Development of a Breakthrough Cancer Pain Assessment Tool

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Declaration of Originality

I, Katherine Webber, hereby declare that this thesis contains the results of my own work except where otherwise acknowledged. The studies in this thesis were conceived and designed with the assistance of my supervisors, Professor Cowie and Doctor Andrew Davies. In addition, statistical support was received from the Imperial College statistical adviso(ry service. Information derived from the work of others and discussed in this thesis is referenced in the text and listed in the bibliography. No part of this thesis has previously been submitted in application for a higher degree.

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Abstract

Breakthrough cancer pain (BTCP) is a type of pain characterised by transient pain exacerbations on the background of stable and well-controlled pain. It is a significant problem in cancer patients, however, there are no fully validated diagnostic or measurement instruments to identify and assess this type of pain. The aim of this study was to develop and validate a clinical tool to diagnose and quantify BTCP.

This study consisted of two stages. Stage one involved the development of a BTCP diagnostic algorithm, which was tested for diagnostic accuracy in 135 cancer patients. The 'gold-standard' BTCP diagnostic test for comparison was a comprehensive clinical assessment with a cancer pain expert. The sensitivity of the diagnostic algorithm to detect 'true cases' of BTCP was 0.54 (i.e. 54% of expert diagnosed BTCP cases screened positively), specificity 0.78 (78% of non-BTCP patients screened negatively), positive predictive value 0.84 (84% of cases that screened positively had the condition of BTCP), and negative predictive value 0.60 (60% of those that screened negatively did not have the condition).

Stage two involved the development of a BTCP measurement instrument from first principles according to international standards. This instrument was then tested on 100 BTCP patients to assess for measurement properties of validity, reliability, responsiveness and acceptability.

Reliability testing confirmed that there was an acceptable degree of measurement error. Validity testing confirmed two underlying BTCP dimensions in the instrument. All items and summary scores correlated appropriately with external measures of BTCP. The instrument demonstrated responsiveness by correlating with the patient impression of change and clinical measures of change.

In summary, this is the first measurement instrument with robust validity and reliability data for the clinical diagnosis and quantification of BTCP. The measurement instrument met all required standards to recommend its general use however, the diagnostic tool had a lower than expected ability to detect 'true' cases

of BTCP. The clinical implications of this study mean that once BTCP has been identified the measurement tool could be used to quantify the severity of BTCP, and monitor BTCP experience over time.

Publications arising from this thesis

Presented abstracts

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Publications

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Glossary of Terms

Breakthrough cancer pain (BTCP): a transient exacerbation of pain that occurs spontaneously or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain.

Construct validity: the extent to which a scale conforms to logical relationships with clinical anchors and other measures.

Content validity: the extent to which the content of a scale is representative of the conceptual *domain* it is intended to cover.

Discriminant validity: demonstrated by evidence that a scale is not related to measures of different constructs.

Domain: pain domain is the term used to refer to different subcategories of the concept of interest e.g. pain intensity or *interference.* Also referred to as a 'dimension.'

Effect size: an objective and standardised measure of the magnitude of an observed effect.

Eigenvalue: numerical value of the substantive importance of each dimension (or factor) in a *factor analysis*.

End of dose failure: a type of pain related to analgesic dosing. Some authors regard this as a subtype of breakthrough pain.

Factor analysis: a technique for identifying whether the correlations between a set of observed variables stem from their relationship to one or more of the dimensions (or factors) in the data.

Interference: the term used to refer to the impact of pain on aspects of function e.g. interference with activities of daily living secondary to pain

Minimal important difference (MID): the numerical value of the measurement instrument that reflects a clinically relevant, either positive or negative, difference.

Neuropathic pain: pain secondary to abnormal function of the somatosensory nervous system

Nociceptive pain: pain that arises from actual or threatened damage to non-neural tissue and is due to activation of nociceptors (sensory pain receptor)

Non-volitional incident pain: a subtype of breakthrough cancer pain that refers to pain precipitated by an involuntary act e.g. coughing.

Performance status: refers to a patient's general physical condition and is classified according to the Eastern Cooperative Oncology Group (ECOG) performance status ratings, 0=fully active, no restrictions, 1=restricted but ambulatory and able to carry out light work, 2=ambulatory but unable to carry out work, up and about more than 50% of waking hours, 3=capable of limited self care, confined to bed or chair for more than 50% of day, 4=completely disabled, confined to bed or chair

Procedural pain: a subtype of breakthrough pain related to a therapeutic intervention e.g. wound dressing

Reliability: the extent that a score on a measurement instrument is free from error assessed by the ability of the measure to produce consistent results when the same entities are measured under different conditions.

Responsiveness: the ability of a measurement instrument to detect any change in a trait it is designed to measure.

Scree plot: a graph plotting each factor in a *factor analysis* against its associated *eigenvalue*. It shows the relative importance of each factor.

Spontaneous pain: a subtype of breakthrough cancer pain that occurs unpredictably without a specific trigger. May also be known as 'idiopathic pain.'

Validity: the ability of an instrument to adequately measure the desired construct of interest.

Volitional incident pain: a subtype of breakthrough cancer pain that refers to pain precipitated by a voluntary act e.g. walking. This may also be referred to as 'movement related pain.'

Chapter 1. Introduction

1.1 Definition of pain

Pain is a symptom that affects a significant proportion of patients with a cancer diagnosis [1], 70% of patients with incurable cancer and 45% of patients in the last week of life [2]. However, pain is a 'private personal experience' and due to its subjective nature can be difficult to assess and quantify [3].

The International Association for the Study of Pain (IASP) Subcommittee on Taxonomy proposed a definition of pain as follows: 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or is described in terms of such damage' [4]. This definition is the standard for the majority of pain texts and refers to pain as a psychological state, as opposed to a pathophysiological state [5]. The stimulation of pain receptors and pathways does not always result in pain being experienced. Pain is instead the result of this stimulation in conjunction with the interpretation and expression of such stimuli by higher pathways in individuals [3,6].

1.2 Pain dimensions

The different aspects of pain experience are referred to as pain dimensions. The above IASP definition broadly refers to pain as having both sensory (pain receptor stimulation) and emotional dimensions (cognitive processing of stimuli) and it is universally acknowledged that pain is a multidimensional experience [6,7].

The multidimensionality of pain was initially hypothesised by Melzack and Wall in 1965 [8]. They proposed that pain consisted of three dimensions: 1) sensory-discriminative (sense of the intensity, location, quality and duration of pain); 2) motivational-affective (unpleasantness and urge to escape unpleasantness); and 3) cognitive evaluative (cognitions such as appraisal, distraction, and cultural values). They theorised that pain intensity was not simply determined by magnitude of pain stimulus but 'higher' cognitive activities that altered the intensity and unpleasantness. Thus suggestion or placebo may modulate the affective-

motivational dimension whereas excitement or distraction in war or games may block all dimensions. The paper described that: 'Pain can be treated not only by trying to cut down the sensory input…but also by influencing the motivational-affective and cognitive factors as well'. This is the basis of modern pain theory and treatment, which consists of detailed history taking and multidisciplinary management to identify and address the various factors that influence the different pain dimensions [5].

Since this initial hypothesis regarding pain multidimensionality was published various techniques have been developed to further investigate and identify the pain dimensions that exist in different populations.

The most commonly used methods to assess the dimensional nature of pain are multidimensional scaling technique and factor analysis. Multidimensional scaling (MDS) is a general term for a class of techniques developed to deal with problems of measuring and predicting human judgement [9]. Subjects are required to assess the similarity of all possible pairings of a set of pain descriptors and the data is linearly transformed to calculate the number of dimensions that explain the descriptor pairings. One study using MDS in cancer patients reported three pain dimensions, pain intensity, emotional quality and somatosensory [10].

Factor analysis is a statistical technique used to understand the structure of a set of variables by identifying the underlying common dimensions, or factors. It is often used in the context of exploring data or hypothesis testing theories about pain questionnaires in stages of development [11,12].

Factor analysis studies of pain in cancer patients has shown a minimum of two dimensions [13-15]. These are described as sensory (experience of pain intensity, location, duration) and reactive (impact of pain on physical, psychological and social functioning). Some studies using the same technique have described three dimensions with the reactive dimension split into separate physical and psychological components [16,17]. The majority of these studies involved factor analytical techniques on items in a pain questionnaire (Brief Pain Inventory-BPI) (Appendix A)[13]. The exploration of pain dimensions was therefore limited by the

items in the questionnaire, which consisted of enquiries about pain intensity and the impact of pain on social functioning (interference).

In summary, it is acknowledged that pain is a multi-dimensional phenomenon. There remains a lack of consensus, however, about the nature and number of pain dimensions that exist [7]. The dimensions described depend on the population studied and methods employed.

1.3 Classifications of pain

The ability to categorise pain according to various characteristics e.g. cause of pain (aetiology) or type of injury (pathophysiology) provides information that can be used to dictate management strategies and inform patients [18]. Information is also provided that enables clinicians to evaluate different pain dimensions, e.g. pain related to cancer may be accompanied by cognitive-evaluative aspects (fear of worsening disease and death), which can influence pain intensity experienced.

Pain can be categorised in different ways and the most common classifications used are according to 1) aetiology, 2) pathophysiology, or 3) temporal characteristics (i.e. changing profile over time) [4,19,20].

The aetiology of pain refers to the underlying disease process that is causing the tissue damage (e.g. tumour, rheumatoid arthritis). Another way of classifying pain is according to the pathophysiology of the tissue damage (i.e. mechanism causing the problem). Neuropathic pain is pain secondary to abnormal function of the somatosensory nervous system whereas nociceptive pain is pain that arises from actual or threatened damage to non-neural tissue and is due to activation of nociceptors (sensory pain receptor) [4].

Temporal characteristics of pain are a way of classifying pain according to the changing profile of pain intensity over time. Pain is rarely of continuous uniform intensity and the proportion of time that pain is under acceptable control, and the presence and frequency of transient, more severe, episodes, can alter pain management strategies [21,22]. Pain is divided into two categories for this purpose, background pain and transient, or transitory, pain [23].

The term background pain is used interchangeably with baseline pain and is broadly defined as pain that is present for the majority of the time. Transient pain refers to a discrete pain episode of higher intensity than the background pain. [23,24]

1.4 Breakthrough cancer pain

1.4.1 Definition of breakthrough cancer pain

Breakthrough cancer pain (BTCP) refers to a type of pain classified according to temporal characteristics, and requires transient exacerbations of pain to occur on a background of generally controlled pain [23]. There is no consensus on the exact definition of BTCP and many have been presented in the literature (Table 1). However, despite this lack of precise agreement in wording the definitions are broadly similar and require a patient to have 'adequately controlled' background pain with episodes of transient more severe pains (breakthrough episodes).

Table 1: Breakthrough cancer pain definitions

Author	Definition of BTCP
Portenoy and Hagen 1989 [23]	A transitory increase in pain to greater than moderate intensity which occurs on a baseline pain of moderate or less
Portenoy and Hagen 1990 [24]	A transitory exacerbation of pain that occurs on a background of otherwise stable pain in a patient receiving chronic opioid therapy
Hanks 1998 [29]	A transitory exacerbation in otherwise stable analgesia for stable pain
Mercadante 2002 [21]	A transitory exacerbation of pain that occurs in addition to otherwise stable persistent pain
Caraceni 2004 [30]	Baseline pain intensity aggravated by flaring episodes of pain of any duration
Portenoy 2005 [28]	A transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled pain
Hagen 2008 [31]	A transient exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain. Breakthrough pain can be an exacerbation of baseline pain or it can be a pain that is different from baseline pain.
Davies 2009 [22]	A transient exacerbation of pain that occurs spontaneously or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain
Lasheen 2010 [32]	Episodic worsening of pain of any intensity on a background of continuous pain of any intensity or prescribed around the clock analgesics

The issues with the above BTCP definitions are how to objectively define background and transient pains, and more importantly how to define 'controlled' background pain. Background pain broadly refers to pain present for the 'majority of the time' and attempts have been made to describe it more objectively as follows: 'pain present for half the waking days' [33], 'pain experienced for 12 or more hours during 24 prior hours' [22,24,34], or 'pain that is almost always present and may be steady or constant' [25].

The majority of authors agree that background pain needs to be controlled to diagnose BTCP [21-24], however in certain studies BTCP is reported without the requirement for controlled background pain [26,32,35]. Background pain can also be partly or completely masked by analgesia, which needs to be accounted for when evaluating such pain control. The criteria used to define 'controlled background pain' will be discussed in the next section.

1.4.2 Diagnosis of breakthrough cancer pain

BTCP is diagnosed by a variety of methods in observational and pharmacological studies [22]. Certain observational studies have used a clinical diagnosis to identify BTCP patients by providing physicians, nurses [36,37] or researchers [38,39] with a BTCP definition, which they apply by means of a clinical pain consultation. The majority of BTCP definitions used have terms such as 'adequately controlled' and 'relatively stable' to describe background pain, and health professionals and patients may interpret such imprecise language differently. Attempts have therefore been made to apply more objective criteria to diagnose BTCP.

Studies that have applied such criteria initially require a patient to have controlled background pain [27]. There are two methods described to evaluate this phenomenon, firstly by requiring the patient to be taking a stable dose of background pain medication (analgesia that is taken on a regular basis) [40-47], and secondly by requiring the patient to rate the intensity of their background pain below a certain level on a pain intensity rating scale [24,30,33,42,43,46,48].

All pharmacological studies evaluating opioid analgesics for BTCP episodes required patients to be receiving a stable dose of regular opioid therapy to be diagnosed with 'controlled background pain'. The opioid dose was required to be a minimum 'mean equivalent daily dose' of 60mg morphine and had to have been 'stable' for a period of time. The time period required for 'stability' varied between studies (1 month to 1 week) as did the definition of 'stable opioid therapy' [40,41]. Some studies defined as 'less than 20% increase in opioid dose per day for 2 consecutive days' [40] or 'not a rapidly escalating dose' [41]. However it was often not clearly defined.

The other criteria used to diagnose controlled background pain required a patient to rate the intensity of their background pain on a standardised pain intensity scale. The scales most commonly used were 1) a verbal rating scale (VRS) where a patient rates the intensity of their background pain using pain severity descriptors (e.g. as 'none', 'mild', 'moderate' or 'severe'], and 2) a numerical rating scale (NRS) where a patient must rate pain intensity between zero and ten (e.g. 0='no pain', 10='worst pain imaginable').

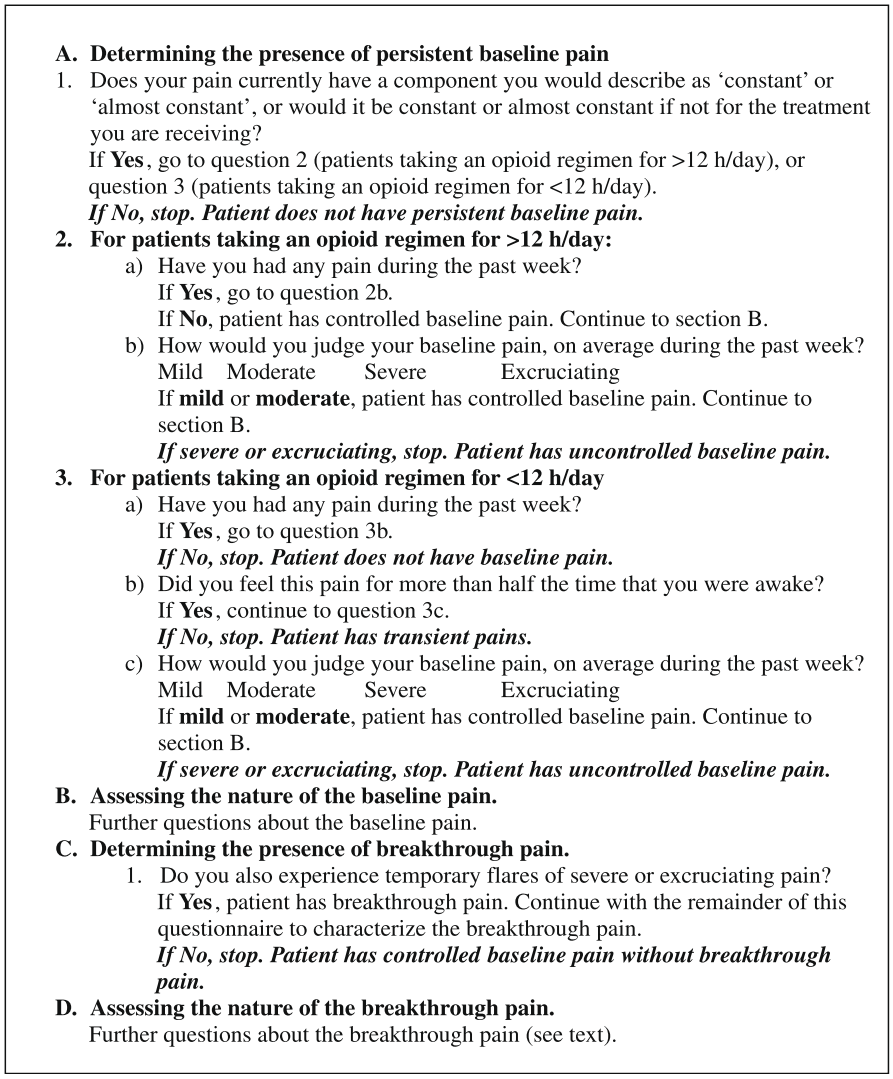
The majority of studies used a VRS to assess background pain [33,42-3,46,48-50]. However there were differences between studies in pain descriptors that defined 'controlled' background pain. Certain studies required patients to rate the intensity of their background pain as 'none', 'mild', or 'moderate' to be considered 'controlled' [33,42-3,46,48-9] whereas others required it to be 'none' or 'mild' [50].

Studies that used a NRS to assess background pain generally required a score of four or less to define 'adequately controlled' [45,47,51]. However Slatkin et al [44] required an overall average pain intensity, which incorporated both background and breakthrough episodes, of seven or below on a NRS to enter their study investigating the efficacy of a fentanyl lozenge versus placebo. Many studies, however, stated that background pain should be 'relatively stable' or 'well controlled' but do not define further [41,52-5].

Once controlled background pain has been diagnosed the next step was to determine the presence of 'breakthrough pain' episodes. Breakthrough episodes of pain are commonly required to be 'transient exacerbations' however there is less consensus regarding what time period constitutes 'transient' and what level of pain severity signifies an 'exacerbation'. Breakthrough episodes have been defined as those requiring additional opioid analgesia [33,41,53-4], as episodes of pain of severe to excruciating intensity on a VRS [33,46,55], or as an episode of pain of greater intensity than background pain [26,50].

Two diagnostic methods have been reported and used to further standardise the diagnosis of BTCP [33,50]. They are both algorithms, a step-by-step process, which categorise a patient's pain based on their answer at each stage. Portenoy et al presented an initial algorithm (Figure 1) [24,33] that required a patient to have background pain present and controlled to a level of moderate or less with breakthrough episodes of 'severe' or 'excruciating' in the previous 24 hours. This algorithm has been replicated to diagnose BTCP in other prevalence studies [48,49] and amended slightly to detect BTCP in non-cancer patients [25].

Figure 1: Diagnostic breakthrough cancer pain algorithm (Portenoy et al 2006)



A. Determining the presence of persistent baseline pain

1. Does your pain currently have a component you would describe as 'constant' or 'almost constant', or would it be constant or almost constant if not for the treatment you are receiving?
   If **Yes**, go to question 2 (patients taking an opioid regimen for >12 h/day), or question 3 (patients taking an opioid regimen for <12 h/day).
   If No, stop. Patient does not have persistent baseline pain.
2. **For patients taking an opioid regimen for >12 h/day:**
   a) Have you had any pain during the past week?
      If **Yes**, go to question 2b.
      If **No**, patient has controlled baseline pain. Continue to section B.
   b) How would you judge your baseline pain, on average during the past week?
      Mild Moderate Severe Excruciating
      If **mild** or **moderate**, patient has controlled baseline pain. Continue to section B.
      If severe or excruciating, stop. Patient has uncontrolled baseline pain.
3. **For patients taking an opioid regimen for <12 h/day**
   a) Have you had any pain during the past week?
      If **Yes**, go to question 3b.
      If No, stop. Patient does not have baseline pain.
   b) Did you feel this pain for more than half the time that you were awake?
      If **Yes**, continue to question 3c.
      If No, stop. Patient has transient pains.
   c) How would you judge your baseline pain, on average during the past week?
      Mild Moderate Severe Excruciating
      If **mild** or **moderate**, patient has controlled baseline pain. Continue to section B.
      If severe or excruciating, stop. Patient has uncontrolled baseline pain.

B. Assessing the nature of the baseline pain.
Further questions about the baseline pain.

C. Determining the presence of breakthrough pain.

1. Do you also experience temporary flares of severe or excruciating pain?
   If **Yes**, patient has breakthrough pain. Continue with the remainder of this questionnaire to characterize the breakthrough pain.
   If No, stop. Patient has controlled baseline pain without breakthrough pain.

D. Assessing the nature of the breakthrough pain.
Further questions about the breakthrough pain (see text).

An alternative diagnostic algorithm was published by Davies et al (Figure 2) [22,50]. In this diagnostic algorithm background pain was required to be 'none' or 'mild on a verbal rating scale to be considered controlled and the transient exacerbations of pain needed to be more severe than background pain but not of a specific rated intensity.

Figure 2: Diagnostic breakthrough cancer pain algorithm (Davies et al 2011)

Q1.Do you have pain related to your cancer?
Yes / No

If no, do not proceed with remainder of questionnaire

Q2. Is the pain present most of the time*, or would be present if not taking painkillers?
(* pain present for ≥12 hr/day during the last week)
Yes / No

If no, do not proceed with remainder of questionnaire

Q3. Is the pain well controlled for most of the time*?
(* pain rated as 'none' or 'mild' but not as 'moderate' or 'severe', for ≥12 hr/day during the last week)
Yes / No

If no, do not proceed with remainder of questionnaire

Q4.Do you have short - lived exacerbations of the pain ('breakthrough pain')?
Yes / No

If no, do not proceed with remainder of questionnaire

Q5.Are you taking a strong painkiller* for the constant pain ('background pain')?
(* e.g. morphine, fentanyl, hydromorphone, methadone, oxycodone)
Yes / No

If no, do not proceed with remainder of questionnaire

Both algorithms diagnosed background pain by requiring the patient to be prescribed fixed scheduled opioids and answering affirmatively to a statement that the pain was, or would be, present for greater than 12 hours per day or half the waking day. They both required the patient to have controlled background pain but differed in their criteria to diagnose this; i.e. 'mild' pain or less versus 'moderate' pain or less on a VRS. There are no published validity data to determine if either of these algorithms accurately diagnosed patients with BTCP, and which value for pain severity most accurately correlated with controlled background pain. In addition, there is no consensus on the period during which background pain was required to be stable to be deemed 'controlled' and reports vary between 24 hours [24,33] and 1 week [22,50].

If the background pain is not considered controlled, then pain is referred to as 'uncontrolled background pain'. A patient may still experience variations in pain intensity with uncontrolled background pain. It should be noted that individual patients vary in their ability to rate and categorise different pains, and also have different multi-faceted reasons for whether they consider their background pain control acceptable [36]. The application of clinician-determined criteria to define 'controlled background pain' may not correlate with a patient's level of acceptability with their level of pain control [56].

In summary, there is currently no universally recognised validated standardised criterion to diagnose BTCP, which has led to a diverse range of patients being recruited to different academic and commercial studies of this condition.

1.4.3 Classification of breakthrough cancer pain

Breakthrough cancer pain can be classified according to different criteria, and often more than one criterion is used. Firstly, similarly to generic pain, BTCP can be classified according to the pathophysiology of the pain process. The majority of studies classify BTCP this way using the categories: 1) nociceptive 2) neuropathic and 3) mixed (combination of nociceptive and neuropathic)[27]. Cancer pain pathophysiology is complex and classification can vary according to individual interpretation despite the above internationally recognised criteria [57]. Tumours can cause both tissue and nerve damage, but it can be difficult from clinical and radiological assessment to determine which mechanism predominates in individuals [29].

Secondly, BTCP can be classified according to aetiology: 1) direct effect of the cancer 2) indirect effect of the cancer (i.e. secondary to disability) 3) effect of anti-cancer treatment (i.e. chemotherapy induced neuropathy), or 4) unrelated to the cancer (i.e. caused by concurrent illness) [24,27,33].

Finally, BTCP is classified according to its relationships with specific events. This classification is unique to the phenomenon of BTCP. Spontaneous pain, which occurs unexpectedly, and incident pain which is precipitated by certain events (e.g. movement). Incident pain is subclassified into three categories 1) volitional pain,

meaning pain precipitated by a voluntary act (e.g. walking) 2) non-volitional, secondary to non-voluntary act (e.g. coughing) 3) Procedural, related to a therapeutic intervention (e.g. wound dressing) [58].

End of dose failure is often described as a third category of BTCP that is related to analgesic dosing (e.g. prior to administration of regular painkillers) however some authors perceive this type of pain as background pain that is inadequately controlled [59]. As the diagnosis of BTCP relies on the presence of 'adequately controlled background pain', the majority of authors classify end-of-dose failure as a type of BTCP if it fits this clinical criterion and background pain is still controlled for the majority of the time [35,58].

1.4.4 Epidemiology of breakthrough cancer pain

The reported prevalence of BTCP is 16-93% (Table 2). The variation in prevalence between studies is due to the varying criteria used to diagnose BTCP, as well as the different patient groups recruited. As previously discussed, there are a number of criteria used to determine if a patient has controlled background pain, which can alter prevalence data. Furthermore some prevalence studies do not require a patient to have controlled background pain at all [32,35,59,60]. BTCP prevalence is often reported as a proportion of a select patient group (e.g. patients with controlled background pain) meaning the data are not applicable to a general cancer pain population [24,33,49]. Many prevalence studies also recruited small numbers and so the data have large confidence intervals. Without objective standardised criteria, and a consistent definition, it is difficult to determine the true prevalence of BTCP from the literature. Nevertheless it is apparent that a sizeable proportion of patients do have exacerbations of pain that cause significant morbidity.

Table 2: Prevalence of breakthrough cancer pain

Study	Population	Diagnostic criteria	Prevalence of Controlled Background Pain (CBP)	Prevalence of BTCP
Portenoy 1990 [24]	90 hospital inpatients-USA	Algorithm (Figure 1)	70%	46% (of total patients) 63% (of patients with CBP[1])
Portenoy 1999 [33]	178 Inpatients in US cancer centre on fixed dose opioid	Algorithm (Figure 1)	92%	47% (of total patients) 51.2% (of patients with CBP)
Petzke 1999 [35]	631 inpatient and outpatient new patient referrals to German pain service	Any transitory exacerbation of pain distinguishable from stable background pain	Not applicable	39% (of total patients)
Zeppetella 2000 [49]	381 hospice admissions with cancer	Algorithm (Figure 1)	64% (245) had background pain	57% (of total patients) 89% (of patients with pain)
Swanwick 2001 [59]	132 UK hospice inpatients with pain	Pain of episodic nature	Not applicable	93%
Fortner 2002 [60]	Phone survey of 1000 US cancer patients	On scheduled analgesics Flares of pain that occurred between doses of analgesics	26% taking regular analgesia	16% (total sample) 63% (patients on regular analgesics)
Gomez-Batiste 2002 [38]	397 Palliative care patients-Spain	A transitory increase of pain of higher than moderate intensity, that occurred suddenly over a relatively well-controlled chronic pain level, which was, at least, moderate in intensity	Not reported	41%
Hwang 2003 [48]	74 US oncology inpatient and outpatients with pain	Algorithm (Figure 1)	Not reported	70% (36% after 1 week)

Study	Population	Diagnostic criteria	Prevalence of Controlled Background Pain (CBP)	Prevalence of BTCP
Caraceni 2004 [30]	1095 cancer patients on opioid analgesics in 24 countries	Following definition applied by physician 'Baseline pain intensity aggravated by flaring episodes of pain of any duration	Not reported	65%
Portenoy 2006 [25]	717 US pain treatment centre patients (non cancer)	Algorithm (Figure 1)	32%	23% (of total patients) 74% (of patients with CBP)
Holtan 2007 [61]	872 Hospitalised cancer patients-Norway	Short episodes of intense pain when your pain treatment otherwise has been generally effective?	52% had pain	37% (of all patients)
Valeberg 2008 [63]	1549 oncology outpatients	Short episodes of increased pain on top of usual pain	Not reported	35% of patients with pain and/or using analgesics
Mercadante 2009 [64]	101 cancer patients at home-Italy	No criteria given	70.2% receiving analgesics	35% (total sample) 49.2% (patients on regular analgesics)
Lasheen 2010 [32]	100 cancer patients referred to US palliative medicine service	Clinical pain evaluation. Episodic pain but did not have to have controlled background pain	Not reported	60%
Mercadante 2010 [65]	302 admissions to oncology centres-Italy	No standardised criteria given	171 (39%) had continuous pain	49% (total patients) 87.1% (of patients with continuous pain) BTP incidence decreased over time
Bhatnagar 2010 [66]	100 Indian head and neck patients	Fixed opioid dose for 1 week with good pain relief and intermittent flares of acute pain	100% (CBP was inclusion criteria)	48%

[1]CBP=controlled background pain

The association of BTCP with demographic and diagnostic features has been investigated in Caraceni's international survey of 1095 cancer patients [30]. The authors found that BTCP was associated with worse performance status (ability to perform daily activities and well being), presence of metastases, bone pain syndrome (especially vertebral column pain) and neuropathic pain syndromes. BTCP was diagnosed by application of a definition by a physician (Table 2) and the comparison group was other cancer pain patients receiving opioids. Other studies have also associated BTCP with bone pain syndrome [48] and neuropathic pain syndrome [35]. The presence of BTCP has not been associated with age, gender or tumour site [30,35,51]. Interestingly, Green et al compared different BTCP characteristics between white patients and 'minority' patients (Black, Hispanic, Arabic, native American) and found the minority group reported higher severity levels of BTCP [51].

1.4.5 Clinical features of breakthrough cancer pain

In the majority of cases BTCP is reported as occurring in one site and is usually related to background pain [24,33,48-9]. Incident pain is the most common subtype of BTCP, followed by spontaneous pain then end-of-dose failure [24,33,38,48,50]. BTCP is also reported as predominantly nociceptive and related to the cancer itself, as opposed to cancer treatment or a concomitant problem[24,33,49].

It is often reported that BTCP is positively associated with an increased severity of background pain [30,33]. However, this only appears to be the case in studies where BTCP patients are compared with those with 'controlled background pain' without breakthrough episodes. When the comparator group also contains patients with uncontrolled background pain this association is not apparent [35].

There is great variation in reported duration of BTCP episodes, from a minimum of <1 minute to maximum of 8 hours [24,33,48-50]. The average duration of BTCP episodes varied in different studies from 15 minutes to one hour [24,33,36,38,48-50]. The majority of the literature does not describe any specific time required to define a breakthrough episode. The average frequency of BTCP episodes also varied from one to six per day [24,33,36,38,48-50]. The median time for the BTCP to reach

peak intensity is often reported in studies and varied from 3 minutes to 15 minutes [24,33,50].

1.4.6 Complications of breakthrough cancer pain

BTCP has been associated with a number of physical and psychological problems. Observational studies of BTCP patients have reported high levels of interference with physical functional, as well as emotional, and social, well being [33,48,50,59].

Certain studies have assessed physical, psychological and social complications of BTCP patients with non-BTCP comparator groups. Portenoy et al reported on 164 US oncology patients and found significantly higher pain related interference scores (degree to which pain interferes) in patients with BTCP (47% total sample) with regard to different aspects of function [33]. This was assessed by the interference scales of the Brief Pain Inventory (BPI) (re: general activity, sleep, waking, work, relations with others and enjoyment of life) (Appendix A). The total summary score for this scale was 70; patients with BTCP had a mean score of 24.8 compared with 16.7 for those without BTCP ($P<0.001$). BTCP was defined using an algorithm (Figure 1) and the comparator group consisted of patients with controlled background pain and no transient exacerbations, i.e. those with uncontrolled background pain were excluded. Portenoy also reported significantly higher levels of psychological symptoms in BTCP patients, as measured by the Beck Depression and Anxiety Inventory.

Caraceni et al reported BPI interference data on 436 cancer patients on opioids in 24 countries and only noted differences between BTCP and non-BTCP patients in general activity, walking and working using the same interference scale as the above study [30]. All patients were taking opioid analgesics. BTCP was diagnosed by clinical assessment (Table 2) and the comparator group were those that did not comply with the BTCP definition i.e. included those with uncontrolled background pain.

Hwang et al studied 74 US oncology inpatients and outpatients using an algorithm to diagnose patients with BTCP and non-BTCP (Figure 1)[48]. There were no differences in BPI interference scores between groups at baseline. However, after

reassessment and implementation of pain treatments at 1 week there were significant differences between these groups in all BPI interference scores. A lower proportion of patients had BTCP at this second time point (36% versus 70%) suggesting that pain treatment was optimised in a proportion of patients improving scores in the non-BTCP comparison group. Hwang reported no greater burden of social or emotional well being in BTCP patients according to the Functional Assessment of Cancer Therapy Scale (FACT-G).

Fortner et al aimed to investigate the relationship between BTCP and direct medical costs in the United States using a telephone survey of 1000 cancer patients identified from a national database [60]. Patients were asked about their experience of pain and pain medication as well as hospital, emergency department and doctor visits because of pain. BTCP was defined as any flare of pain between doses of fixed scheduled analgesics, thus the BTCP group would also include patients with uncontrolled background pain. A non-BTCP comparator group consisted of patients taking analgesics on a fixed schedule who denied any pain 'flares' in between doses. Fortner calculated that patients with BTCP had significantly more annual hospitalisations, emergency department attendances and visits to the physician than patients without BTCP since diagnosis. Estimated health care costs were thus greater for patients with BTCP ($1.9 million compared to $227 000 for non-BTCP patients).

Patients with BTCP were reported as requiring higher doses of opioid in two studies of 164 US oncology patients and 631 German oncology patients presenting to pain clinics [33,35]. However despite a trend for higher overall opioid consumption this did not reach statistical significance.

Fine et al attempted to study BTCP characteristics described by 22 UK hospice patients and their caregivers at home [36]. Interestingly, the patients had difficulty differentiating and allocating separate pain intensity scores for breakthrough and background pain. No other studies reported such a problem. There was poor concordance between the patient and caregivers assessment of the frequency, duration, severity and time to relief of BTCP as well as the amount of pain relief provided by analgesia. This demonstrated a disparity in perception of pain severity

between cancer patients and caregivers that has been reported in the literature. Overall the trend is for caregivers to overestimate the frequency and distress caused by symptoms [67-9]. The reasons for this are multiple and include anxiety about the origin of symptoms, lack of visual cues, and inadequate knowledge to assess the symptom in question. Also it is possible that caregivers may project their own feelings onto the reporting of the patient's symptoms and their emotional state be associated with symptom severity [68-9]. Caregivers also feel that patients underreport symptoms to health professionals to avoid being a burden and therefore overcompensate when reporting. This disparity is reduced over the time period that the symptom is present suggesting familiarisation with the distress caused [67].

In summary, the above studies all report impairment with physical, psychological and social functioning in BTCP patients. However, there are variations when comparisons are made between BTCP patients and non-BTCP patients. This could be explained by the small sample sizes in the majority of studies, as well as the comparator groups consisting of patients with different levels of pain severity, patients with controlled background pain only versus those with uncontrolled background pain.

1.4.7 Treatment of breakthrough cancer pain

BTCP is a heterogeneous condition and as such treatment is highly individualised. Management consist of assessment, treatment of the BTCP and reassessment [21-2]. The BTCP treatment often consists of one or more of the following 1) treatment of the underlying cause of pain (e.g. radiotherapy for bone metastases) 2) treatment of precipitating factors (e.g. constipation) 3) non-pharmacological management 4) pharmacological management [58].

Non-pharmacological methods are commonly used by patients to manage their BTCP and include heat pads, distraction techniques and stopping the activity that causes the pain [35-6,50,59]. Pharmacological treatments include modification of the background analgesic regimen (e.g. increasing dose of analgesics, addition of co-analgesics) or the use of breakthrough analgesics [48,58].

The most commonly used breakthrough analgesics are opioids, although non-opioids are used by a proportion of patients (e.g. paracetamol, non-steroidal anti-inflammatory drugs), and often patients use a combination of analgesics [26,39,50]. The opioids most commonly used for BTCP are normal-release preparations of oral opioids (morphine and oxycodone) [50]. There is concern that the pharmacokinetic profiles of these drugs do not match the temporal characteristics of average BTCP episodes [21,70]. The median duration of a BTCP episode is 15 to 60 minutes whereas the onset of action for morphine to treat a BTCP episode is 20 minutes, and the time taken to achieve meaningful pain relief is 30-40 minutes. Oxycodone (strong opioid painkiller) has onset of action of 30 minutes and takes up to 45 minutes to achieve meaningful pain relief [39,50].

Fentanyl is an alternative opioid analgesic with preparations available that are administered via the oral or nasal sub mucosa. This gives the pharmacokinetic advantage of more rapid absorption and distribution than the oral opioid preparations and thus theoretically onset of action would be more rapid. [71]

Oral transmucosal fentanyl preparations consist of a fentanyl-impregnated lozenge applied to the buccal mucosa, fentanyl buccal tablets, and fentanyl sublingual tablets. All oral transmucosal fentanyl preparations provided statistically significant reductions in BTCP intensity, and improvements in pain relief, when compared with placebo at multiple fixed time points for a transient pain episode [41,44-5,52-4]. These differences were apparent at 15 minutes post administration for the fentanyl lozenge [54], and at 10 minutes post administration for the fentanyl buccal and sublingual tablets [41,44,52]. Differences were sustained throughout the 60-minute study period. Time to meaningful effect of the oral submucosal fentanyl preparations was 10-15 minutes when assessed in other non-commercial studies [39,50].

