PROTOCOL TITLE:

Pilot Trial of Early Interventional Pain Management for Patients with Advanced Malignancies

SHORT TITLE:
Early Interventional Treatment for Cancer Pain

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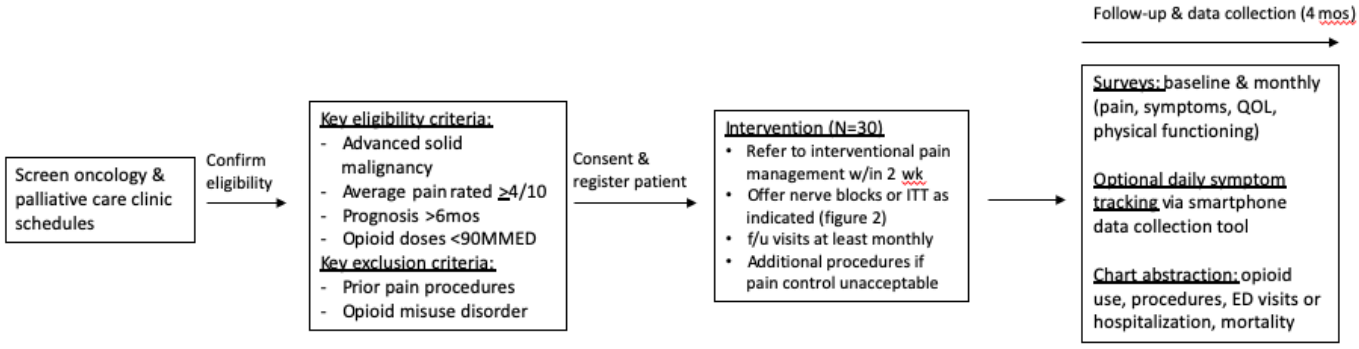
1.0 STUDY SCHEMA



2.0 INTRODUCTION

2.1 STUDY OVERVIEW

In this single arm pilot study, patients with advanced solid tumors and moderate-to-severe pain who are not already on high-dose opioids will be prospectively assigned to early referral to an anesthesia-trained interventional pain management specialist. Specialists all practice at the Brigham and Women's Hospital or its affiliated clinics (e.g., at 850 Boylston, Faulkner Hospital, or Foxboro). These clinicians have a strong affiliation with the Dana-Farber Cancer Institute, and have extensive experience in managing cancer pain with a variety of interventional pain management procedures (e.g. celiac or hypogastric plexus blocks, intrathecal TDD).

Patients will be evaluated for interventional pain management strategies (including, but not limited to, nerve blocks and intrathecal TDD); they will be followed longitudinally with frequent reassessment and management guided by a standardized treatment pathway. This pathway is designed to make the intervention transferrable and ultimately scalable if it is proved effective.

Patients will be followed for 4 months with monthly surveys, and the option to report daily symptoms using a HIPPA-compliant pain-tracking smartphone application. Study staff will also complete structured chart abstractions at end-of-study to assess pain management interventions, opioid use, and healthcare utilization (e.g. hospitalizations/ED visits for pain), and survival.

Primary outcomes of this pilot study will relate to feasibility and acceptability, including recruitment and retention rates, number of completed interventional pain management consultations, the types of interventions offered and the proportion of patients accepting those interventions, and patients' satisfaction with the intervention. We will also explore time trends in clinically relevant outcomes including pain severity/interference, physical functioning, QOL, opioid dose, healthcare utilization and survival.

2.2 Background and Significance

Pain is a common, distressing, and costly complication of cancer. Pain affects approximately half of all patients receiving cancer treatment, a third of survivors, and up to 90% of those in the terminal phase of illness.[1-5] Poorly controlled pain has devastating consequences to cancer patients' quality of life, mood, relationships, and functional wellbeing.[5] Pain is also among the most frequent reasons cancer patients receive emergency department[6,7] and hospital-based care,[8,9] making better pain management a priority for healthcare systems,[10] in addition to patients and their families.

For patients living with advanced incurable cancers, the burden of pain is particularly great. Cancer is the second leading cause of mortality in the US, with 606,880 expected to die from it in 2019.[11] According to a 2016 meta-analysis, the prevalence of pain among patients with advanced stage cancers is 66.7%,[2] with rates exceeding 90% for several common cancer types (e.g. pancreatic) and near end-of-life.[5] Advanced cancer pain can be notoriously severe as tumors invade nearby nerves, bones, and other tissues. Moreover, poorly controlled pain poses a significant burden to patients' emotional wellbeing, and their ability to function physically and to fulfill important life roles.[12-14] Due to recent therapeutic advances (e.g. immunotherapy, targeted therapies), patients are living much longer with their disease, and can consequently live for years with chronic cancer pain. It is therefore essential that pain be managed in a way that enables patients to remain engaged in life.

Systemic opioids are considered the cornerstone of treatment for advanced cancer pain;[15,16] however, medical management alone is often inadequate. Up to 60% of advanced cancer patients experience inadequate pain relief despite access to opioids.[5,17,18] Moreover, several cancer pain syndromes (e.g. visceral, neuropathic) are characteristically opioid-resistant[19,20] – leaving some patients on extremely

high doses with only marginal benefit. Side effects including constipation, fatigue, sedation, and mood changes are extremely common,[21-23] and can prevent patients from engaging in meaningful aspects of their lives. Patients are often given multiple pain medications, at variable doses, making self-management confusing and difficult.[24] Moreover, there is a literature to suggest that opioids may promote tumor progression and shorten patients' survival. In light of growing safety concerns about opioids, many have called for further research into non-pharmacologic strategies to manage advanced cancer pain.[25-27]

Recognizing the limitations of pharmacologic management for advanced cancer pain**, expert organizations including the National Comprehensive Cancer Network (NCCN) recommend consideration of interventional pain management strategies** such as regional neurolysis procedures, intrathecal targeted drug delivery (TDD), vertebroplasty, or percutaneous tumor ablations. Randomized trials suggest that many of these approaches are effective for cancer pain. For example, celiac neurolysis has been found to improve pain, and potentially reduce opioid consumption among patients with pain from advanced pancreatic tumors.[28,29] TDD has been shown in a randomized study to improve pain and reduce opioid consumption and toxicity[30] and possibly extend survival,[31] with a recent retrospective database analysis suggesting cost savings.[32] Unfortunately, patients are usually referred for interventional pain management strategies very late in the disease course, often near the end-of-life, or during a hospitalization for refractory pain. By this time, many patients have been suffering from poorly managed pain for many months, and their pain syndromes may be relatively unresponsive to any treatment because of prolonged exposure to high-dose opioids.

