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Coláiste na Tríonóide, Baile Átha Cliath

The University of Dublin

**The assessment, identification and management
of Circadian rest-Activity Rhythm Disorders in
patients with advanced Cancer (CARDiC)**

A thesis submitted to the University of Dublin for the degree of Doctor
of Philosophy in Clinical Medicine
School of Medicine

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Declaration

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
BMAL1	Brain and Muscle ARNT-Like 1 gene
bPSQI	Brief Pittsburgh Sleep Quality Index
BLT	Bright light therapy
BMI	Body mass index
CARD	Circadian rest-Activity Rhythm Disorder
CBT-I	Cognitive behavioural therapy for insomnia
CFS	Cognitive Functioning Scale
CLOCK	Circadian locomotor output cycles kaput gene
CR	Circadian rhythms
CRP	C-reactive protein
cry	cryptochrome
DLMO	Dim light melatonin onset
ECOG	Eastern Cooperative Oncology Group
EFS	Emotional Functioning Scale
ESS	Epworth Sleepiness Scale
ET	Evening type
GDI	Global Distress Index
GHS	Global Health Status
I<O	Dichotomy index
ISI	Insomnia Severity Index
KPS	Kessler Psychological Distress Scale
LPA	Low level physical activity
MEQ	Morningness-Eveningness Questionnaire
MSAS-SF	Memorial Symptom Assessment Scale – Short Form
MT	Morning type
MVPA	Moderate to vigorous physical activity
NPV	Negative predictive value
NREM	Non-rapid eye movement
OSA	Obstructive sleep apnoea

per	period
PFS	Physical Functioning Scale
PSG	Polysomnography
PPV	Positive predictive value
PSLP	Percent sleep
PPI	Patient and public involvement
QoL	Quality of Life
r24	24-hour autocorrelation coefficient
RAR	Rest-activity rhythms
REM	Rapid eye movement
RFS	Role Functioning Scale
RLS	Restless leg syndrome
SCN	Suprachiasmatic nuclei
SFS	Social Functioning Scale
SE	Sleep efficiency
SOL	Sleep onset latency
WASO	Wake after sleep onset

ABSTRACTS

Simple abstract

People with cancer may experience restless nights and be less physically active during the daytime. People with cancer may also find that the amount of time they spend being physically active or resting changes a lot between days. Research has found a link whereby people with these changes in their rest and physical activity tend to have more worse symptoms, poorer quality of life and a shorter lifespan. However, it was unclear how common the problem was and who tends to get it. There was also no agreed way of diagnosing the problem, or of treating it. The purpose of this research project was to provide some answers to these questions. At first, a group of experts created a standard way to assess and report on people's daytime and nighttime levels of rest and physical activity, and a way to diagnose people who have a problem in these patterns. A set of questions, created to identify people that are at risk of unusual rest and physical activity patterns, failed to recognise those people. However, a study did show that up to 60% of people with advanced cancer have a problem with their rest and physical activity patterns. The study showed that people with more severe disease and those who are less able to carry out their daily activities are examples of factors associated with the problem. People with the problem are also likely to have more symptoms, including feeling more tired and drowsy, have more distress from their symptoms, poorer quality of life and are less able to function as well as they would like. A second study aimed to improve the rest and physical activity patterns of people with advanced cancer, using a sleep course, daily light therapy, and a personalised activity plan. People felt able, and happy to, take part in the study and early data suggests potential benefits in improving people's activity patterns, symptoms and quality of life.

Scientific abstract

In health, people demonstrate a circadian, or 24-hour, physical activity pattern with more physical activity in the day and less physical activity at night. A sub cohort of patients with cancer experience nighttime restlessness and daytime sedentariness, altered physical activity spread across the 24-hour period, or a significant change in activity patterns between days. These changes are more likely in advanced cancer. When this occurs, research highlights that patients have increased symptoms, worse quality of life and a shorter survival. An international e-Delphi study has identified important features of circadian rest-activity rhythm disorders (CARDs), including diagnostic criteria, and standardised assessment methodology. An observational study failed to demonstrate validity of a related screening tool to detect circadian rest-activity rhythm disorders. However, the study highlighted CARDs to be common (60%) and several patient-related factors associated with circadian rest-activity disruption including metastatic organ involvement and higher inflammatory status, for example. It also highlighted significant associations with a CARD diagnosis and increased symptom burden, including fatigue and daytime sleepiness, increased symptom-related distress, poorer global quality of life and poorer functioning subscales. A subsequent feasibility study has proven the acceptability, usability and preliminary efficacy of a multimodal non-pharmacological intervention consisting of cognitive behavioural therapy – insomnia (CBT-I), bright light therapy, and a personalised activity plan. Improvements were seen in important clinical outcomes (symptoms and quality of life measures) and circadian rest-activity rhythm parameters (dichotomy index and 24-hour autocorrelation coefficient).

AIMS OF THE THESIS

1. To outline the physiology and assessment of circadian rhythms
2. To identify the current evidence-base for circadian rhythm disorders in patients with cancer
3. To develop and validate diagnostic criteria and a screening tool to identify circadian rest-activity rhythm disorders in patients with cancer
4. To characterise circadian rest-activity rhythms in patients with advanced cancer
5. To identify associations between circadian rest-activity rhythm disorders and patient characteristics and patient outcomes
6. To identify potential interventions to improve circadian rest-activity rhythm disorders in patients with advanced cancer
7. To assess the feasibility and acceptability of a multi-modal interventional approach to improving circadian rest-activity rhythm disorders in patients with advanced cancer

CHAPTER 1. CIRCADIAN RHYTHMS AND THEIR INVESTIGATION

Aims of chapter 1:

- 1 To outline circadian rhythm physiology, terminology and influencing factors
- 2 To describe investigative approaches to circadian rhythms, including strengths and limitations
- 3 To highlight complications associated with circadian rhythm disorders and the relevance to patients with advanced cancer
- 4 To highlight how circadian rhythm disorders may be classified and diagnosed

1.1. Circadian rhythm physiology

Circadian rhythms (CRs) are complex physiological processes that occur in a temporal fashion around a 24-hour period (1, 2). Within the human body, this includes 24-hour patterns of sleep, appetite, cognition and mood (3). CRs were first studied in 1729 by the French astronomer, Jean Jacques Ortous de Mairan (4). De Mairan noted the rhythmical curling and uncurling of plant leaves across the course of the day, even when kept in darkness.

Three main clocks (a solar, biological and social clock) influence our daily habits (5). Coordination of the biological clock involves input signals (zeitgebers), a central coordinating centre (pacemaker), and output processes which communicate with peripheral centres throughout the body (2). A 'master clock', situated in the two suprachiasmatic nuclei (SCN) of the anterior hypothalamus, contains an abundance of 'clock cells' and oscillatory machinery (6-8). At a cellular level, throughout the body, processes occur in a coordinated autoregulatory fashion through the expression of various genes and transcription-translation feedback loops (1, 6, 7). Several genes are implicated in circadian regulation, with a significant role attributed to the period (*per*), cryptochrome (*cry*), circadian locomotor output cycles kaput (*CLOCK*) and Brain and Muscle ARNT-Like 1 (*BMAL1*) genes (7). Circadian genes have been identified within the central

'master' clock, the suprachiasmatic nucleus (SCN), and peripherally in individual cells (7).

Circadian gene transcriptional feedback loops, and the generation of circadian components, are central to rhythmicity (7). Early studies on drosophila flies found that mutations in *per* genes impacted the circadian rhythm of adult fly emergence and locomotor activity (9). These mutations included the absence of a circadian rhythm (*per*⁰), a short 19 hour rhythm (*per*^s) and a long 29-hour rhythm (*per*^l) (9). The *CLOCK* gene also has a role in circadian function, with mutations resulting in altered rhythm periodicity (10).

Cellular rhythmicity begins with *BMAL1*, identified at circadian clock sites, combining with *CLOCK* to form a heterodimer (11). The *CLOCK*-*BMAL1* heterodimer then binds to the E-box element proximal to relevant circadian genes, including *per* and cryptochrome (*cry*) genes, with subsequent activation of the negative transcription regulator proteins, *per* and *cry*, and the accumulation of associated mRNA as the day progresses (7, 11-13). *CLOCK*-*BMAL1* activities are communicated to the rest of the cell via circadian output genes (3). Negative feedback to *CLOCK* and *BMAL1* transcription is provided by the heterodimer activating the orphan receptor *REV-ERB* α , and the accumulation of *cry* and *per* proteins (7, 12). Inhibitor proteins are subsequently degraded during the circadian night, allowing the cycle to begin again (3).

Although autonomous circadian rhythmicity is seen within SCN neurons and peripheral cells in culture, the central SCN clock is able to coordinate and synchronise peripheral clocks (7). The importance of the SCN in circadian rhythms was highlighted following arrhythmicity developing in subjects with SCN damage (14). Following SCN transplantation, the host animal develops the donor's rhythmicity and, if a donor SCN is transplanted into a host with a partial SCN lesion, then dual rhythmicity may be observed (14).

The SCN, containing around 10,000 gamma-aminobutyric acid (GABA)ergic neurons, is made up of a core region and a more active shell region which is

presumed to be the main pacemaker (3, 6, 13). The core region receives input from four principal sources including the retinohypothalamic tract (RHT), the geniculohypothalamic tract (GHT), the median raphe nucleus and other nuclei within the brain (8, 15). The SCN then integrates external signals through neural responses and neurotransmitter release before communicating with, and orchestrating, peripheral clock rhythms (8). The core neurons communicate with the remaining SCN primarily through vasoactive intestinal peptide, gastrin-releasing peptide and gamma-aminobutyric acid (GABA) (6). The shell region neurons communicate with other cells by releasing arginine vasopressin and GABA, to play a role in various rhythms, including behaviour (6, 13). Output from both core and shell regions travel within the hypothalamus and has projections to the central nervous, limbic, sleep-arousal, autonomic nervous, and endocrine systems, along with peripheral oscillators (6, 8, 13, 16).

Neuroendocrine and neurotransmitter release, along with autonomic neural activity, are amongst several SCN outputs (3). SCN neurons have a spontaneous firing rate (SFR), cycling between >10 and <1 Hz in culture, with heightened activity in the circadian day (3). SCN output, including GABA and neuropeptide release, is predominantly to hypothalamic and thalamic nuclei (3, 8). These feed into the control of feeding-fasting, temperature and hormonal rhythms, including fluctuations in blood pressure, blood glucose and drug metabolism, for example (3). Neural output is predominantly via the autonomic system (7). This includes local projections to nuclei within the hypothalamus and thalamus, and further projections to areas including the preoptic nucleus and pineal gland (8). Projections to the pineal gland release noradrenaline during the nighttime, activating beta-1 and alpha-1 adrenergic receptors, and trigger melatonin release (15). Melatonin has short-term actions, including suppressing SCN neuronal activity, and long-term actions, including circadian phase shifts and rhythm amplification (8).

CRs are endogenous in nature but they are susceptible to environmental influence (17). CRs can be entrained, whereby circadian oscillators are synchronised to the environment (1, 6, 18). Entraining signals, or zeitgebers, include light, temperature, feeding and exercise (1, 6, 18). In order to be effective, the organism needs to be

sensitive to the zeitgeber and be able to synchronise several circadian clocks with the environment (17).

The most powerful synchronising zeitgeber is light which is detected by specialised autonomous retinal photosensitive ganglion cells (rPGCs) within our eyes (6, 19). rPGCs contain melanopsin, a photopigment, which is particularly sensitive to blue light (20). The RHT, in response to light activation of the rPGCs, releases glutamate and pituitary adenylate cyclase-activating peptide which triggers increased SCN firing (6-8). This input is modulated by serotonin via the median raphe nuclei, with an enhanced effect during the daytime and inhibitory effect at night (8). During circadian day, the SFR is high and light has minimal impact on the circadian clock (3). However, towards the circadian night, light is able to influence the SFR (3). Following light exposure in the evening, the sleep-wake phase shifts and nocturnal melatonin production is inhibited (7).

To a lesser degree, feeding habits can also impact CRs. Studies in mice have shown that a 12-hour adjustment to scheduled feeding can advance peripheral clocks, although rest-activity rhythms remain more closely aligned with the peripheral clock status than the feeding schedule (21).

1.2. Circadian rhythm terminology

Circadian rhythms occur cyclically over a given time scale or 'period' (2). Timing of events within a period, such as the peak level of a given biomarker, is known as the 'phase' and this can occur earlier (be advanced) or later (be delayed) in relation to its original or expected timing (2). In cyclical rhythms, the timing between successive phases can be reflected by the period of the rhythm, which in circadian rhythms is roughly 24 hours (2).