Nasal fentanyl preparations were also significantly more effective than placebo in terms of pain intensity reduction and pain relief at 10 minutes after administration [40-1]. Intranasal fentanyl spray has also been compared with the oral transmucosal fentanyl lozenge and was found to have a statistically superior reduction in pain intensity at all time points from 5 minutes [47]. Time to meaningful pain relief was

11 minutes for the nasal fentanyl spray, compared with 16 minutes for the fentanyl lozenge. A fentanyl pectin nasal spray was compared with immediate-release morphine sulphate for the treatment of breakthrough pain episodes [46]. The nasal spray was found to be statistical superiority in terms of pain intensity difference at 15 minutes post administration. Fifty eight per cent of episodes treated with the pectin nasal spray showed significant changes in pain intensity at 5 minutes post administration.

Interestingly, a large proportion (77%) of patients prescribed breakthrough medication are reluctant to use it for every episode due to side effects and having episodes of BTCP not severe or long enough to warrant use [26,50].

In summary, there are different treatment options for BTCP with varying pharmacokinetic properties. Intranasal and oral transmucosal fentanyl products have meaningful pain relief between 10 and 15 minutes whereas oral opioids take between 30 to 45 minutes. This emphasises the need for individualised assessment and reassessment of patients with BTCP to determine appropriate therapy is given and monitored for effectiveness.

1.4.8 Assessment and measurement of breakthrough cancer pain

There are a number of validated assessment instruments for generic cancer pain that are widely used and validated in cancer populations however these do not assess the specific characteristics unique to BTCP (e.g. frequency, duration, breakthrough treatment efficacy) [72-3]. The Brief Pain Inventory (BPI) (Appendix A) is the most widely used generic pain instrument but predominantly requires a patient to rate the average, worst and least pain severity and thus provides no information regarding whether BTCP episodes are present [74]. The BPI also has seven items that measure the impact that pain has on different aspects of physical and social functioning (general activity, mood, walking ability, sleep, relations with others, work, enjoyment of life). A patient is required to rate on a zero to ten numerical rating scale the amount the pain has interfered with a certain activity (0 is 'does not interfere', 10 is 'completely interferes'). These interference questions theoretically are also applicable to BTCP, and have been used in a number of studies to present the impact of BTCP on a patients' functioning [24,30,33,48,50].

There are three assessment instruments specifically for BTCP that have been published, the Breakthrough Pain Questionnaire [25], Episodic Pain Documentation Sheet [75] and the Alberta Breakthrough Pain Assessment Tool [31]. These will be discussed in turn.

1.4.8.1 Breakthrough Pain Questionnaire

The Breakthrough Pain Questionnaire (BPQ) was developed by Portenoy and Hagen to assess the characteristics of BTCP in a cohort of cancer patients [23-5] (Appendix B). The BTCP domains used in the BPQ are described in Table 3. The BPQ has subsequently been used in three further studies to assess BTCP characteristics in different populations [33,48-9] and has been published in full in an article on BTCP in non-cancer patients [25]. The BPQ was derived from principles of cancer pain assessment and the clinical experience of the authors. There is no documented patient involvement in any aspect of the instrument development, and no published validity data available. Certain items within the BPQ have been changed over time, and despite the majority of BTCP domains being assessed, there are no questions about BTCP interference.

1.4.8.2 Episodic Pain Documentation Sheet

The other instrument published in full is the Episodic Pain Documentation Sheet designed to be completed by a clinician assessing a patient with BTCP [75] (Appendix C). This was designed by one author and presented in relation to a case study and review. It is a concise instrument and encompasses the majority of BTCP domains (Table 3), with the exception of BTCP interference. However, no other published study has used this instrument, and there are no validity or reliability data available.

1.4.8.3 Alberta Breakthrough Pain Assessment Tool

The Alberta Breakthrough Pain Assessment Tool was developed for research purposes and published in 2008 [31](Appendix D). It consists of 21 total questions to be answered by the patient, 15 core questions detailing various clinical features of their BTCP (3 questions consist of 2 items), and 3 free text questions asking the

patient for descriptions of their background and BTCP. There is also a section to be completed by the clinician detailing the aetiology and pathophysiology of BTCP.

The authors initially developed 17 core BTCP questions, to be answered by the patient, based on published literature, existing pain assessment tools, and authors' knowledge and experience. Specific questions were then eliminated or revised based on interviews with five patients, and review by the study team. The tool was then sent to national experts (Canada) to assess the items and response formats for relevance and clarity, and subsequent revisions were made by the research team. The tool was then appraised by international experts and similarly revised. Finally, cognitive interviews were performed with cancer patients to assess for clarity, readability and ambiguity.

The national and international experts were asked to indicate their level of agreement with the relevance and clarity of the instrument items and with the adequacy and appropriateness of the response formats and options. Level of agreement was quantified with a five-point scale (-2 strongly disagree, -1 disagree, 0 neither agree or disagree, +1 agree, +2 strongly agree). Consensus was defined as >50% of respondents being in agreement with a statement. Only 1 BTCP item had a consensus of less than 50% in the two expert surveys, and this was reworded however two items were eliminated by the research team based on expert comments despite achieving consensus. Whilst thorough and detailed information was collected about items from a range of experts, a consensus of 50% necessary to define agreement is low compared to standardised consensus guidelines which requires 75% consensus to define agreement [76].

The initial development and formulation of the Alberta tool was by the research group and despite revisions being made on the basis of five patient interviews this process was not explicitly explained as advised by international guidelines [77-8].

The domains included in the Alberta tool are detailed in Table 3, and whilst the majority of domains are included, there are no items detailing BTCP interference. Despite the response options achieving consensus in the expert survey, the majority are verbal rating scales with no associated numerical score. Adjectival verbal responses are reliant on a patient's literacy level and their understanding of the

words in their own context [11]. The Alberta tool also has no published construct validity or reliability data and no other studies have used this instrument.

In summary, despite a well-described development process from investigator, patient and expert sources, the Alberta Tool was designed for research purposes, and there are no validity or reliability data to support its clinical use.

A further eight BTCP questionnaires have been described in the text of individual studies but not published in their own right [26,35-6,38-9,50,59,79]. These studies have used author-designed questionnaires to report characteristics and clinical features of BTCP in different populations. However, none has published the questionnaires used in full and none of these questionnaires have been validated.

Thus there is currently no clinical BTCP diagnostic or measurement instrument developed and validated according to international standards. BTCP is currently assessed, quantified and managed by clinical assessment and reassessment [21-2]. This involves a detailed clinical pain history and thorough clinical examination [28].

Table 3: Description of items in existing breakthrough cancer pain tools

BTCP domains	Breakthrough Pain Questionnaire [25]	Episodic Pain Documentation Sheet [75]	Alberta BTCP Assessment Tool [31]
Intensity	Worst (none/mild/moderate/severe/excruciating)	Severity (mild/moderate/severe/excruciating)	Worst (mild/moderate/severe) and (NRS[1] 0-10)
Temporal factors[2]	Frequency (daily-free text) Duration (free text) Onset (gradual/severe) Relationship to fixed dose analgesia	Frequency (daily and weekly-free text) Duration (free text) Onset (gradual/sudden) Onset (time to max intensity)	Frequency in 24 hrs. Is this usual frequency? (Usual/better/worse) Last BTCP experienced Time from onset to peak intensity (minutes) (0-10/10-30/ 30+/ hard to tell)
Localisation	List of 15 locations	Body map	Body map
Quality	List of 9 pain descriptors		15 pain descriptors
Precipitating factors	Open question Predictability (never predict/ sometimes/often/almost always/always)	None/spontaneous/ incident/non-volitional Predictable (yes/no)	15 options Predictability (never predict/rarely predict/ sometimes/ often/ always)
Number of different BTCP	How many experienced (number)	Each pain to be marked on a separate sheet	Each pain to be marked on a separate sheet
Interference	Not assessed	Not assessed	Not assessed
Relationship to background pain			BTCP separate to background pain
Treatment effect	What lessens your pain? (Free text) Does it work successfully (yes/no)	Background pain (none/uncontrolled/controlled) Scheduled analgesia (none/ insufficient/sufficient)	Relieving factors (18 options) Time until pain relieved (minutes) (0-10/10-30/30+/not on medication) Amount of pain relief (none/slight/good/very good/complete/ not applicable)) Onset of pain relief (minutes) Satisfaction with pain relief (7 point VRS[3] very satisfied to very dissatisfied) Satisfaction with onset of pain relief (response as above)

[1]NRS=numerical rating scale, [2]temporal factors=items describing the variable pattern of BTCP, [3]VRS=verbal rating scale

1.4.9 Breakthrough cancer pain domains

There is no consensus about the items, or questions, which should be included in a BTCP assessment instrument. However, the three published instruments include a number of common items that adhere to general principles of pain assessment and specific issues associated with BTCP (Table 3). As BTCP is a 'transitory increase' in pain it makes sense that to describe such episodes one would need information regarding the frequency of such exacerbations as well as the duration. The relationship of the BTCP to precipitating factors as well as whether it can be predicted also seems relevant in this context.

Pain items are often grouped into broader categories referred to as domains, e.g. 'temporal factors' is the term used to describe the varying pattern of BTCP, and includes items such as onset, frequency and duration. Interference with daily living and quality of life, whilst being important domains to assess, were not included in the published assessment tools, and were often evaluated in studies by the use of different validated instruments (detailed in section 1.4.6).

Recommendations have been published about BTCP assessment and management [21-2]. Mercadante et al reported from a consensus conference of an expert working group of the European Association of Palliative Care and stressed the importance of individual assessment of BTCP due to the heterogeneity of the condition [21]. They described how individual variations in pathophysiology and characteristics of BTCP, as well as absorption and distribution of painkillers, meant assessment of intensity, frequency and duration of episodes are necessary to inform treatment decisions. They emphasised that the use of, and response to, analgesics is also of key importance. The domains recommended to assess BTCP were equivalent to those charted from existing pain instruments in Table 3. They recommended that BTCP intensity be measured using a visual analogue scale (VAS), numerical rating scale (NRS), or verbal rating scale (VRS) repeatedly during each episode. BTCP physical and psychological interference should be assessed using the Brief Pain Inventory interference items and Beck Depression and Anxiety Inventory.

Davies et al reported recommendations of a task group of the Association for Palliative Medicine of Great Britain and Ireland and suggested that in the absence of

a validated clinical tool a framework for history taking should be based on the use of standard pain questions to determine clinical features of BTCP [22]. This included all domains discussed above but also response to non-pharmacological interventions and associated features of the BTCP (e.g. sensory changes that would indicate neuropathic pain). Davies et al emphasised the need for individualised management of BTCP as well as the need for re-assessment to ensure that such interventions were effective and tolerated, and to monitor changes in BTCP. Standard pain scales, such as NRS or VRS, were suggested to assess response to treatment, and choice of scale should be relevant to the patient/situation.

Response to analgesics, or treatment effect, is a BTCP domain of recognised importance with respect to on-going clinical evaluation of a patient. Analgesic response has been evaluated using a variety of methods, such as 'time to meaningful pain relief ' [39,47], time to onset of pain relief [31], reduction in pain intensity[40-7], amount of pain relief [31,40-7], global satisfaction with painkiller [31,54] and effectiveness of painkiller [33]. Whilst these all intend to measure a similar concept the individual questions do not completely correlate [50,80] suggesting each question evaluates a different aspect of a patient's experience with BTCP medication.

Commercial studies evaluating pharmacological preparations to treat BTCP episodes have predominantly used pain intensity differences at set time points as the primary outcome measure [40-7,52-5]. Pain intensity was most commonly measured using a numerical rating scale (anchors, 0= no pain, 10= pain as bad as you can imagine). Secondary outcomes included pain relief measured on a 5-point verbal rating scale (0=none, 4=complete), patient assessment of total pain relief (0=none, 4=complete) and patient rating of global medication performance (0=poor, 4=excellent). One study used time to meaningful pain relief as the primary outcome measure [47]. Each study used a variety of outcomes to demonstrate efficacy of the treatment in order to apply for marketing authorisation from the relevant bodies.

There is a common set of domains used in the majority of studies to assess BTCP. However the questions and response options used to characterise each domain vary and may therefore not be comparable between studies. There is therefore a need for

a standardised and validated BTCP assessment instrument that would allow comparative data between studies. However, consensus regarding the appropriate items needed to evaluate BTCP would be needed in such an instrument.

1.5 Patient-reported outcome measures

A patient-related outcome measure (PROM) refers to any instrument that quantifies a self-reported health condition. The report comes directly from the patient, without interpretation by a clinician or anyone else, and can be used to assess an aspect of disease or treatment effect [81].

1.5.1 Purpose of patient-related outcome measures

PROMS can be used to assess levels of health and need in populations, as well as evidence of the outcomes of services for the purposes of audit quality assurance and comparative performance evaluation. Health policy makers have recommended that PROMs should have a greater role in the United Kingdom's National Health Service [82], and they are now a contractual requirement for patient's undergoing certain surgical procedures (e.g. hip replacements, hernia repairs) [83].

PROMs are also an essential part of clinical research, used to evaluate whether interventions are effective at reducing symptom burden, and improving function and quality of life [81]. The use of a PROM is advised when measuring a concept best known by the patient or best measured from the patient perspective. The demonstration of an improvement in PROMs has led to the approval of pharmaceutical interventions by regulatory bodies [77], however for such interventions to be approved the PROMs must meet certain standard criteria to be accepted as an valid end point.

A patient's illness experience can be a difficult concept to quantify, and can vary between individuals and within individuals over time. In order to develop PROMs that are representative of patients' needs, it is necessary to accurately define and represent the concept of interest, and to adequately encapsulate the different aspects (domains) relating to this concept in a format acceptable to patients [84].

1.5.2 Standardised criteria for health status instrument development

The first published criteria for the development of a measurement instrument were by the American Psychological Association (APA) in 1954 (APA standards for educational and psychological testing) [85]. The APA standards provided a comprehensive reference to test construction, evaluation and documentation, as well as the application of such tests. They have been revised 6 times, most recently in 1999 [86]. They were originally developed for educational and psychological testing, but are cited in many health-related outcome studies and provide the international framework for test development in other disciplines (e.g. education, social sciences) [11,78]. Despite being a comprehensive guide to test development these guidelines were not developed specifically for healthcare purposes. Subsequently standardised criteria based upon the APA standards have been published regarding instrument development to assess patient's health experiences. These are described below.

The United States Food and Drug Administration (FDA) and European Medicine Agency (EMEA), both responsible for drug approval, have published recommendations about the development of PROMs to ensure that drugs are appropriately and consistently evaluated [77]. These recommendations provide a framework for the creation of new instruments, and a means of determining if existing instruments are adequate. The FDA used these criteria to ensure the instrument and resultant outcome data collected during a trial provided valid information about the patient perspective of the intervention.

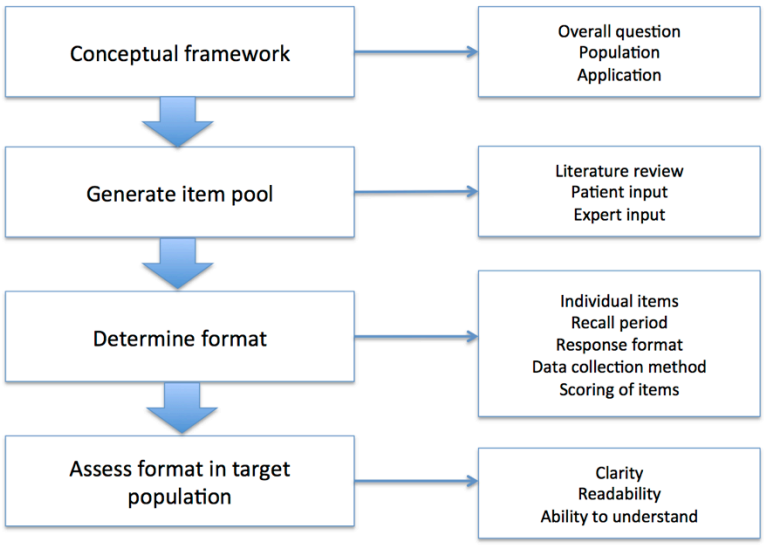
The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) is a working group consisting of academics, clinicians, patient advocates, and representatives of the National Institutes of Health and the FDA that has developed recommendations for PROMs specific to pain. The IMMPACT group meets periodically to develop recommendations with respect to different aspects of pain research. One IMMPACT meeting led to consensus recommendations for evaluating the adequacy and appropriateness of existing measures for clinical trials of pain interventions. Recommendations were published detailing methods that should be used for developing new PROMs [78]. These guidelines were based on the

APA standards but gave more detailed guidance on the processes involved in development of a pain measurement instrument. The sections below describe the recommendations for instrument development based upon the frameworks described by the above bodies.

1.5.3 Designing an instrument

The initial stage of PROM development involves the drafting of an instrument that measures the concept of interest [87-8]. The recommended process for this, by the FDA and IMMPACT groups, is by a series of sequential steps (Figure 3). There is little difference between the guidelines for this process.

Figure 3: Recommended process for patient-related outcome measurement instrument development



The process begins with the identification of an initial framework and is followed by generation of items, or questions with appropriate response formats. The adequacy of a purported instrument depends on this item generation process.

The conceptual framework is established by clearly defining the intended purpose and application of the instrument as well as the target population. A draft

instrument can then be created with questions generated from the above concepts after consultation with experts and patients. All guidelines recommend patient input in the generation of a new instrument, and the FDA and IMMPACT guidelines specify that in-depth patient interviews or focus groups should be performed to identify content domains that are relevant to those with the condition. Individuals with a range of symptom severity and demographics should be used as this may affect priorities and preferences.

Once items have been developed attention must be given to determine the format of the instrument. Individual items, or questions, and response formats must be consistent with the purpose and intended use. It is essential for wording, for both anchors (descriptions attached to response scales representing opposite extremes of item) and instructions, to be clear and appropriate, with no bias in the direction of response.

The recall period for the instrument must be decided based on the instruments purpose and intended use. Long recall periods can undermine content validity as response is influenced by current state at time of recall so advice is for shorter recall periods describing current and recent state.

Items should have appropriate numerical scores assigned to each answer category based on the most appropriate scale of measurement, and evidence presented that summary scores are appropriate.

Items, domains and general scores must reflect what is important to patients and must be understood by patients. Patient understanding of item and response content, clarity and readability should be evaluated using cognitive interview studies. Cognitive interviewing explores how people approach the task of answering questions and highlights those items that are causing problems. The instrument must not cause undue physical, emotional or cognitive strain on the patient. The degree of tolerable burden depends on patient condition and illness severity. Missing data and refusal rate are indications of inappropriate respondent burden or inappropriate items or response options.

The processes involved in the preliminary instrument development must be documented along with any appropriate modifications based on any of the above processes. Following the above steps ensures that the instrument has adequate content validity (i.e. the content of the scale is representative of the concept it is intended to cover).

1.5.4 Testing of an instrument

Once an instrument has been developed the next stage is to test the instrument in the intended population to ensure that it has an acceptable degree of measurement error (reliability), measures 'what it is supposed to' (validity) and has the ability to detect relevant clinical changes over time (responsiveness). The broad term used to refer to this process is 'psychometric testing' which means a series of tests performed to evaluate the properties of an instrument designed to measure a concept without a single 'gold-standard' comparator.

The FDA guidance provides a detailed account of measurements necessary to establish reliability and validity of a new instrument [77]. These measurement properties are based on the APA standards, and standard psychometric theory texts, and are widely used throughout healthcare research to evaluate new and existing measures [11,86,89,90]. The IMMPACT guidelines do not go into detail about specific psychometric tests but instead refer the reader to those methods detailed in the APA standards 1999 publication. The psychometric properties that should be assessed according to the FDA and APA standards are described in more details below.

1.5.4.1 Reliability

Reliability refers to the extent to which a score is free from errors of measurement [11]. Many factors, apart from the construct of interest, could potentially influence a patient's response to a pain measure or scale. Such factors might include the assessment setting (e.g. clinic versus laboratory), the person administering the measure, other subjective experiences (e.g., being more or less fatigued or upset), or motivational factors (e.g. desire to appear stoical, desire to not affect treatment decisions) [91]. Another potential source of measurement error is if items are

difficult for patients to understand, especially if the patient group have limited cognitive abilities [92]. Variance associated with each of these factors, which don't reflect the specific domain of interest, are referred to as error variance.

The main method to determine reliability in pain assessment research is to calculate a reliability coefficient, which can be used to estimate stability over time (test-retest coefficient) or association among items in the scale (internal consistency coefficient alpha) [93-4]. To determine the test-retest coefficient a patient completes the test twice over a specific time period where the underlying measurement concept is stable. The time period chosen must ensure the underlying state has not changed but must be long enough to minimise memory effects from the first test. If the test time period is too long results may reflect actual change as opposed to measurement error.

1.5.4.2 Validity

In addition to content validity, it is necessary to determine other types of validity. Construct validation ensures that the instrument is measuring 'what it is supposed to' by conforming to prior hypotheses concerning logical relationships that should exist with other measures and/or characteristics of these patient groups. For example, physical activity should relate to the performance status of a cancer patient. Documented relationships between results gathered using the instrument and results gathered using other measures should be consistent with these pre-existing hypotheses. Relations with other variables can be correlative, (e.g. relationships with other test scores or clinical measures) or experimental (e.g. whether PRO scores can distinguish between different clinical groups). [11,77,86,89]

Criterion validity is the extent to which scores of a PROM are related to a gold standard measure of the same concept (e.g. medical school entry exam compared with criterion of graduating from medical school). For most PROMs, criterion validity testing is not possible because the nature of the concept to be measured does not allow for a single 'gold-standard' criterion measurement to exist. [77]

1.5.4.3 Responsiveness and minimal important difference

Responsiveness is the ability of a measurement tool to detect any change in the trait it is designed to measure. In health care outcomes the desired effect of an intervention is to induce a clinical change for the patient so it is important that a newly developed instrument is able to reflect such a change. The minimally important difference (MID) is the numerical value of the measurement instrument, which reflects a clinically relevant, either positive or negative, difference. Clinically relevant change is a difficult concept to define and measure, and is most frequently based on a change that is perceived by a patient as beneficial or harmful, or one which would lead a clinician to consider a change in treatment. This change is determined by comparing clinical and patient-based end points with PROM scores over time, or the change in PROM score after the application of a treatment of known and demonstrated efficacy. [95-6]

Knowing the MID of a PROM allows a sample size calculation to be estimated in future studies using this measure to enable conclusions to be drawn about whether statistically significant effects of interventions are also clinically relevant [95].

The Food and Drug Administration (FDA) guidance on the use of outcome measures as endpoints in clinical trials stated that the ability of an instrument to detect change would be reviewed, but more detailed information on methods to determine such change have not yet being published [77].

The Centre for Health Outcomes and IMMPACT group have published recommendations for evaluating responsiveness and MID for PROMs [97-8]. There are three recommended methods that can be used to determine MID, and often more than one is used. Anchor-based methods use an external indicator to group patients into those reflecting no change, negative changes or positive changes in clinical or health status. Clinical trial experience makes it increasingly possible to understand MID for different PROMs, based on demonstrated differences between active and placebo treatments in clinical trials. Distribution-based methods are anchor free, and estimate the MID using statistical methods based on the distribution of observed scores in a relevant sample.

1.5.4.3.1 Anchor-based methods

The anchors can be clinical (i.e. clinician ratings or laboratory measures) or patient ratings (i.e. global rating of change). The patient's perspective is recommended to be given most weight [97-8]. However retrospective self-reports can be subject to recall bias, and clinician perspective often influences the treatment decisions [99,100]. It is therefore advised to use multiple anchors to confirm and examine responsiveness and to determine the amount of change on the anchor that is a reasonable indicator of minimal change [77,98].

It is also necessary to ensure that the anchor is relevant to the disease state and therefore there needs to exist an understanding of the overall disease trajectory in terms of health outcomes to evaluate responsiveness. Other factors that lead to variation in the estimation of MID are whether people are evaluated as high or low on the measure at baseline, whether they improve or decline over time, and whether they have similar demographic and clinical characteristics. [97]

1.5.4.3.2 Clinical trial experiences

As the literature on PROMs increases it is possible to understand MID based on systematic reviews of demonstrated differences between two active drugs, or an active drug and placebo. For example, a systematic review found consistent evidence that an asthma treatment resulted in a 0.3 point improvement in an asthma quality of life questionnaire [100]. When these effects are seen consistently across studies and they correlate with other parameters of improvement they provide a valuable source of data for the MID of that PROM. However, there are observations that the MIDs determined from clinical trial data may differ from the above anchor-based methods and it is only recommended to use this method when multiple outcome studies are available [102].

1.5.4.3.3 Distribution-based methods

Distribution methods for estimating clinically important changes use statistical measures to generate a relevant result. Research based upon statistical theory and

previous studies show that the effect size may approximate a MID for some PROMs [11,89,98].

The effect size is a calculation of the magnitude of group change over time made by subtracting the mean score at time point 2 from mean score at time point 1 and dividing by the standard deviation of the mean score (time point 1). Cohen proposed criteria to categorise effect size into small, moderate and large effects [11-2]. Therefore if the effect size (i.e. magnitude of change after implementation of treatment) were moderate or large then this would represent a clinically relevant change.

Criticisms of this method are that the calculation includes the standard deviation and thus results may be influenced by the heterogeneity of the sample [98,103]. Also it provides no direct information about the MID, they are just a way of expressing observed change in a standard metric. Although distribution-based results demonstrate that change has occurred, and provide insight into magnitude of change, they do not inform as to whether the change is meaningful.

There is no consensus as to how much data are needed as supportive evidence for the MID of a PRO instrument [96-8]. As with other aspects of construct validity, responsiveness and MID are confirmed based on accumulating evidence from multiple patient-based and clinical anchors. These will almost always result in a range of values for the MID and an absolute value assigned using clinical interpretation of the relevance of different anchors and how closely they are linked with the concept of measurement. Like all aspects of construct validity there is no single gold standard to determine the MID, and it may differ between different patient populations.

1.5.4.3.4 MID in pain instruments in pain populations

In cancer pain measurement Farrar et al [104] defined a clinically meaningful change using the anchor-based method of a patients requirement for additional analgesia during a BTCP episode. This used data from a clinical trial involving 130 patients with BTCP who received either a fentanyl product or placebo for a BTCP episode. If a patient did not require an additional analgesic following administration

of the trial drug they were defined as having a clinically meaningful improvement in pain intensity. The patient's pain intensity ratings (0-10 on NRS, taken every few minutes) were assessed for those with and without a significant improvement, and the change in pain intensity score with optimal sensitivity and specificity recommended. Seventy two percent of patients who did not require an additional dose of analgesia (clinically meaningful improvement) had a reduction in pain intensity levels of 2 or more; 64% who did require an additional dose had a reduction in pain intensity of less than 2. On the basis of this study a reduction of two or more in pain intensity on a zero to ten NRS is often used to represent clinically meaningful change. Using the same criteria a percentage reduction of 33% on a NRS was also recommended as clinically meaningful change.

However, despite this being the optimal cut-off point in the above study one-third of patients did not conform to these values. This could reflect the variability of individuals in the subjective rating of scores i.e. a change of 1 point could represent a large change for one patient and minimal for another. There are also many different variables dictating whether a patient takes additional analgesia, e.g. fear of side-effects, that do not reflect a reduction or clinical improvement in pain score [26]. Another criticism of this study is that they analysed 1268 pain episodes in 130 patients. Measuring multiple episodes in an individual ensures a larger data set but does not improve the applicability of these results to other populations due to individual measurement error.

Another way of assessing a clinically meaningful MID is to ask patients what they would consider an acceptable outcome. Investigators assessed the relative importance of four outcome measures, pain level, fatigue, distress and interference, in 300 fibromyalgia and back pain patients [105]. The patients rated pain as most important followed by fatigue, interference then distress. Interestingly, these patients were also asked to rate on a zero to ten NRS (0=no pain, 10=worst pain possible) what score would need to be achieved to represent a successful treatment outcome for themselves and this score was subtracted from their current pain score. The difference in score required meant a 54% reduction in pain level was needed for the patient to hypothetically determine intervention as successful. This compared

with a 60% reduction necessary in fatigue and distress, and 63% reduction in interference.

In another study 66 patients attending a chronic pain clinic rated their current pain on the Brief Pain Inventory (four pain intensity questions on a 0-10 NRS, and 7 pain interference questions on a 0-10 NRS) (Appendix A), patients then had to complete the same pain tool imagining that the pain had reached an acceptable level [106]. An average reduction of 3 points on each Brief Pain Inventory intensity and interference scale (change >40%) indicated an acceptable outcome. The duration of pain and presence of anxiety were predictors of larger estimates of acceptable levels of pain severity and impact. These are significantly higher percentages than those reported retrospectively using anchor based methods [104,107]. However patients may 'recalibrate' their criteria for success after treatment and this may account for smaller changes when using retrospective judgement [108].

There are inherent problems with any method of measuring the MID in cancer pain PROMs. Thus only the patient can determine what constitutes a meaningful change in their own status but this may be subject to error and influenced by factors other than the measurement construct (e.g. overall health condition). Clinician opinion can also be used to determine MID but when quantifying cancer pain this is based on a clinical assessment of the patient and is thus reliant on the same patient recall error as well as clinical consultation skills. The assessor status can also influence a patient's recall [99]. There are no laboratory parameters that can quantify pain and no specific clinical response criteria for cancer pain (such as the rheumatology response criteria using clinical examination of joints [109]) so clinical opinion is based on a global assessment of change in clinical status which may differ between individual clinicians [99]. Cancer pain may improve in response to different cancer treatments e.g. radiotherapy [110] and it could be possible to calculate MID by observing such responses. However a patient or clinician report would still be required to evaluate if a certain improvement in pain control was clinically relevant.

Anchor-based measures of patient and clinician impressions of change remain the optimal method to determine the MID of a cancer pain PROM and are the most commonly used anchors in the acute and chronic pain literature [98,104,107,111].

Comparisons with other validated measures, such as quality of life instruments with known MID, are limited as they measure different concepts to cancer pain and are thus poorly correlated [112].

In summary, responsiveness and MID are important aspects of validity but cannot be directly defined in PROMs due to a lack of a gold standard comparator, and require multiple anchor-based methods to determine the value. Clinical measures, response of pain to different cancer treatments and usage of pain medications, can be used as such anchors in combination with patient and clinician global assessments [97-8,104,107]. Distribution-based methods can also be used in addition to the above and may add statistical strength to those measures [113].

1.6 Pain measurement instruments

Pain is a complex multifactorial experience and there are multiple issues involved in the assessment and measurement of pain. This section will discuss whether various pain measurement techniques improve pain control in cancer patients followed by which aspects of pain should be assessed and how they should be measured. Specific issues regarding pain measurement from a patient's perspective will also be covered.

1.6.1 Does standardised pain assessment improve pain control?

Cleeland reported that 42% of advanced cancer outpatients with pain were not given adequate analgesic therapy [115]. A discrepancy between patient and physician assessment of the severity of the patient's pain was predictive of inadequate pain management. Underestimation by health care providers of the severity and distress of a patient's cancer pain has been consistently reported in the literature [116-8].

This disparity between patient and health care provider pain ratings indicates that standard assessments are not obtaining accurate information about the patient's pain experience, and subsequently pain control is inadequate. The reasons for inadequate pain assessment are complex and often multifactorial. Firstly, a patient may not disclose fully about the severity of their pain. This can be due to fear of

disease progression, concerns about analgesia (e.g. tolerance or side effects), as well as issues regarding cancer treatment (e.g. delays to chemotherapy)[119-122].

Secondly, health care providers may not have the skills, knowledge or time to adequately evaluate and treat pain in cancer patients. Surveys of physicians and nurses reveal that inadequate assessment is the most significant barrier in their own management of cancer patients with pain [123-4]. This data suggests that conventional medical and nursing training does not equip health care professionals with the skills necessary to assess pain. Standardised pain assessment tools could theoretically be used as a means of addressing the above barriers ensuring that patients report pain issues, and providing health care professionals with a framework to assist with evaluation.

A number of randomised controlled trials have evaluated the effect of standardised pain assessment on cancer pain control [125-8]. The results vary depending on the type of pain assessment used and amount of subsequent intervention (e.g. treatment algorithm) included in the study protocol.

Kravitz et al randomised 78 patients to have pain intensity scores recorded or not on bedside charts by researchers [125]. The intervention did not result in improved pain control as determined by current and worst pain scores on a 0-10 visual analogue scale at 3 and 5 days post initial assessment. The study did not have a reported sample size calculation, and the results had large confidence intervals. The negative results could be due to an inadequate number of patients recruited to detect the required improvement, or the assessment method was not comprehensive enough. The junior medical staff targeted in this study were often caring for patients in both the control and intervention group leading to potential benefits being carried over to control patients.

Trowbridge et al randomised 320 outpatient cancer patients to having their pain assessments (average and worst pain intensity; pain treatment regimen and degree of pain relief) reviewed by the oncologist prior to consultation or not. [126] There were no differences between the groups in any of the self-reported ratings of pain at 4 weeks but the incidence of pain did decrease from 70% to 55% in the intervention

group (P=0.05). The oncologists were also more likely to increase analgesics in this same group (20% vs. 14% in control group, P=0.16).

Cleeland et al studied the impact of standardised pain assessment and analgesic treatment protocol in 136 patients in oncology outpatient units [127]. Different centres were randomly assigned to implement pain assessment, prior to consultation, followed by management as per treatment protocol (oral analgesic regimen created by expert working group), or to standard clinical assessment and treatment. At day 15 worst pain had decreased by 27% (from 6.6 to 4.8) in the intervention group and by 7% in the control group (from 7.3 to 6.8). The proportions of patients responding to pain treatments (worst pain scores changing from moderate or severe to none or mild) were 48% in the assessment and protocol group versus 15% in the control group. These changes were sustained at 29 days and were statistically significant. This study also investigated whether other cancer patients at the intervention site benefitted from 'diffusion of knowledge' by recruiting and comparing additional patients. However despite a higher proportion of patients responding to pain treatments at the intervention site (29% versus 19%) this result was non-significant. This study did not reach its calculated sample size (308) therefore may not have had adequate numbers to detect diffusion effects. The positive outcomes detected in the intervention group compared to previous studies could be explained by a more comprehensive pain assessment (pain type and severity), or by the inclusion of a treatment protocol giving the clinician guidance in management.

Du Pen et al randomised 81 cancer patients to a multilevel treatment algorithm or standard practice [128]. The treatment algorithm consisted of standardised assessment by pain study physician and implementation and titration of analgesia based on pain intensity numerical rating scale scores. The Brief Pain Inventory was the primary outcome measure and revealed that usual pain intensity was significantly reduced in the intervention group at all time points. However despite worst pain intensity, pain relief and pain interference being consistently lower in the intervention group there was no statistically significant difference. There was also no difference in opioid dosage or patient adherence to medication between groups. There was no sample size calculation reported in this study, instead recruitment

was based over a 3 month time period. This could mean that meaningful differences were not detected due to inadequate sample size or the assessment and treatment algorithm used was not adequate to overcome the multiple pain barriers.

In summary, a combined pain assessment and treatment protocol was the most effective intervention to improve pain control however there were methodological differences between studies making comparisons in outcomes non-conclusive. The treatment protocols used were based on pain intensity and aetiology, and subsequent analgesic changes on medication efficacy and tolerability. There were no standardised assessments of other pain dimensions, temporal pattern or patient functioning, which can also impact clinical decision making. However it can be challenging to incorporate the multidimensional experience of pain into a treatment algorithm and study differences may also rely on individual clinician's ability to assess and manage cancer pain. It is likely that interventions to improve cancer pain assessment must be used in addition with other strategies to target patient and healthcare barriers to cancer pain management e.g. pain education programs [114,129].

1.6.2 Domains used to measure cancer pain

The terms 'pain dimensions' and 'pain domains' are used interchangeably to refer to an aspect of pain experience e.g. pain intensity. A pain item refers to a question or a statement describing a domain, or a constituent of a domain e.g. an item describing intensity might ask "how severe is your pain?' There are a number of pain related domains that have been used in studies to assess cancer pain and published recommendations regarding domains to be included in pain measurement instruments for cancer and non-cancer pain. These are described and referenced in more detail below.

The IMMPACT group developed consensus recommendations for a core set of outcome domains to be considered for all clinical trials of treatments for pain [130]. Each participant generated a list of pain domains based on literature provided; consensus was determined by discussion and then a formal vote. Of note, there were no patient representatives on this particular IMMPACT panel though subsequent meetings did involve such participants.

The following six core domains were recommended to be included as outcomes in studies evaluating pain interventions:

1. Pain severity. This incorporated multiple aspects of pain including intensity, location and qualities.
2. Physical functioning defined as the diverse aspects of a person's life, including the ability to carry out daily activities, walking, work, travel and self-care.
3. Emotional functioning. This referred to the evaluation of emotional distress related to a pain condition.
4. Global impression of treatment and satisfaction.
5. Adverse events of treatment, especially drugs. This is an essential component of all therapeutic clinical trials.
6. Participant disposition. This referred to details of those not enrolled in the study, protocol deviations (e.g. treatment non-adherence) and participant withdrawal from the study. This is also a statutory requirement of clinical trial monitoring.

It was noted that the particular outcomes included would depend upon the aims of the study conducted and population under examination so the above served as generic guidance. There were also eight supplemental domains recommended, role functioning, interpersonal functioning, pharmacoeconomic measures, biological markers (e.g. imaging, genetic markers), coping, clinician or surrogate ratings of global improvement, neuropsychological assessments of cognitive and motor function, and suffering and end-of-life issues.