Health systems factors likely play a significant role in limiting advanced cancer patients' access to interventional pain management. First, there are no standardly agreed upon triggers for intervention pain management referral, leading to very late referrals when patients may not even be eligible for certain procedures such as TDD. Second, most interventional pain management specialists operate outside of cancer clinics, making oncologists largely unfamiliar with their capabilities and scope of practice. Third, many pain management specialists lack specific experience with advanced cancer patients, or guidelines needed to integrate interventional techniques into these patients' care. These barriers call for healthcare delivery research to evaluate specific referral processes and treatment algorithms to integrate interventional strategies into the care of advanced cancer patients.

Our overarching hypothesis is that early referral to pain management specialists and systematic consideration of interventional pain management strategies, will improve pain severity, physical functioning, and quality of life among patients with pain from advanced solid malignancies. We also hypothesize that early referral will minimize patients' reliance on systemic opioids, reduce opioid toxicity, unplanned emergency department and hospital-based care for pain, and potentially prolong survival.

This will be a single arm pilot study in which we will identify patients with advanced malignancies who have cancer-related pain, who are not yet on high-dose opioids, and we will arrange for early referral to an interventional pain management specialist at a large center with expertise in cancer pain management. We will evaluate metrics of study feasibility/acceptability needed to plan for a future randomized trial. We will also assess key proximal and distal outcomes needed for a future randomized trial, such as time to completion of the pain management referral, the numbers and types of interventional pain strategies recommended (e.g. nerve blocks, ITT), the proportion of patients accepting those therapies, trajectories of pain severity/interference, opioid doses, and pain-related ED visits and hospitalizations.

3.0 OBJECTIVES

There are three main objectives of this pilot study. Among patients with advanced solid malignancies who have moderate-to-severe cancer pain

1. Determine the feasibility of early referral for consideration of interventional pain management strategies
2. Determine the proportion of participants who are candidates for, and who ultimately receive at an interventional pain procedure
3. Determine patients' satisfaction with their pain management care

4.0 RESEARCH SUBJECT SELECTION

4.1 Methods that will be used to identify potential subjects:

Under a HIPAA waiver, study staff will screen the electronic medical record and scheduling systems in outpatient DFCI oncology and palliative care clinics to identify potentially eligible patients. Study staff may also query Epic, administrative/operations/billing databases, order entry databases, and/or cancer

registry databases to identify potentially eligible participants. Study staff may also accept potential patient referrals from site clinicians. Clinicians will be identified through direct referral from the study PI.

Study Population: Eligible patients will be age greater than 21 years and have an a locally advanced or metastatic solid malignancy, and moderate to severe cancer pain persisting for at least 2 weeks. We are focusing on patients whose pain is from their cancer, or a sequelae of their cancer treatment (ie., not chronic pain that predates their cancer, such as from fibromyalgia or arthritis). We are also focusing on patients who are NOT already taking high-dose opioids (defined as 200MMEs per day), as we are seeking to examine early referral to interventional pain management (rather than referral after escalation to high dose opioids). We will also exclude patients whose primary pain syndrome is sensory peripheral neuropathy as this syndrome is not amenable to interventional procedures. Patients active opioid misuse disorder as documented in the chart, and confirmed by the attending physician will be excluded because their pain is often primarily driven by psychological factors and is poorly responsive to traditional pain treatments. Patients who are not proficient in English will be excluded because the smartphone pain reporting tool is only available in English, and some of the survey measures have not yet been translated into languages other than English.

4.2 Eligibility

Inclusion Criteria:

1. Diagnosis of a metastatic, or locally advanced unresectable malignancy
2. Anticipated prognosis of more than 6 months according to the primary oncologist
3. Age greater than 21 years
4. Persistent pain with an average pain rating of 4 or greater on an 11-point numeric rating scale (NRS) from 0-10, defined by averaging the “worst pain” and “average pain” items from the Brief Pain Inventory long form where 10 is considered the most severe.
5. Pain has persisted for at least 2 weeks
6. Pain is due to cancer or sequelae of cancer treatment

Exclusion Criteria:

1. Primary pain syndrome is sensory peripheral neuropathy
2. Patient is taking more than 200 morphine milligram equivalents (MMEs) per day on average, at the time of recruitment.

3. Currently cared for by interventional pain management specialist
4. Receipt of prior pain intervention for cancer pain (e.g. celiac neurolysis)
5. Bleeding diathesis, uncontrollable infection, or other contra-indications to pain interventions
6. History of opioid misuse disorder
7. Inability to speak English
8. Cognitive impairment or any other disorder that would impede study participation and survey completion
9. If patients are unable to complete the baseline survey, they will no longer be considered eligible for the study; this will serve as an indication of barriers to participation that would make them unable to comply with study procedures.

4.3 Number of Subjects

Up to 31 participants will be enrolled in the study. We anticipate this will take 12 months.

5.0 RESEARCH SUBJECT ENTRY

5.1 Recruitment procedures

A Dana-Farber-based research assistant (RA) will screen provider schedules from participating outpatient solid tumor and palliative care clinics. Of note, an NRS pain score is assessed at every clinical encounter, which will facilitate screening. For potentially eligible patients the RA will email the provider for permission to approach the patient. If the provider either confirms permission or does not opt-out within 3 days, we will then approach the patient for participation. Approaches may occur in person in the clinic, or by phone. After confirming eligibility, interested patients will be consented for the study in writing or via RedCap. The consent form can be found in Appendix AA.