The effect of a zeitgeber, and the magnitude of its influence, differs depending on the timing of exposure and this can be reflected by phase shifts, or changes to the phase time, in phase response curves (PRC) (2, 22). To understand the impact of a zeitgeber, the response should be evaluated over several phases to produce the PRC.(2) For example, SCN neuronal activity is usually diminished during the night,

but with light exposure and RHT activation, neuronal activity is increased and a phase shift occurs (6). Using a bright light impulse prior to the midpoint of the melatonin circadian rhythm delays the reduction of SCN activity, whereas delivery after the midpoint of the melatonin circadian rhythm advances the reduction of SCN activity (22). Exercise can also act as a zeitgeber. Melatonin and physical activity were measured under free-living conditions in 52 young, predominantly sedentary, adults who were assigned to either morning or evening exercise (23). Early morning exercise resulted in significantly phase advancement and earlier sleep onset when compared to the evening exercise group. Exercise did not impact the quality, fragmentation, or duration of sleep. The magnitude of phase advancement was greater for those with a preference for later sleep and wake times, also described as a later chronotype, and advances occurred with both morning and evening exercise. For those with a preference for earlier sleep and wake times, described as an early chronotype, a phase advance was seen with morning exercise and a phase delay with evening exercise.

Circadian rhythms are analysed in various ways with several descriptive terms being used (Table 1). This may include the timing of events, such as peak levels of a measure in relation to the 24-hour clock, or how strong and stable the circadian rhythm is. Rhythms typically show fluctuations of a measure around a mean point, with minimum and maximum values (2). This varied approach to circadian rhythm analysis can be demonstrated using 24-hour rest-activity rhythms. The time of a repeating cycle (period) or time of the maximum activity (acrophase) may be noted (24). The difference between average and highest activity levels (amplitude), timing of the least active 5 hours (L5), timing of the most active 10 hours (M10), or the average activity level (mesor) may be considered (24, 25). The variability of the rhythm compared to the overall amplitude within a 24-hour period (intradaily variability), or the stability of the rhythm over days (interdaily stability) may also be considered (24). Additional methods for assessing and reporting different circadian rhythms will be highlighted throughout the thesis.

Table 1. Descriptive of circadian measures

Circadian measure	Description
General terms	
Acrophase	The timing of peak level (26)
MESOR	The average level over 24 hours (26)
Up-MESOR	The timing of switching between low and high activity (26)
Down-MESOR	The timing of switching between high and low activity (26)
Amplitude	The difference between average and maximum level (25)
Double amplitude	The difference between maximum and minimum levels of the cosine function (27)
Cortisol / melatonin specific	
Area under the curve (AUC)	Total cortisol levels under the curve of all measurements. Larger AUC indicates circadian disruption (28)
F test	To test the zero amplitude hypothesis (29)
Diurnal slope / diurnal decline phase	Rate of decline from cortisol peak (30-33)
Phase angle of entrainment	The timing of the peak of the first waveform relative to awakening (34)
Dim light melatonin onset (DLMO)	Timing when melatonin exceeds a threshold considering mean and standard deviations of melatonin prior to the melatonin rise on 3 days (35)
Diurnal cortisol variability	Difference in cortisol value at earliest collection time and nighttime point (Morning – Night) / Morning (36)
Cortisol variations (VAR)	0800 cortisol – 2000 cortisol / 0800 cortisol (37)
Cortisol awakening response	Cortisol slope after awakening (waking and +30 minutes sample) (31)

CAR_i	Cortisol 30 minutes after awakening – cortisol at awakening (33)
CAR_{auci}	Area under the curve during first 60 minutes after awakening (33)
Cortisol variability	Morning cortisol – night cortisol / morning cortisol (36)
Actigraphy specific – General activity	
Mean activity	Mean of daily activity (38)
Intradaily variability (IV)	A measure of rhythm fragmentation (39)
Interdaily stability (IS)	A measure of rhythm stability between days (39)
VL5	Mean activity value of the 5 least active hours
L5	Mean timing of the 5 least active hours (39)
VM10	Mean activity value of 10 most active hours (39)
M10	Mean timing of the 10 most active hours (39)
Relative amplitude	$(VM10 - VL5) / (VM10 + VL5)$ (39)
R-squared	Rhythmicity coefficient of the sleep wake cycle (26)
Bathypase	Time of lowest activity (40)
Circadian quotient	Amplitude / mesor (41)
Rhythm quotient	$A_{24HR} / (A_4 + A_8 + A_{12})$ (41)
Circadian function index (CFI)	A combined measure of IV, IS and RA (39)
Dichotomy index (I<O)	Activity in bed (I) compared to activity out of bed (O) (26, 42)
Dichotomy index for nighttime restfulness	I<O percentage of activity in bed which falls below median activity out of bed (31)
Dichotomy index for daytime sedentariness	O<I percentage of activity out of bed which falls below median activity in bed (31)
24-hour autocorrelation coefficient (r24)	Correlates activity at same time points between different days, considering consistency and regularity. Higher values are more stable (31, 42)

Day-night activity balance	Ratio of activity during the day and night (41)
Night-day sleep balance	Ratio of sleep during the night and day (41)
Total wake time (day)	Total amount of time spent awake (43)
Movement and fragmentation index	Sum of percent of mobile minutes and immobile bouts <1 minute / no. immobile bouts within a time interval (44)
Rhythm index	A measure of quality and regularity of the inactive state (35)
P1-1	Probability of staying in inactive/rest state (35)
Actigraphy specific - sleep-wake activity	
Bed time (BT) / time of retiring	Time to bed and lights switched off (45, 46)
Get up time (GUT) / time of waking up	Time woke up in the morning (45, 46)
Total time in bed	Time between BT and GUT (45, 46)
Sleep onset latency	Number of minutes to fall asleep. Time between BT and sleep onset (45-47)
Latency to persistent sleep	Number of minutes to persistent sleep (46)
Wake after sleep onset	Sum of all wake periods whilst in bed OR between sleep onset and offset (44, 46)
Total sleep time	Time between bedtime and wake time (44) OR total time in bed scored as asleep (46)
Total nighttime sleep	Sum of all sleep periods whilst in bed (44)
Sleep midpoint	Midpoint of time in bed (45, 46)
Sleep motor activity (SMA)	Mean number of movements in a given epoch (45)
Diurnal motor activity (DMA)	Mean number of movements in each epoch (45)
Wake minutes	Duration of wake during sleep period (38, 46)

Wake episodes / number of awakenings in the night (NWAK)	Number of wake episodes during sleep period (47)
Mean duration of wake episodes	Mean duration of all wake episodes (46)
Long wake episodes	Number of wake episodes lasting 5 minutes/+ (46, 48)
Longest wake episode	Duration of the longest wake episode (46)
Sleep fragmentation index (SFI)	Number of awakenings / total sleep time in minutes (46)
Sleep efficiency	Proportion of time asleep whilst in bed (28, 46)
Short burst inactivity index	Zero activity of 1 minute / zero activity of any duration (46)
Time napping and sleep minutes	Duration of sleep episodes during wake period (38)
Long sleeps	Frequency of long naps lasting 5 minutes/+ (48)
Sleep episodes	Number of sleep episodes during wake period (48) (Grutsch 2011) OR number of blocks of continuous sleep epochs (46)
Mean duration of sleep episodes	Mean duration of all sleep episodes (46)
Sleep episodes 5 min/+	Number of sleep episodes whose duration lasts 5 minutes or more (46)
Longest sleep episode	Duration of longest sleep episode (46)
Time awake spent immobile	The percentage of time spent awake and immobile (49)
Early morning awakening	Period of wakening in the morning lasting 30 minutes or longer (43)
% sleep (up interval)	Percent of time asleep between two attempted sleep periods (50)

% sleep (down interval)	Percentage of time asleep during attempted sleep time (50)

This thesis focusses on circadian, or 24-hour, rhythms. Rhythms can occur over longer and shorter time periods. Infradian rhythms extend beyond 24-hour periods and include monthly menstrual cycles and annual hibernation periods (51). Ultradian rhythms describe periods less than 24-hours, and can often be seen occurring within known 24-hour circadian rhythms, such as changes within the hypothalamic-pituitary-adrenal axis (51).

1.3. Circadian rhythms and their investigation

Various human CRs exist and normal rhythms, or patterns, have been demonstrated in healthy individuals (Figure 1). Commonly investigated CRs (melatonin, cortisol, body temperature, sleep-wake and rest-activity), along with their investigational approaches, will be discussed. Many CRs exist, including the expression of clock genes, but these will not be covered in this chapter (52).

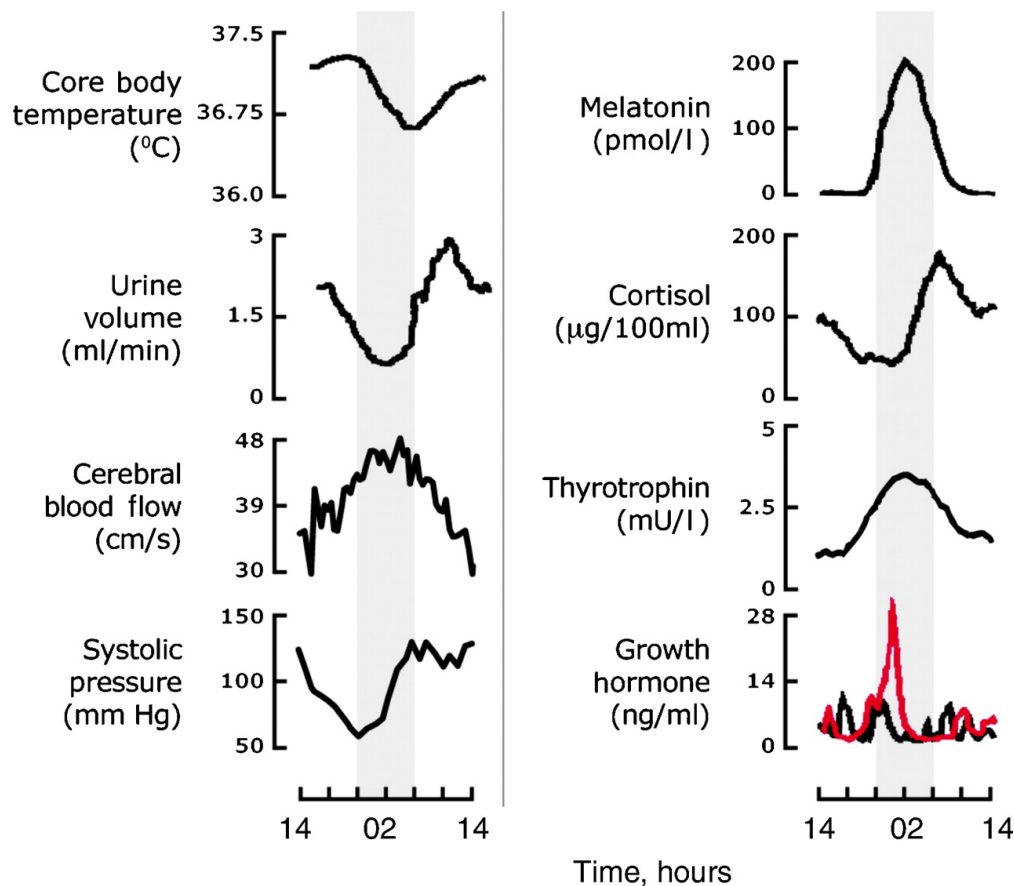


Figure 1. Physiological and endocrine circadian rhythms. Physiological (left) and endocrine (right) rhythms are demonstrated. Subjects remained awake in a controlled environment, with the shaded area representing the usual sleep period. Without sleep, the growth hormone rhythm is lost (black) but returns (red) when sleep is permitted (13).

1.3.1. Melatonin

Melatonin is a hormone which is secreted from the pineal gland in a diurnal pattern, with peak values occurring between 0300 and 0400 (53). Circulating tryptophan is transformed to serotonin and then melatonin before diffusing into blood, cerebrospinal fluid (CSF) and other bodily fluids (53, 54). Circulating melatonin is mainly protein bound and has a wide volume of distribution (53). The liver is responsible for 90% of melatonin breakdown, with further excretion in urine (53). 1% remains unchanged in the urine and reflects circulating levels (53). Significant intra-individual stability in secretion patterns makes melatonin a robust marker of

circadian rhythmicity (53). However, significant inter-individual variability exists and disordered rhythms or altered melatonin levels are noted in several pathophysiological conditions, particularly ocular, neurological, psychiatric and cardiovascular disease (53).

Melatonin rhythmicity is under the influence of the SCN, which itself is directed by light exposure (53). Light exposure inhibits melatonin synthesis to varying degrees (53). Complete suppression is seen with light intensity of 2000-2500 lux and of blue wavelength (446-477nm), whereas usual domestic intensities (50-300 lux) have a lesser impact (53). With prolonged nighttime light exposure, this inhibitory affect is overcome, and melatonin secretion shifts to the morning (53).