Domains used for the measurement of pain have also been identified in published systematic reviews. Jensen performed such a systematic review with the purpose of identifying studies that included data regarding the reliability and validity of cancer pain measures [131]. Potential articles were identified using Medline searches of 6 key word combinations, followed by searches of specific measures identified. One-hundred and sixty four articles were identified that met the following inclusion criteria: 1) study subjects had cancer, 2) at least 1 pain measure was included, 3) the pain measure was adequately described to be able to identify the pain dimension

assessed and type of scaling used, and 4) data were presented that addressed the psychometric properties of the measure. The authors summarised the findings regarding the psychometric properties of such measures. Table 4 charts the pain domains identified and the frequency they occurred in published studies.

Table 4: Frequency of cancer pain dimensions in psychometric studies

Pain dimension	Proportion of studies
Pain intensity	74.4%
Pain intensity and interference[1] combined	29.3%
Pain interference	14.0%
Pain relief	10.4%
Pain quality	10.4%
Affect/unpleasantness	8.5%
Pain site	1.8%
Temporal aspects[2]	1.2%

[1]Interference= extent to which pain interferes with functioning, [2]temporal aspects=variability of pain over time (includes frequency, onset, duration)

Holen et al [72] performed an extensive literature review to examine the content of existing pain assessment tools for cancer pain in palliative care practice and research. The aim was to evaluate pain domains present in existing tools, evaluate the relevance of such domains by consulting an international panel of experts, and to explore the need for additional dimensions. Two literature searches were conducted using keywords in five databases, firstly a search on pain assessment tools used in palliative care populations and secondly a broader search for pain assessment tools in other populations. The authors identified 48 papers that met the criteria of pain assessment in advanced cancer patients receiving palliative care. From a close examination of available tools they were able to devise a list of pain domains and items. The list of pain domains was ranked by an expert panel, six physicians experienced in pain and palliative care from five European countries, in terms of relevance and importance in both clinical and research settings. They also presented

the number of items per dimension represented in the pain assessment tools identified. Table 5 displays these results.

Table 5: Cancer pain domains in palliative care studies

Expert rankings (6 physicians) of importance of domains in palliative care (highest ranked to lowest) (Holen et al)	**Number of items per domain in existing pain assessment tools in palliative care patients (Holen et al)**	**Expert rankings (32 experts) of importance of domains in palliative care (Hjermstad et al)**
Pain intensity	Pain interference 231	Pain Intensity
Temporal pattern	Pain intensity 138	Temporal pattern
Treatment and exacerbating/ relieving factors	Location 93	Treatment
Pain location	Treatment 85	Pain quality
Pain interference	Temporal pattern 29	Pain Location
Pain quality		Pain interference
Pain affect		Pain duration
Pain duration		Pain affect
Pain beliefs		Pain history
Pain history		Pain beliefs

Hjermstad et al on behalf of the European Palliative Care Research Collaborative (EPCRC) updated the above literature search [73] and performed a more detailed survey of forty-five international experts. In this survey, members of European or International pain task forces were asked to rate the relevance of 10 pain domains for palliative care pain assessment, and asked how to measure the dimensions and the most appropriate recall times (past 24 hours etc.).

There was agreement with the previous study (Holen et al) in the order of the top 3 dimensions (Table 5). However pain quality was rated of greater importance than pain interference in this larger survey. Pain quality provides information that assists the clinician in determining the pathophysiology of the pain (e.g. 'shooting' pain can be associated with neuropathic problems), which perhaps accounts for its higher ranking in a larger survey. The history of pain (previous pain experiences) and pain

beliefs (attitudes, coping strategies and beliefs about causes of pain) were deemed the least relevant in both studies.

The expert rankings of cancer pain domain importance in palliative care patients and the frequency of representation of such items in tools did not correlate. In particular only 16% of the tools assessed temporal characteristics of pain despite experts ranking it as second most important domain. The review concluded that there was great variation in the content of existing pain assessment tools, and very few included the top 5 domains as determined by the experts.

Pain interference (extent to which pain interferes with functioning) was the most common dimension featured in existing palliative care pain assessment tools, which contrasts with the Jensen literature review, where intensity was the most frequent dimension. However, there were differences between the reviews. Holen and Hjermstad included only studies with advanced cancer patients whereas Jensen included all cancer patient studies. Jensen evaluated all available studies that assessed psychometric properties of an individual pain assessment measure whereas Holen evaluated each measure once only. More published studies evaluated the psychometric properties of pain intensity whereas pain interference had more items represented in cancer pain assessment tools. This is undoubtedly due to intensity being a dimension that can be evaluated by a single question whereas interference is a more complex concept requiring multiple questions to assess.

The Holen and Hjermstad expert surveys ranked pain dimensions in order of relevance for the assessment of pain in palliative care. These ratings were thus based on individual clinician's knowledge and experience. Holen reported the views of 6 physicians, and Hjermstad 45 clinicians, who were 'experienced international palliative care clinicians and researchers' from task forces of the European Association of Palliative Care and International Association of Pain. These are small numbers when you consider the number of clinicians that assess and treat cancer pain daily and whilst they have the experience to be on task forces of professional bodies it is not known how well they represent overall clinician opinion.

The IMMPACT and FDA guidance on PROM assessment tool development are consistent in their requirement for patient input in the development of new

measures [77,78]. However, the above recommendations do not include information about pain domains from patient sources. There are reported discrepancies between patient and clinicians regarding treatment outcome priorities and preferences [132-4] and it is difficult to know how well expert opinion truly represents the patient.

1.6.3 Domains to measure cancer pain from a patient perspective

People with the pain condition are of great importance in the development of a new measure. Their subjective experience of the condition can reveal different perspectives on the true experience of living everyday with pain. It would seem to be common sense that the outcomes most critical in the measurement of pain are the ones considered important by those with the condition. Regardless of this, there is very little reported in the pain literature about the value that patients place on different outcomes.

One study asked 40 chronic pain patients to describe outcomes they think should be used to evaluate new pain medications under investigation [134]. The patient was asked to describe as many end-points as possible after being presented with four vignettes describing different studies. The most commonly described end point was decreased pain (80%), followed by decreased frequency of scheduled analgesia doses (70%), and decreased opioid dose (68%). Reduced burden of side effects from medication (constipation 45%, drowsiness 42%) featured more commonly than improvement in activities and sleep (30%). The results only reported the frequency of end-points cited by a group of patients and not the relative importance of each and were specific to the evaluation of pharmacological treatments. However it is interesting the emphasis that patients gave to the burden of such treatments compared with the experts in the previous section. The most commonly cited end-point of decreased pain is a broad term that could refer to multiple pain domains (pain severity, frequency, duration) but demonstrates that patients don't categorise pain into different domains and refer to the broader 'pain experience'.

In a multi-centre European study of breakthrough cancer pain (BTCP) 320 patients ranked the most important features of a 'rescue' medication for BTCP episodes [50]. The most important feature was to 'relieve pain completely' (47%), followed by the ability to 'relieve pain quickly' (44%). Interestingly, side-effect burden (4%), ease of

use (2.5%) and cost (0%) were considered less important than effectiveness. Patients had to rank the above outcomes from a list provided and thus did not have the option to rank other aspects of BTCP experience (e.g. improvements in function).

1.6.4 Single-item scales

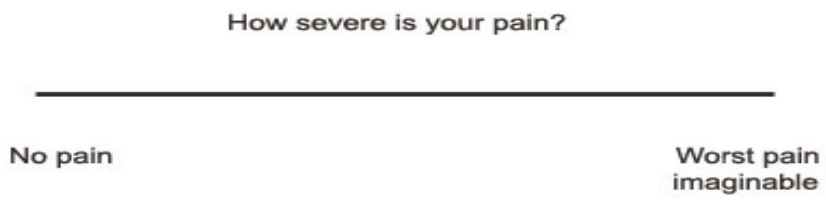
Different types of measure have been used to assess various pain domains, and include single item rating scales and multi-dimensional measures. Single-item rating scales consist of one question and a corresponding response format that measures an individual pain item whereas multi-dimensional measures consist of a number of pain questions.

The most commonly used response formats are visual analogue scales (VAS), numerical rating scales (NRS) and verbal rating scales (VRS). The majority of psychometric data assessing such responses has been for single-item pain intensity questions.

1.6.4.1 Visual Analogue Scale

The visual analogue scale (VAS) consists of a line, usually 100mm in length, with each end labelled with a descriptor, or 'anchor', representing the extremes of the domain being measured (Figure 4) [135]. The subject is required to put a mark on the line to represent the level of the domain that represents their state. The distance measured from the 'no pain' end to the mark is that subject's VAS score.

Figure 4: Visual analogue scale



The majority of research reported on the VAS refers to pain intensity and the validity for this method of measurement has been consistently demonstrated in terms of correlation with other pain intensity ratings [136-8], sensitivity to changes in cancer pain in relation to treatment or over time [139-40], as well as association

with changes in tumour status [141], diagnosis (cancer vs. non-cancer) [142], performance status [141], and quality of life [141,143]. VAS measures of pain intensity have also been shown to successfully quantify experimental painful heat stimuli [144]. Test-retest reliability of the VAS was at acceptable levels when examined over time periods of 5 minutes to 1 week [138,142-3].

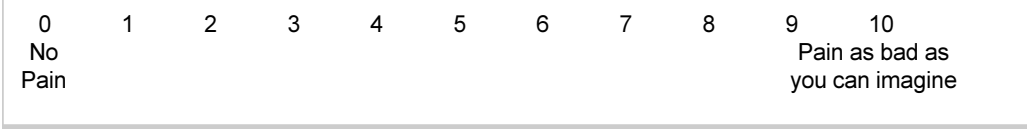
The VAS has a large number of response categories and is considered more sensitive to change than measures with fewer such response options. However it is conceptually complex and requires the ability to convert a sensory concept into a linear format, which some patients may find difficult [145]. This is demonstrated by higher non-compliance ratings compared with other scales [146-7]. Bruera et al found that 16% of patients were unable to complete a VAS even with nursing assistance and this number rose to 84% as disease progressed [147]. Female, elderly patients are reported as having particular difficulty with this method [145].

Seymour studied whether different end-phrases used on a VAS scale to describe extremes of pain intensity altered the scoring pattern used by patients with dental pain [148]. High correlation was found between scales using different phrases, but the scale with the phrase 'worst pain imaginable' was the best choice for comparing present or worst pain between groups.

1.6.4.2 Numerical rating scale

A numerical rating scale (NRS) consists of a range of numbers, usually zero to ten, where the lowest number represents, in terms of pain intensity, no pain, and highest number represents an extreme level of pain (e.g. pain as bad as you can imagine) [149] (Figure 5). The subject is required to write down or circle the number that best represents their level of pain.

Figure 5: Numerical rating scale



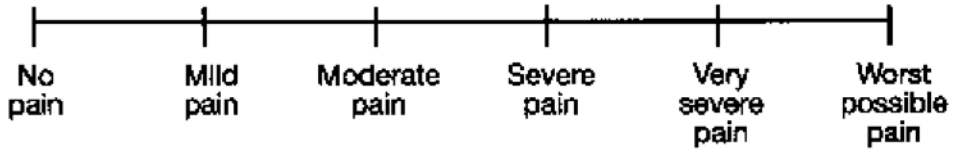
The NRS is closely correlated with the VAS when measuring pain intensity and has similar psychometric properties of validity and reliability [150-2]. NRS's have demonstrated criterion related validity by positive associations with analgesic use [74], dyspnoea [154], pain interference [74,154], performance status [155], mood [155] and negative associations with global quality of life [154,156]. Sensitivity to change has been demonstrated in terms of increases in pain secondary to radiotherapy and physiotherapy and decreases in pain associated with pain treatment [52-55, 157-8]. The change in pain intensity score on a NRS that represents clinically meaningful change has also been determined for the NRS as two points on a 10-point scale (discussed previously) [104]. These data are not available for other types of single item rating scale for pain intensity and as such support the utility of the NRS. The NRS also has better compliance data and is preferred to the VAS in terms of ease of use [159-60]. However it still requires the ability to convert a complex sensory experience into a number that may not suit all patients.

The majority of NRS use an 11-point scale (0-10) however a 101-point NRS or VAS has more response options potentially leading to more sensitive results especially when measuring change. However analysis of patient's use of 101 point scales reveal almost all patients provide responses in multiples of 5 or 10, suggesting that 10 and 20 point scales provide sufficient levels of discrimination [161].

1.6.4.3 Verbal rating scale

The verbal rating scale (VRS) consists of a list of descriptors or phrases (e.g. none, mild, moderate, severe) describing different levels of pain intensity or other pain experience [162] (Figure 6).

Figure 6: Verbal rating scale



A VRS should include descriptors that describe the extremes of that dimension and they range from 4-point scales to 15-point scales [11]. Subjects are asked to choose the phrase that best represents their pain dimension.

Criterion validity has been shown for the pain intensity VRS when compared with anxiety about pain [163], tumour size, tumour stage [164] and survival [165]. The VRS shows sensitivity to change with pain treatment and are correlated with the above measures (NRS and VAS) [145,160,166].

The main advantage of VRSs are that patients, particularly the elderly, prefer the VRS and find them easy to use, and so compliance rates are thus higher than the VAS [145,160]. The disadvantages are the reliance on a patient's ability to read and interpret the multiple words or phrases used. A patient may interpret a word differently depending on the context in which they place such a phrase, or may not find an adequate word to describe their experience [167]. Furthermore the VRS has been reported to have a lower discriminatory capability in distinguishing between background and transient pains as compared with a VRS [168]. Due to the limited fixed number of responses, VRSs' are considered to be less sensitive to change than a VAS or NRS, unless they have more than 10 response phrases (which is unusual in the context of pain intensity) [161].

1.6.4.4 Other response formats

The VAS, NRS and VRS are the most common single-item response formats. However other methods described in the literature are mechanical VAS (similar to VAS but subject required to use a slider to identify pain point) [169], graphic rating scales (VAS with specific markers and labels at fixed points) [170], face scales (drawings of facial expressions represent different levels of pain intensity, commonly used in paediatrics) [146] and a combination of numbers and descriptors [171].

1.6.5 Equivalence of different response formats

A number of studies have attempted to evaluate what pain intensity levels on a numerical rating scale (NRS) are equivalent to verbal rating scale (VRS) responses. Serlin et al compared a culturally and linguistically diverse (from USA, France, China

and Philippines) sample of cancer patients self-reported ratings of 'worst pain' (0-10 NRS, 0='no pain', 10='worst pain possible') with self-rated levels of pain-related interference (0-10 NRS, 0='no interference', 10='completely interferes') of mood, sleep, work, enjoyment of life, relations with others, walking and activity [172](Appendix A). The relationship between worst pain intensity and pain-related interference was non-linear and clustered into three numerical groups on the rating scale, i.e. 1-4, 5-6, and 7-10. These three groups were labelled as 'mild', 'moderate' and 'severe' by the authors. It is not known if these adjectives adequately represent these cluster groups, as they were not 'tested' on patients.

Paul et al repeated this study methodology in cancer outpatients with bone metastases and again found three clusters corresponding with average and worst numerical pain scores [173]. The cut-off point for the second category was however different to the Serlin study, 1-4 (mild), 5-7 (moderate), 8-10 (severe).

Palos investigated a community sample of the general population and asked them to define what pain intensity cut-off level on an NRS represented mild, moderate and severe pain [174]. The cut-points were 1.3-3.6 (mild), 4.3-6.5 (moderate), and 7.4-9.8 (severe). Even though a different population was used this adds strength to the reports by Serlin and Paul. Interestingly, the results in the above studies had no differences across ethnicities, age and gender implying that such cut-offs may be generalizable across different population groups.

1.6.6 Patient interpretation of single-item scales

As discussed previously, pain is a multi-dimensional experience with between two and four dimensions being described by different statistical techniques. As a result a single pain intensity scale lacks specificity, and it is possible that multiple dimensions are contributing to this rating. Patients that respond to a single pain intensity score may differ in how they evaluate such a rating.

Clark et al demonstrated that cancer pain patients differ in how they weight different pain dimensions [10]. Multidimensional scaling was used to determine underlying pain domains and relative importance of each dimension. Two dimensions, sensory and emotional, were yielded in relation to pain intensity; one-

third identified sensory pain intensity as being more important, one-third emotional qualities of pain intensity, and one-third equal weight to both. Thus a score on a single item scale may be dominated by a different dimension depending on that patient and convey little information on that individuals pain characteristics.

Studies that compared NRS pain intensity scores with the Multi-dimensional Affect and Pain Survey (101 descriptors of pain categorised into three cluster dimensions-somatosensory, emotional and well-being) reported that pain intensity ratings were much more determined by the emotional dimension than by the somatosensory dimension [175-6].

Williams performed semi-structured interviews with chronic pain patients regarding their use of a pain intensity visual analogue scale (VAS) and numerical rating scale (NRS) [159]. Patients had inconsistent uses of such pain intensity scales and multiple factors influenced their pain intensity ratings, including impact of pain on activities, distress and fatigue levels. If a patient required help they felt fraudulent if they rated their pain at a low level and tended to rate as they felt a health care professional would expect their pain to be. Interestingly a number of patients redefined the endpoints on the scale with 'no pain' representing their 'normal pain' allowing a greater variation in scoring pains above normal. A separate subset did not use the lower numbers at all as this did not represent their pain.

Due to multiple factors accounting for an individual's pain experience the use of tools to assess domains other than pain intensity are being used more frequently.

1.6.7 Measurement of treatment effect

The majority of research into single-item scales and response formats is in regard to pain intensity. However single-item scales have also been used to measure different aspects of pain treatment [177]. There are a number of outcome measures used to assess pain treatment response including pain intensity difference, pain relief, patient satisfaction with pain control, and global estimations of effect. However, these outcome measures do not measure the same 'thing', and so may give rise to differing treatment effects.

This is demonstrated by a study that evaluated the adequacy of pain treatment in oncology patients by the means of four different outcome measures [80], i.e. pain intensity (average and worst) on a 0-10 numerical rating scale (0='no pain', 10='worst possible pain'), pain relief (0%='no relief', 100%='complete relief'), patient satisfaction (5-point VRS, 'very satisfied' to 'very dissatisfied'), pain management index (PMI, analgesic score (0=no pain medication, 1=non-opioid, 2=weak opioid, 3=strong opioid) minus the pain score (0='no pain', 1='mild pain', 2='moderate pain', 3='severe pain'). 'Adequate' pain treatment was defined individually for each measure based on the literature, not by use of an external comparator. The results are presented in Table 6 and demonstrate the variation in treatment effect depending on which outcome is chosen.

Table 6: Adequacy of pain treatment in oncology patients determined by different outcome measures

Pain outcome measure	% of cancer patients with 'inadequately treated' pain
Percentage of pain relief	16%
Pain Management Index	49%
Pain intensity (average)	60%
Pain intensity (worst)	91%

Interestingly, a factor analysis of these outcome measures revealed that pain relief and satisfaction were correlated and loaded onto a different underlying factor than the pain intensity measures. In other words pain relief and satisfaction are part of a separate pain construct to pain intensity. Selection of a particular outcome measure will depend upon the characteristics of treatment, and the areas of interest to the investigators, but the measures chosen may affect study results significantly [178].

Patients' satisfaction with pain control is frequently used to assess the quality of interventions and services. High satisfaction is a desired outcome, although high levels of satisfaction with pain control often coexist with high levels of pain intensity [179]. This paradox has been documented in oncology patients, as well as other hospitalised patient groups [180-1].

Patients' often consider more than one factor when determining if they are satisfied with treatment for pain, including pain intensity, pain interference with functioning, opioid dose and opioid-related side-effects [182]. As well as efficacious pain treatment the patient-provider relationship was of key significance in a patients' judgements about satisfaction with pain control [183]. In particular, being listened to, treated with respect, having expectations and goals of treatment discussed and being in a partnership with the healthcare team all contributed to a patient's global satisfaction rating [183-4].

Another way of assessing treatment effect is by asking the patient to make a global estimation of pain treatment. Collins et al investigated a simple global estimation ("How effective do you think the treatment was?"-'poor', 'fair', 'good', 'very good', 'excellent') as a measure of efficacy of analgesics [185]. They compared this global estimation with pain relief scores, and found the relationship between a global effectiveness of 'very good' or 'excellent' and 50% of maximum possible pain relief was fair (r^2=0.67). Thus, similar numbers-needed-to-treat were reported using 50% pain relief, and the top two categories of global effectiveness, and they concluded that the global assessment provided similar, though not identical, measures to the pain relief scale.

Pain relief is the only measurement of response to pain treatment that has been shown to be sensitive to the effects of treatment. Farrar described meaningful pain relief as moderate or above on a 5-point VRS ('none', 'slight', 'moderate', 'lots', 'complete') as defined by a patient not requiring additional analgesia for a breakthrough pain episode [186]. However, the most commonly used response option for pain relief involves an evaluation of the percentage of relief (0-100%) and there is no change data reported for this scale [98,115]

An expert working group of the European Association of Palliative Care made recommendations on pain measurement tools in palliative care research [187] and concluded that a VAS or NRS should be used to measure pain intensity and pain relief. The IMMPACT group recommended the use of an 11-point NRS to assess pain intensity in research studies as well as the use of rescue analgesics [188].

1.6.8 Multidimensional scales

The most commonly used multidimensional scale to assess cancer pain is the Brief Pain Inventory short form(BPI)[13,74] (Appendix A). This is also the recommended method of assessing cancer pain by the IMMPACT [188] and European Palliative Care Research Collaborative [73].

The BPI was developed in response to existing pain measures being excessively burdensome for cancer patients to complete [189]. The questionnaire was developed to capture the sensory dimension of pain (i.e. intensity or severity) and the reactive component (i.e. interference with daily function). Patient interviews were used to determine individual items, and the initial version was published in 1983 as the Wisconsin Brief Pain Questionnaire [74], and subsequently renamed as the Brief Pain Inventory (Appendix E).

Initial validation was conducted in cancer patients and construct validity demonstrated by comparison of scores with external criteria of opioid analgesic use and disease severity. The BPI consisted of four pain severity questions, worst pain, least pain, average pain, and pain right now, answered on a numerical rating scale (0=no pain, 10- pain as bad as you can imagine), and seven pain interference questions. The seven questions enquired about interference with walking, working, sleeping, mood, relations with others, general activity and enjoyment of life answered on a numerical rating scale (0-10 scale, 0= no interference, 10=interferes completely). The BPI also recorded information about pain quality (list of descriptors), medication use, percentage and duration of pain relief and non-pharmacological pain relief use. The BPI long form was validated using a recall period of 1 week. [13]

Subsequently a shorter version of the BPI was developed, keeping the pain severity, pain relief and interference questions but omitting pain quality and pain medication use information (Appendix A). The shortened version is more widely used, and has been predominantly validated using a recall period of 1 day [17, 190-3].

Factor analysis of the BPI has revealed an underlying two-factor structure demonstrating the multi-dimensionality of the scale [191]. The BPI has been widely

used and extensively validated in multiple languages by confirmation of the factor structure (confirmatory factor analysis) and correlation of BPI scores with other pain scales and interference scales e.g. European Organization for Research and Therapy of Cancer (EORTC) quality of life questionnaire pain and interference subscales [14-16,194-5].

1.6.9 Specific issues with pain instrument use in palliative care populations

There are a number of issues associated with measuring pain in patients with life-limiting illness including the presence of multiple other symptoms, and deteriorating physical and mental condition. In addition there are many psychological and existential issues associated with disease progression and short life expectancy that can impact on physical symptom experience and perception [196]. Higher levels of psychological distress and lower levels of social support are associated with higher levels of cancer pain [197-8], which demonstrates the complex and multifactorial nature of pain.

Palliative care patients with cancer often have difficulty in completing a multi-item assessment tool. In one study involving consecutive admissions to a palliative care unit 68% of patients were unable to complete any of the multi-item pain assessment tools [146]. This was due to cognitive impairment, communication difficulties and severe physical illness. In another study new referrals to a palliative care unit were invited to complete the Brief Pain Inventory (BPI) over 4 consecutive weeks [199]. Only 41% of patients were able to participate until the end of the study, and 50% of questions were not adequately completed, mostly due to poor physical condition.

To account for the weak physical condition and degrees of cognitive impairment in advanced cancer patients, patient-reported outcome measures (PROMs) developed should be short, simple and clear [187]. Whilst brevity is desirable this must be balanced against appropriate levels of information obtained to allow judgements to be made.

Clinicians often judge PROMs to be burdensome and time-consuming for patients and as such they are not currently widely used in everyday practice [123]. However health policy changes dictate that outcome measurements will be compulsory in

future [200] therefore care must be taken to ensure that appropriate PROMs are developed to represent patients with poor physical conditions.

Chapter 2. Hypotheses and aims

The aim of this study was to develop a breakthrough cancer pain (BTCP) assessment tool for clinical use to allow specialists and non-specialists to rapidly diagnose and quantify BTCP in a variety of clinical settings, as well as monitor changes in BTCP over time. This study therefore consisted of two main phases, the development of an instrument to adequately diagnose cases of BTCP, and the development of an instrument to adequately assess and quantify BTCP.

2.1 Stage 1: Development of a breakthrough cancer pain diagnostic instrument

The aim of this stage of the project was to develop a simple method to allow specialists and non-specialists to rapidly and accurately diagnose BTCP in a clinical setting.

2.2 Stage 2: Development of a breakthrough cancer pain measurement instrument

The second stage of the study aimed to develop an instrument to assess and measure the relevant characteristics of BTCP in a range of cancer patients. The instrument was required to be used in clinical settings to allow specialists and non-specialists to rapidly assess and quantify BTCP and monitor over time. To ensure that the BTCP measurement instrument met this purpose it was necessary to have content relevant to both patients and pain specialists, and meet international standards of reliability, validity and responsiveness in the relevant population. Importantly, it was also needed to be acceptable to the population of interest, in terms of clarity, readability and length.

The following hypotheses were tested:

1. A simple algorithm can be used to detect the presence of breakthrough cancer pain (BTCP) in patients in a range of settings.

2. A clinical BTCP assessment tool can be developed from first principles with relevant content from both expert and patient sources.
3. The clinical BTCP assessment tool developed is able to adequately measure the desired construct i.e. severity of breakthrough cancer pain (validity)
4. The clinical BTCP assessment tool has an acceptable level of measurement error (reliability).
5. The clinical BTCP assessment tool has the ability to detect clinically relevant changes over time (responsiveness).

Chapter 3. General methods

This study consisted of two stages, the development of a BTCP diagnostic instrument, and the development of a BTCP measurement instrument. A brief summary of the methodology for each stage is described below, and then a description of participants recruited for each stage of the study, as well as the approvals obtained.

3.1 Stage 1: Development of a breakthrough cancer pain diagnostic instrument

The research group developed a diagnostic algorithm that produced a diagnosis of BTCP. To determine if the algorithm accurately diagnosed 'true' cases of BTCP it was compared with a 'gold standard' clinical pain interview with a pain specialist. One hundred and thirty five patients were recruited for this stage of the study.

3.2 Stage 2: Development of a breakthrough cancer pain measurement instrument

This stage of the study involved the development of a BTCP measurement instrument with relevant content (content validity) and then psychometric testing of the instrument to ensure it was both reliable and adequately measured the desired construct (validity). The ability to measure clinically relevant change over time (responsiveness) and acceptability of the instrument to patients with the condition was also assessed.

The instrument was developed from expert (quantitative survey) and patient sources (qualitative interviews). Instrument content was subsequently reviewed by the same experts and patients (cognitive interviews). Ten patients were used for each set of interviews. Psychometric testing of the instrument was then performed in 100 BTCP patients and the instrument evaluated against a number of clinical and biomedical parameters.

3.3 Participants

Patient participants for all the above stages of the study were from three different clinical settings: the Royal Marsden NHS Foundation Trust (tertiary referral cancer centre), Royal Surrey County Hospital (District General Hospital and St Luke's Cancer Centre) and St Clare's Hospice. Three sites were chosen to ensure the study was representative of cancer patients at different stages of their disease seen in different clinical environments.

The Royal Marsden NHS Foundation Trust is a tertiary referral cancer centre consisting of two hospital sites based in London and Surrey and receives national and international referrals for cancer treatment. St Luke's Cancer Centre is based at a District General Hospital in Surrey and treats a local cancer population. There is an inpatient oncology unit, extensive outpatient services and a day therapy unit for administration of oncological therapies. St Clare's Hospice is an 8-bedded palliative care inpatient unit in Essex with extensive community and day centre services for cancer patients many of whom are no longer receiving cancer treatment.

To avoid selection bias and to ensure the instruments were applicable to general oncology populations, oncology wards, outpatient oncology clinics and hospice day centre and inpatient unit were screened regularly for patients that met the inclusion criteria for each study stage (described in more detail in individual sections). Written and verbal consent was obtained from all study participants (Appendix F).

3.4 Ethical review and sponsorship

The Royal Marsden Research Ethics committee and Imperial College Research and Development committee approved the study (09/H0801/58) (Appendix G). A substantial amendment was submitted when the definitive BTCP measurement prototype had been drafted to allow further details to be given to the committees about the instrument being used for the psychometric testing in stage 2 (Appendix H).

Chapter 4. Stage 1: Breakthrough cancer pain diagnostic instrument

4.1 Methods

This stage of the project aimed to develop a simple method to enable non-specialists to diagnose BTCP, and to determine if the BTCP algorithm adequately detected 'true' cases of BTCP in a cohort of cancer patients. A secondary aim was to evaluate which background pain severity rating optimally assessed the condition of 'controlled background pain'.

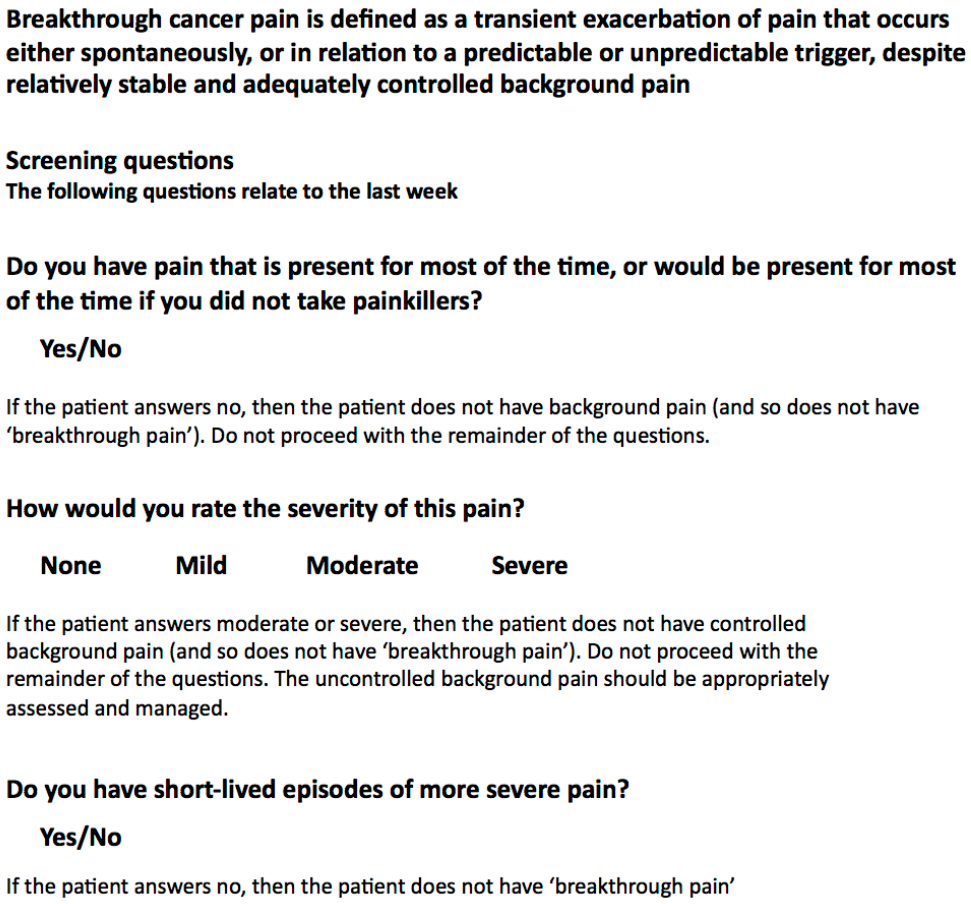
4.1.1 Algorithm

An algorithm (series of questions) was developed to determine if participants had a diagnosis of BTCP (Figure 7). The algorithm was based on a comprehensive review of the literature and consisted of three questions to be answered by the participant. The questions referred to pain experienced over the previous week. The initial question established if a participant had background pain present and allowed for the fact that they may be taking regular painkillers that mask the pain. The second question required the participant to rate the severity of their background pain as none, mild, moderate or severe, and the third question established if transient episodes of pain were present.

The criteria for an algorithm diagnosis of BTCP were:

1. Presence of background pain: affirmative answer to the first question on algorithm
2. Background pain controlled-defined as a rating of none or mild on the verbal rating scale in the second question
3. Transient episodes of pain-affirmative answer on third question

Figure 7: Breakthrough cancer pain diagnostic algorithm



4.1.2 Participants

This was a prospective observational study conducted at three United Kingdom sites (described previously). The inclusion criteria were 1) pain related to cancer or cancer-treatment 2) around-the-clock analgesia prescribed for the previous week 3) age>18 years 4) ability to complete study proforma. The patient must have experienced pain for a period of at least one week. Regular round-the-clock analgesia was defined as any background pain relief medication prescribed over the previous week. The pain relief could be opioid or non-opioid.

The author or a palliative care research nurse screened patients that were referred to the palliative care hospital support team and pain and palliative care outpatient clinics at 2 hospital sites. The same investigators also regularly screened oncology outpatient clinics, oncology wards and oncology day treatment units for appropriate

patients. The author also regularly screened the hospice inpatient unit and attended the day therapy centre twice a week to identify appropriate patients in this environment.

If a patient had a cancer diagnosis and was receiving regular prescribed pain relief the author asked a health professional clinically involved with the patient to approach and enquire if they would be interested in participating in our study. If the answer was affirmative a member of the research team approached and gave them a Patient Information Sheet (PIS) (Appendix I) with further details about that stage of the study and the study in general. It was made clear to the patient at all times that they had no obligation to participate and it would not affect their care. If any issues were identified in the course of the study e.g. unrelieved symptoms, a referral was made to the palliative care team. If a patient agreed to participate written and verbal consent was obtained.

4.1.3 Definition of 'true' cases of BTCP

The 'gold standard' BTCP diagnosis was made by a clinical expert, defined as a Consultant in Pain or Palliative Medicine with specialist knowledge of BTCP. The specialist knowledge required them to work with patients with BTCP, be viewed by peers as an opinion leader and have at least one peer-reviewed publication about BTCP. Two experts agreed to participate in this stage of the study, one expert evaluated patients recruited in the hospice, and the other assessed hospital recruitments.

4.1.4 Assessments

Each patient was administered the algorithm developed. This was followed by a clinical assessment with a pain specialist with specific expertise in BTCP who was blinded to the results of the algorithm. The specialist was required to state if the participant had background pain present, whether they thought the background pain was adequately controlled, and whether episodes of BTCP were present. The clinical assessment diagnosis represented the 'gold standard' of patients with the condition of 'controlled background pain' and BTCP.

4.1.5 Sample size and analysis

The sensitivity (i.e. the proportion of patients with the condition screening positively), specificity (i.e. proportion of patients without the condition screening negatively), positive predictive value (i.e. proportion of patients screening positively that have the condition) and negative predictive value (i.e. proportion of patients screening negatively that don't have the condition) were calculated for the condition of 'breakthrough cancer pain' and 'controlled background pain' at each pain severity cut-off [201]. Table 7 represents the elements used to calculate these results and the equations used for calculation are documented below.

Table 7: General representations of a diagnostic test

		Disease status (expert diagnosis of BTCP)		
		Positive	Negative	Total
Algorithm	Positive	a	b	a + b
	Negative	c	d	c + d
	Total	a + c	b + d	

a=true positive, b=false positive, c=false negative, d=true negative

- Sensitivity= a/(a + c)
- Specificity= d/(b +d)
- Positive predictive value= a/(a + b)
- Negative predictive value= d/ (c + d)

The kappa statistic was calculated to determine the level of agreement between the screening algorithm and expert opinion and represents how much better the study agreement was as compared to chance. It was calculated by initially assessing the proportion of agreements expected by chance and subtracting from proportion of agreements found in study. Kappa has a maximum value of 1.00 when agreement is perfect; a value of zero indicates no agreement better than chance, and negative values show worse than chance agreement. There are no absolute definitions for the interpretation of kappa however the following guidelines are the most commonly used. [201]

Value of kappa:

- <0.20 Poor agreement
- 0.21-0.40 Fair agreement
- 0.41-0.60 Moderate agreement
- 0.61-0.80 Good agreement
- 0.81-1.00 Very good agreement

A sample size of 135 subjects was required to detect a sensitivity of 70%, and specificity of 85% with 95% confidence interval width of 10% assuming 60% prevalence of breakthrough pain [202]. Recruitment continued until the required sample size was achieved.

4.2 Results

135 patients were recruited for the study and completed the algorithm. To recruit 135 patients, 147 were approached and 12 patients declined to participate. Proffered reasons for not wanting to take part were fatigue (6 patients), no reason given (3 patients), did not want to see a doctor (2 patients), and did not want to talk about pain (1 patient). The demographic details are presented in Table 8.

Table 8: Demographic data for breakthrough cancer pain diagnostic tool

Age	Median 62yr (range 33-96yr)
Gender	
Male	76 (56%)
Female	59 (44%)
Cancer diagnosis	
Gastrointestinal	35 (26%)
Breast	26 (19%)
Genito-urinary	25 (19%)
Lung	16 (12%)
Gynaecological	10 (7%)
Head and neck	7 (5%)
Haematological	8 (6%)
Other	8 (6%)
ECOG Performance Status[1]	
0	6 (4%)
1	29 (21%)
2	44 (33%)
3	46 (34%)
4	10 (7%)
Recruitment site	
Royal Marsden Hospital	100 (74%)
St Clare's Hospice	25 (19%)
St Luke's Cancer Centre	10 (7%)
Inpatients	51 (38%)
Outpatients	84 (62%)
Pain pathophysiology	
Nociceptive	75
Mixed neuropathic and nociceptive	58
Neuropathic pain	2

Table 9 displays patient background pain severity ratings as compared to the expert background pain diagnosis (controlled or uncontrolled). Every patient that rated their background pain as 'none' was determined to have 'controlled' background pain by the clinical expert. Eighty-three percent of patients that rated their background pain as 'mild' had expert determined 'controlled' background pain compared with 51% of patients with 'moderately' rated background pain. Interestingly, more patients with a 'severe' background pain rating had 'controlled' rather than 'uncontrolled' background pain (69% versus 31%) as determined by the clinical expert.