- In person approach: A research assistant (RA) will approach the patient in clinic to explain the study and offer participation. Interested participants will then review the study letter with a

research team member (Appendix AB) and if interested provide documentation of consent (either in writing or electronically).

- Remote approach: A study letter will be sent to the patient before remote approaches (either by email or snail mail) with the option to decline further contact if they aren't interested. Alternatively, if the treating clinician introduces the study to the patient, and the patient requests that they are contacted, we will call the patient at the same time as sending the study letter.

Consent forms will be sent either by mail or electronically through a secure and personalized link in the FDA and HSSH compliant Mass General Brigham/Partners REDCap database. The consent forms will be IRB approved. During the consent discussion, study staff will emphasize that the study is voluntary, patients may withdraw from the study at any time, and that withdrawal of consent will not affect their medical treatment in any way. Consent discussions can be completed via phone or Zoom.

5.1.1. Materials that will be used to recruit subjects: See Appendix AB for study letter.

5.1.2. Duration of subject's participation in the study: Participants will be on the study for 4 months.

5.1.3. Duration anticipated to enroll all study subjects: We anticipate that it will take 6 months to enroll 31 participants to the study

5.2. Informed Consent

Written consent will be obtained from all patient participants. Remote consenting will be permitted as an alternative to in-person consents.

If a patient is being contacted by phone, the patient will be asked to confirm their identity and verify their personal information (i.e. date of birth, address). Consent forms will be sent by mail or electronically through a secure and personalized link in the FDA and HSSH compliant Mass General Brigham/Partners REDCap database. During the consent discussion, the study staff will emphasize that participation is voluntary and the participant may stop participating at any time. Consent discussions may take place over the phone or HIPAA compliant Zoom.

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore as required by DF/HCC Policy REGIST-101.

6. STUDY DESIGN AND METHODS

6.1. Study Design/Type

Design: Single-arm pilot feasibility study

6.2. Selection of Instruments

Feasibility: As the primary goal of this study is to assess feasibility of the early intervention pain management intervention, our study team will track the following measures of feasibility

- Feasibility of recruitment: we will track the number of patients screened, the number approached, the proportion who consent to the study (and reasons for study refusal)
- Feasibility of the intervention: we will track the following
    - Proportion of participants who undergo a consultation with an interventional pain specialist, and the proportion who do so within the target timeframe of 4-weeks
    - Proportion of participants who are offered an interventional pain procedure, and the type of procedure offered (e.g. nerve block, steroid injection, epidural or intrathecal pump)
    - Proportion of participants offered a procedure who accept the procedure, who undergo that procedure, and the timeframe of the procedure
    - Proportion of patients who receive more than one pain intervention
- Feasibility of study assessments: We will keep track survey response rates and reason for non-completion
- Feasibility of retention: We will track the number of patients who complete the study, and reasons for drop-out

Survey assessments will occur at baseline, 2-months, and 4-months. Measures are selected because we expect them to be covariates, primary or secondary outcomes of a future efficacy study.

Pain severity: pain severity will be assessed by averaging the least/average/worst pain rating from the Brief Pain Inventory (BPI) short-form (0-10 numeric rating scale, NRS).[33] Pain interference: interference of pain on patients' general activity, mood, walking ability, work, relationships, sleep, and enjoyment of life will also be assessed by the BPI short-form (0-10)[33]

Quality of life: will be assessed with the Functional Assessment Cancer Therapy: General (FACT-G)[34] including its physical wellbeing, social/family wellbeing, emotional wellbeing, and functional wellbeing subscales.

Anxiety and depression: will be measured using the 4-item PROMIS depression short-form, and 4-item PROMIS anxiety short form

Opioid-use: patients' opioid and non-opioid analgesic regimen will be abstracted from the chart at baseline and end-of-study. Patients will also be asked to report on adherence to scheduled pain medications and the number of breakthrough opioid doses they take in a day

Symptoms: the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) will assess relevant symptoms most relevant to pain or opioid side effects including constipation, concentration, fatigue, insomnia.[35]

Pain Catastrophizing: This will be measured from the 13-item pain catastrophizing scale

Care satisfaction: 5-items adapted from the Hospital Consumer Assessment of Healthcare Providers and Systems will assess satisfaction with pain management care. Patients will also be asked whether they received any interventional pain procedures, and if so – how much relief they received for their pain.

Healthcare utilization will be assessed through structured chart abstraction (see Appendices BA and BB)

- ☐ Pain-related ER visits

- ☐ Pain-related hospitalization, unplanned and planned
- ☐ Intervention types, location, results,
- ☐ Interventions – if placement of a TDD pump - report catheter tip location, complications, medication and dose at the time of implant and at end-of-study, any related procedures required.

Optional remote daily symptom reporting:

*Due to application development barriers, the study team had to close version 1 of the *MyPainPal* app before version 2 was fully developed and functional. So, participants recruited after April 4th, 2023, were not offered the optional remote daily symptom reporting.

Patients will also be given the option of completing daily pain assessments using a smartphone application developed by Dr. Enzinger and the study team. *MyPainPal,* is an Android and iPhone-compatible smartphone app that hosts patients analgesic and laxative medications (inputted by the study assistant), it delivers symptom surveys, and provides tailored psychoeducation relevant to cancer pain. The app will send a reminder to complete a brief symptom survey twice per week which will include the following 6 items, which are estimated to take no longer than 5 minutes to complete. Assessments used for this study can be found in appendix C.

- Pain severity (4 items): patients will rate their pain at its least, worst, and average over the past 24 hours on a scale from 0-10, and their pain at present, and whether their pain is acceptable to them
- Opioid use: patients indicate the number of doses of breakthrough opioids they used in the last 24 hours, and they are asked how much relief it provided
- Pain interference (3 items): patients will rate the extent to which pain interferes with general activity (scale, 0-10) sleep, and mood also derived from the BPI-SF
- Constipation: including last bowel movement and laxatives taken.

