

Right to refuse or Withdrawal:

The decision to participate in this study is entirely up to you. You may refuse to take part in the study at any time without affecting your relationship with the investigators of this study or MTRH. Your decision will not result in any loss of benefits to which you are otherwise entitled. You have the right not to answer any single question, as well as to withdraw entirely from the interview at any point during the process;

additionally, you have the right to request that the interviewer not use any of your interview material.

Part II: Certificate of Consent:

I have read or have had read to me the description of the research study. The investigator or his/her representative has explained the study to me and has answered all of the questions I have at this time. I have been told of the potential risks, discomforts as well as the possible benefits (if any) of the study. I freely volunteer to take part in this study and appended my signature below and that I have understood the information provided above.

I will be given a signed and dated copy of this form to keep, along with any other printed materials deemed necessary by the researcher.

Name of Patient	**Signature of Patient/thumbprint**	**Date**

Name of Representative/Witness	**Signature of witness/thumbprint**	**Date**

Name of person Obtaining Consent	**Signature of person Obtaining Consent**	**Date**

Consent to follow up via phone: (*to be filled if patients accept to be contacted via phone*)

I hereby append my signature below as a sign of consent to be contacted via phone during the duration of follow up of this study.

Name of Patient	**Signature of Patient/thumbprint**	**Date**

Appendix 2: Numerical Rating Scale

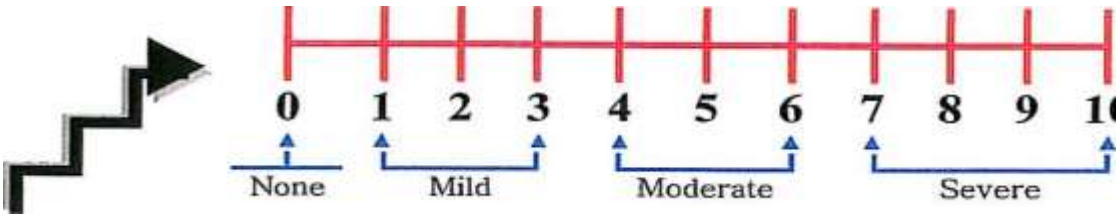
NATIONAL INSTITUTES OF HEALTH

WARREN GRANT MAGNUSON CLINICAL CENTER

PAIN INTENSITY INSTRUMENTS

JULY 2003

O — 10 Numeric Rating Scale (page 1 of 1)



Indications: Adults and children (> 9 years old) in all patient care settings who are able to use numbers to rate the intensity of their pain.

Instructions:

1. The patient is asked any one of the following questions:
    - What number would you give your pain right now?
    - What number on a 0 to 10 scale would you give your pain when it is the worst that it gets and when it is the best that it gets?
    - At what number is the pain at an acceptable level for you?
2. When the explanation suggested in #1 above is not sufficient for the patient, it is sometimes helpful to further explain or conceptualize the Numeric Rating Scale in the following manner:
    - 0 = No Pain
    - 1-3 = Mild Pain (nagging, annoying, interfering little with ADLs)
    - 4 6 = Moderate Pain (interferes significantly with ADLs)
    - 7-10 = Severe Pain (disabling; unable to perform ADLs)
3. The interdisciplinary team in collaboration with the patient/family (if appropriate), can determine appropriate interventions in response to Numeric Pain Ratings

Adopted for use from McCaffery & Beebe, (1993).

Appendix 3a: Interviewer-based Study Questionnaire

Title: Pain management among patients with bone malignancies at Moi Teaching and Referral Hospital

Study Name: _____ **Form Serial Number:** _____ **Date:** _____

Participant's Initials: _____ **Participants study Code** _____ **Telephone No** _____

Participant type: Outpatient☐ or Inpatient☐ **Entry Ward/Clinic:** **Sex: Male☐ Female☐** **Age**

Part 1. Social Demographics

Physical Address: **County:** _____ **Subcounty:** _____

History of smoking: **YES:☐ NO:☐**

Current or previous Occupation:

Education Level: *[tick highest level completed]* **None☐, Primary☐, secondary☐, Tertiary☐, University☐**

Present Marital status:	Single ☐	Married ☐	divorced/separated ☐	Widowed ☐	Cohabiting ☐	Others *[please state]*

Nationality: _____ **Ethnicity:** _____ **Do you have NHIF Cover?** **YES: ☐ NO: ☐**

How often do you drink alcohol? **Never ☐** **Less than monthly ☐** **Monthly ☐** **Weekly ☐** **Daily or almost daily ☐**

On average how much do you earn per month?		
	A) Below: 5000 ☐	E) 40,001 – 55,000 ☐
	B) 5,000 – 10,000 ☐	F) 55,001 – 75,000 ☐
	C) 10,001 – 25,000 ☐	G) 75,001 – 100,000 ☐
	D) 25,001 – 40,000 ☐	H) Above 100,000 ☐

Part 2. Medical History

Serostatus: **Negative ☐** **On HAART ☐** **Not on HAART ☐** **Unknown ☐**

Other Co-current illness: _____

Site of Primary tumor: _____ **State the Pathological name of Primary tumor:** _____

Date of Diagnosis of primary tumor: **Site (s) of Bone Malignancy:** _____

Number of Bone Lesions **Solitary Bone Lesion ☐** **Multiple Bone Lesions☐**

[if multiple Bone Lesions record site(s) and number of lesions present] _____

Radiological Investigations performed to diagnose the Bone Malignancy?