Table 9: Patient background pain severity ratings compared with clinical expert background diagnosis

Patient's rating of background pain intensity	N	Expert diagnosis	
		'controlled background pain' N=95	'uncontrolled background pain' N=40
'None'	9	9 (100%)	0
'Mild'	60	50 (83%)	10 (17%)
'Moderate'	53	27 (51%)	26 (49%)
'Severe'	13	9 (69%)	4 (31%)

Table 10 displays the sensitivity and specificity of two different background pain severity cut-off levels for the clinical diagnosis of 'controlled background pain'. The sensitivity of a background pain severity rating of mild or less to accurately categorise controlled background pain was 0.69 compared to 0.97 for severity of moderate or less, however this was balanced by a higher specificity rating for mild or less, 0.78 compared to 0.2

Table 10: Sensitivity analysis of patient background pain severity ratings compared with diagnosis of controlled background pain

	Patient rating of background pain intensity	
	'None', 'mild'	'None', 'mild', or 'moderate'
Sensitivity	0.69	0.97
Specificity	0.78	0.2
Positive predictive value	0.84	0.68
Negative predictive value	0.6	0.77

The experts diagnosed 65 (48%) patients with breakthrough pain. The algorithm had a sensitivity of 0.54 i.e. 54% of patients with the 'true' condition of breakthrough cancer pain screened positively (using the pre-specified cut off score of mild) and a specificity of 0.76. The positive predictive value was 0.7 and negative predictive value 0.62 (Table 11).

The kappa value for the screening algorithm as compared to the clinical expert was 0.39.

Table 11: Sensitivity analysis of the algorithm screening test compared to expert diagnosis of breakthrough cancer pain

	Algorithm diagnosis of breakthrough pain N=135
Sensitivity	0.54
Specificity	0.76
Positive predictive value	0.70
Negative predictive value	0.62

Comparisons between recruitment sites revealed that the sensitivity of the algorithm to diagnose BTCP was lower in hospice patients compared with those from the hospital sites (0.36 versus 0.61) (Table 12). This was predominantly due to hospice 'true' cases of BTCP rating their background pain intensity as 'moderate' or 'severe'. The average age of hospice patients was higher (70 years versus 59 years) (P>0.001) and performance status was worse; 92% of hospice patients had an ECOG performance status of 3 or 4, compared with 30% of hospital patients (P>0.001).

Table 12: Sensitivity analysis of algorithm screening test by recruitment site

	Recruitment site	
	Hospital site N=110	Hospice site N=25
Sensitivity	0.61	0.36
Specificity	0.75	0.82
Positive predictive value	0.70	0.71
Negative predictive value	0.67	0.82

Further analysis revealed that the sensitivity of the algorithm to diagnose BTCP was higher in patients under the age of 65 (0.63 versus 0.44) (Table 13), and in patients with a better performance status (0.66 versus 0.41)(Table 14). However, there was little difference in algorithm sensitivity according to pain pathophysiology (Table 15) or inpatient status (Table 16).

Table 13: Sensitivity analysis of algorithm screening test by age

	Age	
	Under 65 N=82	**65 and over N=53**
Sensitivity	0.63	0.44
Specificity	0.68	0.88
Positive predictive value	0.67	0.80
Negative predictive value	0.65	0.61

Table 14: Sensitivity analysis of algorithm screening test by performance status

	Performance status	
	ECOG 0-2 N=79	**ECOG 3-4 N=56**
Sensitivity	0.66	0.41
Specificity	0.66	0.89
Positive predictive value	0.68	0.79
Negative predictive value	0.64	0.62

Table 15: Sensitivity analysis of algorithm screening test by pain pathophysiology

	Pain pathophysiology	
	Pain with neuropathic features N=60	**Nociceptive pain N=75**
Sensitivity	0.52	0.59
Specificity	0.65	0.83
Positive predictive value	0.67	0.74
Negative predictive value	0.52	0.71

Table 16: Sensitivity analysis of algorithm screening test by inpatient status

	Inpatients N=51	**Outpatients N=84**
Sensitivity	0.53	0.58
Specificity	0.71	0.78
Positive predictive value	0.73	0.69
Negative predictive value	0.52	0.69

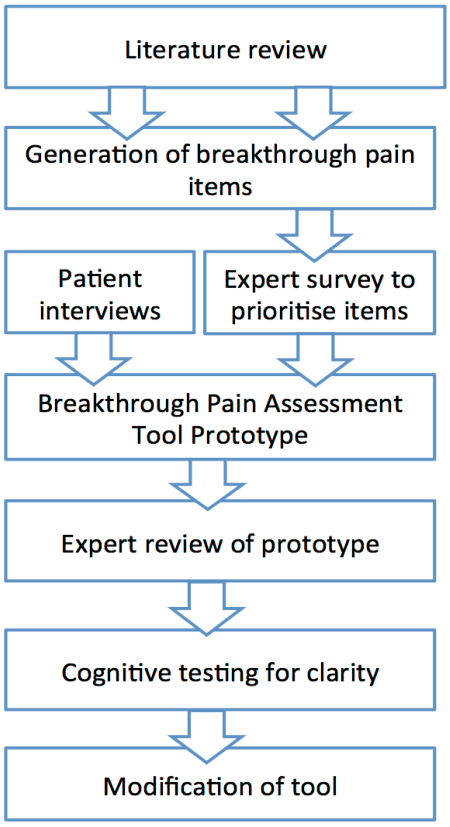
Chapter 5. Stage 2: Breakthrough cancer pain measurement instrument: generation of tool content (content validity)

5.1 Methods

Efforts were made to develop the BTCP measurement tool to international standards of instrument development. A multi-method qualitative and quantitative process was employed to ensure that content of the BTCP measurement tool was relevant to and representative of the targeted construct. In accordance with IMMPACT (Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials) and FDA guidelines both expert and patient opinion was obtained [77-8].

Figure 8 summarises the sequential process used to develop the content of the BTCP assessment tool.

Figure 8: Content validity method



A literature review generated a list of items to characterise and describe BTCP, which clinical experts then rated in terms of importance and relevance in the clinical assessment of BTCP. Interviews were conducted with BTCP patients and the analysis of these, together with the expert survey, formed the basis of the initial instrument prototype. The prototype was then reviewed by both experts and patients and revised accordingly.

5.1.1 Expert survey to determine relevant pain items

United Kingdom experts evaluated items for inclusion in the BTCP assessment tool from a quantitative survey.

5.1.1.1 Participants

The expert was defined as a Consultant (Nurse or Doctor) with specialist expertise in BTCP or pain instrument development and viewed by peers as opinion leaders i.e. author on at least one peer reviewed publication in the field. All experts were based in the United Kingdom (U.K.) as the instrument was to be tested and validated in a U.K. population, and meanings of certain phrases or words could differ depending on linguistic and cultural context. The survey was sent to each expert with a covering letter (Appendix J) and consent was implied by completion and return of the survey.

5.1.1.2 Data collection

The experts were initially contacted via e-mail to inform about the study and asked if they were willing to complete a questionnaire. If yes, the experts were mailed the list of BTCP items and asked to rate their level of agreement with the relevance of each item in the clinical assessment of BTCP on a 5-point Likert scale (strongly disagree, disagree, no preference, agree, strongly agree) (Appendix K). The experts were also asked about the most relevant time recall period for such an instrument to assess BTCP over.

5.1.1.3 Analysis

Definition of agreement was predetermined as a minimum of 75% of experts indicating ‘agree’ or ‘strongly agree’ on the Likert scale [76,203]. Any item with this

level of agreement was considered to be included in the assessment tool and justification was necessary to not include it, e.g. item not representative of patient experience, or item measured similar concept to other relevant included item. Any item with less than 75% agreement was considered not to be included in the tool unless relevant justification e.g. recurring theme in patient interviews.

5.1.1.4 Sample size

A sample size of fourteen experts was aimed for to provide adequate numbers for agreement according to the RAND/UCLA (Research and Development corporation/ University of California, Los Angeles) appropriateness manual guidelines [76]. The RAND corporation is a non-profit institution that helps improve policy and decision-making through research and analysis that, together with the University of California, produced a manual of step-by-step guidelines with the purpose of utilising the collective judgement of experts to inform clinical practice. These guidelines have been incorporated into decision making for international and national health care policy (e.g. NICE) and are considered the current standard for determining consensus among experts [204-5].

5.1.2 Patient interviews

Semi-structured interviews were performed with ten individuals with BTCP to ensure their views and experiences were represented in the BTCP assessment tool. Individual interviews were chosen to allow participants to talk in personal terms about their BTCP and a semi-structured format to enable flexibility in the sequence of questions dependant on the participant's response. As BTCP is a subjective phenomenon interview prompts were designed to elicit feelings about aspects of multiple BTCP domains, including the extent to which they were considered to be important.

5.1.2.1 Participants

English-speaking adults attending a United Kingdom cancer centre with a diagnosis of advanced cancer and BTCP (diagnosed clinically) were eligible for the interviews.

Purposive sampling was designed to obtain people with a range of gender, age, and cancer diagnoses.

Each participant was given a Patient Information Sheet (Appendix L) detailing this part of the study and had 24 hours to consider if they were willing to enter. If the patient agreed, an interview date was arranged and written consent was obtained.

5.1.2.2 Data collection

An in-depth interview was conducted with each participant (duration of 30-60 minutes) in a private room at a place of their convenience. At the beginning of each interview the researcher defined BTCP for the participant and explained that the purpose of the interview was to learn about their experience of this type of pain. Each interview was audiotaped, transcribed verbatim and reviewed prior to the subsequent interview. File notes were written immediately after each interview.

5.1.2.3 Analysis

Content analysis method was used to organise data and identify emerging themes [206-10]. This involved initial coding of units of text noted by hand in the margins of the transcript. The initial codes were systematically classified into categories of similar meaning and themes were identified. The researcher repeatedly read through all transcripts to gain an overall understanding of the texts and to aid in the identification of themes common to all participants, and overarching themes. A second person, nurse consultant/lecturer with expertise in qualitative research methodology, reviewed the coding and themes, and discussion was held with the researcher until both parties agreed. The themes were compared to the preliminary framework and revised accordingly by researchers.

5.1.3 Formulation of breakthrough pain assessment tool prototype

The research team drafted questions and response formats for each item to be included from the expert survey and patient interviews. In some cases patient's words were used to phrase the questions. Each question and response format was worded as simply as possible to be clear and avoid ambiguity.

5.1.4 Expert review of breakthrough pain assessment tool prototype

The United Kingdom experts (same as above) were mailed the BTCP assessment tool prototype and asked to comment on the questions and the response formats. They were asked for their comments in relation to clarity, wording, relevance and representativeness. The research team carefully evaluated all comments and modified the prototype accordingly.

5.1.5 Patient cognitive testing

The BTCP assessment tool prototype (modified after above expert review) was tested on a convenience sample of ten patients for readability and clarity.

The participants had a diagnosis of BTCP. A member of the research team approached and gave them a Patient Information Sheet (PIS) (Appendix M) with further details about that stage of the study and the study in general. If the patient agreed, an interview date was arranged and written consent was obtained.

The 'think-aloud' method was used, which involved encouraging patients to explain their thought process whilst completing the assessment tool [211]. Careful consideration was given to any problem expressed by a patient. If a problem was encountered on 2 occasions then the question was reworded or substituted. The research team modified the tool and a final version was produced.

5.2 Results

5.2.1 Literature review and expert survey to determine relevant breakthrough cancer pain items

The BTCP domains and items generated by the literature search, as well as the expert ratings of each item, are presented in Table 17. All fourteen experts returned the initial survey rating the clinical relevance of BTCP items. The majority of experts (>75%) considered every BTCP clinical item to be relevant, except for radiation of BTCP, duration of average episode of BTCP, average BTCP intensity and time of last BTCP.

Table 17: Expert ratings of BTCP items

Domain	Items	% experts rating item as clinically relevant
Location	Location of breakthrough pain	100%
	Radiation of breakthrough pain	71%
Quality	Similarity to baseline pain	100%
	Quality of pain	93%
	Associated features	86%
Intensity	Worst breakthrough pain intensity	86%
	Intensity of each episode	79%
	Average breakthrough pain intensity	57%
Temporal features	Daily frequency of pain	100%
	Duration of each episode	86%
	Date breakthrough pain started	79%
	Time between onset and peak intensity	79%
	Duration of average episode	64%
	Date/time of last breakthrough pain	50%
Exacerbating factors	Exacerbating factors	100%
	Predictability	93%
Treatment	Frequency of usage of BTCP medication	100%
	Amount of pain relief	100%
	Side effects of painkillers	100%
	Type of breakthrough pain medication	93%
	Dose of breakthrough pain medication	93%
	Time to meaningful pain relief	93%
	Non-pharmacological relieving factors	93%
	Time to onset of pain relief with medication	86%
	Satisfaction with breakthrough medication	86%
	Ease of use of painkillers	86%
Interference	Activities of daily living	100%
	Walking/ movement	93%
	Sleep	93%
	Work	93%
	Social Activity	93%
	Relationships	86%
	Mood	86%
	Enjoyment of life	86%
Psychological issues	Quality of life	93%
	Distress caused by pain	93%
	Meaning of pain	79%

5.2.2 Patient interviews

A content analysis identified themes of communication, isolation, and BTCP management. Further details about all themes and sub-themes have already been published 'Breakthrough pain: a qualitative study involving patients with cancer' (Appendix P) [212]. The issues identified and used specifically in the development of the BTCP assessment tool are discussed below.

The BTCP domains referred to by all patients were intensity, location, interference, temporal factors and relieving/ treatment factors. The meaning of BTCP for the patient was often expressed in association with fear of disease progression and implications on prognosis. Characterisation of the pain was most commonly made in terms of intensity and location. Interestingly, the patients had often learnt to live with a certain level of pain and even used terms such as 'my usual pain episodes'. The severe BTCP episodes, when pain was at its worst, were referred to extensively and patients used emotive terms to describe such occasions; 'made me want to scream', 'very distressing'.

There were multiple issues expressed by each patient regarding physical and social functioning, and the range of interference items discussed was incredibly varied. Patients often discussed interference in quite general terms; 'I wish I could live a normal life', 'I wish I could do the things I used to do'. Psychological interference was emphasised strongly by the majority of patients especially the ability of pain to affect their mood and cause high levels of distress. Patient's expressed temporal factors of frequency and duration often and typically used language such as 'a burst of pain', or 'on-going nagging pain' to describe the duration of an episode. Frequency was often variable and related to activities performed in a day and interestingly also related to mood and psychological state.

BTCP management, in particular medications, featured frequently. There were many issues expressed regarding opioid analgesia, balanced by the ability to carry on with life if BTCP was appropriately assessed and managed. Specialist pain services were perceived as providing the necessary expertise to perform this management however concern was expressed about continuity of care and seeing different health care professionals who perceived their pain descriptions differently. One patient

talked about having to use different terms and higher pain ratings when he felt certain health professionals were not taking his pain as seriously. Side effects from painkillers featured strongly in all patient interviews, and often patients preferred to live with a level of pain rather than experience adverse effects from their analgesics. Patients often described painkillers in terms of their general effectiveness, 'quite effective', 'worked well', rather than the amount of pain relief provided or their satisfaction with the painkiller.

5.2.3 Formulation of breakthrough pain assessment tool prototype

It was apparent in the initial analysis of the above results that there were 2 distinct categories of question to be included in the tool: 1) items to characterise BTCP 2) items to measure the severity of the BTCP.

It was essential that the tool be as brief as possible to ensure it was easy to use in clinical practice by patients who often have difficulty completing a large number of questions due to fatigue, time pressures, and concentration issues. Thus, careful consideration was paid to each pain domain, and if determined of low clinical value, either from expert survey, patient interviews or literature review, items were rejected.

5.2.3.1 Rejected items

Individual items within each domain were evaluated separately. From the original domains the following were rejected:

1. *Radiation* of BTCP was the domain of least importance as rated by the experts. We decided this domain would not significantly alter assessment and characterisation of the pain.
2. Experts rated *similarity to background pain* as highly relevant however the literature reports that >95% of BTCP is an exacerbation of the background pain therefore this question would be applicable only to the minority of patients; asking about the location of the BTCP would adequately cover the clinical information necessary.

3. Experts rated the *quality/character* and *associated features* of BTCP as relevant. In the patient interviews pain was most often characterised in terms of severity. We considered quality and associated features to be of limited clinical value due to their inability to discriminate underlying pathophysiology, and their wide variability [213].
4. The *onset of BTCP* did reach meaningful consensus in the expert survey however, was rated less relevant than duration and frequency of BTCP. The time between onset and peak intensity was difficult for patients to calculate and varied significantly in the literature. Clinically, if duration of the episode is known, speed of onset of pain is of limited value in determining management options and was thus not included.
5. The *meaning of BTCP* for the patient was a major theme in the patient interviews associated with fear of underlying cancer progression, and fear of dying. It was decided, after lengthy discussion, that despite the importance of this item in overall pain assessment and management, it reflected too many different underlying constructs to have meaningful value in the measurement of BTCP specifically.
6. The *history of BTCP* included the items 'time of last BTCP' and 'date BTCP started'. The experts rated these domains as less relevant than others and information generated was unlikely to alter the current clinical management of BTCP.

5.2.3.2 Questions

The following items were included and formulated into questions by the researchers. The aim of each question was to have as few words as possible with no ambiguity. Clarity and simplicity were considered essential.

1. *Location* of BTCP
2. *Exacerbating* and *relieving* factors were considered highly relevant by both expert and patient sources.
3. *Intensity*. *Worst pain intensity* was rated highly by experts and featured significantly during patient interviews and was therefore included. However clinically it was necessary to know whether the 'worst intensity' represented

all BTCP episodes. In our interviews the patients often referred to their 'usual' breakthrough episodes therefore a question was added enquiring about intensity of a '*typical* episode' of BTCP. The term average was not used as that required a patient to make a mental calculation of all episodes and experts did not rate the information as relevant.

4. *Frequency* of BTCP was rated highly by experts and is an item included in all observational BTCP studies. It was therefore considered necessary to include to clinically evaluate BTCP.
5. *Duration* of each episode was rated highly by experts, however average duration was deemed to be of lower clinical value. Patients expressed that duration was variable thus agreeing with the limited clinical value of averaging out such an experience. Practically it was difficult to ask, and to expect a patient to remember, the duration of each BTCP episode therefore a question was formulated asking the patient to state the duration of a 'typical' BTCP episode to represent the duration of most importance to them. We decided to ask about duration for a typical episode where painkillers were not taken. This was because the duration of a BTCP episode with analgesia would be assessed by questions regarding treatment effects (see below).
6. *Interference*. Psychological interference featured prominently in patient interviews and it was decided to use the patient's own term of 'distress' to formulate a question to address emotional response to the pain. Other types of interference described were incredibly varied and to limit the number of questions in the instrument, and thus patient burden, it was decided to use one general question to address this wide range of issues. Again the patient's own term was used, 'I can't do the things I want to do' and formulated into a question.
7. *Treatment*. The mainstay of therapy for BTCP is pharmacological treatment and assessment of analgesic efficacy was rated highly by experts. However, there are many different questions used to evaluate painkillers and the expert survey did not satisfactorily distinguish between such items. The patients talked about analgesia in terms of 'effectiveness', rather than amount of pain relief, and therefore we used this term to formulate a question. 'Time to meaningful pain relief' was also used as clinically this gave information

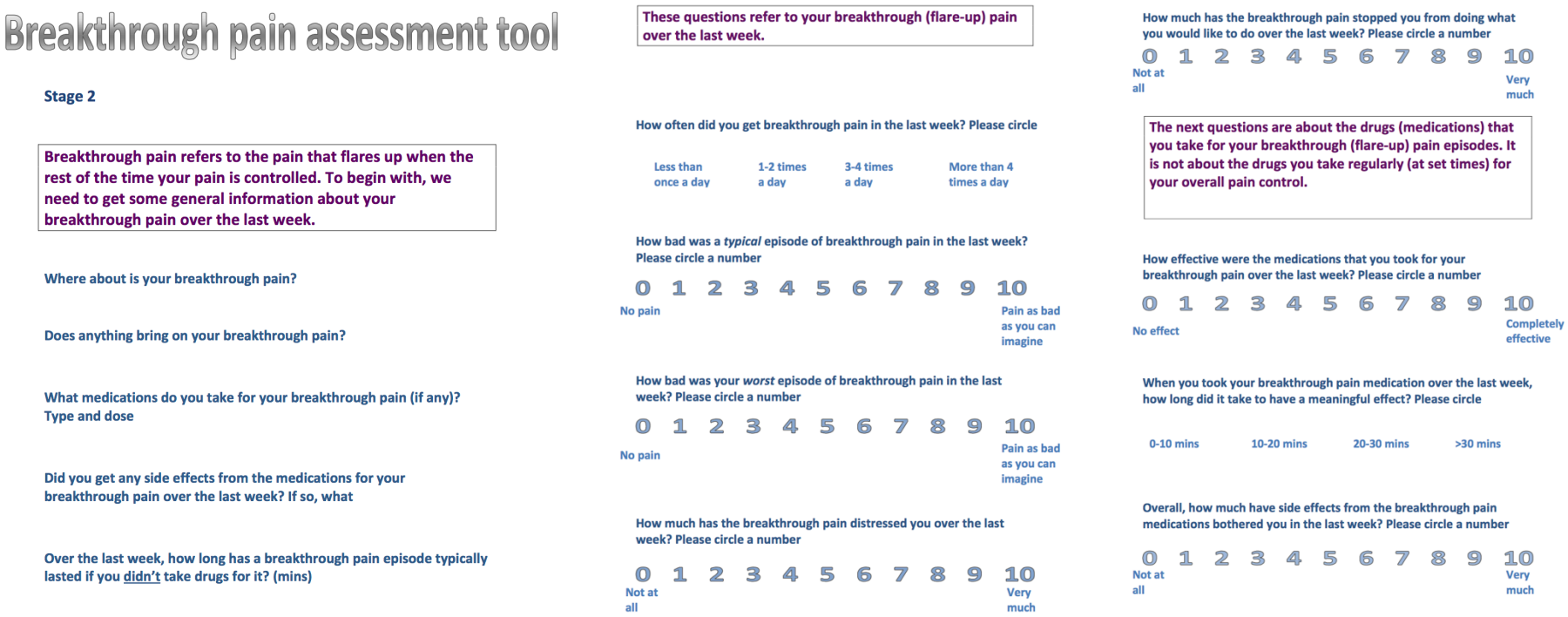
regarding whether BTCP therapy was appropriate for the BTCP duration the patient experienced. Side effects were enquired about after being raised by all patients in interviews, and clinically this information is necessary to guide decisions on titration and tolerance of BTCP painkillers.

5.2.3.3 Response formats

Numerical rating scales have been recommended as the preferred response format for palliative care research, and consistently had greater compliance and ease of use than a visual analogue scale as well as having more data points to calculate responsiveness than a typical verbal rating scale. For these reasons a NRS has been used for questions where appropriate. The anchors chosen for the NRS response were words that represented extremes of severity for that item and the same anchors were used where possible to aid with clarity.

There were 2 quantifiable questions where a NRS was not appropriate, frequency and time to meaningful pain relief. Four response options were chosen for each item based upon the literature and clinically relevant cut-off values. For example, time to meaningful pain relief response options were based on results of commercial studies regarding painkillers prescribed for BTCP, 10-20 minutes for oral transmucosal and nasal fentanyl preparations, and greater than 30 minutes for oral opioid. An initial BTCP assessment tool prototype was developed (Figure 9).

Figure 9: Breakthrough cancer pain assessment tool initial prototype



5.2.3.4 Expert and patient review of breakthrough cancer pain assessment tool prototype

Nine experts returned the BTCP assessment tool prototype with their comments and cognitive 'think aloud' interviews were performed with 10 patients with BTCP. Revisions of the initial BTCP assessment tool prototype were made based upon expert and patient comment (Table 18).

Table 18: BTCP assessment tool (BAT) revisions after expert and patient reviews of prototype

	BTCP tool prototype	Expert comments	Patient comments	Revisions made
Definition of BTCP for patient	'Breakthrough pain refers to the pain that flares up when the rest of the time your pain is controlled	'needs to conform to standard definition' '"flare-up" introducing a new term'	'Need good explanation at the top as can be confusing what breakthrough pain is'	'Breakthrough pain refers to the short-lived increases in your cancer pain'
Completion instructions	None present	"what if there is more than 1 breakthrough pain'		Instructions added 'If the patient has more than 1 breakthrough pain then a tool must be completed for each pain.'
Time frame	Each question incorporates 'over last week' in phrasing	'Include time frame in initial instructions' All experts agreed with 1 week recall	'Kept forgetting it was over the last week'	At top of each page 'The following questions relate to your breakthrough pain over the last week' 'over last week' removed from individual questions
Layout	Page 1=characteristics Page 2 and 3=measurements	'Group questions into relevant domains e.g. all questions regarding medications together' 'Use black text, not colour'	Frequency was talked about before answering 'exacerbating factors' question	Layout altered into domain groups. Frequency asked before 'Does anything bring on your pain?' Text changed to black
Location	'Where about is your breakthrough pain?'	'Not correct English!' Add body map		'Where is your breakthrough pain?' Body map added
Frequency	How often did you get your breakthrough pain?	Agreed with question and response formats	Good question but needs to be asked earlier	No change in question but moved to earlier in questionnaire
Exacerbating factors	'Does anything bring on your pain?'	'Answer is yes or no, also need to ask to specify'	"I thought this just meant medication, maybe need to specify'	'If yes, please write down' '(Painkillers or other)' added

	BTCP tool prototype	Expert comments	Patient comments	Revisions made
Relieving factors	Medication efficacy questions-see below	'Need to ask about factors other than medications'		Question added: 'Does anything relieve your pain? If yes, please write down This question would also cover predictability of BTCP
Duration	How long has a breakthrough pain episode typically lasted if you didn't take drugs for it?'	'Many different questions being asked here?' 'What if they take medication for every episode?'	'Difficult to answer. Would help to have response options' 'Episodes vary, need to ask about normal episode or longest.'	'How long does a typical episode of breakthrough pain last?' Response options added
Intensity	'How bad was a typical episode of breakthrough pain?' 'How bad was your worst episode of breakthrough pain?'	'Change bad to severe' 'Response format good'	Patients answered worst severity first and then had to change it when read second question,	'How severe is the worst episode of breakthrough pain?' 'How severe is a typical episode of breakthrough pain?' Order reversed
Interference	'How much has the breakthrough pain stopped you from doing what you would like to do?' 'How much does the breakthrough pain distress you?'	'Unusual question-who does what they want to do?'	"Prefer more general questions to asking about individual activities' 'Good question as pain does distress' 'Distress is more associated with panic than emotional pain'	'How much does the breakthrough pain stop you from living a normal life?'
Breakthrough medication efficacy and tolerability?	'How effective were the medications that you took for your breakthrough pain?' 'When you took your breakthrough pain medication how long did it take to have a meaningful effect?	'Will the words effective and meaningful be understood?' 'Add "no effect" as response option' 'Need to standardise the term used for breakthrough pain medications throughout, maybe to drugs or painkillers.'	'What if you take different painkillers? Maybe need to add more instructions.' All patients understood term 'effective' Implies 'when it starts to work' or 'when it reduces pain' or 'how long until pain goes away'	'How effective is the painkiller that you usually take for your breakthrough pain?' 'How long does the painkiller for you breakthrough pain take to have a meaningful effect?' 'No effect added as response option.'

5.2.3.5 Breakthrough cancer pain assessment tool scoring system

The final version of the BTCP assessment tool was drafted and called the BAT (Breakthrough cancer pain Assessment Tool). The BAT is shown in Figure 10. The scoring system used for the BAT is highlighted in red and described in this section. The BAT is a 14-item instrument and consists of three questions that characterise the pain: location (with body site map), exacerbating and relieving factors (free text answers); two questions to measure the intensity of the BTCP (0-10 NRS responses); two questions to quantify BTCP-related interference (0-10 NRS); and two questions to assess temporal features, frequency (four verbal rating scale (VRS) ordinal response options) and duration of BTCP (five VRS ordinal response options). Three questions ask about treatment for BTCP: BTCP therapy taken (free text), effectiveness of painkillers (0-10 NRS) and time to meaningful pain relief (five VRS ordinal response options); two questions enquire about side effects of BTCP treatment: presence of side effects (free text) and impact of side effects (0-10 NRS). In total there are six questions with 0-10 NRS responses, and three questions with VRS ordinal responses (two questions with five categories, one question with four categories).

For purposes of analysis it is preferable for the BAT to have a scoring system to enable calculations of a single score to define the underlying characteristic. The easiest way to calculate such a score is to simply add up the scores of the individual items and this is the most commonly used approach [11]. The BAT, however, has different response options for different questions making the scoring system slightly more difficult. The different response formats were unavoidable due to the nature of items required to assess BTCP, intensity can be quantified on a NRS, whereas BTCP duration cannot and therefore a VRS was used. A NRS is the preferable method of measurement and this was used where possible and this numerical response can be directly used towards calculation of the total score. However, the three VRS responses needed to be assigned numerical scores to allow such items to be included in the calculation. As the minimum score for the NRS was zero and maximum was ten, it made sense to use multiples of two to score each sequential VRS response to allow the maximum numerical value to be equivalent. As such the questions with five VRS responses were given ascending numerical values of two,

four, six, eight and ten and the four-item VRS response similar with maximum score of eight.

Figure 10 shows the BAT with the VRS responses numerical equivalents in red, these scores were not on the patient version.

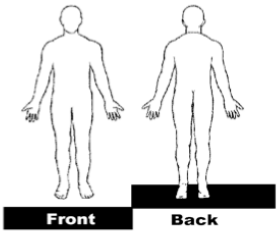
In summary, the nine questions with response formats are used to calculate a BAT total score. The six questions with zero to ten NRS responses simply use the score indicated, and the higher the score the worse the BTCP. The exception is the question asking about effectiveness of BTCP painkiller which is reverse phrased i.e. the higher the score the greater the effectiveness, and thus the score must be reversed before adding to the total. The ordinal responses are numbered in multiples of 2, again with the higher score indicating a worse BTCP experience. The lowest score for each question is 2, least frequent and shortest duration BTCP, and highest score eight (frequency four categories) or 10 (duration and time to meaningful pain effect, five categories). The maximum BAT score is thus 88 (six x 10 NRS+ two x 5 option VRS + one x 4 option VRS).

Figure 10: Breakthrough Pain Assessment Tool

Breakthrough pain Assessment Tool-BAT

The following questions relate to your breakthrough pain over the last week. Breakthrough pain refers to the short-lived increases in your cancer pain.

Where is your breakthrough pain?
Please indicate on picture with a cross (X)



How often do you get breakthrough pain?
Please circle one answer

Less than once a day (2) (numerical score)	1-2 times a day (4)	3-4 times a day (6)	More than 4 times a day (8)

Does anything bring on your breakthrough pain?
If yes, please write down

Does anything relieve your breakthrough pain? (painkillers or other)
If yes, please write down

How long does a typical episode of breakthrough pain last?
Please circle one answer

< 5 min (2)	5-15 min (4)	15-30 min (6)	30-60 min (8)	> 60 min (10)

How severe is your *worst* episode of breakthrough pain?
Please circle one number

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

How severe is a *typical* episode of breakthrough pain?
Please circle one number

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

Breakthrough pain Assessment Tool-BAT



The following questions relate to your breakthrough pain over the last week
Breakthrough pain refers to the short lived increases in your cancer pain

How much does the breakthrough pain distress you?
Please circle one number

0	1	2	3	4	5	6	7	8	9	10
Not at all										Very much

How much does the breakthrough pain stop you from living a normal life?
Please circle one number

0	1	2	3	4	5	6	7	8	9	10
Not at all										Very much

What painkillers do you take for your breakthrough pain (if any)?
Please write down type and dose of painkillers

How effective is the painkiller that you usually take for your breakthrough pain?
Please circle one number (note-reverse scored)

0	1	2	3	4	5	6	7	8	9	10
Not at all effective										Completely effective

How long does the painkiller for your breakthrough pain take to have a meaningful effect?
Please circle one answer

No effect (10) 0-10 min (2) 10-20 min (4) 20-30 min (6) >30 min (8)

Do you get any side-effects from the painkiller for your breakthrough pain?
If yes, please write down type of side effect

How much do side-effects from the painkillers for your breakthrough pain bother you?
Please circle one number

0	1	2	3	4	5	6	7	8	9	10
Not at all										Very much

Chapter 6. Stage 3: Breakthrough cancer pain measurement instrument: psychometric testing

6.1 Methods

6.1.1 Study design

This was a prospective observational, longitudinal study in patients with BTCP. Comparisons were made between the BTCP assessment tool (BAT) and multiple clinical parameters.

6.1.2 Participant recruitment

Patients with BTCP were recruited from three United Kingdom sites (described previously).

Inclusion criteria were deliberately wide and included any cancer diagnosis, BTCP of any origin (cancer-related, cancer-treatment related) experienced over the previous week, prescribed around-the-clock pain relief, and age greater than 18 (no maximum age limit). BTCP was defined as 'a transitory exacerbation of pain on the background of relatively stable and adequately controlled pain' and was determined by clinical assessment. The patient must have experienced BTCP for a period of one week. Regular around-the-clock pain relief was defined as a patient taking any background pain relief medication on a regular prescribed basis over the previous week. The pain relief could be opioid or non-opioid.

The author or a palliative care research nurse screened patients that were referred to the palliative care hospital support team and pain and palliative care outpatient clinics at 2 hospital sites. The same investigators also regularly screened oncology outpatient clinics, oncology wards and oncology day treatment units for appropriate patients. The author also regularly screened the hospice inpatient unit and attended the day therapy centre twice a week to identify appropriate patients in this environment.

If a patient had a cancer diagnosis and was receiving regular prescribed pain relief the author asked a health professional clinically involved with the patient to approach and enquire if they would be interested in talking to a member of the research team about their pain. If the patient agreed they were approached by the author and screened by a brief clinical interview to determine if they had BTCP. If they fulfilled the entry criteria, a verbal explanation of the study and patient information sheet were given (Appendix N). If any issues were identified during the course of the study, e.g. unrelieved symptoms, appropriate referral was made to optimise care. Additionally, if a patient did not consent to enter the study or did not fulfil the criteria a referral was still made to the clinical palliative medicine team, if necessary, to further manage pain and symptom issues.

Written and verbal consent was obtained from each subject and a screening log was kept to record the total number of patients seen, number of patients eligible, and the number who declined to participate.

6.1.3 Instruments

The BTCP assessment tool (BAT) was developed during the initial stage of this study and described in detail previously (Figure 10).

The BAT was compared with certain questions on the Brief Pain Inventory (BPI). The BPI is an instrument designed to measure the subjective intensity of generic cancer pain and the impairment caused by the pain (Appendix E). The BPI has been extensively validated in cancer patients with pain [15-18,191,214]. The BPI includes four questions related to pain severity and seven questions related to pain interference with function. It also includes questions about pain quality, pain relief, and general attitudes towards pain experience.

The pain severity items (pain now, worst pain, average pain, least pain) are presented as numerical rating scales (NRS), with 0= 'no pain' to '10=pain as bad as you can imagine'. The pain severity index is calculated by adding the four responses. The seven pain interference items requires a patient to rate how much pain interferes with general activity, enjoyment of life, mood, walking, work, relations with others, and sleep. These items are presented on a NRS, with 0='does not

interfere', and 10='completely interferes'. An interference index is calculated by adding the interference item scores. There is also one question where a patient is required to rate the percentage of pain relief provided by pain treatments, with 0%='no relief', and 100%='complete relief'.

6.1.4 Measurements

As well as the pain assessment tools a number of clinical parameters were assessed at each consultation with the pain expert (Appendix O). The researcher collected the following demographic information: age, sex, cancer diagnosis, recruitment site, and inpatient/outpatient status. Detailed information was also collected about stage and treatment of the patient's cancer: local vs. metastatic disease, anti-cancer treatment given (chemotherapy/radiotherapy/hormonal therapy/no treatment), site of metastases (bone/visceral/both/none). If a patient was receiving no anti-cancer treatment the reason why was documented e.g. stopped due to progressive disease or end of course, treatment not initiated. The Eastern Cooperative Group (ECOG) performance status was assessed for each patient whom received a score based on their level of physical function (0=fully active, no restrictions, 1= restricted but ambulatory and able to carry out light work, 2= ambulatory but unable to work, 3=limited self-care, confined to bed/chair >50% waking hours, 4=completely disabled).

The type and dose of breakthrough and background analgesia was recorded, as well as the frequency of administration of breakthrough analgesia per day. The pain clinician was required to record the following during their consultation: global assessment of whether BTCP was adequately controlled (yes/no); changes to BTCP management e.g. analgesic alterations or referral for pain procedure (vertebroplasty/nerve block); aetiology of BTCP (cancer-related/ cancer-treatment/ concomitant factor); pathophysiology of BTCP (nociceptive/neuropathic/mixed) and subtype of BTCP (volitional incident/ non-volitional incident/ spontaneous).

The patient was also require to make a global assessment about their BTCP; 'do you think your breakthrough pain is adequately controlled?' (yes/no), and about their BTCP management; 'do you think changes need to be made to your breakthrough pain management? (yes/no/not sure). At follow up visits both clinician and patient

were required to rate their global impression of change of BTCP status since the previous consultation by answering the following questions: 'how do you think your breakthrough pain is compared to when you last filled in this questionnaire?' and 'how would you rate this patient's breakthrough pain compared to the last time you assessed them for this study?' (better/same/worse).