Survey results from *MyPainPal* are visible immediately within a password-protected, HIPPA-compliant research portal. The study assistant will monitor this portal daily. For any severe symptoms, the study assistant will notify the patients' care team within that business day. Results from the symptom surveys will be used to algorithmically generate an end of survey summary screen on the patients' app after completing the survey, and if needed, recommend the patient to reach out to their care team regarding

their symptoms. This summary screen includes tailored psychoeducational messages regarding pain management and includes links to *MyPainPal* resources. These resources can also be accessed in the app at any point by the patients and feature psychoeducational content relating to cancer pain, opioids, other pain medications, laxatives, relaxation techniques, and other relevant educational material. The application also features a medication screen tailored to each patient's prescribed medications that relate to cancer pain and symptom management, such as short-acting and long-acting opioids, other pain medications, and laxatives. These medications are listed and categorized, and the app displays the patients most updated prescriptions. Patients are also suggested content from the resource library for each of their prescribed medications, which includes information about the medication, usage, and side effects. Example screenshots of the end of survey summary screen, psychoeducational resources, and medication summary screen can also be found in appendix C.

To ensure safety, if a patient reports potentially serious symptoms, they are specifically instructed to notify their care team by calling or paging after hours. Symptoms that prompt this alert include worst pain of 9 or 10, worst pain of 7-8 that is identified as new, or endorsement of any so-called "red flag" symptoms (severe weakness, light headedness, obstipation, vomiting 2 or more times, fever, chest pain, shortness of breath, new/worsening back pain, new weakness/numbness in legs, hallucinations, inability to eat/drink). For symptoms that are poorly controlled (but not categorized as potentially serious), patients are still encouraged to contact their provider. These symptoms also are highlighted as "red" within the researcher/clinician portal and will be monitored daily by the research team. Any "red" symptom will result in an email or Epic inbasket alert to the patients' care team. The application also includes clear disclaimers that it is not monitored continuously or outside of business hours, and patients are reminded to rely on normal modes of communication for any urgent issues: *"My Pain Pal is not constantly monitored. It is not monitored at all outside of regular business hours. For urgent problems, contact your care team by phone (link to clinic number) or call 911."*

MyPainPal contains a HIPAA-compliant researcher-facing web portal. Within the portal, a dashboard will present trended symptom data, opioid use, and specific recommendations for poorly controlled symptoms. Severe symptoms will prompt patients to contact their care team and trigger clinical alerts. Summary reports (with trended symptom data, opioid-use data, and management recommendations) will be distributed to oncologists prior to clinic visits, facilitating productive interactions and timely

medication adjustments. The research team will monitor the portal where patient survey responses are presented. If a severe symptom is reported, the research team will contact the relevant nursing staff for clinical follow-up (as per the above paragraph, patients are always advised to contact their care teams for safety concerns, and there is no expectation for immediate nurse outreach). If they choose, nurses and physicians involved in the care of participating patients will be permitted to create an account to access to patient symptom data on the portal.

This is an overview of the functions of the patient-facing app and clinician-facing portal:

Table 2. Summary of *MyPainPal* app functionalities:

The main patient-facing tools include the following (accessed via app):
1. **Reminders** → Reminders about when surveys are available 2. **Alerts** → Notifications instructing patients to immediately contact their care team if severe or potentially dangerous symptoms are reported. 3. **Daily Symptom Reporting** → Surveys that will allow patients to report symptoms 4. **Education** → Evidence-based symptom management tools, ranging in form (long-form texts, quick, bite-sized tips, videos, swipe-through texts) 5. **Activities** → Recorded relaxation exercises/meditations and quizzes 6. **Medication List** → House patient medications (opioids, laxatives, etc.)
The main researcher-facing tools include (accessed via computer):
1. **Alerts** → Systems to highlight severe symptoms within clinician portal 2. **Visualizations** → Display previously reported PROs for a given patient 3. **Reports** → Display patients who are enrolled in the program, view results across multiple patients, and identify patients who did not report PROs on schedule. Include a copy/paste report for use in medical records/email that draws from application data

Only participants recruited before April 4th, 2023, were given the option to use the *MyPainPal* app, and if participants opted in, they completed an additional acceptability measure in the final survey.

MyPainPal Acceptability: Acceptability of patient symptom reporting through the *MyPainPal* app will be assessed with 5 acceptability questions regarding the patients' experience with the app.

TABLE 3: Measures to be Collected

Measures collected via patient assessments		Survey			App data	Chart review
Assessment	**Measure**	**BL**	**2-month**	**4-month**		
Co-variates						
Socio-demographics	Standard	x				x

Pain catastrophizing	PCS	X				
Depression and Anxiety	PROMIS measures	x				
Pain and Symptoms						
Pain severity/interference	BPI – short form[36]	x	x	x	x	
Patient reported outcomes	PRO-CTCAE	x	x	x		
Quality of life	FACT-G[34]	x	x	x		
Opioid use[4]	Self-report	x	x	x	x	
Healthcare utilization						
Satisfaction with care	Adapted from HCAHPS		x	x		
Pain medication changes, pain management interventions	-					x
ED visits, hospitalizations	-					X
MyPainPal Acceptability*	-		x			

*****Applicable to participants recruited before 4/4/2023.

Long-term study follow-up: patients will be consented for survival follow-up, which will be supplemented by an existing DFCI research process which obtains data from the National Death Index

7. Description of research procedures being performed

7.1. Survey Assessments

Patient will complete surveys at baseline (window 0-2 weeks), 2 months (window 7-13 weeks), and 4 months (window 15-19 weeks) (see appendices DA, DB and DC respectively).

The surveys can be completed remotely though a link to a Partners Healthcare compliant electronic survey system (e.g. REDCap), over the phone with the RA, over Zoom with the RA; or in person with pen and paper or on a tablet. The Baseline survey will assess socio-demographics pain severity/interference,[36] opioid use,[4] symptoms,[37] and quality of life,[34] with metrics shown in Table 3. of study survey will largely replicate the baseline survey, additionally, patients will rate their satisfaction with their pain management care. See appendix DA for the Baseline survey items

Patients recruited before April 4th, 20203 were also be given the option of completing daily pain assessments using a smartphone application. M*yPainPal,* developed by study PI, Dr. Andrea Enzinger*,* is an Android and iPhone-compatible smartphone app that delivers symptom surveys and tailored cancer pain psychoeducation geared toward advanced cancer patients using opioids. Patients will be pushed twice weekly surveys, optional for study participation, and are included for exploratory longitudinal analyses to examine the pre-post effects of specific pain interventions.