The role of melatonin remains poorly understood but largely relates to signalling darkness to the body and is considered an endogenous synchroniser of circadian rhythmicity (53). Sleepiness, melatonin secretion and a fall in body temperature all coincide (53). Melatonin administered in the evening may advance sleep-wake rhythms, whereas melatonin administered in the morning may delay sleep-wake rhythms (53).

Several factors influence melatonin secretion including age, light exposure (including artificial light sources), season, posture, exercise, sleep and/or sleep deprivation, caffeine, and medication such as non-steroidal anti-inflammatory drugs (NSAIDs) (16, 54). Melatonin secretion is reduced by alpha-2- and beta-1-adrenergic adrenergic blockers, and some benzodiazepines, and is reinforced by monoamine oxidase inhibitors and antidepressants, including tricyclic antidepressants, fluvoxamine and desipramine (53, 54). Oral melatonin supplementation does not mimic physiological melatonin due to rapid release, a short half-life, and supraphysiological levels, but can advance SCN circadian phases when given late in the day (52, 53).

Melatonin enhances antioxidative enzyme levels, reduces pro-oxidative enzymes and is a potent free radical scavenger (53). Melatonin also augments the immune response and interacts in a bi-directional manner with interleukins and cytokines (53). Alongside antioxidant properties, if melatonin is administered in a circadian-

dependent fashion, anticancer defences are augmented and antiproliferative effects are displayed (53).

Saliva or plasma samples can be used to assess melatonin levels, or urine samples to assess melatonin metabolites, such as 6-sulfatoxymelatonin (16). Samples taken across a 24-hour period reflect the circadian rhythm but can be time-consuming and inconvenient (16). As light exposure can suppress normal melatonin secretion, accurate sampling is often performed under dim light conditions and reported as the dim-light melatonin onset (DLMO) (16, 54). The DLMO reflects the time when melatonin levels begin to rise and can be used to identify both the phase and period of the circadian rhythm (16, 54). A standardised method for melatonin sampling, assessment of the DLMO and threshold values has not been agreed (54). Threshold values consider the degree of melatonin increase compared to peak values, commonly as a percentage or standard deviation, or absolute values measured in pg/ml (54).

Although melatonin sources are correlated, they are not equivocal (54). Plasma melatonin levels, for example, are 3 times higher than salivary melatonin levels (54). In ideal circumstances, samples should be collected between the evening and morning hours, with more frequent samples providing more accurate data (54). Samples should be obtained under dim light conditions, and if using saliva samples, the individual should not brush their teeth or eat in the 30 minutes before sampling (54). Blood samples require centrifuging with serum removal and freezing (54). Urine samples may be stable for up to 5 days and saliva samples are either frozen immediately or stored in refrigerators when collected in the home setting (54). Radioimmunoassay and enzyme-linked immunosorbent assay (ELISA) are the most common methods for analysing samples (54).

1.3.2. Cortisol

The hypothalamus responds to physical or psychological stress triggers by stimulating the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis (52). As a result of HPA activation, glucocorticoids (GC) are produced, and aim to control the initial stress reaction (52). Adrenal gland GC

secretion is largely influenced by corticotropin (ACTH), with 60- to 90-minute oscillations occurring throughout the day (52). Complex interactions between central and peripheral clocks, and the hypothalamus, pituitary gland and adrenal glands, control GC release (52). Cortisol production peaks in the early morning, around 0800, and then decline across the day, with the lowest levels seen in the late evening, around 0000 (52, 55, 56). The difference between peak and trough cortisol levels is one of the largest that is measurable in human endocrine systems (52). GC receptors are present throughout the body, including the central nervous system, and are thought to have a role in synchronising other circadian rhythms (52).

Acute changes to the light-dark, rest-activity, or feeding patterns are not immediately followed by synchronisation of cortisol rhythms, which in turn limits the synchronisation of other 'clocks' (52). However, this delay in reacting to acute environmental changes makes cortisol a strong marker of circadian rhythm (52). GCs display variable influence on circadian clocks, with the lung and kidney clocks being more easily reset (52). GCs are also able to augment the SCN response to light, aiding in synchronisation (52). GCs have widespread actions, and the strength of influence depends upon timing. In response to stress, GCs mobilise glucose, encourage the diversion of blood to brain and muscle, and improve cognitive function (52). If stress becomes chronic, contrasting effects are seen, including cardiometabolic disturbances, muscle degradation, memory deficits, and immunosuppression (52).

Low cortisol levels coincide with sleep initiation and a cortisol peak, occurring 3-4 hours after sleep onset, coincides with rapid eye movement (REM) sleep (52). Throughout the sleep period, cortisol peaks coincide with awakenings, and the main cortisol peak coincides with the final awakening (52).

The significant morning peak includes a brisk cortisol rise within 20-45 minutes of waking, and this can be measured by the cortisol awakening response (CAR) (52, 55, 57). The CAR is not seen following short naps, nor is it seen when waking in the middle of the night (55). Cortisol levels may rise by up to 75% from waking and this response is dampened by administering dexamethasone (55). The CAR

demonstrates high intra-individual stability and consistency across ages (55). The CAR is sensitive to light exposure and is independent of cortisol levels throughout the day (57). There also appears to be minimal influence on the CAR from gender, menstrual cycle and oral contraception (55). There is conflicting evidence concerning physical and psychiatric disease and its influence on the CAR. A larger CAR is often observed with earlier awakening (55). The CAR does appear to be higher in individuals experiencing increased physical or psychological demands (55).

Similar to melatonin, cortisol can be sampled from blood, saliva and urine (57). Timing of sampling, particular home saliva sampling, is of paramount importance, particularly when calculating the CAR, and is therefore open to inaccuracies (57). Salivary samples reflect free serum cortisol and may be more accurate than total serum cortisol (16). Self-reported and actual wake times can differ significantly and therefore influence self-sampling methods (57). Saliva cortisol may also be influenced by smoking, eating and drinking, brushing teeth, caffeine, nicotine and blood glucose levels (57). Importantly, physical activity, body position, high protein meals and light exposure can all influence cortisol levels (16, 57). Additionally, shift work, jet lag, intercurrent illness, psychological stress, endocrine disorders and medication can influence levels (16, 57). Additional influencing factors include sleep quality and duration, light exposure, age, and sex (57).

Aside from the CAR, cortisol levels vary across the day can also be measured as the average level of cortisol across the day, and as the change from morning peak to evening trough levels, known as the diurnal cortisol slope (DCS) (58). Various terminology can be used to describe the DCS and various approaches to investigating the DCS have been used (58). This may include multiple sampling approaches, or comparing the difference between wake and bed levels or peak and bed levels, for example (58).

1.3.3. Body temperature

Body temperature is detected peripherally by sensory receptors and centrally by hypothalamic receptors (59). Sensory input is processed in thermoregulatory

centres within the hypothalamus with output signals to muscle, skin, vascular tissue, and brown adipose tissue to counteract any temperature deviations (59, 60). Although a direct link has not been found between the thermoregulatory centres and the SCN, it is postulated that the SCN regulates the circadian rhythm of body temperature (61). Regularisation of body temperature between 36.5-37.5°C optimises several physiological processes, and circadian fluctuations can entrain gene regulation processes (60, 61). A circadian temperature rhythm, mirroring sunset and sunrise, occurs with peak values in the late afternoon and trough levels towards the end of the sleep phase (59-61). Overall cooler temperatures, of around 0.2°C, are noted in the winter and, in females, a 0.25-0.5°C increase in temperature occurs around ovulation (61). As humans age, the temperature circadian rhythm is dampened, inter-daily variability heightened and they are less able to synchronise their temperature rhythm to environmental changes (61, 62). Within patients with cancer, circadian body temperature disruption has been noted, particularly those with a poor performance status and those receiving chemotherapy (61).

Body temperature acts as a synchroniser for other peripheral clocks, a stabiliser of various circadian rhythms, and has a role in the regulation of sleep (62). Body temperature is also influenced by other rhythms, such as melatonin whereby melatonin release encourages peripheral vasodilatation and a subsequent hypothermic effect (62). Core body temperature is susceptible to influence from meals, external temperature and bright light, for example (16).

The central, or core, body temperature is the most accurate method of assessment and may be measured using rectal probes (61). Despite variance in the measurement of peripheral temperature, oral or axillary methods are often more acceptable and convenient (61).

1.3.4. Circadian physiological changes

As mentioned previously, CRs are seen in multiple body systems. Examples include peak blood pressure occurring around 2100 followed by a fall in blood pressure (52). Similarly, a fall in heart rate is also seen in the initial phases of sleep (52). Altered rhythms, such as an absence of this nocturnal blood pressure change, is associated with worse cardiovascular outcomes and mortality (52). Circadian patterns may also be seen at a cellular level, including for immune cells. Leucocytes, for example, peak during the night and after the GC morning peak: levels fall as they migrate to the bone marrow (52).

1.3.5. Sleep-wake and rest-activity

Sleep-wake and rest-activity circadian rhythms are distinct entities but there is overlap in how they are assessed and how the 24-hour rhythms are controlled. Most rest periods occur during sleep and most active periods occur during wake. Wake periods however can include restful activities, and sleep periods can be restless. The two circadian rhythms will be discussed independently before reviewing the similar approaches to assessment. Similarities and differences between the two circadian rhythms will be highlighted.

1.3.5.1. Sleep-wake circadian rhythms

Sleep is a complex physiological process with important roles in health and daytime functioning, including cognitive processes such as memory and learning, attention and emotional wellbeing (1). During sleep, individuals cycle between phases of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep (1, 63). NREM sleep is made up of 4 different stages and is characterised by sleep spindles, slow waves, K complexes and reduced muscle tone (1, 63). Stage 1 NREM is often the first to be entered upon sleep initiation, lasting between 1 and 7 minutes and is the NREM stage an individual is most easily awoken from (63). Stage 2 NREM is the most predominant of the NREM phases, lasting between 10 and 25 minutes and becomes progressively longer during sleep (63). Stage 2 NREM is important for learning and memory formation (63). Stages 3 and 4 NREM

(slow-wave sleep), occur predominantly in the first third of the sleep period with stage 3 lasting short minutes and stage 4 lasting between 20 to 40 minutes (63). Stage 4 NREM is the deepest sleep requiring most arousal to result in awakening (63). REM phases are interspersed between NREM phases, occurring every 90-110 minutes, and become progressively longer as the sleep period continues (1, 63). REM sleep is characterised by sawtooth waves, desynchronised EEG patterns, phasic eye movements and atonic muscles (1).

As humans age, the sleep time required to feel refreshed shortens and short periods of sleep, or naps, increase (1). With advancing age, slow wave sleep and the amount of time spent asleep whilst in bed (sleep efficiency) reduces, it takes longer to fall asleep (sleep onset latency), and the sleep-wake period occurs earlier (a phase advance) (1, 63-65). Slow wave sleep periods have a high arousal threshold and therefore older people, with less slow wave sleep, have more frequent wake episodes during sleep (63, 64).

Multiple sleep regulation models exist. A common model highlights the role of sleep-promoting, or homeostatic, processes (Process S) and wakefulness-promoting, or circadian, processes (Process C) (16, 63, 66). Process S relates to sleep debt, which increases as the day progresses and decreases with sleep (63, 66). At its peak, sleep is encouraged, and at its trough, awakening is encouraged (66). Process C builds throughout the day to encourage alertness but falls in the late evening to help with sleep consolidation (63). It then builds again in the early morning prior to awakening (63). Without process C, sleep can be seen distributed across the 24-hour period (63). Currently, Process S and C are thought to undergo a continuous interaction whereby high homeostatic pressure correlates with low circadian pressure, for example (66).

The forebrain, hypothalamus and brainstem also play roles in sleep and wakefulness. Arousal systems, within the brainstem, activate the forebrain and promote wakefulness (63). This arousal system can be dampened by neurons, predominantly within the preoptic area, with resulting sleepiness (63). Digestive processes are also interpreted by the brainstem and can influence sleep (63). Furthermore, the SCN communicates with sleep-wake systems to ensure

coordination with the day-night cycle (63). In addition, temperature plays a role in sleep-wake regulation. A sleep-promoting relative hypothermia is seen towards the end of the day and a wake promoting relative hyperthermia in the morning (63).

1.3.5.2. Rest-activity circadian rhythms

Research has focussed on sleep-wake circadian rhythms or the impact of physical activity on other measurable circadian rhythms. Rest-activity rhythms have been characterised in different populations but there is little evidence on the control of physical activity in rest-activity rhythms.