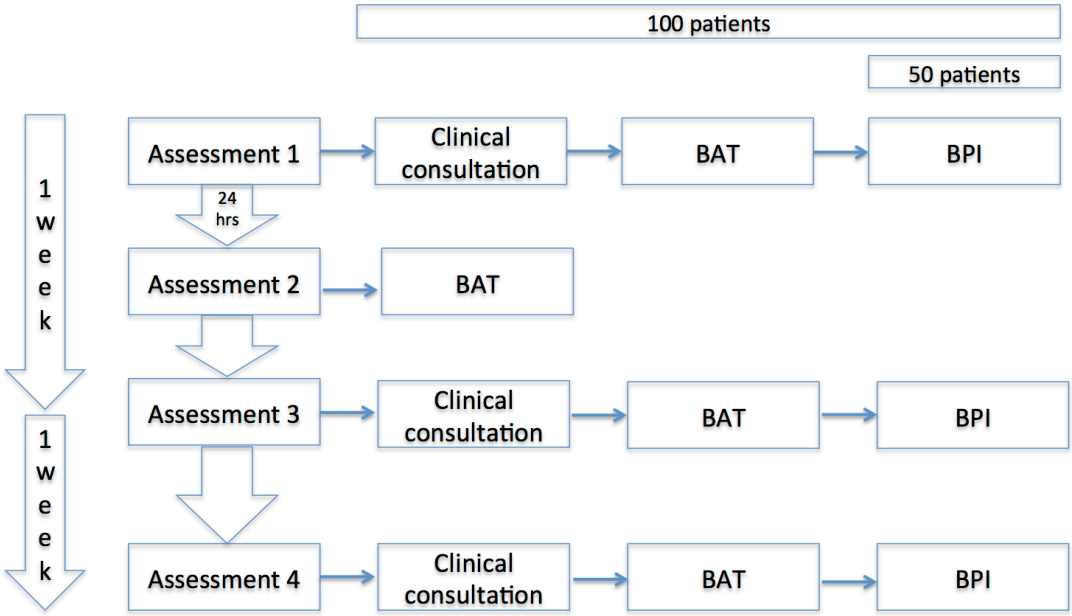
6.1.5 Study protocol

Figure 11 displays the study protocol. The patients completed the Breakthrough Pain Assessment Tool (BAT) on 4 separate occasions. Assessment 1 required the patient to complete the BAT and (Brief Pain Inventory) BPI and have a corresponding consultation with a pain expert (Consultant in Palliative Medicine/ Pain Medicine). At assessment 2 (conducted 24 hours after assessment 1) the patient completed the BAT only (for test-retest purposes).

Assessment 3 occurred approximately 1 week after assessment 1 and required the patient to complete the BAT, BPI and have a follow up clinical consultation with the same pain specialist. Assessment 4 occurred at least 1 week after assessment 3 and again required to patients to complete the BAT, BPI and have follow up consultation.

These consultations occurred when the patient was attending the hospital for appointments or treatments (chemotherapy/radiotherapy) or were present as inpatients. The author or a palliative care research nurse collected all relevant measurements at each assessment.

Figure 11: Study protocol (BAT=Breakthrough Assessment Tool)



6.1.6 Sample size

A sample size of 50 was required for test-retest reliability to detect a clinically acceptable level of correlation (0.85) with 80% power and a significance level of 5%. [215]

A sample size for validity testing was calculated using a previous BTCP study as reference, which compared Brief Pain Inventory (BPI) interference scores between patients with and without BTCP [33]. This study reported a mean score of 4.0 (S.D. 1.1) on a 0-10 numerical rating scale relating to the impact of BTCP on activity compared to a mean score of 2.7 (S.D. 1.4) in a group with no BTCP. Assuming our study obtained similar results for different clinical groups of BTCP patients, a sample size of 70 would be required at 90% power and a significance level of 5% to detect a statistically significant difference between the groups. A sample size of 100 would give at least validity and reliability of this precision and allow for dropouts. Based on previous questionnaire studies in advanced cancer patients, it is assumed that up to one third will not complete follow up [199] due to fatigue, cognitive impairment and rapidly deteriorating clinical condition. We therefore aimed for a sample size of 100 patients at weekly follow up with at least 50 completing the 24-hour test-retest.

The study started with patients completing the BAT and having a clinical assessment however at midterm review it was recommended to administer a validated generic pain tool to the remaining patients, as well as the other measures, to provide more data for analysis. Therefore fifty patients completed the BAT only and fifty completed the BAT and BPI. As the above sample size was based on a between groups analysis, a sample size of 50 was considered adequate for a correlative analysis between the two pain assessment tools [11].

6.1.7 Data analysis

Psychometrics describes the field of study concerned with theory and technique of psychological measurement. A series of psychometric tests are required to assess the performance of an instrument if there are no gold standard measurements to compare with. Psychometric testing is thus required to evaluate health-related outcome measures and works on the principle that certain psychometric properties are required to be demonstrated to ensure the instrument conforms to international standards and recommendations [11,77-8] (Table 19).

Relevant psychometric tests were conducted on the BAT to establish these properties, and consisted of a number of stages of psychometric statistical analysis. The psychometric analysis was performed according to well-established methods and standards [11,86,89]. This statistical analysis was applied to measurement items within the BAT i.e. items that a patient is required to quantify on a numerical or verbal response format. The BAT scoring system used for the purposes of psychometric evaluation has been described previously.

The BAT data were entered into a database and SPSS software was used to perform statistical analysis [12]. The psychometric tests conducted are described in more detail in the text below

Table 19: Psychometric tests definitions

Psychometric property	Definition/ Test
Item analysis/reduction	Ability of scale to represent a multidimensionality construct with no redundant items
Reliability	Ability of scale to measure construct of interest consistently with acceptable degree of measurement error
Internal consistency	The extent to which items comprising a scale or subscale measure the same construct
Test-retest reliability	The degree of error of a measurement instrument assessed by administering the instrument to respondents on two different occasions and examining the correlation between test and retest scores
Validity	Ability of scale to adequately measure concept of interest
Content validity	*The extent to which the content of a scale is representative of the conceptual domain it is intended to cover; assessed during the instrument development stage*
Construct validity	*Extent to which scale conforms to logical relationships with clinical anchors and other measures*
Known groups analysis/ hypothesis testing	The ability of a scale to differentiate between groups that hypothetically have significantly different scores in domain of interest
Convergent validity	Evidence that the scale is correlated with other measures of the same or similar constructs Correlations between the BAT and clinical outcome measures Correlations between the BAT and patient-based outcome measures (BPI)
Discriminant validity	Evidence that scale is not related to measures of different constructs
Responsiveness	Ability of scale to detect clinically significant change Effect size calculated using Cohen's coefficient Minimal Important Difference (MID): smallest difference in score perceived as clinically beneficial
Acceptability	Patient's ability to comprehend and complete all relevant questions Assessed by completeness of data

6.1.7.1 Item analysis and reduction

The first stage of analysis established the underlying dimensionality of the BAT items. Pain is a multi-dimensional experience and studies have shown that cancer pain has a minimum of two underlying dimensions, sensory (intensity) and reactive (interference). The BAT should therefore reflect the multidimensional nature of pain with a minimum of two underlying dimensions, and these dimensions are likely to be similar, but not identical, to those identified for all cancer pain. The BAT contained questions about BTCP medication efficacy and these items could potentially account for an additional dimension (treatment response was not assessed for dimensionality in the cancer pain literature).

The dimensionality of the BAT was determined initially by exploration of relationships between BAT items. If the majority of patients assigned similar scores to two different BAT items then they are said to correlate with each other, the degree of correlation would depend on the proportion of patients scoring the items similarly. If every patient gave two BAT items an identical score they would be perfectly correlated but in practice this is rare. A correlation coefficient is the term used for the calculation of correlation between two items and is an analysis based on the graphical representation of two continuous variables. This calculation gives correlation coefficient values ranged between -1 and +1, a value of +1 implies perfect positive correlation, and zero implies no correlation.

A correlation coefficient was calculated for each BAT item, compared to each other BAT item, and a matrix of correlation coefficients drawn for all items. The matrix of values indicated whether all items correlated highly with each other or whether there were groups of items that clustered together accounting for multiple underlying dimensions. Items in a measurement tool designed to measure the same underlying construct should have a moderate correlation with at least one other item (correlation coefficient >0.25). If an item did not correlate with any other item it should be omitted or rewritten as it is measuring an unrelated construct to all other items and may affect validity of the tool. If two items had a correlation coefficient of >0.75 this indicated they correlated highly and one could potentially be redundant and should be considered for omission.

More detailed information regarding relationships between BAT items and underlying dimensions was obtained using a statistical technique known as factor analysis. Factor analysis is used primarily to explore the underlying dimensionality of a newly developed measurement instrument (exploratory factor analysis) or to test prior hypotheses regarding dimensionality (confirmatory factor analysis). There are different types of exploratory factor analysis but solutions generated are often similar and the most commonly used, and least complex, in health research is principal component analysis (PCA). PCA uses the above correlation matrix to establish how strongly an individual item correlates with each underlying BTCP dimension, and thus how many different BTCP dimensions account for all the BAT items. For the purposes of PCA each BTCP dimension is referred to as a 'factor'.

Strictly speaking there are the same number of underlying factors as there are items, as all items measure a slightly different aspect of BTCP experience. Subjects completing the BAT will have rated items, and sets of items, differently, meaning there will be a spread of data, also known as variability. PCA calculates factors based on what underlying correlation of items accounts for the maximum amount of variability, or variance, among scores across subjects. The first factor calculated accounts for the maximum amount of variance among scores across subjects, and the second factor is calculated to account for the maximum amount of variance that remains and so on. The first few factors account for the majority of variance within the scores and thus represent the predominant BTCP dimensions represented by the data. The numerical measure of substantive importance of each factor is an eigenvalue i.e. the larger the eigenvalue the higher the substantive importance of that factor.

The SPSS software generated a list of factors found within the correlation matrix, with corresponding eigenvalues and percentage of variance among scores accounted for by each factor. To determine which factors were important and accounted for the underlying dimensionality of the BAT the following criteria were used:

1. Retain the factors with an eigenvalue of one or greater (Kaisers criteria)[216]. This is most commonly used.

2. The cut-off point on a scree plot (graph plotting each factor against its associated eigenvalue) for the optimal number of factors to be retained is at the point of inflexion of the curve (point where slope of line changes dramatically)(Cattell's criteria) [12]. This is used if there is a factor or factors with eigenvalues of close to 1.

Once a factor structure was found, it was important to decide which BAT items predominantly contribute to each factor. SPSS generated a factor loading matrix where there was 1 row for each BAT item and 1 column for each retained factor. There was a value for each BAT item called a factor loading value. The factor loadings of each item are a gauge of substantive importance to a given factor and are thus used to place items into factors. A factor loading is calculated from the eigenvalues and gives a value between zero and one, the higher the value of the factor loading, the greater the importance of the item to that factor. In other words the factor loading can be thought of in terms of the degree of correlation between a factor and an item. A factor loading value of greater than 0.3 was considered to be important for each item.

Often, once factors have been extracted there is a tendency for items to have high loadings on the most important factor and smaller loadings on other factors. A technique called factor rotation was used to discriminate more effectively between factors. Rotation of the factor structure can clarify which items load preferentially onto which factor. There are two main types of rotation, oblique and orthogonal, oblique rotation is used when underlying factors correlate with each other and orthogonal when factors are independent. Hypothetically the factors of the BAT should correlate therefore an oblique rotation was applied to the data.

Missing data can be accounted for in three different ways during a PCA. The subjects with missing data can be excluded from the analysis (preferable and most precise method), the data can be replaced with the mean value (preferable if large amounts of missing data or small sample size) or the individual calculations requiring the missing data can be omitted. For the purposes of this analysis the subjects with missing data were excluded from the analysis.

6.1.7.2 Reliability

Reliability is a calculation of measurement error and estimates whether the measure consistently reflects the construct that it is measuring. Reliability was assessed in two ways in this study, using internal consistency and test-retest methods.

Internal consistency is a statistical technique based on the idea that individual items, or sets of items, that measure the same underlying concept, should produce results that correlate with the rest of the questionnaire. Practically this means that if all the BAT items are measuring BTCP then a patient with high levels of BTCP should have a high overall BAT score, and if the BAT is reliable then any randomly selected items should also be high.

The simplest way of calculating this is by randomly splitting the data in two, and if the scale is reliable the scores for each half should be the same (or similar) [217]. The reliability statistic calculated is the correlation between the 2 halves of data; high correlation values are a sign of reliability. The problem with this method is that there are several ways that data can be split which could influence the results. To overcome this problem the data can be split in two in every possible way, calculating the correlation value for each split and averaging these values [217-8]. This method was originally developed by Cronbach in 1951 [93] and is the most commonly used measurement of reliability in health research. The correlation coefficient value produced is referred to as Cronbach's alpha. Cronbach's alpha is a value between zero and one with a higher score indicating a greater degree of reliability. A value of greater than 0.7 is the most often quoted acceptable value to indicate a reliable scale [218], however, this value depends on the number of items in the scale i.e. as the number of scale items increases the value of alpha increases, therefore if a scale has less than five items a value of greater than 0.5 implies acceptable reliability [219]. It is recommended that Cronbach's alpha should be calculated separately for individual factors or subscales within a scale as results may be affected by correlations between individual items.

Test-retest reliability assessed the correlation between test scores completed by the same person on two different occasions. Theoretically, if the underlying construct remains stable the participant should get the same score on the instrument and any

difference in score would be due to measurement error. It is important that tests are completed far enough apart so that the participant doesn't remember previous answers but not over a long enough period that the underlying construct may change. For the purpose of this study a period of 24 hours was used between tests. Test-retest reliability was assessed using the intraclass correlation coefficient, this was calculated by the ratio of variance between patients to error variance. As with all previously discussed correlation coefficients, the value was between zero and one, and a value of >0.8 indicated the scales reliability for summary scores.

For the purpose of the above reliability analysis any reverse-phrased items must be reversed. In the case of the BAT the question asking about effectiveness of BTCP medication was reverse scored i.e. highest score indicated maximum effectiveness whilst higher scores indicated worse BTCP outcomes for all other items, and was thus reverse scored for all calculations.

6.1.7.3 Construct validity

Construct validity refers to the ability of a newly developed scale to measure the concept it was designed to by conforming to a number of prior hypotheses concerning logical relationships that should exist with other clinical measures and characteristics of distinct patient groups. This is assessed using a series of psychometric tests comparing the BAT with other clinical data collected.

6.1.7.3.1 Known groups analysis

The initial method used to demonstrate construct validity of the BAT was to assess if clinical groups that hypothetically had differences in BTCP severity were able to be significantly differentiated by the BAT items. The mean scores for individual questions, and total BAT scale, were compared between these different clinical groups using the independent t-test, and significance level defined as <0.05.

The first clinical groups compared were defined according to the patient and clinicians global assessment of adequacy of BTCP control. For each assessment the patient and clinician independently rated BTCP as 'adequately' or 'inadequately'

controlled. It was hypothesised that the BAT scores should be higher in the groups deemed as having 'inadequately controlled BTCP' by patient or clinician.

The second clinical group comparisons were related to changes made to pain management at clinical consultation. This could relate to changes made to pain medication or procedures initiated to assist with pain control (nerve block). At each assessment any management changes initiated by the clinician was recorded, and the patient was also asked if they thought changes should be made (yes/no/not sure). It was hypothesised that BAT scores would be higher in the clinical groups requiring alterations to their pain management.

The other group comparisons made used biomedical criteria related to cancer and performance status to differentiate clinical groups. It was hypothesised that the total BAT scores would be higher in patients with metastatic disease versus local disease, and in patients who have stopped, or not started anti-cancer treatment compared to those having treatment. Worse performance status i.e. patients with lower levels of physical function were also hypothesised to have higher BAT scores.

6.1.7.3.2 Convergent validity

Convergent validity provides evidence that the scale is correlated with other measures of the same or similar constructs. The criteria for acceptability rely on the degree of conceptual similarity between the BAT and other validation measures. To establish convergent validity the BAT was compared with clinical outcome measures and patient-based outcome measures.

The clinical outcome measures used as external comparators were background and breakthrough pain medication doses. It was hypothesised that BTCP would be more highly correlated with breakthrough pain medication than background pain medication. As such, a moderate correlation would exist between the BAT scores and breakthrough medication frequency of administration, and this relationship would be stronger than between the BAT and background analgesia dose. Background pain medication was converted to standard morphine equivalent 24-hour dose.

The patient-based outcome measures used comparators were individual item scores and summary scores of the Brief Pain Inventory. The BPI was described in detail previously and is included in 0. The BPI was designed to measure generic cancer pain and therefore theoretically the BAT and BPI measure related aspects of pain experienced. Certain BPI questions are more relevant to BTCP experience than others and should therefore hypothetically correlate more strongly. It was postulated that moderate correlations would exist between the BAT scores and BPI average pain intensity score (one item), and BPI total pain severity score (sum of four pain intensity items, average, worst, least, and 'right now'). Theoretically higher correlations should be seen between the BAT and BPI worst pain intensity item and BPI interference items as these are more easily extrapolated in terms of BTCP experience. Worst pain intensity on the BPI and the worst BTCP intensity item on the BAT should have high degrees of correlation.

The BAT was compared with these clinical and patient-based parameters using bivariate correlations to assess whether there was a relationship between values i.e. as medication usage increased, did BAT scores also increase in the same proportion. This analysis resulted in a correlation coefficient for each comparison. The value of the coefficient lies between -1 and +1; a value of +1 indicates that the two variables are perfectly positively correlated, as one variable increases, the other does by a proportional amount. The correlation coefficient is a standardised measure of an observed effect and values of +/-0.1 represent a small effect or amount of correlation, values +/- 0.3 a medium correlation and +/- 0.5 a large correlation.

6.1.7.3.3 Discriminant validity

Discriminant validity provides evidence that the scale is not correlated to measures of unrelated constructs. The BAT should theoretically have low correlation with a patient's age or gender and, correlation coefficients were thus calculated between BAT scores and these parameters.

6.1.7.4 Responsiveness

Responsiveness refers to the ability of a scale to detect change and was assessed by a number of methods. Firstly, an effect size was calculated which is an objective and

standardised measure of an effect over time. The most common measure of effect size is Cohen's and is defined as the difference between the two means at different time points, expressed in standard deviation units (mean difference/SD at baseline). In the context of comparing group averages, a small effect size is 0.2; a medium effect size is 0.5, and a large effect size is 0.8. It was hypothesised that BAT scores would improve overtime with known efficacious treatment, in this case regular assessment and input by specialised pain service, and would have a minimum of a medium effect size.

The minimally important difference (MID) was defined as 'the smallest difference in score in the domain of interest which patient's perceive as beneficial and which would mandate a change in the patient's management.'. The MID was calculated using a range of anchor-based methods.

In this study we defined a clinically significant difference i.e. beneficial effect, using the patient's global assessment of their BTCP over time. If a patient indicated their BTCP was 'better' this was considered a beneficial effect. The mean difference in BAT values were calculated between initial consultation and subsequent follow up for all patients and minimal important difference was the numerical difference in BAT score for the patients defined as 'better' minus those who describe their BTCP as the 'same'.

These calculations were repeated using different parameters to define clinically significant difference: expert global assessment of BTCP at follow up; and patients requiring analgesia adjustments at initial follow up (defined as not improved).

6.1.7.5 Burden and acceptability

The acceptability of a newly designed scale to the users is of paramount importance, and when developing scales for use in advanced cancer patients the burden must also be considered. Evaluating the amount of missing data assessed this.

Missing data was coded according to three categories: reason not known, patient unable to answer question or question not applicable to the patient. As the latter does not represent a patient's ability to complete the questions appropriately,

missing data were defined by the first two categories. Acceptability of the instrument was defined as missing data <5% for each item.

6.2 Results

6.2.1 Recruitment and follow up

One hundred patients were recruited to complete the BAT. To recruit 100 patients, 161 were approached, 38 were ineligible (did not have BTCP) and 23 declined to enter. The reasons for not entering the study were: no reason given 14; too unwell/fatigued 6; not wanting to participate in research 3.

Sixty-two per cent of patients completed the final study assessment; the number of participants at each site that completed the follow up stages of the study is reported in Table 20.

Table 20: Study completion at each stage by recruitment site

	BTCP tool initial assessment	BTCP tool 1 week clinical follow up	BTCP tool 2 week clinical follow up
Royal Marsden Hospital	45	37 (82%)	28 (62%)
St Clare's Hospice	20	14 (70%)	7 (35%)
Royal Surrey County Hospital (RSCH)	35	30 (86%)	27 (77%)
Total	100	81	62

The predominant reason for participants not completing assessments 3 and 4 were due to clinical condition (Table 21).

Table 21: Reasons for non-completion of study by recruitment site

	1 week follow up			2 week follow up		
	RMH[1]	STC[2]	RSCH[3]	RMH	STC	RSCH
Died	1	2	2	6	3	3
Unwell	4	1	2	5	5	2
Lost to follow up	1	3	1	4	5	3
Withdrew	2			2		
Total	8	6	5	17	13	8

[1]Royal Marsden Hospital, [2]St Clare's Hospice, [3]Royal Surrey County Hospital

6.2.2 Demographic data

Table 22 shows the demographic details of patients who entered the study.

Table 22: Demographic data at initial consultation

Age	61 (range 27-89)
Male	54 (54%)[1]
Female	46
Diagnosis	
Gastrointestinal cancer	27
Genito-urinary	22
Lung	16
Breast	14
Haematological	7
Head and neck	5
Gynaecological	4
Other	5
ECOG	
0	3
1	27
2	34
3	23
4	13
Recruitment site	
Royal Marsden	45
St Clare's Hospice	20
Royal Surrey County Hospital	35
Inpatients	45
Outpatients	55
Anti-cancer treatment	
Chemotherapy	31
Radiotherapy	11
Hormonal therapy	4
Trial drug	11
Pre-treatment	3
No planned or further treatment	40
Cancer status	
Local disease	15
Metastatic disease	85
Site of metastases	
Bone	31
Visceral	36
Both	18

[1]100 patients recruited so percentage is same as number of patients for all values

6.2.3 Characteristics of breakthrough pain

Descriptive data about the BTCP experienced by patients at first consultation is reported in Table 23. The majority of patients (86%) experienced BTCP solely related to their cancer and a small number had pain from more than one different cause (5%).

Volitional incidental BTCP (precipitated by voluntary act e.g. walking), and spontaneous BTCP (pain occurring unexpectedly), or a combination of the two, were much more common than non-volitional incident pain (precipitated by an involuntary act e.g. coughing).

The majority of patients were prescribed an oral opioid as background (65%) or breakthrough medication (80%) at first consultation; 13% were prescribed a buccal or sublingual fentanyl preparation and in half these cases this was in addition to an oral opioid. Thirteen patients were prescribed more than one medication for their BTCP episodes (7 oral or intravenous opioid and non-opioid, 6 oral opioid and buccal/sublingual fentanyl product). Ninety-nine percent of patients had been prescribed a medication for their BTCP episodes.

Table 23: BTP descriptive data at first consultation

Aetiology of BTP	No of patients
Cancer-related	86 (86%)[1]
Cancer treatment-related	8
Concomitant problem	1
Cancer and cancer treatment related	2
Cancer-related and concomitant problem	3
Pathophysiology of BTP	
Nociceptive	72
Neuropathic	2
Mixed	26
Subtype of BTP	
Volitional incident pain	39
Spontaneous	32
Spontaneous and volitional	20
Non-volitional incident pain	7
Volitional and non-volitional incident	2
Background pain medication	
Morphine	41
Oxycodone	24
Fentanyl patch	23
Codeine preparation	6
Tramadol	1
Buprenorphine patch	2
Pregabalin	2
Nortryptiline	1
Breakthrough pain medication	
Morphine	43
Oxycodone	25
Buccal or sublingual fentanyl	7
Non-opioid	7
Codeine	4
Intra-venous opioid and non-opioid	1
No medication	1
Oral opioid and fentanyl product	6
Oral opioid and non-opioid	6
Frequency of taking breakthrough medication (in previous week)	
0	15
Less than once per day	19
1-2 times per day	39
3-4 times per day	21
More than 4 times per day	6

[1]100 patients recruited so percentage is same as number of patients for all values

6.2.4 Item analysis and reduction

A matrix of correlation coefficients for each BAT item compared with each other BAT item is presented in Table 24. A correlation coefficient value of >.3 indicates a medium correlation, and >.5 a large correlation. The matrix shows that there is a range of correlation values across items with certain items forming separate clusters of medium to large correlations indicating there are multiple underlying dimensions.

Interestingly, BTCP intensity (typical and worst) and BTCP distress correlated strongly with BTCP impact on living a normal life suggesting they are contributing to one underlying BTCP dimension. There were medium correlations between BTCP duration, effectiveness of BTCP painkillers and time to meaningful pain relief demonstrating that these items may contribute towards a different dimension.

There was no correlation of >0.75 between items (indicating item redundancy) and all items had at least a medium correlation with a minimum of one other item. This indicated that BAT items were all measuring distinct aspects of the same underlying construct and no item reduction was necessary

Table 24: Item correlation matrix between breakthrough pain assessment tool items

	How often do you get BTCP?	How long does a typical episode last?	How severe is your worst episode?	How severe is a typical episode?	How much does the BTCP distress you	How much does BTCP stop you from living a normal life	How effective is the BTCP painkiller	Time until meaningful effect of BTCP painkiller	How much do side effects from painkillers bother you?
How often do you get breakthrough pain (BTCP)?	1	-.216	***.302***	***.391***	.146	.237	.086	-.080	.203
How long does a typical BTCP episode last?	-.216	1	0.072	.062	.095	.125	-237	***.428***	-.003
How severe is your worst episode of BTCP?	***.302***	.072	1	***.623***	***.461***	***.579***	-.161	.123	-.191
How severe is a typical episode of BTCP?	***.391***	.062	***.623***	1	***.404***	***.614***	-054	.064	.239
How much does the BTCP distress you?	.146	.095	***.461***	***.404***	1	***.615***	.054	.228	***.334***
How much does the BTCP stop you from living a normal life?	.237	.125	***.579***	***.537***	***.615***	1	.166	.124	.254
How effective is the painkiller that you usually take for your BTCP?	.086	.237	.161	.108	.054	.166	1	***.293***	.026
How long does the painkiller for your BTCP take to have a meaningful effect?	-.08	***.428***	.123	.064	.228	.124	***.293***	1	.085
How much do the side effects from your BTCP painkillers bother you?	.203	-.003	.191	.239	***.334***	.254	.026	.085	1

[2]correlation coefficient values of >.1 represent a small correlation, ***>.3 medium***, **>.5 high**

The item correlation matrix identified clusters of item correlations indicating multiple underlying BTCP dimensions. A principal component factor analysis (PCA) with oblique rotation (Oblimin) was performed on these nine BAT items to further explore the underlying dimensions and establish which items contributed to each underlying dimension or factor.

An initial PCA was run to obtain eigenvalues for each factor in the data, the larger the eigenvalue the higher the importance of each factor i.e. the factor accounts for greatest amount of score variance. Two factors had an eigenvalue of >1 (Kaiser's criterion to retain factors), the values were 3.026 and 1.658, and these accounted for 52% of variance in the data (Table 25). It was clear that these 2 factors were important and accounted for the majority of the item scores given by patients. The third factor fell slightly below this criterion and had a value of 0.997 therefore further tests were run to establish if this factor should be retained.

Table 25: Factor extraction by principal component analysis of breakthrough pain assessment tool

Factor	Eigenvalues[1]	% of variance[2]	Cumulative variance %
1	3.026	33.618	33.618
2	1.658	18.426	52.044
3	.997	11.073	63.117
4	.891	9.902	73.019
5	.658	7.310	80.330
6	.606	6.732	87.061
7	.486	5.400	92.462
8	.354	3.937	96.399
9	.324	3.601	100.000

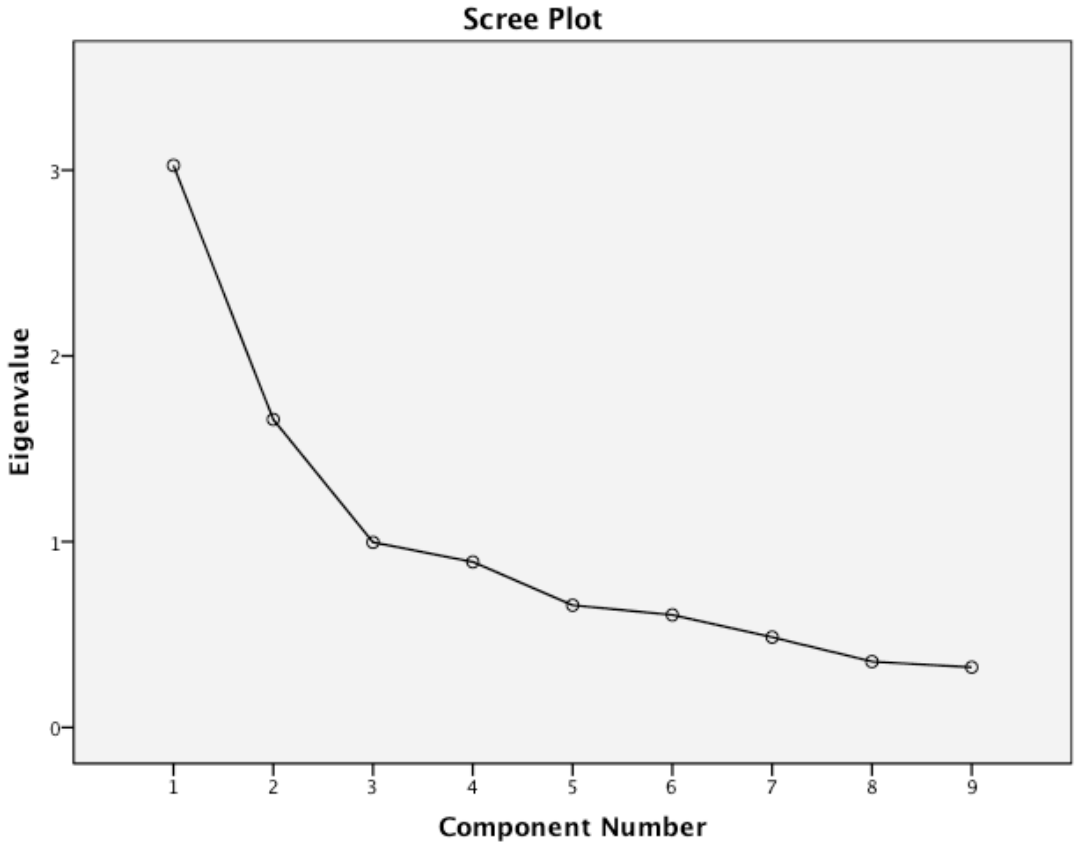
[1]Eigenvalue is a numerical value that denotes the importance of each factor,[2]percentage of variance in BAT scores accounted for by each corresponding factor

A scree plot was drafted which showed a point of inflexion that would justify retaining 2 factors (Figure 12) however, there was also an inflexion point after 3 factors. From these two criteria it would be reasonable to retain either two or three factors depending on which made the most clinical sense in the use and interpretation of BAT items.

For this PCA the sampling adequacy was calculated as good (Kaiser-Meyer-Olkin=0.745) and the correlations between items were sufficiently large to have

acceptable results (Barlett's test of sphericity had a significance value of less than 0.001).

Figure 12: Scree plot of eigenvalues



The initial PCA revealed a preferential two factor solution (2 underlying pain dimensions) to account for all BAT items, however the methods used could also support a three factor solution depending on further analysis of individual items. Factor loadings were thus calculated for each BAT item to determine how strongly they correlated, or loaded, onto each factor.

Table 26 displays the rotated factor loadings for each item in the BAT onto the two factors with eigenvalue >1.

Table 26: Factor loading with oblique rotation for the breakthrough pain assessment tool

	Factor	
	1	2
How often do you get the breakthrough pain?	***.568***	
How long does a typical episode last?		***.801***
How severe is the worst breakthrough pain?	***.787***	
How severe is a typical breakthrough pain?	***.800***	
How much does the breakthrough pain distress you?	***.695***	
How much does the breakthrough pain stop you from living a normal life?	***.787***	
How effective is the painkiller for your breakthrough pain?		***.531***
How long does the breakthrough painkiller take to have a meaningful effect?		***.779***
How much do the side effects from your breakthrough painkiller bother you?	***.468***	

All items loaded onto one of these two factors with a value of >.3 (criteria stated for minimum importance of item). The two BTCP intensity items (worst and typical), two interference items (BTCP distress and impact on normal life), BTCP frequency and breakthrough painkiller side effects questions loaded onto the first factor. The second factor consisted of items that evaluated the effectiveness of breakthrough painkiller, time to meaningful effect of breakthrough painkiller and BTCP duration. The two factor solution thus accounted for each item in the BAT in a clinically representative manner and as such was kept as the preferential solution for the data.

Theoretically this created two subscales within the BAT: a BTCP severity and impact subscale (six questions), and a BTCP duration and medication efficacy subscale (three questions).

Interestingly, the BTCP severity and impact subscale (severity subscale) also included the item about breakthrough painkiller side effects, and the BTCP duration and medication efficacy subscale (treatment subscale) included the BTCP duration item.

Using the scoring system developed for the BAT, the severity subscale has a maximum score of 58, and the treatment subscale has a maximum score of 30 (maximum total BAT score=88).

6.2.5 Reliability

The reliability of the BAT was assessed by calculation of the internal consistency and test-retest coefficients. Internal consistency was determined by calculating Cronbach's alpha coefficient. The value of Cronbach's alpha for the total BAT score was 0.70 (>0.7 recommended standard for scales of more than 5 items), indicating the BAT is a reliable scale. The BAT consisted of two subscales and the Cronbach's alpha coefficient value for the BAT severity subscale (six items) was 0.75, and for BAT treatment subscale was 0.552 (>0.5 recommended standard for scales of 3-5 items) indicating these subscales were also reliable according to this method.

Test-retest reliability was calculated using the intraclass correlation reliability coefficient equation. Table 27 displays the test-retest reliability coefficients for the total BAT score, BAT subscales and individual items. The test-retest coefficient for the total BAT score was 0.89 (recommended standard >0.8) indicating an acceptable degree of measurement error. The BAT subscale scores also had acceptable levels of reliability when assessed by this method (severity subscale 0.80, efficacy subscale 0.92). Test-retest analysis of individual BAT questions showed varied values of reliability coefficient. Interestingly, the items assessing BTCP typical intensity and BTCP distress had the lowest values i.e. these item scores varied the most in individual patients whilst the underlying concept remained stable.

Table 27: Test-retest coefficients of the breakthrough pain assessment tool

	Intraclass correlation coefficient
BAT total score	0.88
Severity subscale	0.80
Efficacy subscale	0.92
How often do you get breakthrough pain?	0.68
How long does a typical breakthrough episode last?	0.78
How severe is your worst breakthrough pain?	0.69
How severe is a typical breakthrough pain?	0.54
How much does the breakthrough pain distress you?	0.55
How much does the breakthrough pain stop you from living a normal life?	0.71
How effective is the painkiller for your breakthrough pain	0.76
How long does it take the painkiller for your breakthrough pain to have a meaningful effect?	0.79
How much do side effects from breakthrough painkillers bother you?	0.70

All values have significance <0.001, recommended standard for acceptability >0.8

6.2.6 Construct validity

6.2.6.1 Known groups analysis

Comparisons in mean BAT scores were made between different clinical groups that hypothetically had significantly different scores in the domain of interest. The first clinical groups were determined according to the patient and clinician's global impression of adequacy of BTCP control. Comparisons were made between BAT scores for patients who globally rated their BTCP as 'adequately controlled' versus 'inadequately controlled' and the same calculations were made according to the clinician's impression. Table 28 presents the BAT scores for these clinical groups.

The BAT total score, severity subscale score and treatment subscale scores were all significantly higher, indicating worse BTCP, in the expected clinical groups (patient and clinician 'inadequately controlled BTCP'). Interestingly, there were much greater overall differences in scores between the clinical groups determined by patient opinion than clinician opinion. This is seen further when evaluating differences in scores between individual items, with the majority of individual BAT items having significantly higher scores in the patient 'inadequately controlled' BTCP group, whereas only three individual BAT items had such scores in the clinician 'inadequately controlled group' (BTCP painkiller effectiveness and time to meaningful effect, and impact on living a normal life). Interestingly, 34% of patients considered their BTCP 'inadequately controlled', in contrast to the 72% of patients that the clinical experts defined as having 'inadequately controlled BTCP'.

The second set of clinical groups analysed were determined according to BTCP management changes. BAT scores were compared between patients who indicated they needed changes to their BTCP management versus those that didn't. Comparisons were also made between patients who had BTCP management changed by the clinician and those who didn't. Table 29 presents the mean scores between these clinical groups determined by changes to pain management.

The total BAT score, severity subscale and treatment subscale had higher scores in the expected patient and clinical groups (changes needed to painkiller). All these scores reached statistical significance except for the treatment subscale in the clinically determined group. Interestingly, 57% of patients stated their BTCP management needed changing, compared to 71% who actually had such changes, and all BAT scores correlated more strongly with the patient opinion group than with the changes actually made by the clinician. The only BAT items that significantly correlated with the clinical changes were effectiveness of BTCP medication, and impact of BTCP on normal life.

There was no significant difference in total or subscale BAT scores between patients having anti-cancer therapy (radiotherapy, chemotherapy, hormonal therapy) and those who were not (no planned treatment, treatment stopped). Total or subscale BAT scores were not significantly higher in patients with metastatic disease

compared to those with local disease. There was also no difference in BAT scores according to ECOG performance status.