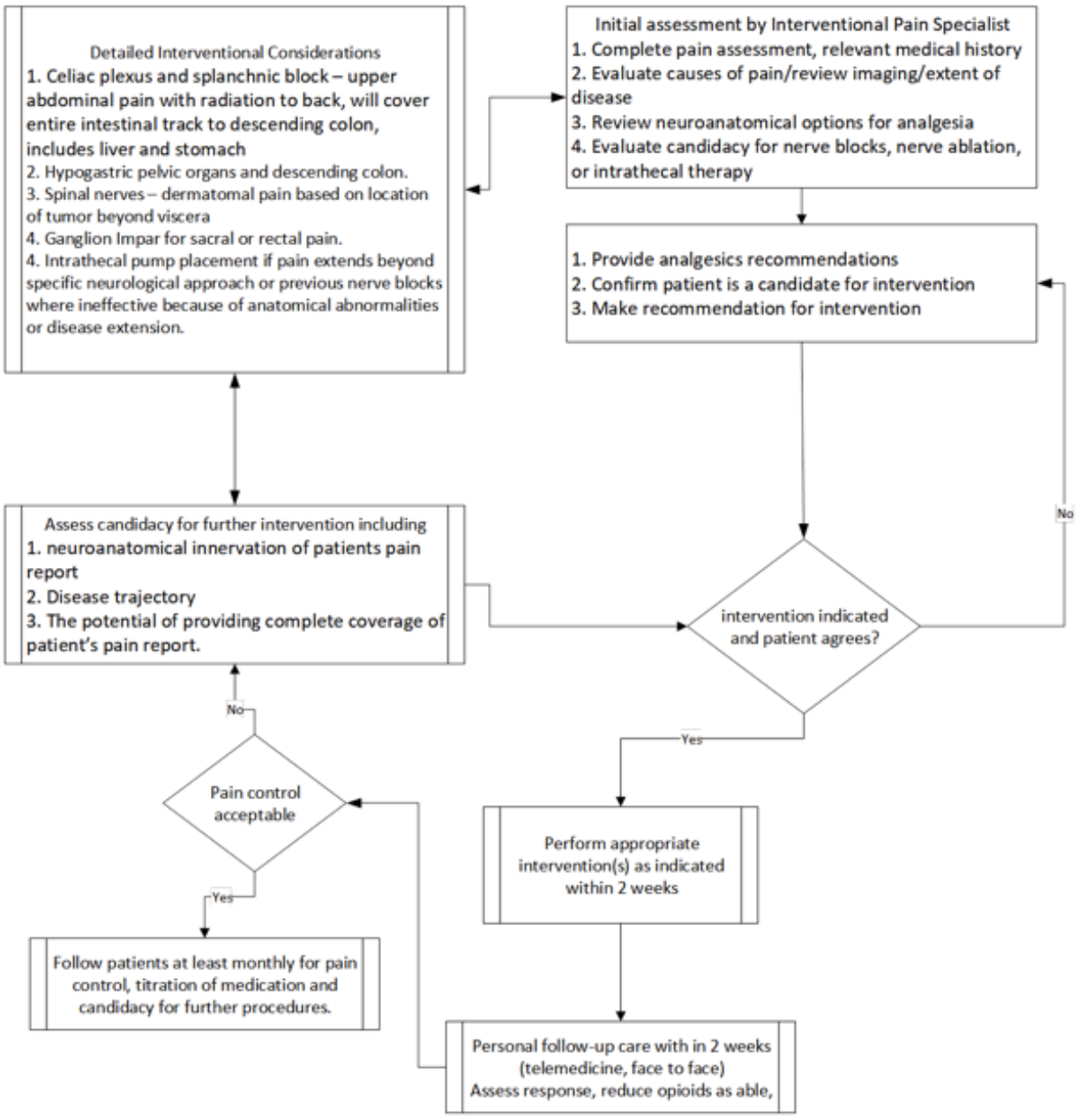
7.2. Intervention

Patients will be referred for evaluation by an anesthesia pain specialist at the Brigham and Women's Hospital or Brigham and Women's Faulkner Hospital (which share clinic faculty), the partner hospital of the Dana-Farber Cancer Institute. This large group includes 5 fellowship-trained physicians who have a particular focus on cancer pain and extensive experience with advanced procedures including intrathecal TDD for cancer pain. The initial consultation will occur either in person or via a telehealth video-conference within 4 weeks of enrollment.

Patients will be scheduled for at least monthly visits in the pain clinic (in person or virtual) throughout the study period, or as defined by the treatment algorithm presented in figure 2. While treatment will be guided by figure 2, care will be at the clinical discretion of the treating physician and as acceptable to the patient participant. The initial consultation will focus on evaluating the patient's pain syndrome and assessing candidacy for interventional procedures including plexus or somatic nerve blocks and intrathecal therapy. The physician will make recommendations to optimize the patients' analgesic regimen, and will offer appropriate interventional therapies. If the patient consents to an intervention, it will be scheduled as soon as possible (ideally within 2 weeks). Patients will be monitored closely for

improvement. If pain relief is inadequate, medications will be optimized and the patient will be considered for alternative interventions (e.g. intrathecal therapy) with potential for benefit. If the patient initially responds an intervention and subsequently develops new or recurrent pain, they will likewise be considered for repeat intervention or a different intervention as clinically indicated (see figure 2 for more details).

The study team will hold bi-weekly meetings with study investigators to review all patients on the study including their cancer history, pain syndrome, their candidacy for interventional procedures and outcomes. This will facilitate the team's ability to track adherence to the treatment algorithms and the outcomes of any interventional pain management procedures.