Rest-activity patterns have been assessed in adults using accelerometry-based physical monitoring. Compared to men, women have higher average and peak activity levels, more consolidated rhythm patterns during the day and more stable rhythm patterns (67). Peak physical activity occurs around 14:42 (67). As humans age, the mean and peak activity levels fall and the pattern becomes more fragmented (67). Peak activity occurs around an hour earlier in the day for older adults than younger adults (67). Racial differences have also been noted. For example, the Asian population have a later peak activity to the Caucasian population, and the Black population have lower activity levels and less inter-daily stability than the Caucasian population (67).

1.3.5.3. Sleep-wake and rest-activity assessment

Sleep can be assessed in various ways. This may include the timing of sleep within the 24-hour period, the architecture of sleep itself and the duration of different aspects, sleep preference, sleep efficiency and sleep quality. Similarly, activity assessment may consider frequency, timing, duration, or intensity of rest or active periods. Investigative approaches to sleep and activity should focus on the outcome of interest. Direct observation of behaviours can be used to assess activity using pre-determined criteria, to provide contextual information, and to validate more novel approaches to physical activity assessment (68, 69). With adequate assessor training, direct observation is a valid and reliable measure, but is associated with significant burden for both the researcher and participant (68).

Participants may also adjust their behaviour when knowingly being observed (68). Activity may also be observed using wearable cameras, which can collect information across the day and again, provide contextual information (68). However, privacy issues may arise with the method and there is increased burden in analysing the information (68). Alternatives to direct observation include objective measures, such as polysomnography, accelerometry, and heart rate monitoring, and subjective measures, such as patient questionnaires and diaries. Of note, any device which provides feedback to the individual, has the potential to influence behaviour and therefore activity (70). Prolonged monitoring may also provide a more accurate reflection of real-life activity (70). When choosing an assessment method, the type of activity data (duration, frequency, intensity and type), cost, and burden to participant and research should be considered (71). There is no gold standard for measuring physical activity (70).

1.3.5.3.1. Polysomnography

The gold standard sleep investigation is overnight polysomnography (PSG), whereby individuals have continuous brain electrical, muscle and eye activity monitored by electroencephalography (EEG), electromyography (EMG) and electrooculography (EOG), respectively (1, 72, 73). PSG also utilises video recordings to monitor physical movement, nasal pressure and chest or abdominal sensors to monitor respiratory effort and airflow, pulse oximetry to monitor blood oxygen saturation level, and electrocardiography to monitor heart rate and rhythm (72). For a sleep study, PSG findings are analysed in 30-second periods, or epochs, to determine different sleep phases and presence of cortical awakening (72, 73). PSG has additional uses, including the assessment of sleep-related breathing disorders, such as obstructive sleep apnoea, movement and behaviour disorders, such as parasomnias, seizure disorders, restless leg syndrome and periodic limb movements (72, 74). PSG may not be required to make a diagnosis, but can be supportive of a diagnosis or aid when multiple conditions co-exist (74). PSG is a component in the assessment of sleep and needs to be considered alongside a clinical history and examination (74).

PSG reports allow an understanding of a patient's sleep architecture, as well as behaviours during sleep and the timing of the sleep episode. Time spent in bed, time to sleep onset (sleep onset latency), time spent sleeping, times spent within NREM and REM stages, and awaking times can be noted (75). Sleep efficiency, the time spent asleep whilst in bed, can be grossly calculated but may miss short periods of wakefulness (75). Sleep efficiency may be reduced in the event of a long time to fall asleep or time between sleep onset and lights on time or out of bedtime (75). Time spent awake after sleep onset (TASO) can also be reported and may reflect more accurate sleep fragmentation as it does not consider wakefulness prior to sleep onset (75). If used on multiple nights, total wake time can also be reported. When considering circadian rhythm sleep-wake disorders, the focus of investigating sleep is the timing of the sleep episode within a 24-hour period and the regularity of sleep across 24-hour periods. PSG is therefore able to consider the circadian rhythm of sleep.

PSG is often carried out in a standardised, inpatient setting, which is artificial to the patient and findings may relate to the "first-night" effect (72). This describes poor sleep quality and reduced sleep time in the laboratory (72, 75). Due to the associated cost and limited availability, PSG studies may be time limited and a single overnight study is unable to reflect night-to-night variability (72). In the artificial setting, a sleep diary prior to the sleep onset allows consideration of the patient's usual sleep habits when interpreting the results (75). Home PSG monitoring is possible and more natural to the patient, but if technical issues arise they cannot be addressed by a sleep technologist in the middle of the study (72). Manual scoring of PSG results is labour intensive, considers gross changes, rather than continuous dynamic change, and has significant intra- and inter-scorer variability (73).

1.3.5.3.2. Accelerometry and Inclinometry

Accelerometers provide a non-invasive measure of acceleration and magnitude in various directions using uni-, bi- or tri-axial sensors which can be worn for prolonged periods (69, 70, 76). This may be in the form of a watch-like, wrist-worn device, also known as actigraphy, and is able to capture activity information over

a 24-hour period (77). As most individuals rest during sleep and are active during wake, accelerometers can reflect sleep and wake periods. As accelerometers can detect velocity, the frequency, duration and intensity of an activity can be assessed (70, 71). Due to a lack of consensus over thresholds it can be difficult to assess intensity (70). Accelerometers are also unable to provide information on the actual activity being undertaken (69).

Accelerometry devices are typically worn on the wrist, thigh, hip or ankle and can be performed in the home setting (71, 76, 78). The hip location better reflects energy consumption in a laboratory setting, but the wrist location is felt to be more acceptable to adults (76). Both hip and wrist locations correlate well with moderate-to-vigorous activity ($r=0.80-0.84$), but less so for low-intensity activity ($r=0.18-0.63$) and may miss static exercise (70, 76). When assessing physical activity intensity in young adults, using four accelerometer locations versus direct observation, a thigh worn device demonstrated superior sensitivity and specificity compared to wrist- or hip-worn devices (79). The thigh-worn device also accurately detected breaks in sedentary behaviour, whereas other locations overestimated breaks in sedentary behaviour (79).

Tri-axial, compared to uni-axial, sensors are more closely correlated with energy expenditure (70). When tri-axial sensors are compared with indirect calorimetry, they overestimate activity energy expenditure, and when compared with the doubly labelled water method, they underestimate activity energy expenditure (AEE) (70). Accelerometers are expensive, require technical expertise to analyse the information and lack standardised protocols to manage the data (71).

Activity counts can be used to categorise activity intensity with <100 counts/minute reflecting sedentary behaviour, 100-1951 counts/minute reflecting light physical activity (LPA), and ≥ 1952 counts/minute reflecting moderate to vigorous physical activity (MVPA) (79). The latter study however used controlled environments and may not reflect free-living conditions or all groups (79). Additional challenges with the use of thresholds includes a lack of consideration for posture and therefore sedentary activities may not be differentiated from standing or other forms of LPA (79).

Accelerometers assess activity within time periods (epochs) of 1 second to 5 minutes, with 30-60s being commonly used, which can then be interpreted as resting or moderate-to-vigorous active periods (16, 70, 76, 77). Using shorter epochs provides more detailed information (76). Accelerometers have significant storage capacity and can provide detailed information for prolonged periods (71). Continuous accelerometer monitoring has better compliance, as there is less chance that the user forgets to reapply the device, and less bias, as the user is not selecting the time frame to be assessed (68). Accelerometer devices may also incorporate light sensors and event marker buttons to indicate pre-specified activities, such as getting into bed (77).

When investigating circadian rhythms, resting or sedentary periods also need to be accurately assessed. Sedentary behaviour, muscle inactivity, is associated with poor cardiometabolic health, morbidity and mortality (68, 79). Prolonged, rather than intermittent, periods of sedentary behaviour are worse (79). Restful activities, such as sitting and squatting, may involve skeletal contraction, and by incorporating inclinometers within accelerometers, this additional information may be captured (68). The activPAL, an inclinometer, worn on the thigh, is the “gold standard” to accurately assess sedentary time and has been validated against direct observation in various settings (68). The device demonstrate excellent agreement with direct observation of transitions between upright and sedentary positions, steps, and time spent sitting, lying and upright (80). Inclinometers are a valid and reliable measure of sedentary activity, but are costly (68). Accelerometers, when worn on the thigh, act similarly and have high validity and reliability for detecting total sedentary time (68). When worn on the wrist, accelerometers lack the validity to measure sedentary time and may lack postural information (68). Algorithms detecting sedentary time when using wrist accelerometers do exist, but difficulties arise during static postures where the arm is bent, such as standing at a desk (68). Hip accelerometers also struggle to differentiate between passive and active non-ambulatory postures (68).

Adults, particularly the elderly due to physical restrictions, often have steady activity levels across the day and prolonged periods of sedentary activity (71).

Devices therefore that are unable to accurately assess low intensity activities, such as walking, are not ideal for adult and elderly populations (71).

Algorithms, most commonly the Cole-Kripke algorithm, can be applied to the accelerometry data to generate information about several sleep parameters and can distinguish sleep up to 88% of the time (77, 78). Sleep-wake criteria differ when using PSG and accelerometry. PSG defined sleep initiation coincides with EEG changes, whereas actigraphy defined sleep begins with immobility (81). Accelerometry data can be analysed using several approaches, most commonly Cosinor and non-parametric analyses, but can also include wavelet-based, fourier and data adaptive approaches (82, 83). A traditional parametric cosinor analysis assumes a diurnal pattern over 24 hours and uses a regression model to fit the accelerometry data to a cosinor curve, whereas the alternative non-parametric approach does not assume the diurnal pattern and considers fragmentation within the rhythm or between cycles, for example (82, 83). The acrophase, amplitude, mesor, dichotomy index and 24-hour autocorrelation coefficient parameters are commonly used (Figure 2).

In healthy populations, actigraphy provides a reliable and valid alternative to polysomnography in assessing sleep, but it is less reliable when sleep becomes fragmented (16, 77). Actigraphy tends to overestimate sleep efficiency and sleep duration, particularly in individuals with long periods of in-bed wakefulness (i.e. insomnia) (81, 84). Similarly, actigraphy tends to underestimate wake episodes, sleep onset latency and wake after sleep onset (81, 84). A retrospective study of mixed inpatient cohorts found that actigraphy, compared to PSG, had good sensitivity (0.965) but poor specificity (0.329) (81). Research demonstrates a lack of standardisation in actigraphy devices, the device settings, reported parameters and scoring algorithms (81). Despite low quality evidence, the American Association of Sleep Medicine (AASM) recommend the use of actigraphy, for a minimum of 72 hours, in the assessment of circadian rhythm sleep-wake disorders in adults (85). The AASM highlight that actigraphy offers objective measures with minimal risk and low patient burden (78).

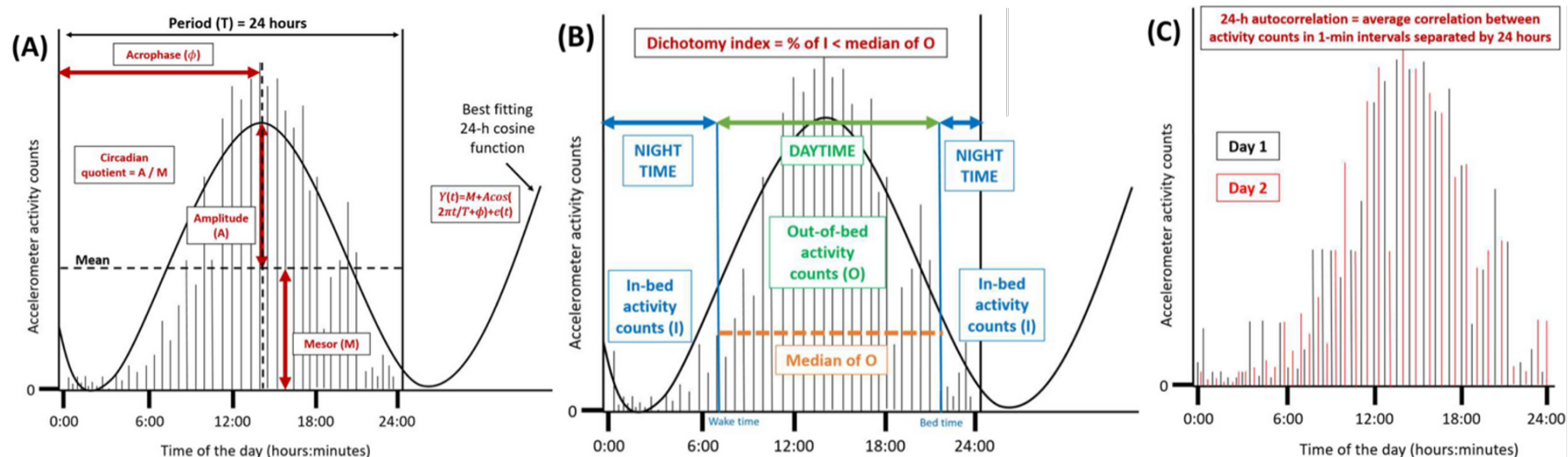


Figure 2. Circadian rest-activity rhythms (25). Activity counts (black lines), typically for each minute, are plotted along a time frame. The height of the lines, representing the level of activity, typically increase during the waking day and reduce during the night. (A) Illustrates the period (time frame) of the rhythm, acrophase (time of peak activity), amplitude (difference between the mean and peak activity counts), and mesor (24-hour rhythm adjusted mean of activity counts). (B) Illustrates the dichotomy index ($I < O$) which describes the percentage of activity counts in bed that are below the median activity counts whilst out of bed. (C) Illustrates the 24-hour autocorrelation coefficient (r_{24}) which compares activity counts at the same time point separated by 24-hours.