Table 28: Comparisons of breakthrough pain assessment tool scores determined by impression of BTCP control

	Patient's global impression of BTCP			**Clinician's global impression of BTCP**		
	Adequately controlled N=65	**Inadequately controlled n=34**	***P value***	**Adequately controlled n=28**	**Inadequately controlled n=72**	***P value***
Total BAT score	43.15	54.62	***0.000***	41.54	49.25	***0.005***
BAT severity subscale	30.03	39.26	***0.000***	29.5	34.68	***0.019***
BAT treatment subscale	13.12	15.82	***0.023***	12.04	14.77	***0.027***
How often do you get breakthrough pain?	5.07	6.18	***0.009***	5.43	5.47	*0.922*
How long does a typical episode of breakthrough pain last?	6.03	6.79	*0.182*	6.07	6.34	*0.654*
How severe is your worst breakthrough pain?	7.06	8.26	***0.003***	7.04	7.68	*0.135*
How severe is a typical breakthrough pain?	5.51	6.39	***0.019***	5.62	5.86	*0.544*
How much does the breakthrough pain distress you?	5.14	7.41	***0.000***	5.18	6.21	*0.095*
How much does the breakthrough pain stop you from living a normal life?	5.47	7.36	***0.002***	4.89	6.66	***0.005***
How effective is the painkiller for your breakthrough pain (reversed)?	2.68	3.87	***0.022***	1.89	3.54	***0.002***
How long does the painkiller take to have a meaningful effect?	4.90	6.02	***0.013***	4.52	5.58	***0.028***
How much do the side effects from your breakthrough painkiller bother you?	2.10	4.40	***0.002***	1.81	3.21	*0.076*

Table 29: Comparisons of breakthrough pain assessment tool scores between groups determined by changes to BTCP management

	Patient's opinion regarding BTCP management			**Clinical decision made to BTCP management**		
	'I don't need changes to painkillers' n=41	**'I need changes to painkiller' n=55**	***P value***	**No changes to painkillers n=29**	**Changes to painkillers N=71**	***P value***
Total BAT score	42.67	53	***0.000***	42.83	48.83	***0.029***
BAT severity subscale	29.98	37.73	***0.000***	30.10	34.51	***0.045***
BAT treatment subscale	4.74	6.19	**0.010**	12.72	14.52	*0.143*
How often do you get breakthrough pain?	5.13	5.90	***0.06***	5.31	5.52	*0.633*
How long does a typical episode of breakthrough pain last?	5.93	6.77	*0.13*	6.21	6.29	*0.899*
How severe is your worst breakthrough pain?	7.18	7.93	***0.06***	7.21	7.61	*0.336*
How severe is a typical breakthrough pain?	5.74	6.00	*0.473*	5.62	5.85	*0.566*
How much does the breakthrough pain distress you?	5.04	7.12	***0.000***	5.31	6.17	*0.161*
How much does the breakthrough pain stop you from living a normal life?	5.07	7.50	***0.000***	5.00	6.64	***0.009***
How effective is the painkiller for your breakthrough pain (reversed)?	2.54	3.68	***0.022***	2.17	3.44	***0.016***
How long does the painkiller take to have a meaningful effect?	4.73	6.00	***0.005***	4.79	5.48	*0.151*
How much do the side effects from your breakthrough painkiller bother you?	3.31	3.60	***0.045***	2.11	3.11	*0.201*

6.2.6.2 Convergent validity between the BAT and clinical outcome measures

Comparisons were made between the BAT and background and breakthrough pain medication. There was a much stronger correlation between the BAT and breakthrough medication parameters than between the BAT and background medication dosage.

The correlation between the frequency of breakthrough medication administration and the BAT total and subscale scores was moderate in size (total score 0.495, severity subscale 0.414. treatment subscale 0.349) (Table 30). Interestingly, BTCP frequency and intensity (worst and typical) were more highly correlated with breakthrough medication administration than other items i.e. patients with more intense and frequent BTCP took breakthrough medication more often.

Table 30: Convergent validity between BAT and frequency of administration of breakthrough analgesia

	Correlation with frequency of taking breakthrough painkillers [1,2]	**Correlation with background medication dosage**
Total BAT score	**.495**	.184
BAT severity subscale	**.414**	.163
BAT treatment subscale	**.349**	.109
How often do you get breakthrough pain?	**.387**	-.024
How long does a typical episode of breakthrough pain last?	.210	.095
How severe is your worst breakthrough pain?	**.321**	.136
How severe is a typical breakthrough pain?	**.384**	.045
How much does the breakthrough pain distress you?	.146	.093
How much does the breakthrough pain stop you from living a normal life?	.282	.219
How effective is the painkiller for your breakthrough pain (reversed)?	.223	.124
How long does the painkiller take to have a meaningful effect?	.182	.017
How much do the side effects from your breakthrough painkiller bother you?	.213	.137

[1]All correlation coefficients have P values <0.05

[2]correlation coefficient values of >.1 represent a small correlation, **>.3 medium, >.5 large**

6.2.6.3 Convergent validity between the BAT and patient-related outcome measures

Table 31 presents the correlation coefficients between the BAT and Brief Pain Inventory (BPI). The total BAT score had a high correlation with BPI total interference subscale (0.565) and a moderate correlation with BPI pain intensity subscale (0.398). The BAT severity subscale correlated highly with BPI worst and average pain intensity items as well as with the BPI interference subscale. The BAT treatment subscale did not correlate well with any BPI measurements.

The BAT worst BTCP intensity item and BPI worst pain intensity item had a very strong correlation, and BTCP worst intensity also correlated moderately with BPI average pain intensity. Interestingly, frequency of BTCP correlated with BPI 'worst' and 'average' pain intensity, as well as 'sleep' and 'general activity' interference

items, whereas duration of BTCP only correlated with the BPI mood interference item.

Impact of BTCP on normal life correlated highly with BPI 'general activity', 'walking' and 'work' items, whereas distress from BTCP correlated moderately with 'enjoyment of life', 'working', 'walking' and 'mood' BPI items. Interestingly, the BPI sleep interference item did not correlate with either BTCP 'distress' or 'impact on normal life' questions but did have an association with BTCP intensity.

The effectiveness of BTCP painkiller item correlated with BPI walking interference item and BPI pain relief item. However, the BAT items measuring time to meaningful pain relief and side effects of painkillers did not correlate with any BPI items.

Table 31: Convergent validity between BAT and brief pain inventory (BPI) pain intensity scores[1,2]

	Brief Pain Inventory pain intensity items						**Brief Pain Inventory interference items**							
BAT items	**Worst pain**	**Least pain**	**Average pain**	**Pain now**	**Total pain severity score**	**% of Pain relief**	**General activity**	**Mood**	**Walking**	**Work**	**Relations with others**	**Sleep**	**Enjoyment of life**	**Total**
Total BAT score	***.485***	.129	***.496***	.271	***.398***	-.165	***.456***	***.473***	***.35***	***.399***	***.377***	.208	***.485***	**.565**
BAT severity subscale	**.560**	.089	**.537**	.278	***.435***	-.077	***.456***	***.481***	***.348***	***.451***	***.466***	***.311***	**.54**	**.632**
BAT treatment subscale	-.008	.134	.092	.105	.071	-.224	.214	.240	.120	.031	.001	-.154	.114	.113
How often do you get breakthrough pain?	**.344**	.201	**.354**	.216	.295	-.196	***.309***	-.008	.012	.165	.216	***.316***	.262	.239
How long does a typical episode of breakthrough pain last?	-.052	.066	.088	.142	.089	-.141	.136	***.374***	.119	.068	.189	-.199	.105	.167
How severe is your worst breakthrough pain?	**.891**	.111	***.399***	.157	***.476***	-.065	***.346***	.266	.233	.210	.127	***.396***	***.448***	***.427***
How severe is a typical breakthrough pain?	**.545**	.213	***.473***	***.431***	**.559**	-.017	***.405***	***.342***	.216	.283	***.478***	***.365***	***.362***	**.522**
How much does the breakthrough pain distress you?	***.402***	-.185	***.320***	.011	.151	.104	.126	**.3**	***.355***	***.342***	.253	.175	***.362***	***.396***
How much does the BTCP stop you from living a normal life?	***.366***	-.029	.252	.019	.195	-.110	**.672**	**.5**	**.615**	**.571**	***.336***	-.01	***.48***	**.636**
How effective is the painkiller for your breakthrough pain?	.028	.172	-.027	.010	-.009	***.483***	.211	-.019	***.304***	-.073	-.124	-.049	.079	.051
How long does the painkiller for your breakthrough pain take to have a meaningful effect?	-.151	.051	-.016	-.037	-.073.	.156	.103	.031	-.167	.003	-.124	-.08	-.021	-.075
How much do side effects from your BTCP painkiller bother you?	-.058	.087	.292	.234	.117	-.024	.012	.245	-.04	.155	.263	.128	.154	.151

[1]All correlation coefficients have P values <0.05

[2]correlation coefficient values of >.1 represent a small correlation, ***>.3 medium***, **>.5 high**

6.2.6.4 Discriminant validity

There was no statistically significant difference in BAT scores (individual items, subscale or total score) between male and female patients. Patients' age had a poor correlation with all BAT scores (Table 32).

Table 32: Discriminant validity between BAT scores and age

BAT question or subscale	Correlation with age[2]
Total BAT score	-.084
BAT severity subscale	-.006
BAT treatment subscale	-.185[1]
How often do you get breakthrough pain?	.203[1]
How long does a typical episode of breakthrough pain last?	-.25[1]
How severe is your worst breakthrough pain?	-.105
How severe is a typical breakthrough pain?	.064
How much does the breakthrough pain distress you?	-.042
How much does the breakthrough pain stop you from living a normal life?	-.021
How effective is the painkiller for your breakthrough pain (reversed)?	-.016
How long does the painkiller for your breakthrough pain take to have a meaningful effect?	-.132
How much do the side effects from your breakthrough painkiller bother you?	-.062

[1]All correlation coefficients have P values <0.05
[2]correlation coefficient values of >.1 represent a small correlation, >.3 medium, >.5 high

6.2.7 Responsiveness

The initial calculation of responsiveness was the Cohen's effect size. This was calculated by the difference in mean BAT scores divided by the standard deviation. The total mean BAT score at first assessment was 47.09 (standard deviation 12.52), and mean total BAT score at first clinical follow up was 36.59. The difference in scores was 10.86 thus the effect size for the total BAT score was 0.87 (10.86/12.52). This was a large effect size as defined by standard criteria (>0.8).

The minimal important difference (MID) was calculated using different anchor-based methods. The first method compared changes in mean BAT scores with the patient impression of change of BTCP (Table 33). The patients who categorised their BTCP as 'better' had an improvement in total BAT score of 16.98; compared with an improved BAT score of 4.5 in those whose BTCP remained the same. The difference in scores (MID) according to patient-reported opinion was 12.48.

Table 33: Difference in BAT scores over time categorised by patient impression of change

Patient impression of change of BTCP at initial follow up	N	Mean difference in total BAT score between first assessment and initial follow up	P
Better	49	16.98 (18.35)	<0.0001
Same	20	4.5 SD (10.6)	<0.0001
Worse	10	-6.9 (18.5)	<0.0001

The same calculations were performed to determine the MID according to the clinician's impression of change (Table 34). The MID using this criterion was very similar to the above value 12.88.

Table 34: Differences in BAT scores over time categorised by clinician impression of change

Clinician opinion of BTP at follow up	N	Mean difference in total BAT score between first assessment and initial follow up	P
Better	45	17.87	<0.0001
Same	26	4.96	<0.0001
Worse	9	-8.0	<0.0001

The MID for the BAT severity and treatment subscales, as well as each individual BAT item, using the above patient and clinician global change criteria are presented in Table 35. The MID for the severity subscale (maximum score=58) was 9, according to patient criteria, and 10.27, according to clinician, whereas the MID for the treatment subscale (maximum score=30) was 3.72 (patient criteria) and 2.92 (clinician criteria). The MID could not be calculated for certain individual items

(effectiveness, meaningful effect and side-effects) as the change in score was not statistically significant. Interestingly these items all evaluated BTCP treatments.

Table 35: Differences in BAT item and subscale scores over time categorised by patient and clinician impression of change

Difference in mean score between first assessment and initial follow up	**Patient**				**Expert**			
	Better N=49	**Same N=20**	**Worse N=10**	***Minimal important difference (MID)***	**Better N=45**	**Same N=26**	**Worse N=9**	***MID***
Total BAT score (max score =88)	16.98	4.5	-6.9	*12.48*	17.87	4.96	-8.0	*12.91*
Severity subscale (max=58)	12.2	3.2	-4.5	*9*	12.84	2.57	-4.0	*10.27*
Treatment subscale (max=30)	5.02	1.30	-2.4	*3.72*	5.30	2.38	-4.0	*2.92*
Frequency	1.33	0.4	-0.89	*0.93*	1.59	-0.24	-0.22	*1.83*
Duration	1.95	0.30	-1.2	*1.65*	1.90	0.88	-1.33	*1.02*
Worst BTP intensity	2.3	0.55	-1.3	*1.75*	2.44	0.19	-0.11	*2.25*
Typical BTP intensity	2.1	0.65	-0.6	*1.45*	2.04	0.27	0.67	*1.77*
Normal life	2.88	1.0	-2.22	*1.88*	3.00	0.92	-2.22	*2.08*
Distress	2.04	0.32	-1.33	*1.72*	2.24	0.42	-1.78	*1.82*
Effectiveness[1]	-0.87	0.5	0.67		-1.05	0.17	1.14	
Meaningful effect[1]	0.51	1.07	-0.67		0.59	1.04	-1.42	
Side-effects[1]	1.17	-0.67	-1.33		1.12	-0.27	-0.43	

[1]No statistically significant differences between mean scores in better, same, worse categories

Table 36 reports another anchor based method for determining MID and categorises mean BAT scores between patients who did and did not require changes in BTCP management at their initial follow up. All items had significant differences in mean scores between the 2 groups. Using this method the MID in BAT score was 20.78.

Table 36: Difference in BAT scores over time categorised by change in pain medications at consultation

Difference in mean score between first assessment and initial follow up	**Pain medications changed by clinician at follow up visit**		
	Yes=36	**No=44**	***Minimal important difference***
Total BAT score difference (max=88)	-0.67	20.11	*20.78*
Severity subscale (max=58)	-0.53	14.27	*14.77*
Treatment subscale (max=30)	-0.14	6.14	*6.28*
Worst BTP intensity	0.14	2.48	*2.34*
Typical BTP intensity	0.31	2.13	*1.82*
Effectiveness	-0.68	1.32	*2*
Normal life	0.14	3.07	*2.93*
Distress	-0.44	2.64	*3.08*
Duration	0.17	2.10	*1.93*
Frequency	-0.17	1.62	*1.79*
Meaningful effect[1]	0.13	0.94	*0.81*
Side-effects	-0.57	1.43	*2*

[1]No statistically significant differences between mean scores

6.2.8 Acceptability

Table 37 presents the missing data from the initial BAT completion. The missing data from questions about BTCP painkiller use were not applicable to certain patients who had not been taking such pain relief during the last week. Two patients were unable to answer questions regarding duration and typical BTCP severity due to episodes varying so widely. Two patients were also unable to evaluate the effect BTCP had on their 'normal life' responding that their cancer meant they were no longer living a normal life. However, the majority of patients were able to respond to the questions and only one was omitted with no reason attached.

The BAT met the aforementioned standard of having less than 5% of missing data per question (excluding missing data due to question not being applicable).

Table 37: Missing data from initial breakthrough pain assessment tool completion

	Missing data	Reasons for missing data		
		Question not applicable to patient	Reason not known	Patient unable to answer
How often do you get your breakthrough pain?	0			
How long does a typical episode of breakthrough pain last?	3		1	2
How severe is your worst breakthrough pain?	0			
How severe is a typical breakthrough pain?	2			2
How much does breakthrough pain distress you?	0			
How much does breakthrough pain stop you from living your normal life?	2			2
How effective is your breakthrough painkiller?	6	6		
How long does breakthrough painkiller take to have a meaningful effect?	7	7		
How much do breakthrough painkiller side effects bother you?	7	7		

Chapter 7. Discussion

7.1 Summary of aims

The original aim of this study was to develop a breakthrough cancer pain (BTCP) assessment tool for clinical use to allow clinical specialists and non-specialists to rapidly diagnose and quantify BTCP in a variety of settings, as well as monitor changes in BTCP over time. This aim involved the development of two instruments: one to diagnose patients with BTCP, and a second to assess and measure the relevant clinical characteristics of BTCP.

The aim of the diagnostic instrument was to adequately detect cases of BTCP in a range of cancer pain patients. The aim of the BTCP measurement instrument was to adequately encapsulate and quantify patients BTCP experience by meeting certain standards of validity, reliability and responsiveness in the relevant population, and have acceptable clarity and content. The BTCP assessment tool thus required multiple stages of development and testing to meet these aims.

7.2 Breakthrough cancer pain diagnostic instrument

This stage of the study involved development of a diagnostic BTCP algorithm and assessed whether this algorithm adequately detected 'true' cases of BTCP. The algorithm was developed by the research team, based upon the literature and clinical experience, and validated in a cohort of cancer pain patients against the condition of 'true BTCP' (defined by clinical consultation with a pain expert).

The diagnostic BTCP algorithm detected 54% of patients with 'true' BTCP (sensitivity). This was a lower than expected value; acceptable values for a screening test depend on the reason for screening, however >70% is widely accepted as the minimum to implement a test in clinical practice [201]. The exact reasons for this result are unknown, however there were multiple factors that potentially could have contributed.

There is no universally accepted definition of BTCP, and despite most published definitions being similar the wording is vague (e.g. background pain must be

'adequately controlled') and subject to individual clinical interpretation. This is reflected in the large range in reported prevalence of BTCP [59-66]. As such, the condition of 'true BTCP' is difficult to define and interpret. The 'gold-standard' method of diagnosing BTCP in this study was a detailed pain consultation with an expert. However this method of diagnosis may produce variable results depending on the interaction and information elicited from the patient, as well as in the application of BTCP definition. Different clinical experts may have different judgements and applications of BTCP definitions depending on their individual opinions and experiences. A 'gold-standard' diagnosis for a complex multi-dimensional pain experience that relies on patient history and recall can be difficult to achieve, especially when there is no consensus among experts regarding the definition of BTCP. However, every effort was made in this study to recruit clinical experts that had particular expertise in BTCP and were assessing patients on a regular basis, as well as having an in depth understanding of the literature. Having each patient assessed by two clinicians may have highlighted diagnostic differences between individuals but due to time and availability for this study it was not possible.

The patient was required to quantify their background pain on a verbal rating scale (none, mild, moderate, severe). The terms 'background pain' and 'breakthrough pain' are medical definitions and the majority of patients were unfamiliar with these terms [36]. As such, patients were not used to categorising background pain separately from BTCP episodes. The algorithm aimed to avoid the term 'background pain' for this reason, and instead referred to pain that is present for 'most of the time' however patients often expressed difficulty in understanding what this phrase referred to and asked for more detailed verbal explanations. It was difficult to simply encapsulate the complex concept of background pain in the format of a question easily understood and interpreted by patients. The severity and frequency of BTCP episodes can also alter a patient's background pain perception and rating with higher intensity of background pain reported in those with BTCP episodes [30].

The condition of 'adequately controlled' background pain is generally accepted to be required for a patient to be diagnosed with BTCP [21-2]. In the literature a verbal rating scale is the most commonly used instrument to quantify background pain.

However the pain intensity values used to define 'controlled' levels of background pain have differed between studies from 'moderate', 'mild' or 'none' [24,33] to 'mild' or 'none' [50]. A secondary aim of this study was to investigate which of these criteria optimally assessed the true condition of 'controlled background pain'.

The controlled background pain criteria of 'moderate', 'mild' or 'none' accurately detected 97% of 'true' controlled background pain cases, whereas the 'mild' or 'none' criteria detected 69%. However, despite having such high sensitivity values the 'moderate' or less criteria included a high number of false positives i.e. uncontrolled background pain cases, meaning specificity was low (20%). The 'mild' criteria, despite having lower sensitivity, detected fewer false positives and specificity was 78%.

Interestingly, the background pain rating of 'moderate' was used almost equally by individuals defined with the true condition of 'controlled' and 'uncontrolled' background pain indicating that this adjective may not be adequate to discern the complex concept of 'adequate' pain control. An issue with using a verbal rating scale to measure the level of background pain is that words have different meanings based on experiences and contexts of individual patients [167]. A patient may not want to describe their background pain as mild in case it trivialises it and they are not taken seriously. Alternatively, the term moderate is often determined to be adequate by some but not others [145].

The background pain rating of 'severe' was used more frequently by those considered to have 'controlled' background pain than those with 'uncontrolled' pain. The reason for this is unclear but the numbers were small in this group (N=13) meaning a few spurious results could result in large percentage changes. Such results could occur if a patient had severe transient pain episodes and could not distinguish between background and exacerbations of pain from the algorithm questions. The pain experience could be so overwhelming that all pain ratings are given as 'severe' and anecdotally this did seem to be the case. The disparity with expert ratings in this group could also be due to the patient underplaying pain experience to the expert for a variety of reasons, e.g. stoicism, reluctance to alter medication, fear of underlying cause of the pain [114,220-1]. This result again

highlights the difficulty of determining a 'gold-standard' diagnosis of a complex subjective phenomenon.

Background pain is described in previous studies as pain experienced 'more than half of waking hours' or 'more than 12 hours per day' [24,33,50] . In this study we decided to allow the patient to determine what they considered to be appropriate by asking about their pain experienced 'most of the time'. This enabled the patient to consider the background pain in relation to his or her own life but has the disadvantage of variability in individual patient's interpretation. The first question of the algorithm is automatically affirmative if a patient is on regular analgesia however a patient will often not know if their pain would be mostly present if they stopped their analgesia. This perhaps could have been phrased more clearly to account for this; 'Do you have pain that is present for most of the time?' or 'Do you have pain that requires you to take regular painkillers?'

The second algorithm question, 'how would you rate the severity of this pain?' referred to the 'pain that is there most of the time' in question one. The term background pain was avoided as evidence indicates that patients don't understand this term [36]. However, many patients required clarification at question two regarding which pain we were referring to and it was reiterated by the researcher that it was the pain' present for most of the time'. This again could have been phrased more clearly such as 'how would you rate the severity of this pain (pain present for most of the time)?

In this study we assessed pain experienced over the previous week. This was to reflect clinical practice in so far as many pain patients are seen weekly on an outpatient basis and are required to express their pain experience over this time period. Pain can vary in individuals on a day-to-day basis and a patient with only a 24-hour period of controlled background pain will need further assessment to establish if this pain level is sustained. Evaluation over a week to determine a diagnosis of breakthrough pain would more likely reflect a truer state. Recall bias is a documented problem and studies have shown that a number of different factors can influence a patient's evaluation of their pain state over a period of time [99,100,222]. This can lead to test error however in clinical practice a clinician is

required to evaluate information provided by a patient over a certain time period and as the comparisons in this study required the same information this effect would be minimised. Other potential sources of error are the patients' memory being triggered by the algorithm allowing them to have more enriched details when they saw the clinician.

It is interesting that the algorithm had a lower sensitivity in the cohort of hospice patients compared to hospital patients. These differences could be due to issues regarding the 'gold-standard' diagnosis of BTCP as a different expert was used at this site. Alternatively this patient group was significantly older and had a poorer performance status than the hospital cohort and it is possible that certain pain descriptors may have different meanings and interpretations depending on age or a patient's clinical scenario. This is further evidenced by the algorithm achieving a higher sensitivity in patients under the age of 65 and with a better performance status, i.e. younger and fitter patients. There was little difference in algorithm performance according to outpatient status and underlying pathophysiology of pain. However, it must be noted that few patients had solely neuropathic pain with the majority having at least a nociceptive component.

In summary, the ability of an algorithm to categorise patients as having breakthrough pain has a good positive predictive value but limited sensitivity using a cut-off score of mild to define 'controlled background pain'; when the cut-off level is changed to moderate the sensitivity increases but specificity is significantly reduced. Many patients had difficulty understanding the algorithm and required explanations from the research team questioning whether these results would be as valid using different personnel to screen. A comprehensive clinical assessment remains the preferred method to diagnose BTCP however diagnostic issues still remain making a 'gold standard' diagnosis difficult to define. A diagnostic algorithm has been used in a number of commercial and observational studies to diagnose BTCP without any validity testing [24,33,42-3,46,48-9,50]. The results from this study question the appropriateness of this method to diagnose BTCP in future studies without corroborative clinical assessment.

7.3 Breakthrough cancer pain measurement instrument

The aim of this stage of the study was to develop a clinical BTCP instrument that appropriately assessed and measured BTCP to allow health professionals to rapidly evaluate and monitor BTCP over time. To achieve this purpose the instrument was required to contain items to elicit the most relevant BTCP information (content validity) and to conform to a number of psychometric properties in order to demonstrate the instrument's ability to adequately measure the desired construct consistently and reflect relevant changes over time. A series of phases were necessary to determine the validity, reliability and responsiveness of the instrument.

7.3.1 Content validity

The content validity of the BAT (Breakthrough pain Assessment Tool) was established sequentially according to international recommendations for tool development from the FDA, APA and IMMPACT group [77-8,86]. In accordance with these guidelines cancer patients were involved in different development stages of the project. Qualitative interviews were performed with patients to explore BTCP experience and the themes identified from these interviews were considered for inclusion in the BAT. Patients' exact words were used to formulate questions and responses to further represent their view. After the initial BAT was drafted further interviews were performed with patients to ensure clarity, readability and lack of ambiguity of items and responses. As patient interviews were time and labour intensive, only ten patients were used however, care was taken to ensure they represented a range of ages, cancer stages and diagnoses.

Development of the BAT also conformed to international guidance by the inclusion of an expert survey to rate the clinical relevance of BTCP items and standardised criteria were used to determine consensus. Every effort was thus made to ensure the content of the BAT was clinically representative for both experts and patients in accordance with international guidelines.

There were a number of further psychometric properties of the BAT that were assessed during this study. These were item analysis and reduction, reliability

testing, construct validity testing and assessment of the instrument's ability to detect clinically relevant change.

7.3.2 Item analysis and reduction

The original hypothesis was that the BAT would measure two to three underlying pain dimensions based on analysis of generic cancer pain measurement instruments. Item analysis revealed that the BAT did indeed conform to this hypothesis and items loaded onto two underlying factors (dimensions).

These identified factors allowed the formation of two separate BAT subscales, referred to as the severity subscale and treatment subscale. The severity subscale consisted of six items: BTCP worst intensity, BTCP typical intensity, BTCP distress, impact of BTCP on normal life, frequency of BTCP, and side effects of BTCP painkillers. It is interesting that the BTCP interference item correlated with the BTCP intensity items. This contrasts with the underlying dimensionality of the Brief Pain Inventory (BPI) where pain intensity and pain interference items formed two separate underlying dimensions. This could indicate that BTCP is a conceptually different pain experience or that the more global interference question asked in the BAT, 'how does BTCP stop you from living a normal life?' evaluated a different dimension to the BPI specific interference items (general activity, sleep, relations with others, work, mood, enjoyment of life, walking).

Another unique finding was that the side effects from medication correlated more with BTCP intensity and interference than with measures of BTCP medication effectiveness. This indicated that side effects from painkillers were incorporated in a patient's evaluation of daily living. Painkiller side effects were of great importance to patients in the interview stage of this study as well as clinically relevant for professionals in order to make management decisions. Quantitative data about side effects are rarely included in cancer pain assessment instruments but these results demonstrate that this item is relevant to clinical management of BTCP and patient's everyday lives [223].

The treatment subscale consisted of three items, duration of BTCP, effectiveness of BTCP painkiller and time to meaningful effect of BTCP painkiller. The correlation of

the two items that assessed painkiller efficacy is not surprising, as well as these questions forming a separate dimension to the items assessing intensity and interference. However, BTCP duration correlated with the treatment pain dimension whereas frequency with the severity dimension, in fact duration and frequency correlated very poorly with each other. These two items are unique to BTCP measurement, as a patient must experience transient exacerbations of pain to be able to quantify these items, and there is little data regarding their relationships with other pain items. The duration of the BTCP was correlated with 'time until meaningful effect' of BTCP painkiller. This implied that BTCP painkillers were taken for the majority of episodes and patients interpreted the 'meaningful effect' of a painkiller as a time period similar to that of the BTCP duration. The term 'meaningful' can be interpreted differently by individual's depending on their understanding and contextual experience of such a term. Time until meaningful pain relief is a frequently used outcome in pharmacological BTCP studies [39,47] however there is little research into the interpretation of such a term by patients.

7.3.3 Reliability

Reliability was assessed using two standard methods, test-retest and internal consistency. Test-retest reliability assessed the BAT score over a period of time over which the underlying construct was stable [11]. Any change in the scores was thus related to measurement error as opposed to changing underlying condition. The test-retest coefficient met recommended standard levels for the BAT total score and subscale scores, which confirms that the measurement instrument has an acceptable level of measurement error.

The internal consistency coefficient (Cronbach's alpha) assessed relationships between the individual BAT items. To be a reliable instrument relationships should exist between questions designed to measure the same underlying construct. Cronbach's alpha coefficient scores also met standard criteria indicating that the BAT met multiple criteria of reliability.

Referring to the test-retest data, evaluations were also made on individual items. The BAT items that had the most variation over a 24-hour period were typical BTCP intensity and distress caused by the BTCP. In patient interviews it was evident that

the term ‘distress’ had different meanings for different individuals. It could reflect psychological response to pain or a greater worry associated with progression of the cancer. The variation in this item whilst the BTCP condition was stable perhaps reflects this wide interpretation. A typical BTCP episode intensity rating may have varied depending on events of the previous 24 hours implying that even when asked about recall over the past week when rating this particular item the recent history is considered.

7.3.4 Construct validity

Construct validity was evaluated by calculating BAT scores in clinically distinct groups that theoretically should have differences in BTCP severities. There were a number of different groups assessed. Firstly groups were categorised by a patient or clinicians global assessment of adequacy of BTCP control, and whether pain medication was considered to need altering. Secondly, biomedical markers of stage of cancer, performance status, site of metastases and anti-cancer treatment were used to determine groups. Patients with more advanced cancer, poorer performance status and not receiving anti-cancer treatment were hypothesised to have more severe BTCP.

The groups defined by patient and clinician global impression of BTCP adequacy revealed that significantly more clinicians considered patients to have inadequately controlled BTCP (72%) than patients themselves (35%). Despite this the expert made changes to BTCP medication in 71% of cases thus clinical management was based upon the clinician’s overall assessment rather than the patients. A patient’s global assessment of adequacy of control of BTCP could be influenced by a number of factors other than BTCP severity. Studies that assessed satisfaction with pain control demonstrated that global satisfaction was influenced by quality of communication with health care professionals, a clear pain management plan, and confidence in the pain professional’s expert knowledge [182-3]. In this study the patient’s global assessment could reflect these other factors. This is supported by the fact that despite 35% of patients claiming their BTCP was inadequately controlled, 55% thought they needed changes to their pain medication.

The total BAT score and subscale scores were significantly higher in clinical groups defined as having 'inadequately controlled' BTCP by both clinicians and patients. Clinical decisions regarding medication are complex and require the assimilation of multiple clinical items to create a global impression of a patient's health status, as well as an understanding of the patient's expectations and acceptability of certain changes. The decision is often made in collaboration with the patient so it is an outcome agreed with and understood. The fact that the BAT total score and severity subscale correlated with clinician and patient global assessment indicates the validity of the tool in comparison with a complex clinical interaction.

Disease stage, anti-cancer treatment, performance status and site of metastases did not correlate with the BAT i.e. BAT severity scores were not higher in patients with more advanced cancer, poorer level of performance or with bone metastases. It is interesting that the BAT scores correlated more strongly with patient and clinical perceptions and assessments of BTCP rather than with biomedical anchors of disease. Pain is a multi-dimensional experience and evaluations of individual scores consist of sensory, emotional and evaluative components [8]. The BAT is representative of this complex experience and this is reflected in the correlation with judgements of those most familiar with the experience of BTCP (patient) and assessment of BTCP (clinician) rather than with biomedical markers, which don't reflect the cognitive and emotional complexities of pain.

Patients receiving anti-cancer treatment (hormonal therapy, chemotherapy, or radiotherapy) did not have significantly different BAT scores compared to those whose treatment had been stopped, or not started, due to advanced disease state. The majority of patients having anti-cancer therapy were receiving with palliative intent, with aims of prolonging life and improving symptoms. It is interesting that those having such treatments did not have less severe levels of BTCP. Reasons for this could include patient selection i.e. patients with severe BTCP are more likely to be referred to the pain team by their oncologists thus not being fully representative of the range of BTCP patients having treatment. Other reasons could be that anti-cancer treatment doesn't effectively treat BTCP without concurrent analgesia management and specialist pain assessment, which all BTCP patients received in this study. The treatment group were also analysed as one whereas they are in fact a

heterogeneous group receiving different therapies for different cancers at varying stages of disease and treatment. This broad analysis may have not been specific enough to detect any such differences.

In conclusion these results provide construct validity evidence that the BAT is a valid measurement of BTCP according to both patient and clinician criteria however biomedical anchors did not correlate with BTCP multi-dimensional experience.

7.3.5 Convergent validity

Convergent validity measured relationships between the BAT and continuous clinical outcome variables (pain medication) and patient outcome variables (generic pain assessment tool). The BAT scores were compared with BTCP medication administration and background analgesia dose. As expected, there was a stronger correlation between the BAT and frequency of BTCP medication administration than background medication dosage. BAT questions assessing BTCP frequency and intensity were the most highly correlated with BTCP medication, which makes intuitive sense and is described as a common reason for taking BTCP analgesia [26].

The literature does report higher doses of background opioid used in BTCP patients however, this was in comparison to those without BTCP [33]. The results from this study show that higher background analgesic dose is not associated with more severe BTCP. This contrasts with validation studies of the BPI where background analgesic dose was found to correlate with the scores [74].

The BAT was also compared with the brief pain inventory (BPI); a generic pain tool that evaluated worst, average, least and current pain intensity and seven pain-related interference items (sleep, work, walking, general activity, relationships, mood, enjoyment of life), as well as pain relief from treatments. The four BPI pain intensity items total a sum 'pain intensity' subscale and seven BPI interference items total a 'pain interference scale'.

As predicted the worst BTCP intensity score correlated highly with BPI worst pain intensity score confirming that these items were measuring an almost identical construct. Also, as expected the BAT severity subscale correlated moderately with

both the BPI intensity subscale and BPI interference subscale confirming that the scales were measuring related but not identical constructs.

Many interesting relationships were observed between BAT and BPI items. Firstly the BAT treatment subscale did not correlate with any BPI item. The BAT treatment subscale consists of items regarding BTCP duration, and effectiveness of BTCP painkillers and time to meaningful effect of BTCP medication. These items are unique to the BAT and the experience of BTCP meaning that a correlation did not exist with any generic pain measures. Effectiveness of BTCP painkiller was however, moderately correlated with percentage of pain relief from 'all pain measures' on the BPI showing that they measure similar constructs.

Distress from BTCP was moderately correlated with mood and thus assessed the psychological component of pain. However BTCP distress was also correlated with walking, work and enjoyment of life demonstrating that 'distress' encompassed a range of pertinent issues. The item regarding the impact of BTCP on 'living a normal life' correlated with all BPI interference items, except sleep. This demonstrated that this question has validity in encompassing multiple aspects of pain interference without the burden of answering multiple questions. Sleep was not correlated with BTCP distress and ability to live a normal life. This corresponded with previous BTCP literature where sleep had the lowest interference scores and was not as impacted by BTCP as daytime activities [50].

Duration of BTCP was only correlated with BPI general activity, whereas frequency of BTCP only correlated with BPI intensity and general activity. This demonstrated that items unique to BTCP experience were not reflected by the majority of BPI questions supporting that BTCP is a separate construct from generic pain, and not comprehensively assessed by the BPI.

These results demonstrate that the BAT has acceptable levels of convergent validity by correlating in an expected fashion with different clinical and patient-related outcome variables.

7.3.6 Responsiveness

The ability of the BAT to demonstrate clinically relevant changes over time is an important part of its validity in application to clinical practice. This was assessed by calculating the overall effect size and the difference in BAT score that represented clinically significant change (minimal important difference). The effect size of the total BAT was large which indicated that patient's BTCP had improved over the course of the study due to regular clinical assessment, reassessment and appropriate intervention. BTCP has been reported as an independent predictor for worse pain outcomes [224]. This large effect size, coupled with nearly 50% of patients reporting an improvement in BTCP after 1 pain consultation, emphasises the response of BTCP to specialist pain assessment and intervention in accordance with recent guidelines [22].

The minimal important difference (MID) in total BAT score required to represent a clinically important change was calculated using different external anchors. Firstly, patient and clinician impression of change of BTCP was used. BTCP rated as 'better' indicated clinically significant improvement, and a reduction in BAT score of 12.5 and 12.9 respectively represented the MID (total maximum BAT score=88). Secondly, the criterion of analgesic changes at follow up consultation was used to represent change. Using this anchor the MID was much higher (20.7). Different anchors will inevitably lead to different results however the similarity in MID using patient and clinical opinion anchors indicates the consistent responsiveness of the BAT.

The much larger difference in MID when using changes in analgesia requirement as the anchor-based comparison method implies that that the patients having such changes represent a more severe BTCP group than those whose global difference in BTCP is described as 'worse'. However, the significant differences in BAT scores over time between distinct clinical groups indicate that the BAT is a valid instrument for assessment of clinically relevant changes.

It can be concluded from the extensive psychometric testing of the BAT measurement instrument that it is a reliable and valid measure in the population tested.