7.3. Data Collection:

Three survey assessments (at baseline, 2-months, and 4-months) will assess future outcomes and covariates needed to plan a future randomized clinical trial, including patients' pain, functional wellbeing, and quality of life. The daily symptom reporting using a smartphone platform will enable

exploratory longitudinal analyses of response to pain procedures. Structured chart abstractions will assess treatment compliance, opioid prescribing, changes in pain management, and healthcare utilization (i.e. hospitalization, ED visits).

Survey assessments: Patient will complete surveys at baseline, 2 months and 4 months. We anticipate pre-post differences in pain severity scores from baseline to 4 months to be our future primary outcome in a randomized clinical trial. 4 months is a relevant timeframe, because we anticipate it will be sufficient for a patient to be evaluated and treated with at least one interventional pain procedure, and any needed secondary procedures if response is insufficient.

The baseline survey will assess socio-demographics, characteristics and severity of pain, symptom burden and quality of life, and psychological characteristics known to influence pain (e.g. pain catastrophizing, perceived stress, anxiety, depression, sleep). Subsequent surveys will be brief and will focus on pain severity, functional interference, and quality of life.

7.3.1. *Structured chart abstractions*: A study assistant will abstract clinical characteristics at baseline (e.g. tumor type and location of metastases, date of diagnosis, current treatment). At the end of study, the RA will also conduct a detailed abstraction to evaluate the following (see appendices BA and BB):

- Any interventional pain management procedures, and dates of procedures
- Opioid doses (MMEDs) and dates of medication changes
- Unplanned and planned hospitalizations for pain
- Emergency department visits for pain
- Survival (which will be augmented by the National Death Index, which is integrated into the DFCI research database OnCORE through an existing process)

7.3.2. *Smartphone based symptom reporting*: * As described in section 6.2, this is not applicable to patients recruited to the study after April 4th, 2023.

Patients will be given the option to use a secure smartphone application to report on daily symptoms and to track their objective activity levels. Patients will be incentivized $5 for each week that they complete at least 2 daily assessments.

MyPainPal is a secure smartphone application developed, validated, and optimized by Dr. Enzinger. It is fully HIPPA-compliant with all relevant security standards needed to protect health information, and has demonstrated to have high patient acceptability. The application can be downloaded for free through the Apple Store and Google Play. All data are saved on a secure encrypted password-protected server. The application hosts patients analgesic and laxative medications (including dose and frequency), linked to comprehensive medication education. Patients are pushed a brief daily survey which assesses pain severity and interference from the BPI, mood (use of PRN opioids in the past 24 hours, pain relief, constipation and laxative use. Patients receive custom educational pearls in response to each daily survey spanning medication teaching, psychoeducation and skills training (e.g. activity pacing). The application also includes an educational library covering psychological and medical pain management strategies. See appendix C for screen shots of the application. The advantage of this approach is that the brief daily assessments (pain severity, interference) will overlap with the primary/secondary outcome assessments and it will be used to impute these outcomes should survey data be incomplete. Moreover, these will be rich data that will allow exploration of longitudinal outcomes, responses to specific interventions (e.g. procedures, opioid titration), and relationships between pain severity, interference and QOL.

8. Monitoring Subject Safety and minimizing risks

8.1. Risks to Subjects

Physical risks: Physical risks to subjects include if they are offered a pain management procedure and suffer a complication of this procedure. These specific risks and benefits will be reviewed between the patient and the interventional pain management specialist, and patients will be required to sign a standard institutional informed consent document for that procedure as is customary at DFCI and all Mass General Brigham sites.

Psychological risks: Survey assessments, including reporting pain or depressive symptoms could be distressing for some patients.

Privacy risks: There is a risk of privacy violation or loss of confidentiality. This risk is anticipated to be

minimal, and the study team is committed to guaranteeing adequate protection against risk as described in the following section.

8.2. Protection Against Risks

Recruitment and Informed Consent

Participants will be sent a study letter and given the option to opt out of the study. If they do not opt out, participants will be approached in by the RA in a private and confidential manner. If the patient is eligible and interested in participation, the study letter and consent form will be reviewed with and signed by the participant. The RA will keep all signed documents in a password protected folder or locked cabinet, accessible only to the PI-designated study team member.

The informed consent to participate will adhere to strict standards regarding its content. Required sections include: Introduction; Why is this research study being done? What other options are there? What is involved in the research study? How long will I be in this research study? What are the risks or discomforts of the research study? What are the benefits of the research study? Can I stop being in the research study and what are my rights? What are the costs? What happens if I am injured or sick because I took part in this research study? What about confidentiality? Whom do I contact if I have questions about the research study?

8.2.1. Protection against the 3 types of risk to this study:

Physical Risks: Physical risks would all be attributable to routine clinical care received while participating on this study. This is minimized by the fact that we are referring to an expert group of anesthesiologists who are fellowship trained in interventional pain management and all of whom have extensive experience managing cancer pain. We further mitigate any physical risks by using the treatment algorithm as a guide for management. Furthermore, we will hold bi-weekly meetings with study investigators, Dr. Topiwala, Dr. Enzinger, and Dr. Wright to review all patients on the study including their cancer history, pain syndrome, their candidacy for interventional procedures and outcomes. There is also a risk that patients' may feel a false sense of reassurance in reporting their symptoms on the MyPainPal application. We will mitigate this risk by including a disclaimer in the application that the

reported symptoms are not monitored 24/7 and that they should contact their care team for any severe symptoms. Furthermore, any severe symptoms (e.g. pain level of 8 or greater, report of any "red flag" symptom such as fever, vomiting, obstipation) prompts the patient to call their care team immediately. Moreover, any symptoms that are poorly controlled (but not severe enough to merit an alert to contact their care team immediately) are displayed in red on the MyPainPal portal to alert the study team. The patient's care team (oncology, anesthesia pain and palliative care if relevant) will be notified via an Epic inbasket message or email (depending upon clinic preference).

Psychological Risks: Study assessments use validated instruments which have been used in prior studies without causing any significant distress. Should a patient express severe psychological distress to study staff, we will contact the patients' care team and if needed (e.g. the patient expresses suicidal ideation), the study staff will page an urgent social work consultation.