None ☐ **XRay ☐** **CT-Scan ☐** **MRI ☐** **Others:** _____

State Site(s) of Visceral Metastatic lesions if present: _____

Skeletal Rated Events SREs: *[tick box below where applicable]*

Pathological fractures [Present☐, Absent☐] *State site(s) of Fracture(s)* _____

Spinal Cord Compression [Present☐, Absent☐] **Pain** *[skip! to administer a self-assessment pain Questionnaire]*

Serum Calcium Level *[record level if available]* _____

Which of the following Specific cancer treatment modalities has been used to treat the Bone Cancer?

Chemotherapy ☐	Hormonal Therapy ☐	Bisphosphonates ☐	Symptomatic *[e.g. casting]* ☐	*State duration*
Radiotherapy ☐	*Type of Radiotherapy if known* **[Multiple fraction ☐ or Single Fraction ☐]**		**Surgery ☐**	*[state type of operation done if possible]*

For official use only: **List of only the PRESCRIBED patient's analgesic after review?**

Appendix 3b. Self-administered Questionnaire

Title: Pain Management among patients with bone malignancies at Moi Teaching and Referral Hospital

Study Name: _____ Form Serial Number: _____ Date: _____

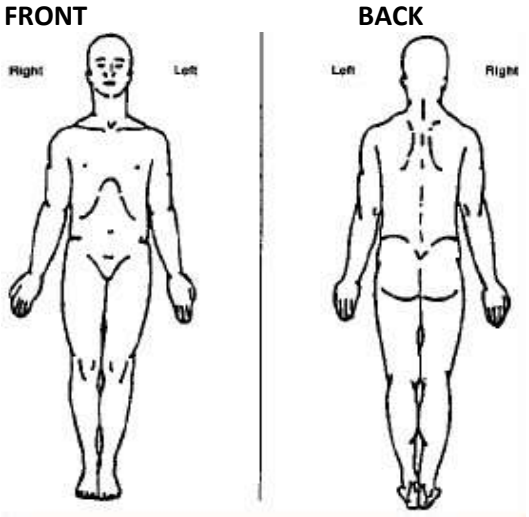
Patient's Initials: _____ Patient's study Code _____ Telephone No: _____

SELF-PAIN ASSESSMENT

1. **Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains and toothaches). Have you had pain other than these everyday kinds of pain today?**

YES☐ NO☐

2. **On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.**



3. **Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐9 ☐ 10

No Pain *Worst Pain You Can Imagine*

4. **Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐9 ☐ 10

No Pain *Worst Pain You Can Imagine*

5. **Please rate your pain by marking the box beside the number that best describe your pain on the average.**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐9 ☐ 10

No Pain *Worst Pain You Can Imagine*

6. **Please rate your pain by marking the box beside the number that tells how much pain you have right now.**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐9 ☐ 10

No Pain *Worst Pain You Can Imagine*

7. **What treatments or medications are you receiving for your pain?**

_____ _____ _____ _____

_____ _____ _____ _____

8. Please record on average the duration of your reported cancer-related bone pain above?

A. Less than 3 Months ☐ B. 3 Months or More ☐

For official use only:

Select the medical cadre who assessed and managed the patient's pain?

☐ Specialist. ☐ Resident. ☐ Medical Officer. ☐ Clinical Officer. ☐ Nurse.

Was the pain assessment Questionnaire Self-administered? A) Yes:☐ B) Assisted:☐

What is the ECOG Functional Status of the patient?

0. (Asymptomatic Fully active): ☐

1. (Symptomatic but completely ambulatory): ☐

2. (Symptomatic, 50% in bed during day. Ambulatory and capable self-care but unable to out and work activities):☐

3. (symptomatic, 50% in bed but not bed bound. Capable of only limited self-care, confined to bed or chair 50%): ☐

4. (Totally bedbound, completely disabled, cannot carry out any selfcare): ☐

Appendix 3c. Follow up Self-assessment Questionnaire

Title: Pain Management among patients with bone malignancies at Moi Teaching and Referral Hospital

Study Name: _____ Day of Follow up: | 1 | 2 | 3 | 4 | 5 | Date: _____

Patient's Initials: _____ Patient's study Code _____ Telephone No: _____

FOLLOW-UP SELF ASSESSMENT QUESTIONNAIRE

(please to be filled after 24 hours of starting the prescribed pain treatment)