7.4 Limitations of study

The first part of this study discussed the development of an algorithm to identify BTCP patients accurately, however the results were not as sensitive as expected. The algorithm was based on the most commonly used objective diagnostic criteria in the literature however patient and expert feedback were not used during the development process of this stage of the study. Using appropriate feedback at earlier stages may have identified issues with the algorithm wording and response formats. Also, only one diagnostic method was tested on cancer pain patients. The development and comparison of different diagnostic algorithms or other methods against the 'gold standard' expert opinion would have allowed us to demonstrate whether any instrument could adequately diagnose BTCP. Other methods that could have been used include a series of statements describing pain where a patient indicated the one that corresponded most closely to their experience, alternatively, a diagram with a graphical representation of different temporal pain intensities that a patient must choose from. The concept of 'adequately controlled' background pain is a difficult one to quantify and it may have been better to evaluate this directly from a patient perspective, 'would you consider your pain is adequately controlled most of the time?' instead of relying on a quantification on a verbal rating scale. The results from this diagnostic study indicate that BTCP is a complex multi-dimensional experience and any method may have had similar issues to the one tested. However, without the data to prove otherwise we cannot make this assumption.

It has already been discussed that using more than one expert to assess each patient would have improved clinical assessment of BTCP diagnosis reliability results however this was not practical due to patient fatigue and other clinician availability and time issues.

The BAT measurement instrument is intended for completion only by patients with BTCP. The BTCP patients used in the above validation study were identified by expert clinical interview, not algorithm diagnosis. As such, validity data presented is from this population of BTCP patients. If the BTCP algorithm is used as a diagnostic screening method for completion of the BAT measurement instrument then patients without the condition may be completing a measure that is not validated and

appropriate for them. As such, we would recommend that BTCP be diagnosed clinically before completing the BAT.

The BAT measurement instrument has been demonstrated to be reliable and valid in the population tested however a limitation of this type of psychometric analysis is that results cannot necessarily be extrapolated onto different cancer populations within the United Kingdom and internationally. Measures taken to ensure applicability of results were the inclusion of patients from three different clinical sites (2 hospital and 1 hospice), to ensure a range of patients. In particular over one third had a performance status where they were confined to bed or chair for the majority of the day (23%) or were completely bedbound (13%) so care was taken to include patients in poor physical condition to ensure the BAT was representative for this patient group. However, data from larger cancer populations would provide additional validity and reliability analysis.

Often in studies that develop new measures in health sciences much longer tools are developed and tested on patients and then the items with the best psychometric properties are selected for use. We intended to represent a wide range of cancer patients, including those with poor performance status and high levels of fatigue. As such a careful and thorough selection process of clinically relevant questions was made with expert and patient input. This created a short tool to be field-tested on patients. However, it must be recognised in rigorous psychometric analysis a larger item pool is often used to extract data. In defence of our method, analysis revealed no redundant items due to high or low levels of correlation indicating that this considered and practical approach to item generation can still produce psychometrically sound results.

Patients received expert pain assessment and intervention whilst participating in the study meaning their breakthrough pain control was optimised. Completing the tool itself may also have improved pain assessment by giving patients prompts about certain items and allowing them to consider aspects of their pain prior to clinical consultation. The tool may therefore perform differently if used in clinical practice without the concurrent assessments performed within the context of the study.

There is no published fully validated clinical BTCP assessment tool and as such construct validity was established from a number of hypotheses based upon clinical experience and literature. There were limitations in the hypotheses regarding BTCP based upon the literature, as these were predominantly small studies with BTCP diagnosed using different methods. Between groups comparisons in these studies were made between those with BTCP and those without. As such, despite associations in the literature between the presence of BTCP and worse performance status and bone metastases [30,49] these biomedical medical markers did not correspond with worse BAT scores. This demonstrates the limitations of using such anchors to categorise BTCP.

The Brief Pain Inventory (BPI) was used as a method to explore the convergent validity of the BAT, and the BAT conformed to the hypothesised relationships. However, the BPI was only tested on a subsection of patients after a midterm evaluation of the study. The reason for not initially including multiple measurement instruments was to reduce patient burden however the BPI analysis provided additional data supporting the validity of the BAT. Ideally, the BPI data should have been collected for all patients. Other tools that could have been used as external comparators of the BAT include various quality of life tools validated in cancer patients. However, it was decided that quality of life was such a distinct concept to BTCP that hypotheses between the tools would be difficult to predict.

A numerical rating scale (NRS) was used as a response category for the majority of the questions. This was chosen based upon recommendations by Palliative Medicine and IMMPACT expert groups made on the basis that it is the easiest scale for patients to complete and has more available data regarding calculating clinically important difference [72-3,187-8]. However, the response categories for duration, frequency and time to meaningful pain relief were represented in a different format, a patient was required to circle the appropriate range of values in which their experience lay. It is recommended that assessment instruments have a consistent format for response options but due to the complexity of BTCP and items needed to gather appropriate clinical information this was not possible. The non-NRS response formats were carefully determined based on clinical practice and available literature

and a scoring system developed to enable responses to be quantified comparably to the NRS answers.

There was a certain amount of missing data, the majority of which was due to the question not being applicable to the patient (e.g. BTCP medication question if patient not taking any painkillers). For the purposes of analysis of summary scores the patients that did not complete all the questions were omitted. Summary score results and responsiveness data cannot therefore be extrapolated onto patients that are unable to complete all the items. Individual question scores may be used but care must be taken to not make summary score comparisons using incomplete patient data. For future validity studies it would therefore be appropriate to have the additional inclusion criterion that the subject must have taken BTCP analgesia in the previous week otherwise their results cannot be analysed.

A proportion of patients were unable to complete the follow up assessments predominantly due to advanced disease. Eighty percent of the original sample completed the first follow up and responsiveness data were calculated on this group. Palliative care studies have well documented problems with follow up data due to the patients having such severe physical illness and this was accounted for in the sample size calculation [146,199]. It was an aim of the study to be as inclusive as possible and as long as a patient was able to understand the patient information sheet and consent to the study we did not aim to exclude those with poor performance status and advanced disease state on the basis that they may not be able to complete follow up.

Finally, it is important for PROMs to be relevant and valid for patients at all stages of their illness and representative of those with poor physical condition. As such patients with cognitive impairment were not automatically excluded from the study. Instead a careful approach was made involving relevant health professionals and family members. If a patient was able to comprehend and evaluate the details of the study, and the family and staff members ensured this comprehension, the patient was deemed fit to participate. This ensured a relevant patient group were adequately represented in the development of this assessment tool.

7.5 Future directions

As discussed in the above section future BAT validation studies would aid in the on-going psychometric analysis of the tool. Such validation studies could be incorporated into clinical trials of interventions to treat BTCP and as such could also provide additional data regarding minimal important differences. Care must be taken in future studies to ensure relevant comparators are chosen for the purposes of validation that take into account the multi-dimensional nature of BTCP and its relationship with interference measures of generic pain.

BTCP can vary daily in patients and the majority of generic pain assessment tools are validated over a 24-hour recall period, however we chose a recall period of 1 week. This was done to reflect clinical practice, which often involves a patient attending a pain clinic weekly, and thus requires them to summarise and express broader conclusions on their BTCP experience over a longer period than 24 hours. However, in a context where a patient is assessed and reviewed more frequently it would be reasonable to consider applying the tool at these intervals. Further studies would be necessary to assess if the BAT remained valid within this context. Another way to further validate the BAT over a recall period of a week would be to give each patient daily pain diaries where daily BTCP episodes and scores are recorded. These could then be compared with the BAT score for accuracy and to assess if current state is influencing recall. When similar studies have been performed in generic cancer pain, a 1-week pain intensity summary score correlated well with daily recordings and it would be interesting to see if such findings are replicated in BTCP experience [100,222].

Validation of the BAT in different languages is also an additional future direction. This would involve relevant translation using standard methods followed by repeating validation methods used in this study to establish reliability, construct validity and responsiveness (e.g. comparison with BPI, global impression of pain).

The BAT was developed according to international recommendations and can therefore be used as a patient-related outcome measure for research purposes. Currently the benefits of certain oncological treatments (e.g. radiotherapy, bisphosphonates) have only been demonstrated using generic pain outcome

measures [225-6] and it would be interesting to assess if these benefits extended to types of BTCP e.g. incident pain.

A changing focus in healthcare towards patient centred care and shared decision making, as well as health care system changes to incorporate PROMs in routine practice make the development of psychometrically sound instruments a growing priority [227-8]. There is some data regarding how the incorporation of routine pain assessment can improve outcomes [127-8]. However, there are no such data for patients with BTCP. It would be interesting to evaluate the BAT in routine clinical practice to see if standardised BTCP assessment and measurement improved outcomes.

7.6 Conclusion

The BTCP assessment tool (BAT) was developed to enable non-experts to rapidly diagnose BTCP and evaluate the relevant clinical BTCP domains. The BTCP measurement instrument (BAT) is a valid and reliable tool in the clinical assessment and quantification of BTCP in cancer patients. Its use can be recommended to quantify BTCP in clinical practice and assess responsiveness to interventions.

This study identified a number of issues with the diagnosis of BTCP, however, the simple diagnostic algorithm developed cannot be recommended as the only method for non-experts to diagnose BTCP. The optimal way to identify patients with BTCP is by comprehensive clinical assessment.

Pain is inadequately controlled in a proportion of cancer patients and whilst the reasons are multiple and complex a clinically relevant tool will allow the collection of pertinent information and highlight those patients that need a specialist pain or palliative care team referral, and allow monitoring of the condition.

The BAT was designed to be brief and relevant however it must be acknowledged that it cannot entirely replace a clinical interview where a patient is allowed to explain in their own words their problems. Instead it is likely to be used as a tool to assist with clinical interview and allow the health care provider to focus on specific areas if scored highly.

Chapter 8. References

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Appendix A. Brief Pain Inventory (Short Form)

Charles S. Cleeland, PhD
Professor and Chair
McCullough Professor of Cancer Research

Department of Symptom Research – Box 1450
Tel: 713-745-3470
Fax: 713-745-3475
E-mail: *ccleeland@mdanderson.org*

October 1, 2010

Ms. Katherine Webber
Royal Marsden Hospital
Downs Road, Sutton, SM2 5PT
London, United Kingdom

Re: Authorization to use the Brief Pain Inventory

Dear Ms. Webber:

I am pleased that you have considered using the Brief Pain Inventory© (BPI) in your upcoming study. The study description you provided seems to be congruent with the intended use of the BPI. You are hereby granted permission to use it in your study. Please note that:

- Your use of the BPI is limited only to the study specified above; to use the BPI in additional studies, you must reapply online at www.mdanderson.org/departments/prg > Symptom Assessment Tools > The Brief Pain Inventory (BPI).
- You are permitted to reproduce the copy of the BPI that is included with this Letter of Authorization; however, you must not remove the copyright notice.
- The BPI may not be modified or translated into another language without the express written consent of the copyright holder, Charles S. Cleeland, PhD. Failure to comply may result in legal action. Permission to alter or translate the instrument may be obtained by contacting me at symptomresearch@mdanderson.org or by mail.

We would greatly appreciate your sending us a summary of your study results after the completion of your project, so that we can continue to evaluate the performance of our instrument.

Sincerely,

Charles S. Cleeland, PhD
McCullough Professor of Cancer Research and Chair
Department of Symptom Research

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: _____/_____/_____ Time: _____

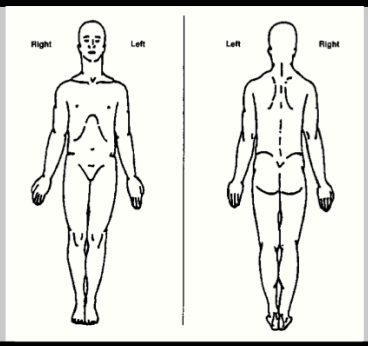
Name: _____ _____ _____

Last First Middle Initial

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 every-day kinds of pain today?

1. Yes 2. 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 circling the one 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										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber 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										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

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

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one 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

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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Appendix B. Breakthrough Pain Questionnaire

Appendix: Pain Assessment Algorithm

This algorithm is designed for patients with controlled, persistent baseline pain. The nature of the baseline pain is assessed. Those with controlled baseline pain are then asked about flares of breakthrough pain. The nature of the breakthrough pain is assessed. Note that the definition of controlled baseline pain depends in part on whether patients are taking opioids more than 12 hours per day (Scenario A) or less than 12 hours per day (Scenario B). Opioid therapy will be known prior to beginning the assessment and it is expected that most patients will be taking opioid more than 12 hours per day.

Determining the presence of persistent baseline pain (determined at screening)

1. **Does your pain currently have a component you would describe as "constant" or "almost constant," or would it be constant or almost constant if not for the treatment you are receiving?**
   0 = No 1 = Yes
   a) If Yes, go to question #2A or #2B
   b) If No, STOP. Patient does not have persistent baseline pain.

Scenario A: Patients taking opioids greater than or equal to 12 hours per day (screening)

2A. Have you had any pain during the past week?
0 = No 1 = Yes
a) If Yes, go to question #3A.
b) If No, patient has controlled baseline plan; skip to question #5.

3A. How would you judge your baseline pain on average during the past week?
1 = Mild 2 = Moderate 3 = Severe 4 = Excruciating
a) If severe or excruciating, STOP. Patient has uncontrolled baseline pain.
b) If mild or moderate, patient has controlled baseline pain. Continue to question #5.

Scenario B: Patients taking opioid less than 12 hours per day (screening)

2B. Have you had any pain during the past week?
0 = No 1 = Yes
a) If Yes go to question #3B.
b) If No, STOP. Patient does not have baseline pain.

3B. Did you feel this pain for more than half the time that you were awake?
0 = No 1 = Yes
a) If Yes, continue to question # 4B
b) If No, STOP. Patient has transient pains

4B. How would you judge your baseline pain on average during the past week?
1 = Mild 2 = Moderate 3 = Severe 4 = Excruciating
a) If severe or excruciating, STOP. Patient has uncontrolled baseline pain.
b) If mild or moderate, patient has controlled baseline pain. Continue to question #5.

5. Assessing the nature of the baseline pain (start of phone interview)

a) Where is this pain? (Indicate "right", "left", or "both", if appropriate).
1 head 2 face 3 neck 4 shoulder (R, L, B)
5 chest 6 arm (R, L, B) 7 abdomen 8 upper back
9 lower back 10 leg (R, L, B) 11 buttock (R, L, B) 12 pelvis (R, L, B)
13 rectal or anal region 14 genital region 15 other_____

b) How long have you experienced this pain? (in weeks)_____

c) What does it feel like? (Indicate one or more than one description):
1 sharp 2 aching 3 crampy 4 radiating or shooting
5 pressing, squeezing or tight 6 burning 7 throbbing 8 stabbing
9 = other (describe)_____

d) Does anything that you do reduce your pain?
0 = No 1 = Yes

e) If Yes, please describe what reduces your pain:
_____

f) Does anything that you do make your pain worse?
0 = No 1 = Yes

Question 6 probes for the presence of breakthrough pain and question 7 assesses the nature of the breakthrough pain

6. Do you also experience temporary flares of severe or excruciating pain?
0 = No 1 = Yes

a) If Yes, patient has breakthrough pain. Continue with the remainder of this questionnaire to characterize the breakthrough pain.

b) If No, STOP. Patient has controlled baseline pain without breakthrough pain.

7. **Assessing the nature of the breakthrough pain**

a) How many different types of temporary flare-ups do you have?
_____
If you had one kind of severe pain flare-up during the past 24 hours, the following questions refer to this. If you have had more than one kind of severe pain flare-up, the following questions refer to the worst flare-up you have had during the past 24 hours. Patients can then describe the second and third worst flare-ups.

b) Where is this pain? (Indicate "right," "left," or "both," if appropriate):
1 head 2 face 3 neck 4 shoulder (R, L, B)
5 chest 6 arm (R, L, B) 7 abdomen 8 upper back
9 lower back 10 leg (R, L, B) 11 buttock (R, L, B) 12 pelvis (R, L, B)
13 rectal or anal region 14 genital region 15 other_____

c) What does it feel like? (Indicate one or more than one description):
1 sharp 2 aching 3 crampy 4 radiating or shooting
5 pressing, squeezing or tight 6 burning 7 throbbing 8 stabbing
9 = other (describe)_____

d) When your pain-flare becomes as bad as it gets, would you say that it is
1 = Severe 2 = Excruciating

e) From the time that you first feel this pain start to flare until it gets to be as bad as it gets, how long does it take (in minutes)?
_____

f) When the pain-flare comes on, does it start mildly and gradually get worse, or does it immediately start out severe?
1 = Gradual 2 = Severe

g) If the pain-flare starts slowly and gradually gets worse, how long does it take from the time that you first start to feel the pain coming on until it goes away?
_____

h) How many times a day do you get this specific kind of pain-flare?

i) Does your pain-flare usually come on after a certain amount of time that you have taken your pain medication?
0 = No 1 = Yes
Describe_____

j) Do you know what causes your pain-flare to come on?
0 = No 1 = Yes

k) If Yes, please describe what causes your pain-flare:
_____

l) How well can you predict when your pain-flare will occur?
1 = Can never predict when it will occur
2 = Can sometimes predict when it will occur
3 = Can often predict when it will occur
4 = Can almost always predict when it will occur
5 = Can always predict when it will occur

m) Does anything help to lessen your painful episode?
0 = No 1 = Yes

n) If Yes, please describe what reduces your pain:
_____

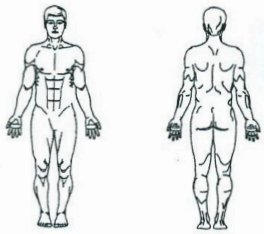
o) If you do know of something that lessens your pain, how sure are you that it will work - does it work successfully each time you try it?
0 = No 1 = Yes
Describe_____

Appendix C. Episodic Pain Documentation Sheet

Patient name: _____ Date: _____

Each pain should be marked on a separate sheet.

Location



Severity

Mild	[ ]
Moderate	[ ]
Severe	[ ]
Excruciating	[ ]

Type

A.	No background pain	[ ]
B.	Controlled background pain	[ ]
C.	Uncontrolled background pain	[ ]

Temporal characteristics

Daily frequency: _____

Onset: Gradual [ ] Sudden [ ]

Time course

Time to max intensity (minutes) _____

Precipitating event

None (spontaneous)	[ ]
Incident	[ ]
Nonvolitional	[ ]

Predictable

Yes	[ ]
No	[ ]

0.	No scheduled analgesia	[ ]
1.	Insufficient scheduled analgesia	[ ]
2.	Sufficient scheduled analgesia	[ ]

Weekly frequency (if less than daily): _____

Total duration (minutes): _____

Pathophysiology

Somatic	[ ]
Visceral	[ ]
Neuropathic	[ ]
Mixed	[ ]
Unknown	[ ]

Etiology

Disease related	[ ]
Treatment related	[ ]
Unrelated to disease/treatment	[ ]

Notes

Appendix D. The Alberta Breakthrough Pain Assessment Tool

Appendix 2
The Alberta Breakthrough Pain Assessment Tool—Research

TO BE COMPLETED BY PHYSICIAN OR NURSE

Instructions:

1. This module should be completed with the patient due to its complexity. The patient or clinician can answer the questions in writing, but if completed by the patient, it must be done under close supervision and help must be immediately available if required.
2. The goal is to have the patient characterize up to three distinct types of breakthrough pain. **To do this, define baseline and breakthrough pain for the patient**. Baseline pain can be defined as "the usual, steady pain you always experience." Breakthrough pain can be defined as "a brief flare-up of pain. It can be a flare-up of the usual, steady pain you always experience (your baseline pain) OR it can be a pain that is different from your baseline pain".
3. First ask the patient to describe his or her baseline pain, which may include a description of the location, severity, quality, or other features of this pain, and complete the table below.
4. Then ask how many different types of **breakthrough pains** he/she typically experiences **in a 24 hour period**. A patient may initially distinguish between breakthrough pains on the basis of any of the following variables: location, provocation, quality, etiology, or any other variable the patient feels is important.
5. Ask the patient to identify up to three of his/her **most bothersome breakthrough pains**, and complete the table below; these breakthrough pains will be the ones that are characterized.
6. Please photocopy the subsequent pages of this module to individually characterize each of the patient's three most bothersome breakthrough pains. Note that a separate Module III should be completed for each of the patient's most bothersome breakthrough pains.

Description of baseline pain	
Describe your baseline pain.	

Descriptions of distinct types of breakthrough pain	
What is your most bothersome breakthrough pain?	
What is your second most bothersome breakthrough pain?	
What is your third most bothersome breakthrough pain?	

Q2. Current breakthrough pain medications: list trade name of formulations [list generic names for all opioid and non-opioid analgesics]	Treatment Regimen		
	Route of Administration	Dose	prn Schedule

TO BE COMPLETED BY PATIENT

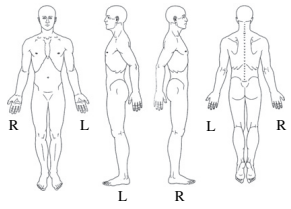
For which breakthrough pain are you completing this form?	

Q1. Relationship to baseline pain Is this pain a brief flare up of your baseline pain or is it a pain that is different from your baseline pain?	☐ Brief flare up of baseline pain ☐ Different from baseline pain ☐ Not sure

Q2. Last time experienced (a) When did you last have this breakthrough pain? (Please refer to your most recent breakthrough pain experience, regardless of whether or not you took medication for it.)	☐ Today ☐ Yesterday ☐ Before then
(b) Beginning at what time, approximately?	

Q3. Frequency (a) Approximately how many times in the past 24 hours have you had this breakthrough pain? (Please include ALL breakthrough pain experiences, regardless of whether or not you took medication for them.)	
(b) During the past 24 hours is this about the usual for you?	☐ Usual ☐ Better ☐ Worse

Q4. Intensity of pain at peak (a) When this breakthrough pain is at its worst, how would you rate this pain on a scale from 0 to 10, with 0 being 'no pain' and 10 being 'worst possible pain'?	
(b) How would you rate the intensity of this breakthrough pain at its worst?	☐ Mild ☐ Moderate ☐ Severe

Q5. Location Where do you feel this pain? (Please **shade in the entire area** in which you experience this pain)	

Q6. Quality What does the pain feel like? (check √ all that apply)	☐ Throbbing ☐ Stabbing ☐ Cramping ☐ Hot-Burning ☐ Heavy ☐ Splitting ☐ Sickening ☐ Punishing-Cruel ☐ Other (please describe):	☐ Shooting ☐ Sharp ☐ Gnawing ☐ Aching ☐ Tender ☐ Tiring-Exhausting ☐ Fearful

Q7. Time from onset to peak intensity When you are awake, on average, how long does it usually take from the time you first feel this pain **until it is at its worst**?	☐ more than 0 and up to 10 minutes ☐ more than 10 and up to 30 minutes ☐ more than 30 minutes ☐ It's hard to say exactly when it started

Q8. Time from onset to end of episode For those pain episodes that you take breakthrough pain medication, how long does it usually take from the time you take your medication until the pain goes away?	☐ more than 0 and up to 10 minutes ☐ more than 10 and up to 30 minutes ☐ more than 30 minutes ☐ I am not on any breakthrough pain medication

Q9. Cause(s) Is there anything that triggers this breakthrough pain? (check √ all that apply)	☐ Movement in bed ☐ Walking ☐ Standing ☐ Sitting ☐ Coughing ☐ Vomiting ☐ Having a bowel movement ☐ Urinating ☐ Swallowing ☐ Eating ☐ Touching area of skin ☐ Breathing ☐ It recurs when I feel my scheduled pain medication wearing off ☐ No, nothing in particular triggers this pain ☐ Unsure ☐ Other (please describe):

Q10. Predictability Can you predict when your breakthrough pain will occur?	☐ I can never predict when it will occur ☐ I can rarely predict when it will occur ☐ I can sometimes predict when it will occur ☐ I can often predict when it will occur ☐ I can always predict when it will occur

Q11. General relief Does anything help to relieve or prevent your breakthrough pain? (check √ all that apply)	☐ Moving ☐ Sitting ☐ Rolling over ☐ Lying ☐ Urinating ☐ Having a bowel movement ☐ Passing gas ☐ Burping ☐ Eating ☐ Sleeping ☐ Applying heat ☐ Applying cold ☐ Breathing ☐ Avoiding coughing ☐ Touching/rubbing/squeezing painful area ☐ Use of breakthrough pain medication ☐ Use of scheduled pain medication ☐ Unsure ☐ Other (please describe):

Q12. Relief from breakthrough pain medication In the past *24 hours*, how much relief has your breakthrough pain medication provided for this breakthrough pain?	☐ No relief ☐ Slight relief ☐ Good relief ☐ Very good relief ☐ Complete relief ☐ Not applicable: I haven't taken any breakthrough pain medication in the past 24 hours (skip questions 13-15)

Q13. Satisfaction with breakthrough pain medication In the past *24 hours*, how satisfied have you been with how well your breakthrough pain medication works for this breakthrough pain?	☐ Very satisfied ☐ Moderately satisfied ☐ Slightly satisfied ☐ Neutral ☐ Slightly dissatisfied ☐ Moderately dissatisfied ☐ Very dissatisfied

Q14. Onset of pain relief In the past *24 hours*, on average, how long has it taken for your breakthrough pain medication to ***begin*** to reduce your breakthrough pain? (Fill in the blank)	____ minutes

Q15. Satisfaction with onset of pain relief In the past *24 hours*, how satisfied have you been with how fast your pain medication ***begins*** to reduce your breakthrough pain?	☐ Very satisfied ☐ Moderately satisfied ☐ Slightly satisfied ☐ Neutral ☐ Slightly dissatisfied ☐ Moderately dissatisfied ☐ Very dissatisfied

TO BE COMPLETED BY PHYSICIAN OR NURSE

Q1. Etiology of breakthrough pain (check √ all that apply)		Pain related to the site of active cancer
		Pain related to the whole body or systemic effects of the cancer disease process (e.g. muscle spasm or bedsores from debility, pain from shingles, etc.)
		Pain related to anticancer treatment (e.g. side effects of radiotherapy, chemotherapy, surgery)
		Pain caused by a concurrent disorder (e.g. osteoarthritis)
		Unknown or uncertain at this time
Q2. Inferred pathophysiology of breakthrough pain (check √ all that apply)		Somatic nociceptive *List damaged tissues:*
		Visceral nociceptive *List damaged tissues:*
		Neuropathic *List damaged tissues:*
		Unknown or uncertain at this time

Note: An administrative manual for the Alberta Breakthrough Pain Assessment Tool serves as a technical appendix for users, and is available by contacting the authors.

Appendix E. Brief Pain Inventory

PROTOCOL # _____ INSTITUTION _____

PATIENT SEQUENCE # _____ HOSPITAL CHART # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory

Date: ___/___/___

Name: _____ _____ _____

Last First Middle Initial

Phone: (___) _____ **Sex:** ☐ Female ☐ Male

Date of Birth: ___/___/___

1) Marital Status (at present)

1. ☐ Single
2. ☐ Married
3. ☐ Widowed
4. ☐ Separated/Divorced

2) Education (Circle only the highest grade or degree completed)

Grade	0	1	2	3	4	5	6	7	8	9
	10	11	12	13	14	15	16	M.A./M.S.		

Professional degree (please specify) _____

3) Current occupation _____
(specify titles; if you are not working, tell us your previous occupation)

4) Spouse's occupation _____

5) Which of the following best describes your current job status?

1. ☐ Employed outside the home, full-time
2. ☐ Employed outside the home, part-time
3. ☐ Homemaker
4. ☐ Retired
5. ☐ Unemployed
6. ☐ Other

6) How long has it been since you first learned your diagnosis? ____ **months**

7) Have you ever had pain due to your present disease?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

8) When you first received your diagnosis, was pain one of your symptoms?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

9) Have you had surgery in the past month? 1. ☐ Yes 2. ☐ No

If YES, what kind? _____

10) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, toothaches). Have you had pain other than these everyday kinds of pain during the last week?

1. ☐ Yes 2. ☐ No

10a) Did you take pain medications in the last 7 days?

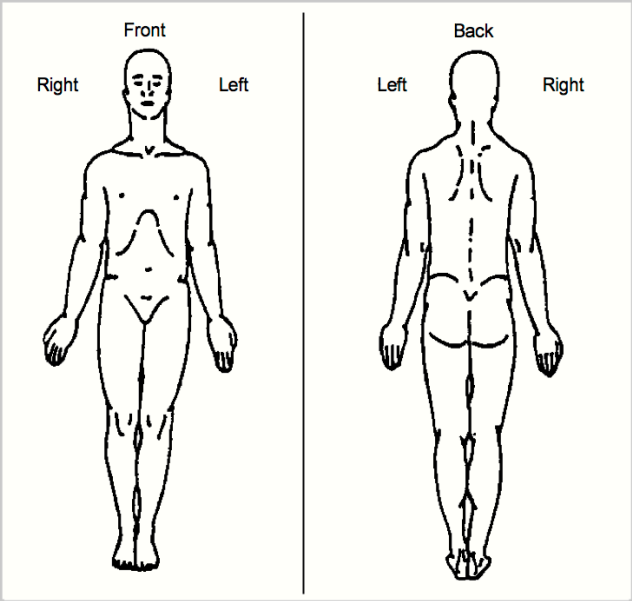
1. ☐ Yes 2. ☐ No

10b) I feel I have some form of pain now that requires medication each and every day.

1. ☐ Yes 2. ☐ No

IF YOUR ANSWERS TO 10, 10a, AND 10b WERE ALL NO, PLEASE STOP HERE AND GO TO THE LAST PAGE OF THE QUESTIONNAIRE AND SIGN WHERE INDICATED ON THE BOTTOM OF THE PAGE.
IF ANY OF YOUR ANSWERS TO 10, 10a, AND 10b WERE YES, PLEASE CONTINUE.

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



12) Please rate your pain by circling the one number that best describes your pain at its worst in the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

13) Please rate your pain by circling the one number that best describes your pain at its least in the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

14) Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

15) Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

16) What kinds of things make your pain feel better (for example, heat, medicine, rest)?

_____

_____

17) What kinds of things make your pain worse (for example, walking, standing, lifting)?

_____

_____

18) What treatments or medications are you receiving for pain?

_____

_____

19) In the last week, how much relief have pain treatments or medications provided? Please circle the one 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

20) If you take pain medication, how many hours does it take before the pain returns?

1. ☐ Pain medication doesn't help at all	5. ☐ Four hours
2. ☐ One hour	6. ☐ Five to twelve hours
3. ☐ Two hours	7. ☐ More than twelve hours
4. ☐ Three hours	8. ☐ I do not take pain medication

21) Check the appropriate answer for each item.
I believe my pain is due to:

☐ Yes ☐ No 1. The effects of treatment (for example, medication, surgery, radiation, prosthetic device).
☐ Yes ☐ No 2. My primary disease (meaning the disease currently being treated and evaluated).
☐ Yes ☐ No 3. A medical condition unrelated to my primary disease (for example, arthritis).
Please describe condition: _____

22) For each of the following words, check Yes or No if that adjective applies to your pain.

Aching	☐ Yes	☐ No
Throbbing	☐ Yes	☐ No
Shooting	☐ Yes	☐ No
Stabbing	☐ Yes	☐ No
Gnawing	☐ Yes	☐ No
Sharp	☐ Yes	☐ No
Tender	☐ Yes	☐ No
Burning	☐ Yes	☐ No
Exhausting	☐ Yes	☐ No
Tiring	☐ Yes	☐ No
Penetrating	☐ Yes	☐ No
Nagging	☐ Yes	☐ No
Numb	☐ Yes	☐ No
Miserable	☐ Yes	☐ No
Unbearable	☐ Yes	☐ No

23) Circle the one number that describes how, during the past week, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

24) I prefer to take my pain medicine:

1. ☐ On a regular basis
2. ☐ Only when necessary
3. ☐ Do not take pain medicine

25) I take my pain medicine (in a 24 hour period):

1. ☐ Not every day
2. ☐ 1 to 2 times per day
3. ☐ 3 to 4 times per day
4. ☐ 5 to 6 times per day
5. ☐ More than 6 times per day

26) Do you feel you need a stronger type of pain medication?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

27) Do you feel you need to take more of the pain medication than your doctor has prescribed?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

28) Are you concerned that you use too much pain medication?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

If Yes, why? _____

_____

29) Are you having problems with side effects from your pain medication?

1. ☐ Yes 2. ☐ No

Which side effects? _____

30) Do you feel you need to receive further information about your pain medication?

1. ☐ Yes 2. ☐ No

31) Other methods I use to relieve my pain include: (Please check all that apply)

Warm compresses ☐ Cold compresses ☐ Relaxation techniques ☐

Distraction ☐ Biofeedback ☐ Hypnosis ☐

Other ☐ Please specify _____

32) Medications not prescribed by my doctor that I take for pain are:

_____

_____

Please sign the back of this questionnaire.

Appendix F. Consent Form

The Royal Marsden NHS Foundation Trust

Consent Form

Development of a breakthrough pain assessment tool

Study Protocol Number

Patient Identification Number:

Principal Investigator: Dr Andrew Davies

Please initial box

1. I confirm that I have read and understand the information sheet dated …….. (Version…….) for the above study and that I have had the opportunity to ask questions ☐
2. I understand that my participation is voluntary and I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I am willing to allow access to my medical records to check that the study is being carried out correctly. I have been assured that strict confidence will be maintained. ☐
4. I agree to take part in the above study. ☐

I would like to be informed of the results of the study. Y/N

I consent to take part in this study:

Name of Patient	Date	Signature
Researcher obtaining consent	Date	Signature

Appendix 12 Version 1.2 : 2nd Dec 2009

Appendix G. Research Ethics Committee Approval

NHS
National Research Ethics Service
The Royal Marsden Research Ethics Committee
St Georges University of London
South London REC Office (1)
Room 1.13
1st Floor - Jenner Wing
Blackshaw Road
Tooting, London
SW17 0RE

Telephone: 020 8725 0252
Facsimile: 020 8725 1897

07 July 2009

Dr Andrew Davies
Consultant in Palliative Medicine
Royal Marsden Hospital NHS Trust
(Honorary Contract Imperial College, London)
Department of Palliative Medicine
Royal Marsden Hospital
Downs Rd
Sutton, Surrey
SM2 5PT

Dear Dr Davies

Study Title: **Development of a Breakthrough Cancer Pain Assessment Tool: Stage 1**

REC reference number: **09/H0801/58**

The Research Ethics Committee reviewed the above application at the meeting held on 15 June 2009.

Ethical opinion

- The Committee discussed non-English speaking participants were part of the exclusion criteria and asked why.
- The safety aspect was raised where proposed home interviews were included. The Committee suggests that alternative arrangements should be made unless unavoidable.
- The Committee commented on how the sample size was decided upon. Part A61 of the application suggested that the final 10 patients going through to testing phase were missing.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Clinical Record File	1.0	
Expert Letter	1.0	29 April 2009
Participant Consent Form: Pre testing patient interviews	1.0	29 April 2009
Participant Consent Form: Patient Interviews	1.0	29 April 2009
Participant Consent Form: Testing validity of an algorithm	1.0	29 April 2009
Participant Information Sheet: Pre testing patient interviews	1.0	29 April 2009
Participant Information Sheet: Patient Interviews	1.0	29 April 2009
Participant Information Sheet: Testing validity of an algorithm	1.0	29 April 2009
Questionnaire: Expert Opinion Survey		
Letter from Sponsor		06 May 2009
Covering Letter		
Protocol	1.0	20 April 2009
Investigator CV		
Application	2.2	11 May 2009

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H0801/58	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

p.p.

Ms Shelley Dolan
Chair

Email: royalmarsden.rec@stgeorges.nhs.uk

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
"After ethical review – guidance for researchers"

Copy to: *Mr Gary Roper, Imperial College*
Ms Jane Lawrence, R&D, RMH

Appendix H. Research Ethics Committee Substantial Amendment Approval

NHS
National Research Ethics Service
The Royal Marsden Research Ethics Committee

St Georges University of London
South London REC Office (1)
Room 1.13
1st Floor - Jenner Wing
Blackshaw Road
Tooting, London
SW17 0RE

Tel: 020 8725 0252
Fax: 020 8725 1897

11 February 2010

Dr Katherine Webber
Clinical Research Fellow
Department of Palliative Medicine
Royal Marsden Hospital
Downs Road
Sutton, Surrey
SM2 5PT

Dear Dr Webber,

Study title: **Development of a Breakthrough Cancer Pain Assessment Tool: Stage 1**
REC reference: **09/H0801/58**
Amendment number: **01**
Amendment date: **21 January 2010**

The above amendment was reviewed at the meeting of the Sub-Committee held on 29 January 2010 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Case Report File	1.2	10 December 2009
Questionnaire: Breakthrough Pain Assessment Tool	1.0	10 December 2009
Participant Consent Form	1.2	02 December 2009
Participant Information Sheet	1.2	02 December 2009
Protocol	2.0	20 January 2010
Notice of Substantial Amendment (non-CTIMPs)	22920/91352/13/847/1826/16 3581	21 January 2010
Covering Letter		20 January 2010

This Research Ethics Committee is an advisory committee to London Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

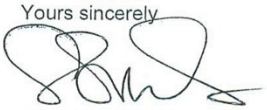
All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

09/H0801/58:	**Please quote this number on all correspondence**

Yours sincerely



Ms Simone Morris
Committee Co-ordinator

E-mail: royalmarsden.rec@stgeorges.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Jane Lawrence, R&D, RMH*
Dr A Davies, RMH

Appendix I. Development of Breakthrough Cancer Pain Diagnostic Algorithm

The Royal Marsden
NHS Foundation Trust

Patient Information Sheet

Diagnosis of breakthrough cancer pain: testing validity of an algorithm

Chief Investigator: Dr Andrew Davies

'We would like to invite you to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your doctor if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.'

What is the purpose of the study?
Breakthrough pain is the name given to pain that suddenly flares up, when the rest of the time your pain is well controlled. It is a specific type of problem and is important to identify to give appropriate advice and therapies. Studies have shown that it can be hard to diagnose this problem so we have developed some simple questions to help with this.