1.3.5.3.3. Pedometer

A pedometer is a simple, portable device that uses a spring mechanism to measure the number of steps taken (69, 70). Pedometers do not collect information about the duration, intensity or frequency of an activity (71). They are easy to use and cheap, but can be influenced by other movements and individuals may adjust their own activity behaviours when receiving feedback from the device (70). Pedometer counts vary depending on the location that they are worn, individual stride lengths and walking speed (70). By taking into account an individual's stride length, walking distance can be calculated (69). Pedometers correlate closely with uni-axial accelerometers and with direct observation (71). Pedometers are less accurate at a slower pace, are unable to accurately capture activities such as swimming or cycling, horizontal movements and upper limb movements (69-71). They may therefore not be appropriate for older individuals with slower or shuffling gaits (71). Pedometers may be less accurate in individuals with a high body mass index (BMI) (71).

1.3.5.3.4. Energy expenditure

Activity may also be considered by assessing an individual's energy expenditure. Total energy expenditure equates to the basal metabolic rate, diet induced energy expenditure and physical activity-related energy expenditure (EE) (69). Calorimetry measures an individual's metabolic rate based on heat production (direct calorimetry) or oxygen use, carbon dioxide production and urine nitrogen loss (indirect calorimetry) (86). A variant of indirect calorimetry, the doubly labelled water (DLW) method, can be performed in any environment and measures the amount of labelled hydrogen and oxygen in blood, saliva or urine that is turned over in the body, across a 7- to 14-day period (86). In everyday living conditions, the doubly labelled water method is the gold standard to measure total EE, but lacks the ability to determine the intensity, duration or type of an activity (69, 70, 86). It is also unable to differentiate between diet- and activity-related EE (69). The DLW has limited large scale application due to cost implications, but may be used to validate other methods (70).

Physical activity involves the EE rising above the resting EE due to contraction of skeletal muscle and can be interpreted to consider the frequency, duration, intensity or mode of activity (70). Activity intensity may be an absolute rate of EE or relative to the individual's level of fitness, and can be categorised using metabolic equivalent of task (MET) into sedentary activity (1.0-1.5 METs), light activity (1.6-2.9 METs), moderate activity (3.0-5.9 METs), and vigorous activity (≥ 6.0 METs) (76). Many individual activities have been coded with a MET value, supported by evidence, to standardise research practice (87). The doubly labelled water method can compare the total EE against resting EE to reflect physical activity (86). The method highlights inaccuracies in self-reported diet and physical activity (86). Insufficiencies in activity monitors, compared to the doubly labelled water method, have been highlighted with significant variation in the performance of devices, and both estimated EE and physical activity level (86). Most devices do not provide a valid estimate of EE (86).

1.3.5.3.5. Heart rate monitoring

Heart rate (HR) can reflect physical activity, considering frequency, intensity and duration of activity, is non-invasive, inexpensive and can be used in a range of circumstances (70). HR changes can be considered in relation to the proportion of an individual's HR reserve, or the maximum HR, to assess activity intensity (70). A linear relationship exists between oxygen consumption, heart rate and moderate-to-vigorous physical activity, but varies depending on the activity and individual characteristics, such as age and fitness level (69, 70). Devices can be calibrated to provide individualised thresholds for activity (69). HR may be assessed in 5-60s epochs and can be individually calibrated to improve accuracy (70). HR monitoring has been validated against EE in young people (70). Accuracy of HR monitoring may be impaired in individuals with a high BMI (71).

Photoplethysmography provides a method for monitoring HR by detecting pulsatile changes within blood vessels using light reflected from, or transmitted through, the skin (88). Heart rate variability can reflect the autonomic nervous system, including changes relating to pain, and the different sleep stages (88). Agreement has been

demonstrated between actigraphy, human scored polysomnography and photoplethysmography in estimating total sleep time, total wake time, wake after sleep onset and sleep efficiency ($p < 0.001$) (88). Photoplethysmography appeared more effective at estimating sleep onset latency.

At lower heart rates, and during sedentary activity, heart rate monitoring lacks validity in assessing activity due to several confounding factors, such as caffeine intake and stress (68, 69). Precision of HR monitoring to assess physical activity, EE and sedentary activity may be improved by combined assessment methods (68, 69).

1.3.5.3.6. Subjective assessments

Physical activity can be assessed subjectively using interviews, patient activity questionnaires or diaries. Subjective measures are open to bias due to a focus on an individual's understanding of activity and activity intensity, inaccurate recall, and social desirability of activity (70, 76). Recall ability may be inadequate with advancing age, cognitive impairment or in inactive individuals (71).

Patient assessment questionnaires may be single-item or multi-item. They are cheap, accessible and easy to use, but variable in detail and duration of assessment (70). Validation studies against DLW have been inconsistent (71). Questionnaires can also assess the mode of physical activity (70). They often underestimate sedentary time, e.g. watching television or sitting at a desk, and activities of daily living, and overestimate vigorous activity, with variable reliability (68, 70). Validity may be improved if used alongside interviews (70). Questionnaires perform better when they consider the time spent performing specific behaviours, but difficulty may then arise if multiple activities have occurred simultaneously (68). If questionnaires are used, assessment of individual activities of interest need to be validated (68). Activities can also be assessed using interviews which discuss events from the previous day (68). This approach is validated against objective measures but often slightly overestimates sedentary activity (68). Interviews collect contextual information and can capture all activities which may otherwise be missed in predefined questionnaires (68).

Activity information can also be collected prospectively in diaries, and consider the type, frequency, duration and intensity of activity, but may be subject to missing data and require individuals to be engaged with the process (68, 70). Diaries can consider different time frames and if METs are taken into account, various activities can be translated into EE (70). The Bouchard activity record, for example, has been validated against objective measures and involves cumulating sedentary activity in 15-minute periods over the 24-hour period (68).

1.3.5.3.7. Chronotype

An individual's preferences for optimal sleep and wake times can reflect their circadian chronotype (89). Chronotypes are broadly classified into morning-type (MT), evening-type (ET) or neither type (NT) (90). The majority of people are classed as NT chronotypes (5). The chronotype highlights a subjective preference for the timing of sleep rather than sleep duration (5). An individual's chronotype also correlates with cognitive attention, where ETs have peak attention at 1200-1600 rather than 1000-1400 as seen for NTs (65). Chronotype can be assessed by several validated questionnaires, including the Morning-Evening Questionnaire (MEQ) and the Munich Chronotype Questionnaire (MCTQ) (5, 90). The MEQ, for example, focuses on an individual's time preferences for activity, sleep and peak alertness (16). The MCTQ considers an individual's actual timing of bedtime, sleep latency and wake time, and differentiates between work and non-work days (16, 91).

An individual's chronotype correlates with several objective measures of circadian rhythmicity, including body temperature and melatonin (92). Sleep studies have shown that subjective "Morningness" and "Eveningness" correlates with earlier and later sleep times, respectively (92). "Eveningness", for example, tends to be found in patients with delayed sleep-phase syndrome whereby their bedtime occurs later in the 24-hour clock (89, 93). A delay in temperature rhythms and the DLMO, by up to three hours, is also found in ET compared with MTs (92). MTs conversely have earlier sleep and wake periods, earlier peak performance and alertness, and earlier biomarkers of the circadian rhythm than ETs (16). The MEQ and Composite Scale of Morningness (CSM) have been validated when considering circadian body

temperature (91). Similarly, MEQ, CSM, Preference Scale and MCTQ have been validated against actigraphy (91). Reliability of MEQ, CSM, and PS range from 0.65-0.90 (91).

“Free” days, reflect days where people have no set commitments such as weekend, and on these days people often sleep later in the day and for longer periods, with a more significant delay for younger individuals (5). MT chronotypes are more likely to report a desire to sleep for longer periods on “free days”. Individuals who spend more time outdoors in daylight throughout the week were also found to have advancement of sleep phases, and this closely correlates with “Morningness” (5).

1.3.5.3.8. Combined approaches

The accuracy of physical activity measurement may be improved using combined methods, such as heart rate monitoring, inclinometers and accelerometers (70). If combined measurements are being used, researchers must consider the added benefit of each method and balance the burden and acceptability to participant and researcher (68). Subjective methods may lack validity in assessing physical activity, but when combined with objective measures, they provide additional contextual information (68).

1.4. Circadian rhythm disorders

Circadian rhythms may be altered in a several ways. This may include a lack of synchronisation with the 24-hour, or day-night, cycle. It may also include a lack of stability within or between the 24-hour periods or a dampening of the usual fluctuation between the peak and trough elements of a rhythm. As highlighted, investigative approaches vary within and between circadian rhythms. Although deviations from the normal human circadian rhythm can be highlighted using these various measures, very few diagnostic criteria exist to highlight a circadian rhythm disorder.

1.4.1. Circadian rhythm sleep-wake disorders (CRSWDs)

A well-defined example of a circadian rhythm disorder, representing alterations to sleep and wake phases in relation to the day-night cycle, is the circadian rhythm sleep-wake disorders (CRSWDs). CRSWDs will be discussed to highlight how a circadian rhythm disorder may be classified and defined.

CRSWDs arise when there is a mismatch between an individual's internal circadian sleep-wake rhythm and their external environment or activities (89, 94). CRSWDs often present with symptoms of insomnia or excessive sleepiness (89). Patients struggle to fall asleep and wake at desired times, with a subsequent impact on education, employment and social functioning (95). This can occur innately in the form of primary circadian rhythm disorders or may be acquired from secondary sources, such as shift work and jet lag. Additionally, a relatively recent term 'social jet lag' represents shifts in circadian rhythms between workdays and free days (96). Individuals with a preference for later sleep times can develop a sleep debt as the week progresses with subsequent compensation during the weekend (96).

The International Classification of Sleep Disorders (ICSD-3) identifies seven CRSWDs (Box 1) (89). This includes delayed sleep-wake phase disorder, advanced sleep-wake phase disorder, irregular sleep-wake disorder, non-24-hour sleep-wake rhythm disorder, shift work disorder, jet lag disorder and circadian sleep-wake disorder not otherwise specified. When sleep rhythms occur earlier in the 24-hour clock this is known as "phase advance" and similarly, when rhythms occur later in the 24-hour clock, this is known as "phase delay" (1).

Delayed sleep-wake phase syndrome (DSPS), characterised by sleeping and waking more than two hours later than conventional sleep-wake times, is more common in young adults and adolescents, with a prevalence of around 7-16% (89, 93). Personal logs and actigraphy demonstrate that sleep onset times are often between 0100 and 0600 with wake times in the late morning or afternoon (89). DSPS individuals who are allowed to sleep at their preferred times demonstrate normal polysomnography, whereas those restricted to acceptable social times have delays in sleep latency and shorter overall sleep time (89). DSPS patients

face extreme difficulty awakening in the morning, and due to shortened sleep time and high sleep propensity, are more likely to suffer cognitive blunting and be at risk of accidents (89). Attempts to correct for delayed sleep onset and offset may encourage the development of symptoms of insomnia, and patients are at risk of substance misuse (89). As DSPS individuals age, the natural phase advancement may offset the phase delay to some degree (89). The pathophysiology of DSPS is poorly understood but several predisposing, precipitating and maintaining factors are postulated. A natural phase delay occurs around the time of adolescents and most DSPS individuals have an evening chronotype (89). 40% of cases have a familial history with genetic polymorphism noted in clock, hPER3, human leucocyte antigen and argylaklylamine N-acetyltransferase (89).

DSPS is also often found in patients with mood disorders, severe obsessive-compulsive disorder and attention deficit hyperactivity disorder (89). For normal circadian control, light exposure in the early morning can cause phase advancements, whereas light exposure in the late evening can cause phase delays (89). Therefore, heightened sensitivity to light may predispose individuals to the development of DSPS (89). Stimulants, including caffeine, and maladjustment to social, work or environmental factors may also precipitate DSPS (89). Measures of circadian rhythm, such as melatonin, can be helpful in the diagnosis of DSPS (89).