Privacy risks: Protection against privacy risks: To monitor the risk of loss of confidentiality/privacy, the study team has ensured that the MyPainPal app is HIPPA compliant and meet the privacy and security standards set by DF/HCC. In addition, all collected study data will be maintained in a secure location and personal identifiers will be removed.

To maximize data security, both REDCap and MyPainPal employ:
User Privileges - To ensure that users have access only to data and information that they are supposed to have within the application, user privileges are utilized within the software. Each user has their own account, and their user account will only have access to information that they themselves have created or to which administrators have granted them access.

Password-protection & Authentication - Both systems are password protected and implement authentication to validate the identity of end-users that log in to the system.

Auto-logout setting will automatically log a user out of the system if they have not had any activity (e.g. typing, moving the mouse) on their current web page for the set amount of time. This prevents someone else from accessing their account and their data if they leave a workstation without properly logging out or closing their browser window.

Logging and Audit Trail - Both systems maintain built-in audit trails that log all user activity and all pages viewed by every user.

9. Statistical Analysis and Sample Size

Power calculations are inappropriate for this pilot feasibility study. We plan to enroll 31 patients over a 6-month period, with 4 additional months for follow-up and 2 months for study preparation and data analysis – based upon projections of clinical volume.

The primary purpose of our analysis is to examine feasibility and acceptability of the intervention. Benchmarks of feasibility/acceptability are as follows

1. Proportion of patients assigned to the intervention that undergo an interventional pain consultation within 4 weeks: $\geq$80%
2. Among patients referred and evaluated by an anesthesia pain specialist, at least 50% will agree and ultimately receive at least one interventional pain procedure
3. Satisfaction with the intervention: At least 80% of patients will be satisfied with the quality of care received in the interventional pain management clinic, defined as rating it a 7 or above on a 0-10 scale.

Analyses will be conducted using an intent-to-treat analysis. Pre-post differences will be assessed and univariate and multivariate descriptive analyses will be performed on all the dependent variables. Statistical significance will be set at $p<0.05$. Chi-square, t-tests, and logistic regression and cluster analyses will be conducted as appropriate. We will calculate the proportion of participants meeting feasibility benchmarks with 95% confidence intervals. Pre-post differences in pain severity (primary outcome) will be examined using a one-sample t-test. One-sample t-tests will also examine pre-post differences in pain interference scores, QOL scores (using the FACT-G), QOL subscales (e.g. physical wellbeing, functional wellbeing), depression/anxiety scores, and opioid MMEs. We will also calculate the proportion of patients undergoing dichotomous outcomes (e.g. occurrence of pain-related ED visits), and the proportion alive at end-of-study. Participants will also be consented for mortality follow-up to allow for examination of survival data.

Missing data will be imputed using a last observation carried forward principle, which will be greatly enhanced by the inclusion of smartphone symptom tracking.

We will fit longitudinal data on pain (derived from the smartphone-based symptom reporting) with linear regressions to estimate the trajectories in pain and to explore the effect of the intervention on pain trajectories, adjusting for each participant's baseline measure. We will also explore the association of potentially moderating variables (e.g. opioid doses, specific interventions patients have for their pain) and clinical characteristics (e.g., stage) with on pain outcomes via linear probability models. These analyses are underpowered, but will be used to explore potentially meaningful differences and estimate a possible effect size and conduct sample size calculations for a future randomized clinical trial.

10. Data Specimen Banking

This study does not involve any specimen collection/banking of any kind.

Personal health information will be collected as part of this study.

All data collected during this study will be stored and used for future research. Any personal identifiers will be removed so that the information cannot be linked back to a patient.

Investigators can request the data collected from this study for new research. Data may also be shared with outside non-profit academic investigators as well as with for-profit pharmaceutical investigators or commercial entities with whom Dana-Farber collaborates. Requests must be sent to the study chair (Andrea Enzinger) and must be approved by the Dana-Farber IRB prior to sharing.

The consent form informs the participant that data collected for this study may be used in the future. By consenting, participants agree. Participants will not be asked to provide additional informed consent for the use of de-identified information in future research.

There is no scheduled date on which the information and data that is being used or shared for this research will be destroyed, because research is an ongoing process.

11. Data Management and Confidentiality

DF/HCC uses a clinical trial management system (CTMS) called OnCore, which is managed by the Office of Data Quality (ODQ).

Patient participants will sign consent and we will collect basic demographic information. Patient participants WILL be registered in OnCore. We will NOT collect each participant's initials and date of birth. We will enter summary/batch accrual information into Dana-Farber's CTMS OnCore.

Data security: PHI data will be collected using multiple the MGB instance of REDCap and MyPainPal, a smartphone-based application developed by Dr. Enzinger at DFCI, which is approved for use on protocol 18-504.

REDCap: For this study, data will be collected using the Partners instance of REDCap (redcap.partners.org). In collaboration with the Harvard Catalyst | The Harvard Clinical and Translational Science Center, REDCap (Research Electronic Data Capture) is a free, secure, HIPAA compliant web-based application hosted by Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS). Vanderbilt University, with collaboration from a consortium of academic and non-profit institutional partners, develops this software application for electronic collection and management of research and clinical study data. Data collection is customized for each study or clinical trial by the research team with guidance from ERIS REDCap administrators. REDCap is built around HIPAA guidelines and is 21 CFR Part 11 capable.

MyPainPal App: The final application will be HIPPA compliant and compliant with DFCI security and privacy standards

To maximize data security, both REDCap and the *MyPainPal* App will employ:

User Privileges. To ensure that users have access only to data and information that they are supposed to have within the application, user privileges are utilized within the software. Each user has their own account, and their user account will only have access to information that they themselves have created or to which administrators have granted them access.

Password-protection & Authentication. Both systems are password protected and implement authentication to validate the identity of end-users that log in to the system.

Auto-logout setting will automatically log a user out of the system if they have not had any activity (e.g. typing, moving the mouse) on their current web page for the set

amount of time. This prevents someone else from accessing their account and their data if they leave a workstation without properly logging out or closing their browser window.