Why have I been chosen?
You have been invited to take part because you are a patient with cancer pain attending the Royal Marsden Hospital or St Clare's hospice. We are inviting 134 patients like you to take part in this study.

Do I have to take part?
It is up to you to decide if you want to take part. If you do decide to take part you will be asked to sign a consent form. If you do not want to take part it will not affect the standard of care you receive.

What will happen to me if I take part?
You will be asked the questions before the doctor sees you. The doctor will then see you as normal. We will compare the results from the questions with the doctor's assessment of your pain i.e. the questions will give us a yes/no answer about whether you have this type of pain and the doctor will decide whether he/she thinks you have this type of pain.
The questions will only take a few minutes, there is a maximum of 3, and the clinical review by the doctor will be part of your regular care.

What are the possible disadvantages of taking part?
Some people may find talking about their pain upsetting however you will be asked a maximum of 3 questions with set answers.

What are the possible benefits of taking part?
We cannot promise the study will benefit you. The information we get from your interview will help improve the assessment of other patients with this problem

Appendix 2 Version 1: 29th April 2009

What if something goes wrong?

If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the investigator (Dr Katherine Webber-see below for contact details). The normal National Health Service complaint mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College Clinical Research Governance Office.

Is there any extra support available?

The Royal Marsden Hospital PALS (Patient Advice and Liaison Service) are available to listen to your concerns, suggestions and experiences. They are independent from the research team and can also provide you with information about agencies and support groups

Will my taking part in this study be kept confidential?

If you agree to take part, a member of the research team, regulatory authority or sponsor organisation (Imperial College) may look at you medical records. Your name will not be disclosed and you will not be indentified in any report or publication that arises as a result of the study.

What will happen to the results of the study?

The results of the study will not be available for about 1 year. The researchers will write a report, which will be publicised at various medical meetings, and in various medical journals. If you would like a summary of results when available please inform your doctor or research nurse.

Who is organising and funding the research?

The study is being organised by the Department of Palliative Medicine at the Royal Marsden Hospital and is sponsored by Imperial College, London. The Palliative Care Research Fund is funding the study. The researchers will not be paid for including you in the study.

Who has reviewed the study?

The Royal Marsden Hospital / Institute of Cancer Research's and Imperial College's Research and Development Committee and Local Ethics Committee have reviewed the study and given it their approval.

Contact for further information

If you would like further information about the study, then please contact the researcher (see below).
Thank you for reading this information sheet, and for considering taking part in this research.

Dr Katherine Webber
Clinical Research Fellow in Palliative Medicine

Appendix J. Covering letter for expert survey

Dear.....,

We are currently embarking on the following research project.

Development of a breakthrough cancer pain assessment tool (BAT)

The principle investigator is Dr Andrew Davies and researcher is Dr Katherine Webber. This is contributing towards Dr Webber's M.D. (Res) at Imperial College, London.

We intend to develop and validate a reliable clinical tool to diagnose and assess breakthrough cancer pain (BTcP) in a variety of settings. There is currently no clinically validated tool for the assessment and diagnosis of cancer related breakthrough pain. We are generating content for the tool by interviews with patients and a survey of experts in BTcP or assessment tool development.

We have identified you as an expert in this field and would be grateful for your opinion in rating which items *you* consider relevant when clinically assessing BTcP. It involves completing the enclosed questionnaire and posting back to me in the envelope provided. If we receive a response we will use the results, together with patient interviews, to formulate a provisional breakthrough pain assessment tool. We will then ask for your opinion about this tool at a later date in a similar way.

Your involvement in the study will be kept confidential. Please do not put your name or other identifying information on the survey if you wish to remain anonymous. The completion of this survey is voluntary, by returning and completing this will indicate that you have given consent to participate.

The development of this tool has been funded by research grants to the Department of Palliative Medicine, Royal Marsden Hospital and is the intellectual property of the developers and the sponsoring academic organization, Imperial College, London.

If you have any questions about this survey, please contact the investigators (listed below).

Thank you for your time and consideration.

Yours Sincerely

Dr Andrew Davies
Consultant in Palliative Medicine
020 8661 3182
Andrew.davies@rmh.nhs.uk

Dr Katherine Webber
Clinical Research Fellow in Palliative Medicine
020 8661 3182
k.webber@imperial.ac.uk

Appendix K. Expert survey of breakthrough cancer pain domains

Breakthrough cancer pain: expert opinion survey

The aim of developing the breakthrough cancer pain clinical assessment tool (BAT) is to have a simple relevant tool that can be widely used in different settings. The tool will consist of 3 parts.

- Part 1: (completed by health professional)

Algorithm to determine whether a patient has a diagnosis of breakthrough cancer pain according to Association of Palliative Medicine (APM) definition; 'transient exacerbation of pain that occurs spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain'.

- Part 2: (completed by patient)

To characterise and assess severity of a patient's multidimensional breakthrough pain experience and its response to treatment.

- Part 3: (completed by health professional)

To complete relevant clinical information, which will determine treatment options

We are conducting this survey to explore the construct validity of the BAT. There are 2 sections. Section 1 consists of a list of pain items, you state your level of agreement with the relevance and importance of each item in the clinical assessment of breakthrough cancer pain. Section 2 consists of a list of factors for which you state your level of agreement in the determination of a management plan.

Please do not put your name or other identifying information on the survey if you wish to remain anonymous.

Section 1

The following items are relevant and important in the *clinical assessment* of breakthrough pain?

Please tick in the box.

	Strongly disagree	Disagree	No preference	Agree	Strongly agree
Location of breakthrough pain					
Radiation of breakthrough pain					
Quality / character of breakthrough pain					
Intensity of each / different episodes					
Average breakthrough pain intensity					
Worst breakthrough pain intensity					
Date breakthrough pain started					
Frequency of breakthrough pain					
Date / time last breakthrough pain					
Duration of each / different episode					
Duration of average episode					
Time between onset and peak intensity					
Predictability					
Exacerbating factors					
Relieving factors					

	Strongly disagree	Disagree	No preference	Agree	Strongly agree
Associated symptoms					
Similarity to background pain					
Distress caused by breakthrough pain					
Meaning of pain for patient					
Breakthrough pain medication (s) - type					
Breakthrough pain medication (s) - dose					
Frequency of usage of breakthrough medication					
Time to onset of pain relief for breakthrough medication					
Time to meaningful pain relief for breakthrough medication					
Amount of pain relief with medication					
Satisfaction with breakthrough medication					
Side effects of breakthrough medication					
Ease of use of breakthrough medication					
Non-pharmacological relieving factors					
Frequency of usage of non-pharmacological Rx					

	Strongly disagree	Disagree	No preference	Agree	Strongly agree
Time to onset of pain relief for non-pharmacological Rx					
Time to meaningful pain relief for non-pharmacological Rx					
Amount of pain relief with non-pharmacological Rx					
Satisfaction with non-pharmacological Rx					
Side effects of non-pharmacological Rx					

Interference with the following	Strongly disagree	Disagree	No preference	Agree	Strongly agree
Movement /walking					
Sleep					
ADLs					
Work					
Social Activity					
Relationships					
Mood					
Enjoyment of life					
Quality of life					

Section 2

The following factors are relevant and important in the determination of a management plan for a patient with breakthrough cancer pain

	Strongly disagree	Disagree	No preference	Agree	Strongly agree
Type of breakthrough pain (i.e. volitional/ non-volitional incident pain, spontaneous pain)					
Aetiology (i.e. cancer-related, cancer treatment-related, concomitant problem)					
Pathophysiology (i.e. nociceptive, neuropathic, mixed)					
Other factors (please state)					

What time factor is most relevant when asking patients about breakthrough pain? Please circle:
Now/ last 24hrs/ last week/ last month / other time period

If you have any further comments please state below:

Thank you for your time in completing this survey.

Appendix L. Patient Information Sheet: Patient Interviews

The Royal Marsden NHS Foundation Trust

Patient Information Sheet

Development of a breakthrough cancer pain assessment tool: patient interviews

Chief Investigator: Dr Andrew Davies

'We would like to invite you to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your doctor if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.'

What is the purpose of the study?

Breakthrough pain is the name given to pain that suddenly flares up, when the rest of the time your pain is well controlled. It is an important problem and studies have shown that it impacts people in different ways. We want to develop a way of assessing this type of pain. In order to do this we need to find out the most important things about the pain and the way it impacts on people with this condition.

Why have I been chosen?

You have been invited to take part because you are a patient with breakthrough cancer pain attending the Royal Marsden Hospital. We are inviting 10 patients like you to take part in this study.

Do I have to take part?

It is up to you to decide if you want to take part. If you do decide to take part you will be asked to sign a consent form. If you do not want to take part it will not affect the standard of care you receive.

What will happen to me if I take part?

A researcher will ask you some questions and encourage you to talk about your pain. The session will be tape-recorded, held in a private room and should take approximately 30 minutes.

What are the possible disadvantages of taking part?

Some people may find talking about their pain upsetting. If this happens, the interview can be stopped at any time. If the interview reveals problems with your pain or other symptoms you will be offered appropriate referral.

What are the possible benefits of taking part?

We cannot promise the study will benefit you other than giving you time to talk about your pain experience. The information we get from your interview will help improve the assessment of other patients with this problem.

Appendix 4 Version 1: Apr 29th 2009

The Royal Marsden NHS Foundation Trust

What if something goes wrong?

If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the investigator (Dr Katherine Webber-see below for contact details). The normal National Health Service complaint mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College Clinical Research Governance Office.

Is there any extra support available?

The Royal Marsden Hospital PALS (Patient Advice and Liaison Service) are available to listen to your concerns, suggestions and experiences. They are independent from the research team and can also provide you with information about agencies and support groups

Will my taking part in this study be kept confidential?

If you agree to take part, a member of the research team, regulatory authority or sponsor organisation may look at you medical records. Your name will not be disclosed and you will not be indentified in any report or publication that arises as a result of the study. The tape recordings will be analysed by the researchers and destroyed when the study ends.

What will happen to the results of the study?

The results of the study will not be available for about 1 year. The researchers will write a report, which will be publicised at various medical meetings, and in various medical journals. If you would like a summary of results when available please inform your doctor or research nurse.

Who is organising and funding the research?

The study is being organised by the Department of Palliative Medicine at the Royal Marsden Hospital and is sponsored by Imperial College, London. The Palliative Care Research Fund is funding the study. The researchers will not be paid for including you in the study.

Who has reviewed the study?

The Royal Marsden Hospital / Institute of Cancer Research's and Imperial College's Research and Development Committee and Local Ethics Committee have reviewed the study and given it their approval.

Contact for further information

If you would like further information about the study, then please contact the researcher (see below).
Thank you for reading this information sheet, and for considering taking part in this research.

Appendix M. Patient Information Sheet: Pretesting Patient Interview

The Royal Marsden NHS Foundation Trust

Patient Information Sheet

Development of a breakthrough pain assessment tool: Pre-testing patient interviews

Chief Investigator: Dr Andrew Davies

"We would like you to take part in a research study. Before you decide it is important for you to understand what it will involve. Please take time to read the following information carefully. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.'

What is the purpose of the study?
Breakthrough pain is the name given to pain that suddenly flares up, when the rest of the time your pain is well controlled. It is an important problem and studies have shown that it impacts people in different ways. We have interviewed patients and doctors about breakthrough pain and developed an assessment tool based on their responses. We need to find out if this assessment tool is clear and easy to follow.

Why have I been chosen?
You have been invited to take part because you are a patient with breakthrough cancer pain attending the Royal Marsden Hospital. We are inviting 10 patients like you to take part in this study.

Do I have to take part?
It is up to you to decide if you want to take part. If you do decide to take part you will be asked to sign a consent form. If you do not want to take part it will not affect the standard of care you receive.

What will happen to me if I take part?
You will be asked to complete the assessment tool with a researcher present. Whilst you complete it you will be asked to 'think aloud' whilst answering each question and to 'talk as much as possible' about your thoughts as you work your way through the form. This session will be tape-recorded and should take less than 20 minutes.

What are the possible disadvantages of taking part?
Some people may find talking about their pain upsetting. If this happens, the interview can be stopped at any time. If the interview reveals problems with your pain or other symptoms you will be offered appropriate referral.

What are the possible benefits of taking part?
We cannot promise the study will benefit you. The information we get from your interview will help improve the assessment of other patients with this problem

Appendix 8 Version 1: 29th April 2009

The Royal Marsden NHS Foundation Trust

What if something goes wrong?

If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the investigator (Dr Katherine Webber-see below for contact details). The normal National Health Service complaint mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College Clinical Research Governance Office.

Is there any extra support available?

The Royal Marsden Hospital PALS (Patient Advice and Liaison Service) are available to listen to your concerns, suggestions and experiences. They are independent from the research team and can also provide you with information about agencies and support groups

Will my taking part in this study be kept confidential?

If you agree to take part, a member of the research team, regulatory authority or sponsor organisation (Imperial College) may look at you medical records. Your name will not be disclosed and you will not be indentified in any report or publication that arises as a result of the study. The tape recordings will be analysed by the researchers and destroyed when the study ends.

What will happen to the results of the study?

The results of the study will not be available for about 1 year. The researchers will write a report, which will be publicised at various medical meetings, and in various medical journals. If you would like a summary of results when available please inform your doctor or research nurse.

Who is organising and funding the research?

The study is being organised by the Department of Palliative Medicine at the Royal Marsden Hospital and is sponsored by Imperial College, London. The Palliative Care Research Fund is funding this study. The researchers will not be paid for including you in the study.

Who has reviewed the study?

The Royal Marsden Hospital / Institute of Cancer Research's and Imperial College's Research and Development Committee and Local Ethics Committee have reviewed the study and given it their approval.

Contact for further information

If you would like further information about the study, then please contact the researcher (see below).
Thank you for reading this information sheet, and for considering taking part in this research.

Dr Katherine Webber

Appendix 8 Version 1: 29th April 2009

Appendix N. Patient Information Sheet: Psychometric Testing of BTCP Assessment Tool

Royal Surrey County Hospital NHS
NHS Foundation Trust

Patient Information Sheet

Development of a breakthrough pain assessment tool

Chief Investigator: Dr Andrew Davies

'We would like to invite you to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your doctor if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.'

What is the purpose of the study?
We have developed a questionnaire to try and assess breakthrough pain in a simple yet effective way. Before we can start using the questionnaire, we need to make sure that it works by comparing it in different patients.

Why have I been chosen?
You have been invited to take part because you are a patient with breakthrough cancer pain attending the Royal Surrey County Hospital. We are inviting 100 patients like you to take part in this study.

Do I have to take part?
It is up to you to decide if you want to take part. If you do decide to take part you will be asked to sign a consent form. If you do not want to take part it will not affect the standard of care you receive.

What will happen to me if I take part?
You will fill in the breakthrough pain questionnaire 4 times in total (followed by another general pain questionnaire). It will ask you some questions about your pain and should take no more than 15 minutes to complete.

1. The first time that you fill it in will be followed by a review from a pain specialist.
2. The second time you fill it in will be a few hours later (this can be done at home if you are not staying in the hospital and will be just 1 pain questionnaire).
3. The third and fourth times that you fill it in will fit round when you attend the hospital. This will be followed by a review from a pain specialist.

What are the possible disadvantages of taking part?
Some people may find it upsetting and tiring to fill in a questionnaire about their pain. If this happens, we can stop at any time and withdraw you from the study. If you withdraw from the study, data already collected would still be used unless you specify otherwise.

What are the possible benefits of taking part?

Appendix 11 Version 1.3 22nd Sept 2010

We cannot promise the study will benefit you other than giving you a chance to answer some questions about your pain. The information we get from you may help improve the assessment of other patients with this problem.

What if something goes wrong?

If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the investigator (Dr Katherine Webber-see below for contact details). The normal National Health Service complaint mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College Joint Research Office.

Will my taking part in this study be kept confidential?

If you agree to take part, your name will not be put on the questionnaires that you fill in. A member of the research team, regulatory authority or sponsor organisation may look at you medical records. Your name will not be disclosed and you will not be indentified in any report or publication that arises as a result of the study. The questionnaires will be destroyed after 10 years.

What will happen to the results of the study?

The results of the study will not be available for about 1 year. The researchers will write a report, which will be publicised at various medical meetings, and in various medical journals. If you would like a summary of results when available please inform your doctor or research nurse.

Who is organising and funding the research?

The study is being organised by the Department of Palliative Medicine at the Royal Marsden Hospital and Royal Surrey County Hospital and is sponsored by Imperial College, London. The Palliative Care Research Fund is funding the study. The researchers will not be paid for including you in the study.

Who has reviewed the study?

The Royal Marsden Hospital, Royal Surrey Hospital and Imperial College Research and Development Committees have reviewed the study and given their approval. The Royal Marsden Research Ethics Committee have reviewed the study and given a favourable ethical opinion.

Contact for further information

If you would like further information about the study, then please contact the researcher (see below).

Thank you for reading this information sheet, and for considering to take part in this research.

Dr Katherine Webber

Appendix 11 Version 1.3 22nd Sept 2010

Appendix O. Case Report File: Psychometric testing of BTCP Assessment Tool

Appendix 10 Case report file Patient ID no.

Development of a breakthrough cancer pain assessment tool

Patient Identification number:

Date of entry:

PI authorisation signature:

Date of signature:

Version 1.3 May 11th 2010

Appendix 10 Case report file Patient ID no.

Data collection: test 1

Date: **Time**

Age	
Gender	
Cancer diagnosis	
Stage of disease	**Stable disease** **Remission** **Progressive disease** **Long term survivor**
Site of metastases	
Anti-cancer treatment	**Pre-treatment** **On treatment-inc date started** **Treatment stopped** **No planned treatment**
ECOG performance status	
Background pain medication	
Breakthrough pain medication and frequency	

Appendix 10 Case report file Patient ID no.

Clinical assessment 1 Date: Time:

1. What type of breakthrough pain does the pt have? Please circle

volitional/ non-volitional incident pain/ spontaneous pain

2. What is the aetiology of the breakthrough pain?

Cancer-related/ cancer treatment-related/concomitant problem

3. What is the pathophysiology of the breakthrough pain?

nociceptive/neuropathic/ mixed

4. Is this patient's breakthrough pain adequately controlled?

Yes/No

5. Are you going to make changes to this patient's medication?

Yes/No If so, document changes and why

6. Are you referring for any other breakthrough pain control management e.g. interventional procedure, radiotherapy?

Yes/ No If so, document here

7. If you think the patient's breakthrough pain is not controlled but are not making any med changes or interventions please document why

Clinician Signature.....

Version 1.3 May 11th 2010

Appendix 10 Case report file Patient ID no.

Data collection test 3

Date

Time

Stage of disease	Stable disease Remission Progressive disease Long term survivor
Site of metastases	
Anti-cancer treatment	Pre-treatment On treatment-inc date started Treatment stopped No planned treatment
ECOG performance status	
Background pain medication	
Breakthrough pain medication and frequency	
Condition since test 1	Disease improved Disease stable Disease Progressed

Appendix 10 Case report file Patient ID no.

Clinical assessment 3 Date: Time:

1. What type of breakthrough pain does the pt have? Please circle

volitional/ non-volitional incident pain/ spontaneous pain

2. What is the aetiology of the breakthrough pain?

Cancer-related/ cancer treatment-related/concomitant problem

3. What is the pathophysiology of the breakthrough pain?

nociceptive/neuropathic/ mixed

4. Is this patient's breakthrough pain adequately controlled?

Yes/No

5. Are you going to make changes to this patient's medication?

Yes/No If so, document changes and why

6. Are you referring for any other breakthrough pain control management e.g. interventional procedure, radiotherapy?

Yes/ No If so, document here

7. If you think the patient's breakthrough pain is not controlled but are not making any med changes or interventions please document why

8. How would you rate this patient's breakthrough pain compared to the last time you assessed them for this study (test 1)?

Better Same Worse

Clinician Signature……

Version 1.3 May 11th 2010

Data collection test 4

Date

Time

Stage of disease	Stable disease Remission Progressive disease Long term survivor
Site of metastases	
Anti-cancer treatment	Pre-treatment On treatment Treatment stopped No planned treatment
ECOG performance status	
Background pain medication	
Breakthrough pain medication and freq.	
Condition since test 1	Disease improved Disease stable Disease Progressed

Appendix 10 Case report file Patient ID no.

Clinical assessment 4 Date: Time:

1. What type of breakthrough pain does the pt have? Please circle

volitional/ non-volitional incident pain/ spontaneous pain

2. What is the aetiology of the breakthrough pain?

Cancer-related/ cancer treatment-related/concomitant problem

3. What is the pathophysiology of the breakthrough pain?

nociceptive/neuropathic/ mixed

4. Is this patient's breakthrough pain adequately controlled?

Yes/No

5. Are you going to make changes to this patient's medication?

Yes/No If so, document changes and why

6. Are you referring for any other breakthrough pain control management e.g. interventional procedure, radiotherapy?

Yes/ No If so, document here

7. If you think the patient's breakthrough pain is not controlled but are not making any med changes or interventions please document why

8. How would you rate this patient's breakthrough pain compared to the last time you assessed them for this study (test 3)?

Better Same Worse

Clinician Signature……

Version 1.3 May 11th 2010

Appendix P. Breakthrough Pain: A qualitative study involving patients with advanced cancer

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ORIGINAL ARTICLE

Breakthrough pain: a qualitative study involving patients with advanced cancer

Katherine Webber · Andrew N. Davies · Martin R. Cowie

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Abstract
Context Breakthrough cancer pain is associated with a high burden of physical, psychological and social problems in quantitative studies. Individual experiences of living with breakthrough pain have not been studied.
Objectives This study aims to explore the individual experience of living with breakthrough cancer pain using a qualitative methodology.
Methods In depth semi-structured interviews were conducted in ten patients with breakthrough cancer pain, and a qualitative content analysis was performed.
Results The overarching themes that emerged were daily living, communication with health care professionals and management of breakthrough pain.
Conclusions Recognising the impact of breakthrough pain and the issues expressed by patients regarding communication and medication gives the clinician a framework for assessment and intervention.

Keywords Breakthrough cancer pain · Palliative care · Pain assessment · Adherence · Cancer · Pain management

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Introduction

Breakthrough cancer pain has been defined as "a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain" [1]. Breakthrough pain is common in patients with cancer pain (40–80%) [2] and is a significant cause of morbidity in this group of patients [3, 4]. Thus, breakthrough pain is associated with morbidity per se, other physical problems (e.g. difficulty mobilising, insomnia), psychological problems (e.g. anxiety, depression), and social problems (e.g. inability to work, social isolation) [3–5].

The aforementioned data are derived exclusively from quantitative studies (usually questionnaire-based studies) and represent the combined experiences of living with breakthrough pain in the population studied. However, breakthrough cancer pain is a heterogeneous condition, and breakthrough pain episodes vary both between individuals and also within individuals (at the same time) [6, 7]. The aim of this unique study was to explore the individual experiences of living with breakthrough cancer pain in patients with cancer using a qualitative methodology.

Methods

Setting and sample

The study was conducted at a large United Kingdom cancer centre, which consists of two hospital sites. The cancer centre serves a local population of 1.7 million and assesses and treats 40,000 patients each year. Referrals are received from throughout the United Kingdom and overseas, and the centre provides surgical and oncological management for a

broad range of cancers at different stages. The inclusion criteria for the study were: (1) age>18 years; (2) diagnosis of cancer; (3) diagnosis of breakthrough cancer pain; (4) ability to provide informed consent; (5) ability to undertake the study interview. To receive a diagnosis of breakthrough cancer pain, a patient was required to have controlled baseline pain (mild or less on a verbal rating scale) with transient exacerbations of more severe pain over the preceding week. A diagnostic algorithm was used to confirm the diagnosis of breakthrough cancer pain [1].

Royal Marsden Hospital's Committee for Clinical Research, Imperial College London's Research and Development Group and the Royal Marsden Hospital's Research Ethics Committee approved the study. All participants received a patient information sheet, were given the opportunity to ask a researcher about the study, were given 24 h to consider entering the study and provided written consent before entering into the study.

Data collection

An in-depth interview was conducted with each participant in a private room at a place of their convenience. At the start of the interview, the researcher defined breakthrough cancer pain (description of the United Kingdom Association of Palliative Medicine definition [1]) and explained that the purpose of the interview was to find out about the participant's experiences of this type of pain. A topic guide (Table 1), based on a review of the literature and discussions within a multi-disciplinary palliative care team, was loosely followed with flexibility in the sequence of topics according to the participant's responses. Interview questions focused on the patients' descriptions of their breakthrough pain, the impact it had on their life, meaning of the breakthrough pain and how they managed the breakthrough pain. The questions were deliberately open to enable participants to describe aspects of breakthrough pain experience important to them, as opposed to a more structured history-taking approach. The initial interview was used as a pilot to assess the participant, understanding and acceptability to the content and sequence of questions. On the basis of this mock interview, it was decided to begin by asking participants about their diagnosis and current treatment to help build a rapport and understanding between interviewer and interviewee. Information from the pilot also deemed it more acceptable to begin with open-ended general questions "Tell me about your breakthrough pain?" to enable the patient to narrate their most significant thoughts before questioning for more specific details about the impact on functioning. The more potentially sensitive questions such as, "Explain how the pain affects you?" and "Does anything worry you about your breakthrough pain?" were asked later in the interview when a rapport had been more firmly established. Each interview was audio taped, transcribed verbatim and reviewed prior to the next interview. In addition, "file notes" were written immediately after each interview. Recruitment continued until data saturation was reached and no new themes emerged from the interviews. A purposive sampling approach was used to try and include a cross-section of characteristics (gender, age, cancer type).

Table 1 Interview topic guide

Opening questions	Tell me about your breakthrough pain?
	What does your breakthrough pain feel like?
Impact on functioning	Can you explain how breakthrough pain has affected you?
	What is it like to live with breakthrough pain?
	How has breakthrough pain changed your life?
	How has breakthrough pain affected your day-to-day activities?
Psychological impact	What do you feel about your breakthrough pain?
	Explain how it affects you as a person
	How does it affect your mood?
Meaning of breakthrough pain	What does the pain mean to you?
	What do you understand about your breakthrough pain?
	Does anything worry you about your breakthrough pain?
Management of breakthrough pain	How do you manage your breakthrough pain?
	What helps you to tolerate the breakthrough pain?
	How do you feel about the medications that you take?
Communication of breakthrough pain	Can you tell me your experience of healthcare professionals listening to you about your breakthrough pain?
	What should healthcare professionals ask you to understand your breakthrough pain?
Concluding questions	What do you hope for in the future regarding your breakthrough pain?

Data analysis

The principal researcher (KW) repeatedly read through the transcripts to gain an understanding of the nature of the interviews. Content analysis methodology was used to initially organise data [8] and subsequently to identify the overarching themes [9]: the initial coding of units of text was performed in the margins of the transcripts; these codes were amalgamated into categories (of similar meaning), and then these categories were used to identify overarching themes. A second researcher reviewed the codes and overarching themes, and discussion was held between the researchers until both parties agreed on these outcome measures.

Results

Ten patients were approached to take part in the study; all the patients agreed to take part in the study, and all the patients completed the study. The characteristics of the participants are summarised in Table 2 (i.e. age, gender, diagnosis). All of the participants talked openly about their experiences of breakthrough pain (duration of interviews: 30–60 min), and there were a number of common experiences within this group of patients. The overarching themes that emerged were interference with daily living, communication with healthcare professionals and management of breakthrough pain.

Interference with daily life

Almost all participants reported that the breakthrough pain had had a major impact on their activities of daily living. Moreover, participants were often overwhelmed by the episodes of breakthrough pain. For example, patient 1 stated that during an episode of breakthrough pain: "It takes up my whole attention and I am just not able to do anything else except screaming and wishing it would stop."

Table 2 Participant characteristics

Pt no.	Sex	Age	ECOG	Diagnosis
1	F	59	4	Metastatic colorectal cancer
2	F	53	2	Metastatic ovarian cancer
3	F	32	1	Metastatic breast cancer
4	M	57	3	Metastatic bladder cancer
5	M	60	3	Metastatic rectal cancer
6	M	76	2	Metastatic prostate cancer
7	F	54	2	Metastatic breast cancer
8	M	60	2	Metastatic oesophageal cancer
9	M	67	2	Metastatic lung cancer
10	F	74	4	Metastatic breast cancer

Loss of control

The occurrence of breakthrough pain was associated with a perception of lack of control over their body. This was particularly apparent in participants with "spontaneous" ("idiopathic") breakthrough pain, i.e. unpredictable episodes of breakthrough pain. Patient 5 commented "you reach a point where you don't know whether you're going to collapse from the pain."

Change of lifestyle

Many participants had changed their lifestyle in order to try to ameliorate the frequency and/or severity of their breakthrough pain. Patient 6 summarized these changes as: "It's like you've had a big accident and you've lost your limbs...and you've got to change your lifestyle." These comments were echoed by patient 7: "You learn to live your life differently...I do think that to live in less pain you have to literally do the things, or not do the things that are going to cause the pain. And you always feel selfish...you have to do a lot of soul searching and coming to terms with what you can and can't do. Why do things that put you in pain?"

In some cases, the change in lifestyle had been extreme, often due to an association between movement and the onset of pain. For example, patient 1 stated: "I am now sort of bedbound and I am afraid to move very much...I mean my whole life is at a halt now." Similarly, patient 4 stated that he was unable to continue to work: "I own a restaurant for the last 36 years...you get up and go there and finding yourself not able to do it." However, patient 2 reported a much lower level of restriction: "I don't think it has affected my life really. I still go out with the girls if I want to on an evening...but I can't walk too far as sometimes that can bring the dull aches on."

It was sometimes difficult for participants to differentiate the impact of breakthrough pain from the other effects of the cancer. Patient 8 commented: "I've lost my day to day activities...if you took away the pain, I'd still have the tiredness...You could say it's to do with weakness, tiredness and pain."

Breakthrough pain was also associated with significant psychological distress: patient 4 stated: "I feel very depressed when that (pain) comes on." Similarly, patient 3 stated: "I think when the pain is not there you can be a lot more positive and get on with a normal life...whereas when the pain is there that kind of goes away a bit."

Pain as a reminder of the cancer

All of the participants had cancer, and all had breakthrough pain related to the underlying malignant disease. Hence, the

occurrence of breakthrough pain was a reminder of the presence of cancer (and in many cases the presence of advanced/incurable cancer). Patient 3 commented: "If you are feeling pain then you are feeling down and the cancer is constantly on your mind and it is kind of like more of an uphill struggle, you feel like you are climbing up a great big mountain."

Communication with healthcare professionals

Expressing subjective experiences

Pain is a subjective phenomenon, and the participants often had difficulty in relating their experiences to health professionals. For example, patient 8 commented: Pain... it's difficult to describe pain...it's really hard to talk to someone about the pain of cancer when the only person who's suffered it is themselves." Similarly, patient 1 commented: "What can you understand about anybody else's pain, everyone has to go through their own. You can imagine how bad it is from anybody but it is always different...it is all terribly subjective."

Often, participants found it easier to describe their breakthrough pain in terms of severity (e.g. 'severe', 'excruciating'), emotions (e.g. 'agony', 'horrible feeling') or impact (e.g. 'makes me groan', 'causes screaming'), rather than in terms of traditional pain descriptors (e.g. 'burning', 'stinging').

Use of language/pain scales

The term "breakthrough pain" was not widely understood by patients, and some participants expressed difficulty in differentiating between continuous background pain and intermittent breakthrough pain. Patient 3 commented: "I think it's been difficult to know what breakthrough pain is... I suppose some of it is around the different definitions...and getting a shared language between patients and health professional."

Patient 6 talked about the difficulty in expressing the severity of pain using numerical rating scales: "And then erm to have a system of 1 to 10. It's alright provided both patient and doctor know what they are talking about. I mean what is 1? What is 10... you can go from 1 to 10 as easy as pie." Patient 9 also commented on the use of numerical rating scales: "On this scale, this 1 to 10, I suppose my version of no pain would be 4."

Impact of language

Patient 7 described how the words used by a particular healthcare professional had influenced her perception of the breakthrough pain: "The doctor said, 'You've all been eaten away here.' Now the pain feels like a rat gnawing at you that couldn't stop." She used this image to describe her pain throughout the interview, and it was clear that the aforementioned consultation had had a significant/negative impact on her experience of the pain.

Need to understand pain

All of the participants stated that it was important to receive a clear understanding of the underlying cause of the breakthrough pain from healthcare professionals ("If I've got a pain I want to understand why I've got a pain [patient 5])."

Patient 2 felt that understanding the cause of the breakthrough pain had alleviated her concerns about the meaning of the pain: "It is the not knowing, I think that is always the worst...if it can be explained it is very helpful if not relieving and reassuring even, to some people." Similarly, patient 3 explained that a better understanding of the pain had led to improvements in the treatment of her pain: "I didn't want my pain to go as it was a way for me to monitor my cancer...I know now that it's not such a link, knowing I can be pain free came as a relief."

Management of breakthrough pain

Conflict regarding medication

Every participant was taking opioid analgesia for their breakthrough pain, and there were many concerns expressed about the use of this group of drugs (e.g. not wanting to mask the pain, morphine as a 'last resort', fear of side-effects, fear of addiction). Indeed, patient 10 stated: "at the moment I'm still trying to keep as much control of my life as I can and I don't want that (morphine) cos I feel too woozy with it and I don't want to sit here sort of in a half silly state, thank you."

However, the concerns were often tempered by the acceptance that such medication was often necessary to manage the breakthrough pain and to maintain a reasonable quality of life. For example, patient 2 stated: "I mean I don't like the idea that I'm on morphine but erm on this level that I'm on it seems to be pretty good. I am just grateful there is something extra that I can take quite honestly... I always make sure I have tablets with me so in the back of my mind I know I'm covered so I can just do whatever I want to do."

Specialist expertise

The participants often stated that their breakthrough pain had been sub-optimally managed by their regular physicians and had only become well controlled after referral to

the palliative care/pain services. Patient 3 commented that: "My G.P. (family practitioner) didn't seem to take me seriously and it took me a while to get tapped into the pain team who were the most help. I think it is best managed by the pain team."

The participants recognised that treatment needed to be individualised and commented that the tolerability of the drug was just as important as the efficacy of the drug. Patient 7 described her experiences: "You've got to go through a trial to see which one works for you and I'm glad I did that...if you're put on the wrong dose to start with and you're as sick as I was then you don't believe the pill's ever going to work...so what you want is something that takes you enough out of pain...but not take you to gaga land."

Discussion

The information derived from this study demonstrates the true impact of breakthrough pain on activities of daily living. Thus, many of the participants had needed to make changes to their lifestyle, and in some cases, the changes in lifestyle were profound (e.g. giving up working). Such lifestyle changes have implications not only for the patient but also for the patient's family and the wider society. However, other participants had needed to make lesser changes to their lifestyle, which may reflect differences in breakthrough pain experience and/or breakthrough pain management. It was evident that lifestyle changes were associated with feelings of 'loss of role' and contributed to psychological distress associated with breakthrough pain.

It has been recommended that the assessment of patients with breakthrough pain should include an appraisal of any interference with activities of daily living [1]. Such information will help to identify potential strategies to help the patient cope with their breakthrough pain (e.g. physical adaptations, social services) [10] and can be used as a surrogate measure of the efficacy of therapeutic interventions [1].

Communication difficulties were identified as a major problem and often related to issues around the assessment of breakthrough pain. Currently, there is no universally accepted definition of breakthrough pain, and the term is used inconsistently within clinical practice [1]. Indeed, the term is frequently/incorrectly used to describe any exacerbation of pain, rather than an exacerbation of pain in a patient with well-controlled background pain. Hence, it is not surprising that some patients were unsure about the meaning of the term "breakthrough pain". Furthermore, patients found it difficult to use conventional pain descriptors and also to use conventional pain scales (i.e. numerical rating scales).

The successful management of breakthrough pain is dependent on a thorough assessment of the pain (and ongoing thorough re-assessment of the pain) [1]. Indeed, inadequate assessment is recognised as one of the barriers to good pain control [11, 12]. It is vital that healthcare professionals ask the "right" questions and equally that patients are clear about what they are actually being asked. Moreover, any medical terminology should be appropriately defined.

Many of the participants highlighted internal conflicts regarding the use of opioid analgesia. Indeed, in some cases, participants would rather suffer from the pain than suffer from the adverse effects of the pain medication. Concerns about adverse effects of pain medication are a common reason for non-adherence [7] and thus common reason for poor pain control [12]. Patients need to be reassured about the safety of pain medication and regularly assessed for the presence of adverse effects; patients with adverse effects should have their treatment reviewed, and (if necessary) should be referred to specialist services (i.e. palliative care/pain services). Thus, there are an increasing number of options for the management of breakthrough cancer pain (http://www.breakthroughcancerpain.org).

There were a number of limitations to this research project. This study was conducted in a specialist cancer centre; therefore, results may not be generalised to other palliative care populations. However, semi-purposive sampling was used to recruit patients with a variety of diagnoses and ages to try and access different views. The sample size was relatively small and provided information that can only be used to generate further hypotheses. The cross-sectional nature of the study did not allow for the examination of changes in breakthrough cancer pain over time. Finally, none of the participants were familiar with the term 'breakthrough cancer pain' and all had had previous episodes of uncontrolled, continuous background pain. As a result, it was often difficult for participants to discuss only their previous breakthrough pain experience and not include the episodes when their pain was uncontrolled. This could mean that many of the themes identified may also be relevant to cancer pain in general. This highlights an important issue for all research into breakthrough cancer pain, and investigators must be aware of participants' difficulty in separating various aspects of their pain experience and always define clearly the pain they are investigating.

Acknowledgements This study was funded by the Royal Marsden Hospital Department of Palliative Medicine Research Fund and a United Kingdom Association of Palliative Medicine research bursary. We would like to thank Natalie Pattison for her valuable support.

Conflict of interest The research sponsor is Imperial College, London that employs the authors Katherine Webber and Martin Cowie. The authors have full control of the primary data and agree to allow the journal to review this data if necessary.

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