Advanced Sleep Phase Syndrome (ASPS) patients have early sleep and wake times with associated advancement in core body temperature and melatonin rhythms (89). ASPS is seen with increasing age, often affecting middle-aged adults, with a population prevalence estimated to be around 1% (89). Earlier onset, seen more so in familial types, may be genetically linked including hPER2 mutations with an associated shorter duration between cycles (89). Other postulated causes include an altered sensitivity to zeitgebers, earlier response to light and an altered ability to delay the rhythm (89). Similarly to DSPS, those with ASPS have a normal polysomnography if allowed to sleep at preferred times, but with enforced times demonstrate short sleep latency and early wakening (89). ASPS individuals are more likely to be MTs and suffer with morning insomnia and excessive evening sleepiness (89). Similar to DSPS, ASPS individuals are at risk

of substance misuse in attempts to manage symptoms and phase advancements (89).

Irregular sleep-wake rhythm disorder (ISWRD) is characterised by a loss of rhythmicity over 24-hour periods and across days (89). ISWRD patients have frequent and fragmented sleep episodes, often lasting less than 4 hours, with associated nocturnal waking (89). Total sleep time within the 24 hour period is often normal (89). ISWD is commonly associated with neurodegenerative conditions and the prevalence follows that of the underlying diagnosis (89). Lack of exposure to entraining agents, including light and activity, predispose and precipitate the disorder. The underlying aetiology is likely multifactorial. Multiple irregular sleep episodes can be captured in sleep logs or actigraphy, and irregular circadian biomarkers and a loss of amplitude (difference between peak and trough levels), is demonstrated (89).

Non-24-hour sleep-wake rhythm disorders (N24HSWD) are free-running rhythms with daily phase delays and usually follow a more than 24-hour rhythm (93, 95). This pattern is more likely in blind individuals who are unable to receive light cues with over half of blind individuals developing the condition (89, 93). DSPS can predispose an individual to N24HSWD and it may be seen in individuals with dementia or intellectual disability (89). Circadian markers demonstrate a degree of asynchrony between sleep-wake times and the circadian rhythm, with a progressive delay in the circadian rhythm (89). This delay can range from minutes to over an hour. Circadian markers at two time points separated by 2-4 weeks can demonstrate a non-entrained rhythm (89).

Box 1. Circadian Rhythm Sleep-Wake Disorders as defined by the International Classification of Sleep Disorders, 3rd edition (89).

General criteria which must be met:

- A. A chronic or recurrent pattern of sleep-wake rhythm disruption primarily due to alteration of endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the sleep-wake schedule desired or required by an individual's physical environment or social/work schedules.
- B. The circadian rhythm disruption leads to insomnia symptoms, excessive sleepiness, or both.
- C. The sleep and wake disturbances cause clinically significant distress or impairment in mental, physical, social, occupation, educational, or other important areas of functioning.

Delayed Sleep-Wake Phase Disorder

- A. There is a significant delay in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidence by chronic or recurrent complaint by the patient or a caregiver of inability to fall asleep and difficulty awakening at a desired or required clock time.
- B. The symptoms are present for at least three months.
- C. When patients are allowed to choose their ab libitum schedule, they will exhibit improved sleep quality and duration for age and maintain a delayed phase of the 24-hour sleep-wake pattern.
- D. Sleep log, and whenever possible, actigraphy monitoring for at least seven days (preferably 14 days) demonstrate a delay in the timing of the habitual sleep period. Both work/school days and free days must be included within this monitoring.
- E. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Advanced Sleep-Wake Phase Disorder

- A. There is an advance (early timing) in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidenced by a chronic or recurrent complaint of difficulty staying awake until the required or desired conventional bedtime, together with an inability to remain asleep until the required or desired time for awakening.
- B. Symptoms are present for at least three months.
- C. When patients are allowed to sleep in accordance with their internal biological clocks, sleep quality and duration are improved with a consistent but advanced timing of the major sleep episode.
- D. Sleep log, and whenever possible, actigraphy monitoring for at least seven days (preferably 14 days) demonstrate a stable advance in the timing of the habitual sleep period. Both work/school days and free days must be included within this monitoring.
- E. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Non-24-Hour Sleep-Wake Rhythm Disorder

- A. There is a history of insomnia, excessive daytime sleepiness, or both, which alternate with asymptomatic episodes, due to misalignment of the 24-hour light-dark cycle and the non-entrained endogenous circadian rhythm of sleep-wake propensity.
- B. Symptoms persist over the course of at least three months.
- C. Daily sleep logs and actigraphy for at least 14 days, preferably longer for blind persons, demonstrate a pattern of sleep and wake times that typically delay each day, with a circadian period that is usually longer than 24 hours.
- D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Shift Work Disorder

- A. There is a report of insomnia and/or excessive sleepiness, accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps the usual time for sleep.
- B. The symptoms have been present for and associated with the shift work schedule for at least three months.
- C. Sleep log and actigraphy monitoring (whenever possible and preferable with concurrent light exposure measurement) for at least 14 days (work and free days) demonstrate a disturbed sleep and wake pattern.
- D. The sleep and/or wake disturbance are not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, poor sleep hygiene, or substance use disorder.

Jet Lag Disorder

- A. There is a complaint of insomnia or excessive daytime sleepiness, accompanied by a reduction of total sleep time, associated with transmeridian jet travel across at least two time zones.
- B. There is associated impairment of daytime function, general malaise, or somatic symptoms (e.g. gastrointestinal disturbance) within one or two days after travel.
- C. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Circadian Sleep-Wake Disorder Not Otherwise Specified (NOS)

- A. Patients meet all the general diagnostic criteria for a CRSWD but do not meet the criteria for one of the specific disorders classified here.

1.5. Circadian rhythms of disease-related events and mortality

Several disease-related events occur in a temporal fashion. A meta-analysis, considering cardiovascular disease, reported an increased early morning rate of acute myocardial infarction and sudden cardiac death (97). Similarly, tachyarrhythmias in patients with implanted cardioverter defibrillators peak between 0700-1100 (98). Blood pressure, heart rate and sympathetic activity, which follow a rhythm throughout sleep and wakefulness, may play a role (99). In particular, REM sleep, which lengthens over the course of the night, has been found to be associated with significant sympathetic activation (99). Other conditions, with observable circadian rhythms, include asthma and epilepsy. A retrospective review reported that 8 of 10 asthma exacerbations within a hospital setting occurred between 0000-0600 (100). Regarding epilepsy, the anatomical origin of the seizure appears related to the peak timing of the event. Although seizures generally follow a unimodal time distribution, as for occipital seizures (1600-1900) and parietal seizures (0400-0700), some seizure types demonstrate bimodal distributions, such as mesial temporal lobe seizures (0700-1000 and 1600-1900) (101).

Furthermore, mortality appears to have a temporal link. A retrospective review of in-hospital deaths reported that, within the non-ICU setting, mortality rates rose from 4am and peaked at 8am (102). A similar distribution has also been found within palliative care settings. Cancer patients within a palliative care unit (PCU), were significantly more likely to die during daytime hours (401; 06:00-20:00) when compared to nighttime hours (225; 20:00-06:00) (103). More specifically, peak times of death within a PCU have been highlighted at 00:00-02:00 and 08:00-10:00 (104). Interestingly, within the same study, no temporal pattern was noted for other hospital patients or for those at home.

1.6. Circadian rhythm disorder associations

Circadian rhythm disruption has been linked with morbidity and mortality. Flatter cortisol rhythms, whereby there is a less marked change between peak and trough cortisol levels, are associated with physical and psychological morbidity (58). This includes depression, obesity, inflammation, fatigue, cancer and mortality (58).

Significant variability in the cortisol circadian rhythm has also been noted in patients with breast and ovarian cancer, including erratic patterns, or persistently elevated or flattened levels (56). Breast cancer patients suffering with fatigue have significantly flatter cortisol rhythms and higher 22:00 levels when compared to those without fatigue (105).

Patients with cancer have been a particular focus of circadian rhythm disruption. Patients with advanced lung cancer demonstrate lower melatonin levels and significant circadian rhythm disruption, more subjective sleep disturbance, worse activity levels and poorer quality of life (106, 107).

Early mice studies found correlations with circadian rhythm disturbance and cancer. More rapid cancer progression and statistically shorter survival times were noted in mice with surgically induced SCN lesions compared to sham operations (108). Attempts to entrain circadian rhythms through meal timing, found that mice fed during light hours has statistically slower cancer progression and prolonged overall survival, compared to mice fed during darkness or *ad libitum* (109). Within humans, flattened cortisol rhythms and a loss of the usual diurnal pattern has been reported to be a significant predictor of mortality for breast and lung cancer patients (110, 111). Metastatic colorectal cancer patients with a proportionally less day to nighttime physical activity have also been identified to have lower levels of quality of life, physical and social functioning, fatigue and loss of appetite (112). Mormont et al monitored rest-activity rhythms using actigraphy in patients with advanced colorectal cancer (113). Patients with increased activity levels whilst receiving chemotherapy had a significant 2-year survival benefit. Similarly, Innominato et al studied patients with metastatic colorectal cancer and found significant independent associations between reduced activity and overall survival (112).

Levi et al demonstrated the significance of the dichotomy index as an independent prognostic factor in a further cohort of metastatic colorectal (114). The dichotomy index (I<O) compares the amount of activity whilst in bed against whilst out of bed. Significant inter-subject rest-activity rhythm differences have been seen in both cancer patients and control groups (35). The I<O index was found to be significantly correlated with the number of metastatic sites, whereby an increasing number of metastatic sites is associated with a lower I<O index (114). Cancer patients with a low I<O have significantly fewer episodes of moderate or highly active states, less difference between their resting and peak activity levels, and less regular inter-daily rest and activity patterns, when compared to patients with a high I<O (35). Cancer patients with a low I<O were also found to have less robust temperature rhythms (35). The evening melatonin rise was more pronounced for high I<O patients and controls compared to low I<O patients (35). Independent prognostic factors, aside from the dichotomy index, included performance status, percentage of liver involvement and the number of previous chemotherapy protocol. The dichotomy index also correlates with progression-free survival (PFS). Patients with a dichotomy index >97.5% had PFS of 9.3 months, compared with 5.8 months in those with an index of ≤97.5% (114).

Studies within other cancers, and cancers at different stages, has also supported this concept. A disrupted dichotomy index in lung cancer patients has been found to be associated with a shorter prognosis, and this effect appears heightened with increasing age (85). In advanced lung cancer patients, performance status and being immobile whilst awake, as measured by actigraphy, have survival implications (49). Indeed, even for patients with a good performance status (ECOG 0-1), immobility whilst awake predicted worse 6-month survival rates. Furthermore, tumour circadian dysfunction in early breast cancer patients undergoing neoadjuvant chemotherapy has been reported as a predictor of survival (115).

1.7. Questions remaining unanswered

1. How should circadian rhythms be investigated in patients with advanced cancer?
2. How common are circadian rhythm disorders in patients with advanced cancer?
3. What associations exist between circadian rhythm disorders in patients with advanced cancer?

CHAPTER 2. CIRCADIAN RHYTHM DISORDERS IN PATIENTS WITH ADVANCED CANCER: A SCOPING REVIEW

2.1. INTRODUCTION

In health, two well documented endocrine circadian rhythms (CRs) are melatonin and cortisol (52). Melatonin and cortisol levels can be measured using several biological samples including serum, saliva and urine (116, 117). Serum melatonin begins to rise from around 22:00, peaking at around 04:00, before falling towards a baseline by 10:00, which persists throughout the day. Cortisol levels peak in the early morning, around 08:00, before falling during the day to a baseline at around 00:00 (52).

Physical activity also demonstrates a circadian rhythm, with peak physical activity occurring around 14:00 and the most restful period centred around 03:00 (118). This may, or may not, coincide with sleep and wake. Sleep and physical activity are assessed primarily using polysomnography and actigraphy (119). Although polysomnography and actigraphy are comparable, actigraphy can be applied to various settings and allows for prolonged periods of monitoring (119). Actigraphy utilises a wrist-worn device to detect physical movement during sleep and wake periods, with subsequent data analysis generating measures of circadian rhythmicity (119). Actigraphy is often accompanied by patient diaries, an approach supported by the American Academy of Sleep Medicine when investigating circadian rhythm sleep disorders (120). However, diaries can be burdensome, inaccurately completed and subject to bias (78). Adult actigraphy research has focused on sleep-wake activity, particularly sleep onset-offset, and the timing of these measures are used within research to describe the robustness of circadian rhythmicity, or the timing and relationship of events (Table 1).