Logging and Audit Trail. Both systems maintain built-in audit trails that log all user activity and all pages viewed by every user.

Study specific procedure to maximize data security:

Controlled access: The REDCap and *MyPainPal* app administrators will set up all user accounts so that each user only has access to their own relevant participant data.

Use of unique study ID numbers: REDCap automatically assigns unique study ID numbers to each new case.

Extensive training: All personnel involved in this study are required to complete and document completion of extensive protocol training. Furthermore, all research personnel are required to have valid certification of human subjects research training.

Quality control: The staff at Dana-Farber will be responsible for monitoring the data for completion, accuracy, and compliance.

12. Provision to Monitor Data to Ensure the Safety of Subjects

The study involves questionnaire-based assessments and symptom reporting and monitoring. The intervention is a care delivery intervention in which patients are referred to a specialty provider who will offer treatments and monitor the patient within the scope of their medical licensure, clinical expertise and practice. This study is not evaluating any investigational procedures or devices. Therefore, any adverse events related to treatment by this specialist would be considered a complication of the routine clinical care received by the patient while participating on the study. Any such complication would be managed by the interventional pain specialist, and the patients' oncology care team. That said, if a patient suffers a serious complication as the result of a pain procedure received while a participant on this study (i.e. a complication that is life threatening, requires hospitalization or prolongation of existing hospitalization, results in significant disability, requires a surgical procedure, death, etc), the study team will notify the IRB within one week of the event. Furthermore, participants will be reminded that participation is voluntary and can be stopped at any time for any reason.

13. Withdrawal of Subjects

The overall DF/HCC study PI, Dr. Andrea Enzinger will make all decisions regarding early termination of the study. The study team will then notify all participants accordingly.

14. Potential benefits to Subjects

Pain management interventions are included in national guidelines for cancer pain management, but are underutilized. My systematic early referral, we anticipate that some patients may benefit by having their pain better managed. This could not only lessen pain severity but also reduce pain interference and improve quality of life.

15. Vulnerable Populations

This research does not involve vulnerable populations of prisoners, children, cognitively impaired adults, or pregnant women. Prisoners, children, cognitively impaired adults, and pregnant women are excluded.

16. Community Based Participatory Study

Not applicable to this study.

17. Sharing of Results with Subjects

Participants will be directed to clinicaltrials.gov for research study results.

18. Setting

This is a pilot study that will take place at Dana-Farber Cancer Institute. Patients will also be referred for pain management care at the BWH pain center clinics – either at the chestnut hill office (850 Boylston), Foxboro office, or the affiliated BWH Faulkner hospital. Research assessments will all be conducted through DFCI study staff and stored on DFCI servers.

19. Resources Available

This study team will be taking place under the Population Sciences Division at Dana-Farber. The Population Sciences Division maintains its own server infrastructure and systems administration staff that provide data storage, data backup, and data security in support of large data analysis projects. The servers are configured as a virtual server pool with virtual server hosts connected to a centralized Storage Area Network (SAN) device. Server virtualization increases the efficiency and flexibility of the server pool while minimizing downtime and cost. The server pool currently has 20 processor cores and a data storage capacity of 9 terabytes. This server infrastructure has a dedicated Systems Administrator to optimize performance, maintain security patches, perform backups, and execute other related tasks. Researchers in the Division have access to additional resources through the Research Computing group. Research Computing provides a variety of services including file server space, backup services, website hosting, and support of some workstation computers.

Additionally, the research team is well-qualified to perform their duties. Drs. Enzinger and Wright have extensive experience in conducting research studies in cancer care delivery and pain management. She has deep knowledge of the clinical and research environments and the patient population and culture at DFCI. Dr. Edgar Ross is an international expert in the management of chronic pain and of cancer pain, and has led numerous observational studies of chronic pain outcomes and therapeutic studies of different pain treatments. Dr. Pritesh Topiwala will replace Dr. Ross as he retires in April of 2023. Dr. Topiwala, a practicing interventional pain management specialist, who was working under Dr. Ross, will be the new clinical champion for this study. Dr. Topiwala has been seeing patients in the interventional pain management clinic, who are enrolled in this study, since the study opened. Dr. Jamison is a pain psychologist, an international expert in chronic pain research, including analysis of longitudinal app-collected symptom diaries.

20. Prior Approvals

Not applicable for this study.

21. Recruitment Methods

See section 5.0 for a detailed description of recruitment procedures.

22. Compensation for Research-Related Injury

Not applicable for this study.

23. Economic Burden to Subjects

Costs that subjects may be responsible for because of participation in the research:
Subjects participating in this study will be asked to complete online surveys and/or report their symptoms from home using an internet-enabled device. Participants will have to use their own hardware (e.g., smartphone, tablet, computer) and their own WiFi or Data Plan which may cost them money; subjects are responsible for these costs. Devices and/or data plans will not be provided by the study.

Patients may also be responsible for parking fees related to visits at the interventional pain management specialist, or costs of the care itself – such as insurance copays or deductibles. Parking fees specifically for visits with the interventional pain management specialist will be reimbursed by the study as necessary. Costs related to the care itself (e.g. insurance copays, deductibles) are considered part of standard care and would not be specifically covered by the study. To compensate for their time, patients will receive $25 at study completion when they have completed their final survey. Patients will also receive $5 for every complete week of surveys completed in the *MyPainPal* app. As described in section 6.2, the *MyPainPal* application will no longer be offered to participants after April 4th, 2023, so therefore the additional compensation will no longer be available.

24. Process to Document Consent in Writing

Documentation of informed consent will be obtained from all patient participants. Patients will have the option of signing a consent in writing, or they may do remote consenting via Redcap (see Appendix AA)

25. Drugs and Devices

Not applicable – this study of a new cancer care delivery model is not examining any drug or device.

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27. Appendices

Appendix AA – Consent Form
Appendix AB – Study Letter
Appendix BA – Beginning Abstraction
Appendix BB – End of Study Abstraction
Appendix C – *MyPainPa*l Application Screenshots
Appendix DA – Baseline Survey
Appendix DB – 2 Month Survey
Appendix DC – 4 Month Survey