1. **How on average would you rate your bone pain after 24 hours of starting the prescribed pain treatments or medications?**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐9 ☐ 10

No Pain — *Worst Pain You Can Imagine*

2. **In the last 24 hours, how much relief have pain treatments or medications provided? Please mark a box below the percentage that most shows how much relief you have received.**

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No Relief — Complete Relief

3. **Please select a box that indicates how on average satisfied you are with your Bone Pain control after 24 hours of starting the prescribed pain treatments or medications?**

A. SATISFIED: ☐ B. NOT SURE: ☐ C. DISSATISFIED: ☐

4. **Please select a box if the prescribed medications were administered in the past 24 hours?**

A. YES: ☐ B. NOT SURE: ☐ C. NO: ☐

5. **If the prescribed medications were not administered in the past 24hrs please state reasons why below.**

_____

_____

_____

6. **Please select a box that best indicates your Adherence Level to the prescribed pain medications or treatment?**

A. GOOD: ☐ B. FAIR: ☐ C. POOR: ☐

8. **If any Modifications in or used any other Self-Prescribed pain medications or treatments please indicate them below?**

_____ _____ _____ _____

_____ _____ _____ _____

_____ _____ _____ _____

Appendix 4. Pain Management Index

The Pain Management Index is used to determine the adequacy of pain management. It is calculated as follows (Cleeland et al., 1994):

The most potent prescribed analgesics are categorized into four basing on the WHO analgesics ladder;

- 0: No analgesics, 1: Non-Opioid Analgesics, 2: Weak Opioid Analgesics, 3: Strong Opioid Analgesics.

Patients' self-reported pain intensity scores are categorized into four basing on severity;

- 0: No pain, 1: Mild Pain (ranks 1 to 3), 2: Moderate Pain (ranks 4 to 7), 3: Severe Pain (ranks 8 to 10).

The Pain Management Index (PMI) for each patient is be calculated by subtracting a patient's pain intensity score from the analgesic score. The Pain Management Index, therefore, ranges from -3 to 3. A negative score suggests potentially inadequate pain management by the prescriber, while a positive score or zero is considered the acceptable recommended treatment for cancer pain. It should be noted that PMI is a conservative assessment tool. It does not account for the patient's adherence, analgesics dosages or other adjuvant pain medications.

Table 14 Showing the Pain Management Index

Analgesics Score	*Pain Intensity Score*			
	0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)
0 (no analgesics)	0	-1	-2	-3
1 (Non-Opioids)	1	0	-1	-2
2 (Weak-Opioids)	2	1	0	-1
3 (Strong Opioid)	3	2	1	0

Appendix 5. IREC Formal Approval

MU/MTRH-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2018/236
Approval Number: 0003262

14th March, 2019

Dr. Kaggwa Andrew,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
14 MAR 2019
APPROVED
P.O. Box 4606-30100 ELDORET

Dear Dr. Kaggwa,

RE: FORMAL APPROVAL

The MU/MTRH- Institutional Research and Ethics Committee has reviewed your research proposal titled: -

"Pain Management among Patients with Bone Malignancies at Moi Teaching and Referral Hospital".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 3262*** on 14th March, 2019. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; hence will expire on 13th March, 2020. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date. You will be required to submit progress report(s) on application for continuation, at the end of the study and any other times as may be recommended by the Committee.

Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. You will also be required to seek further clearance from any other regulatory body/authority that may be appropriate and applicable to the conduct of this study.

Sincerely,

DR. S. NYABERA,
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH
Principal - CHS
Dean - SOP
Dean - SON
Dean - SOM
Dean - SOD

Appendix 6: Approval to conduct Research at MTRH

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone : +254(0)53-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 - 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

19th March, 2019

Dr. Kaggwa Andrew,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Pain Management among Patients with Bone Malignancies at Moi Teaching and Referral Hospital".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

MOI TEACHING AND REFERRAL HOSPITAL
C E O
APPROVED
19 MAR 2019
SIGN
P. O. Box 3 - 30100, ELDORET

19/03/2019

DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc - Senior Director, (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM

Appendix 7: Work plan

Table 15 Study work plan

	2018				***2019***				***2020***				***2021***			
Event	Jan Mar	Apr Jun	Jul Sep	Oct Dec	Jan Mar	Apr Jun	Jul Sep	Oct Dec	Jan Mar	Apr Jun	Jul Sep	Oct Dec	Jan Mar	Apr Jun	Jul Sep	Oct Dec
Proposal Development	■	■	■	■												
Proposal Approval					■											
Pilot Study					■											
Data Collection					■	■	■	■	■							
Data Analysis										■						
Thesis Writing					■	■	■	■	■	■	■	■	■	■	■	■
Department Oral defense											■					
Submission And approval Of abstract												■	■			
Submission of thesis for marking													■	■		
Oral defense														■	■	
Submission of bound thesis														■	■	■