Circadian rhythmicity alters during an individual's lifespan and can impact on health and disease. With advancing age, activity levels decline, peak activity occurs earlier, sleep becomes shorter and more fragmented, and daytime napping increases (67, 121). Circadian rhythm disorders (CRDs), where normal rhythmicity

is altered, can perpetuate cancer, and metabolic, neurodegenerative, psychological and cardiovascular disease (18). CRDs are common amongst cancer patients, affecting up to 75%, and are associated with increased symptom burden, poorer quality of life and shorter survival (56, 113). Interestingly, even misalignment between preferred and actual bedtimes is associated with cancer progression (122).

2.2. AIMS

This scoping review will broadly consider circadian rhythms of cortisol, melatonin, sleep-wake and rest-activity, in patients with advanced cancer, with the aim of:

1. Identifying circadian rhythms in advanced cancer patients, including disordered rhythms
2. Identifying investigative approaches and reported parameters
3. Identifying associations with circadian rhythm disorders, focussing on symptoms, quality of life, survival, and other significant factors

2.3. METHODOLOGY

2.3.1. Data sources

A literature search was performed using PubMed, Embase, Web of Science, Ebsco host (CINAHL, Psychinfo and Psycharticles), Scopus and Cochrane on 20/04/2022. Keywords were restricted to the title and abstract. No other limitations were placed.

2.3.2. Search terms

An example search strategy within PubMed was as follows: ("circadian"[Title/Abstract] OR "sleep wake"[Title/Abstract] OR "rest activity"[Title/Abstract] OR "chrono*" [Title/Abstract] OR "clock"[Title/Abstract] OR "Chronobiology Disorders"[MeSH Terms]) AND (("advanced"[Title/Abstract] OR "progressive"[Title/Abstract] OR "palliat*" [Title/Abstract] OR

"terminal"[Title/Abstract] OR "metast*" [Title/Abstract] OR "end of life"[Title/Abstract]) AND ("cancer*" [Title/Abstract] OR "malig*" [Title/Abstract] OR "tumo*" [Title/Abstract] OR "neop*" [Title/Abstract] OR "oncol*" [Title/Abstract] OR "Neoplasms"[MeSH Terms])).

2.3.3. Eligibility

Studies were eligible for inclusion if the patients were ≥ 18 years old, had a diagnosis of advanced cancer (locally advanced or metastatic) and the study considered objective measures of four markers of circadian rhythm disorders (i.e. sleep-wake rhythms, rest-activity rhythms, cortisol levels or melatonin levels). The studies were also required to be fully translated into English.

2.3.4. Screening and extraction

Two authors independently screened the title and abstract for potential full-text review. Review papers identified in the initial search were also screened for additional full-text review. Full-text articles were reviewed independently by two authors. The reference lists of included articles were searched for any additional articles. Where full-text copies were not immediately available, the leading author or associated research centre, was contacted and if no full-text made available, the article was excluded. Data was extracted by a single author and confirmed independently by a second author. The data extraction tool was then coded into main themes including circadian measures, circadian rhythms patterns, and the association of circadian measures with symptoms, quality of life, survival and other

2.4. RESULTS

The scoping review highlighted 96 articles, which were mainly observational in nature, The review process (Figure 3) is demonstrated and the results from individual studies can be found in Appendix 1.

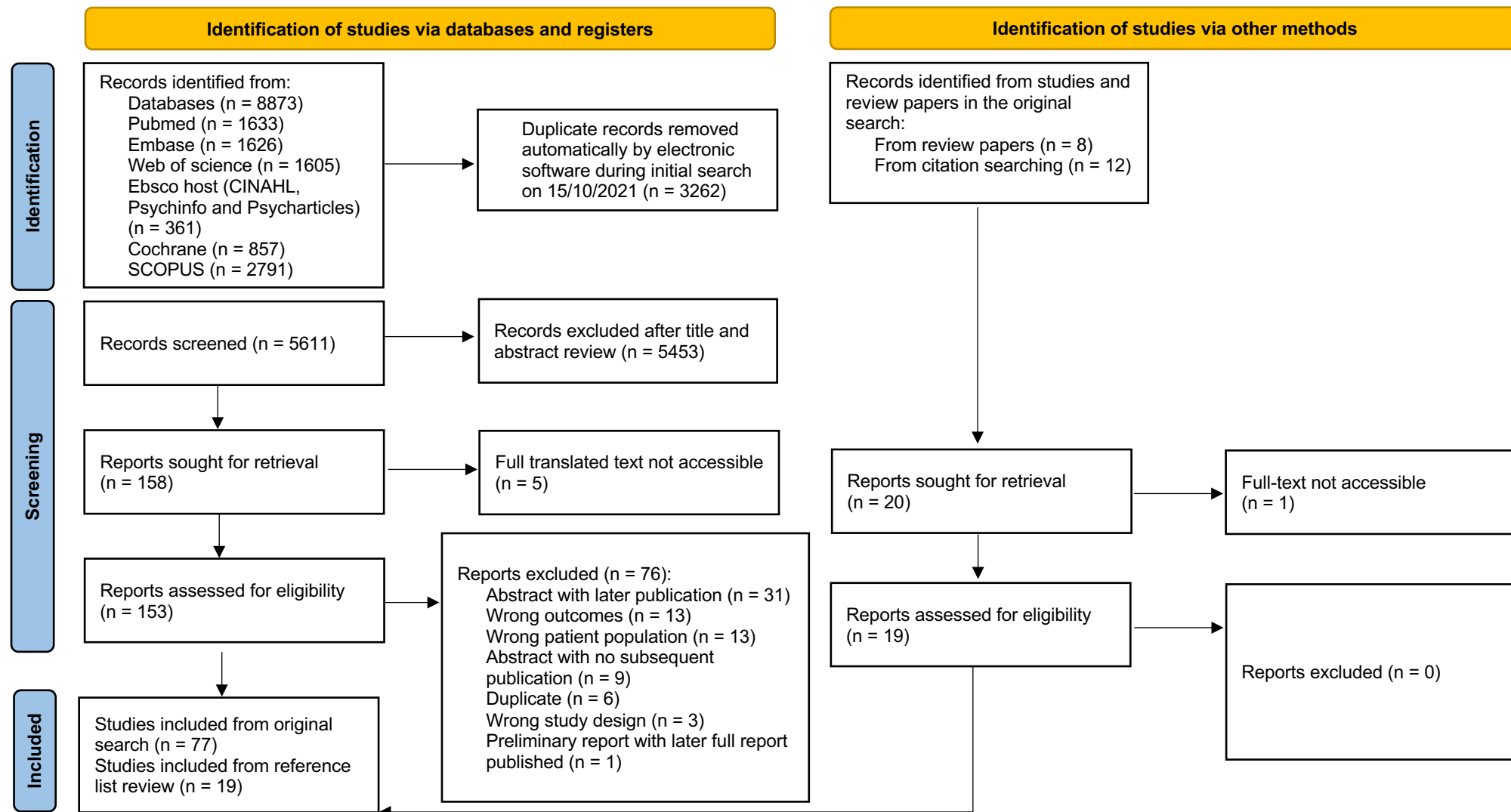


Figure 3. A flow chart of article identification, screening, and exclusion. Flow processes demonstrate identification and screening processes from the original search (left) and from additional sources (right).

Authors utilised actigraphy (n = 33), cortisol (n = 33), combined measures (n = 17), melatonin (n = 11) and polysomnography (n = 2) in their investigation.

Articles focused on several cancer diagnoses, including breast (n = 24), gastrointestinal (n = 22), mixed diagnoses (n = 20), lung (n = 20), gynaecological (n = 7), head and neck (n = 2) and renal (n = 1). All studies included patients with advanced or metastatic cancer; 40 studies focused solely on advanced or metastatic cancer patients.

2.4.1. Investigative and reporting practice

Many articles did not identify normal circadian patterns or values. Variability was noted in the investigational approach, and the reported measures of circadian rhythm. As an example, articles focusing on cortisol measures (n = 48) involved the collection of saliva (n = 23), serum (n = 20), serum and saliva (n = 4), or urine (n = 1) samples. Reported measures included descriptive statistics, MESOR, amplitude, double amplitude, 12- and 24-hour amplitude, acrophase, area under the curve (AUC), diurnal slope, phase angles, cortisol variability, and cortisol awakening response (CAR). Melatonin and cortisol sampling considered 24 hour to 3-day periods for most studies.

Across sleep and wake periods, the timing and duration of activities, the relative proportions between different activities, and the variability both within and between 24-hour periods, were considered. At least 50 different actigraphy parameters were reported. When normal actigraphy values were stated, they differed between studies. The dichotomy index, for example, was reported in 19 studies. Unfavourable, or disordered, I/O values ranged from $<89.5\%$ – $\leq 97.5\%$ (35, 42, 45, 114, 123-127). Favourable, or regular, I/O values varied between $\geq 89.5\%$ – $\geq 99\%$ (26, 35, 40, 42, 45, 114, 123-129). Actigraphy was performed between 2- and 30-day periods in most studies.

2.4.2. Cortisol

2.4.2.1. Cortisol patterns in advanced cancer

13-75% of cancer patients had abnormal cortisol circadian rhythms (27, 56, 129-136). The cortisol acrophase ranged from 04:38 to 09:30 (135, 137, 138). A flattened cortisol slope, reduced diurnal variation, lower morning cortisol rise, and an increased evening cortisol was noted in cancer patients (27, 30, 33, 107, 131, 134, 139-142). This flatter cortisol slope related to higher evening cortisol levels and a lack of the normal decline (34, 143-145). Along with the area under the curve, these changes were more pronounced with later stage, higher grade or metastatic disease and poorer performance status (27, 30, 33, 36, 111, 113, 131, 134, 135, 140, 142, 146-148). A flatter cortisol slope was associated with being male and a smaller CAR was associated with progesterone receptor positivity in breast cancer (111, 144). Studies also noted normal cortisol circadian rhythms in cancer patients (35, 138, 148, 149). A subset of metastatic breast cancer patients were noted to have aberrant cortisol peaks during sleep periods which coincided with wake episodes (149). More wake episodes were also seen with flatter cortisol slopes (110, 150). Mixed findings were noted regarding associations between mean cortisol values and disease stage (30, 143). Cortisol levels were not significantly different between cancer stages and when compared with controls, but the overall mean 24-hour cortisol was found to be higher in cancer patients (107, 147-149).

Salivary and serum cortisol appear positively correlated, particularly when a strong circadian rhythm was present (34, 151).

2.4.2.2. Associations with survival

Flatter cortisol slopes, less diurnal variability and elevated evening cortisol were associated with survival (36, 110, 111, 152, 153). Patients with steep cortisol slopes survived for longer (4.5 years vs. 3.2 years) (110). Cortisol level, area under the curve and CAR were generally unrelated to survival, yet mean cortisol levels were prognostic in patients with metastatic colorectal cancer (111, 134, 154). The disease free interval was not significantly correlated with diurnal cortisol rhythm in

a breast cancer cohort, but was shortened in patients who demonstrated aberrant peak cortisol (149). The cortisol circadian rhythm was also reported to be unrelated to survival (151).

2.4.2.3. Associations with physical symptoms

A smaller CAR and flatter cortisol slopes were associated with total symptom scores, along with the individual scores for fatigue and interference with general activity, work and walking (142). Less diurnal variability was also associated with fatigue and poorer physical well-being (140).

2.4.2.4. Associations with psychological symptoms

Within lung, ovarian, and mixed cancer cohorts, reduced diurnal cortisol variation, elevated evening cortisol, elevated morning cortisol, and higher area under the curve were associated with depression (37, 140, 147, 155, 156). Patients with steeper cortisol slopes, and therefore a healthier circadian rhythm, were found to have a shorter duration of negative affect (32). Antidepressant use was associated with a higher waking cortisol and a lower CAR (144). Those that repress emotions had flatter cortisol slopes (133). Post-traumatic psychological growth after a breast cancer diagnosis was associated with a steeper cortisol slope (157). Other studies reported no significant correlations between cortisol levels, or cortisol slope, and psychological measures (30, 152). In particular, mean cortisol levels were found to be unrelated to depression (156).

2.4.2.5. Associations with quality of life

Flattened cortisol slopes, less cortisol variability and elevated evening cortisol were associated with reduced physical well-being (36, 140). Conversely, cortisol rhythms were also reported to not be correlated with quality-of-life measures (158).

2.4.2.6. Other associations

The cortisol slope, CAR, diurnal variation, and higher cortisol levels were associated with performance status and markers of inflammation (33, 36, 111, 113, 140, 142, 151). The CAR was positively associated with tumour promoting markers, mean cortisol positively correlated with TGF-alpha and IL-6, and circadian cortisol ratio negatively correlated with IL-6 (31, 154).

Flattened cortisol slopes were associated with progressive later waking time and more nocturnal awakenings (110, 146). Aberrant peaks were associated with increased nocturnal wake episodes, metastatic disease, ER negativity and higher initial stage at diagnosis in patients with breast cancer (149). The cortisol rhythm did not predict response to chemotherapy (113). Education, marital status, age, time since recurrence, PR status and metastatic sites were unrelated to cortisol slope (157).

The cortisol slope was correlated with CAR, rather than waking level, and flatter slopes were associated with higher evening cortisol levels and escape from cortisol suppression (144, 145).

2.4.3. Melatonin

2.4.3.1. Melatonin patterns in advanced cancer

17% of metastatic colorectal cancer patients had disordered circadian melatonin rhythms yet many articles found a normal circadian rhythm in cancer patients (107, 129, 148, 159-161). Cancer patients were reported to have absent, time delayed, and time advanced serum melatonin circadian rhythms (29, 161, 162). Reports mainly noted lower mean and peak melatonin values, and a lack of variability throughout the day (29, 107, 161-165). Nocturnal melatonin, AUC and urinary excretion values were lower with more advanced disease (164, 166, 167). Conversely, studies of mixed cancer and gastrointestinal cancer cohorts noted higher melatonin values in cancer patients compared to control (35, 168). Studies also reported maintenance of a circadian melatonin rhythm in lung cancer and

metastatic colorectal cancer patients (107, 148, 159). Circadian parameters were reported to be similar between cancer site, stage and treatment (165).

2.4.3.2. Associations with survival

No significant trend was reported between the melatonin slope and survival (148).

2.4.3.3. Other associations

An inverse relationship was noted between morning melatonin level and performance status (168). Melatonin and tumour necrosis factor (TNF) levels were not correlated (29, 161).

2.4.4. Actigraphy

2.4.4.1. Actigraphy patterns in advanced cancer

Most studies highlighted abnormal actigraphy-defined physical activity (PA) parameters in cancer patients compared to control. Due to several reported parameters, the dichotomy index (I<O), 24-hour autocorrelation coefficient (r24) and sleep efficiency (SE) are noted as examples.

30-54.9% of patients had a disrupted I<O with average group values of 79-98% (individual values of 49-100%) (35, 39, 40, 42, 45, 106, 112-114, 123-126, 128, 136, 154, 169). I<O values were lower in those with metastatic disease, poorer performance status and in males (114, 136). The I<O was reported to be the most discriminative parameter for cancer patients and large inter-subject variability was noted (35, 45).

26-28% of patients had a disordered r24 with average group values of 0.19-0.57 (individual value of -0.06-0.77) (31, 42, 50, 112, 113, 128, 129, 136, 154, 158, 170, 171). r24 values were lower in those with poorer performance status and in African American females (112, 113, 136, 158).

12-88% of patients had disordered sleep efficiency with average group values of 71.0-92% (individual values 20.2-100%) (28, 31, 38, 40-44, 46-48, 50, 106, 126, 128, 150, 153, 172-177).

I<O was correlated with sleep motor activity, wake after sleep onset (WASO), nocturnal awakenings (NA) and SE (45). r24, I<O and mean activity were also correlated (136).

2.4.4.2. Associations with survival

The I<O, r24, physical activity amplitude and MESOR, nighttime restfulness, sleep efficiency, and time awake spent immobile (TASI) were associated with survival (26, 27, 112-114, 153, 154, 178). For example, patients with an I<O <97.5%, or below median I<O, had a reduced overall survival (OS) between 2.1-9.7 months, and reduced progression free survival (PFS) of 4.2 months (114, 123, 124). Similarly, patients with an I<O $\geq$ 99.2% had 11.5 months longer survival than those with an I<O <92.4% (112). The I<O was an independent prognostic factor when accounting for factors including age, gender, performance status, cancer diagnosis and stage, previous chemotherapy and surgery (114, 123, 124). Similarly, SE was an independent risk factor with a greater than double increase in survival for those with a sleep efficiency >85% compared to those with a poor SE (153). However, I<O, r24, mean activity and sleep activity parameters were also reported to not be significantly correlated with PFS (112, 124, 153, 179).

2.4.4.3. Associations with physical symptoms

Circadian activity disruption was associated with pain, fatigue, drowsiness, nausea, vomiting, anorexia and weight loss (38, 46, 113, 127, 136, 154, 159). I<O was specifically correlated with pain, fatigue, anorexia, sleep disturbance or quality, constipation, and dyspnoea (112, 125, 128, 136). r24 was specifically correlated with insomnia, daytime dysfunction, fatigue, anorexia, pain and dyspnoea (38, 48, 112). Sleep efficiency was associated with pain and sleep quality (128, 179). Greater sleep onset latency (SOL), WASO and time in bed (TIB) were associated

with gastrointestinal symptoms (179). Time spent napping was correlated with pain, fatigue and daytime sleepiness (179). Conversely, one study reported no correlation between circadian activity parameters and pain or fatigue (26).

2.4.4.4. Associations with psychological symptoms

Depression correlated with disrupted circadian activity including lower SE, increased time spent napping, time in bed, average wake episodes, I<O, r24 and mean activity (113, 136, 150, 159, 178, 179). Depression was also correlated to shifts in the timing of circadian phases (178). Conversely, anxiety and depression were reported to not be correlated with sleep-activity rhythms, including I<O (26, 35, 41). SOL was negatively associated with perceived stress (150). Intrusive thoughts and avoidant coping were related to lower r24 and more daytime inactivity (171).

2.4.4.5. Associations with quality of life

A more robust dichotomy index was significantly correlated with improved quality of life and health satisfaction (38, 169). Circadian disruption was significantly associated with interference with activity, work, relations, enjoyment of life (125). r24, I<O, and meanAct were positively associated with global quality of life (QoL), along with health, physical, social and functioning subscores (38, 112, 125, 136, 154, 159). Despite the I<O reportedly correlating with all QoL elements, some studies noted circadian parameters were not significantly correlated with the emotional or cognitive subscales (112, 136). A worse global QoL is associated with lower amplitude, MESOR and a later acrophase (26). Global and functional QoL was worse with a higher down-MESOR (26). One study noted that although no parameter was significantly associated with quality of life, the strongest correlation was seen with the r24 (50). TASI negatively correlated with quality of life (49). WASO and r24 were also reported to be unrelated to QoL (158).

Known associations (blue) between actigraphy parameters and symptoms, quality of life measures or survival (Table 2) indicate that the I<O, r24, and sleep efficiency

may have the most impact on patients and therefore could be a focus for future research.

Table 2. The association between actigraphy parameters and clinical outcomes

Actigraphy parameter	Survival	Physical symptoms	Psychological symptoms	Quality of life
Amplitude				
Acrophase				
MESOR				
Down-MESOR				
Dichotomy index				
24-hour autocorrelation coefficient				
Sleep onset latency				
Wake after sleep onset				
Sleep efficiency				
Total sleep time				
Time in bed				
Number of wake episodes				
Time napping				
Time awake spent immobile				
Nighttime restfulness				
Circadian quotient				
Rhythm quotient				

Associations between actigraphy parameters and clinical outcomes are highlighted in blue.

2.4.4.6. Other associations

Some studies reported actigraphy parameters were unrelated to performance status, whilst others reported TASI, I<O, r24 and mean activity to be significantly correlated with performance status (26, 35, 49, 112-114, 136, 154, 159). Analgesic use was associated with more abnormal circadian rhythms (112). There were mixed reports regarding chemotherapy response and circadian rhythmicity. Chemotherapy toxicity and treatment response was unrelated to I<O (124).

Conversely, objective response to treatment appeared to be influenced by the r24 and I<O (113).

More robust circadian rhythms were associated with greater light exposure (26). Subjective and objective activity measures differed, however subjective and objective measures of sleep disturbance were closely correlated (46, 172). Studies reported that measures of activity and mood did not differ significantly between patients who reported their sleep as good or poor (44, 113, 172, 175).

Subjective sleep disruption and circadian disruption can occur separately or simultaneously (40). TST, SE and WASO were reported to be associated with subjective sleep quality (47). Subjective scores of pain and physical function did correlate with objective physical activity (180). Daytime sleep, or inactivity, was related to sleep medication use, nighttime sleep disturbance, daytime dysfunction, nighttime sleep, and sleep quality (48, 122, 181). Circadian disruption was associated with tumour progression markers (31). I<O appeared to correlate with circadian temperature rhythms, self-reported activity and chronotype (35). SE was reported to be correlated with chest metastases, hormone use and radiotherapy (150).

2.4.5. Polysomnography

Patients with cancer spent more time in bed, had multiple nocturnal awakenings and an average SE of up to 77.2% (177, 181, 182). Anticancer therapies were associated with increased SE, and beta blocker use was associated with reduced SE (181). SE was higher in females, white patients, and those with a higher education level (181).

2.4.6. Associations between measures of circadian rhythm

Salivary cortisol levels appeared unrelated to I<O, cortisol rhythmicity positively was correlated with r24, and more robust actigraphy rhythms were associated with a steeper cortisol slope (35, 113, 171). A larger cortisol amplitude was also noted

with a higher I<O (35). Patients with a lower I<O had less pronounced evening melatonin rises and an earlier DLMO (35).

2.5. DISCUSSION

This scoping review highlights that, for several advanced cancer patients, disordered cortisol and activity circadian rhythms are associated with increased symptom burden, poorer quality of life and shortened survival. Activity rhythms and actigraphy appear to be the most common, and melatonin the least common, investigational approaches in this population. Other important associations with CRDs include poorer performance status and raised biomarkers of tumour progression. Various measures of circadian rhythm appear to correlate with one another. Such correlations have previously been seen between PSG and actigraphy, actigraphy and sleep diaries, actigraphy and melatonin and between salivary and serum cortisol (117, 119) Furthermore, the review highlights that several investigational and reporting approaches exist, particularly when using actigraphy.

This review supports, expands upon, and updates previous reviews of circadian rhythmicity in advanced cancer patients. An earlier review reported several disordered circadian rhythms in cancer patients, including changes in cellular activity (mitotic index, dihydropyrimidine dehydrogenase activity), hormonal levels (cortisol, melatonin, prolactin, TSH) and body temperature (183). Similar to this review, studies have highlighted that many cancer patients have stable circadian rhythms and that wide inter-individual variation exists (116, 183). Inter-individual variation is perhaps more evident in the small sample sizes seen in actigraphy circadian rhythmicity research; a finding seen in this review with sample size ranging between 7-439 (78).

Within patients with breast cancer, a review noted that many patients maintain a circadian melatonin rhythm with select patients have smaller melatonin amplitudes and lose their nocturnal melatonin peak (184). Identifying which patients are most impacted by circadian rhythm disorders, and their associations, is important. A

scoping review, focused on rest-activity in advanced cancer patients, noted that CRDs were particularly evident amongst males, those undergoing chemotherapy and those who were symptomatic (185). Similar to this review, CRDs were associated with shorter survival and poorer quality of life (185). The effects may persist beyond cancer treatment with disordered cortisol rhythms being associated with worse biopsychosocial outcomes in cancer survivors (186).

CRDs are not seen solely in cancer patients. Circadian disruption has also been seen in patients with neurodegenerative conditions including Alzheimer's disease, Parkinson's disease, and Huntington's disease (187). Despite conflicting findings, evidence highlights altered rest-activity, body temperature, melatonin and cortisol rhythms within this population and an association between circadian disruption and psychological and physical wellbeing, and quality of life (187).

The review highlights the use of several reporting measures, overlapping definitions and an absence of clear definitions, when investigating circadian rhythms: particularly when using actigraphy. Variability when reporting actigraphy data is not limited to cancer populations. A review of 126 actigraphy studies of children highlighted a lack of standardisation in actigraphy practice, including the reporting of epoch length, artefact detection, and definition of variables (188). Additionally, within cohorts of bipolar disorder patients, over 30 possible actigraphy parametric and non-parametric measures were reported (189). Analysis of actigraphy data takes many forms and lacks standardisation (119, 190). Similarly, variable sampling protocols, analysis and reporting practices has been seen in cortisol and melatonin studies (116, 186).

There are several approaches to hormonal and biochemical investigation, as seen in this review. Serum total cortisol analysis has been proposed as the analysis of choice for cortisol circadian rhythmicity, although salivary cortisol shows promise with further development (117). Benefits and limitations are seen with the various approaches. Although saliva can be obtained in the home setting, oral contaminants need to be considered and there is limited use for overnight study (116). Urine sampling remains a feasible option but often collects samples over a prolonged period and, as a result, reduces the accuracy (116). Plasma sampling

is the most sensitive method and frequent samples are feasible, particularly through indwelling cannulas, but the approach may disrupt sleep and requires hospitalisation (116). Within the context of cortisol, frequent sampling is required to accurately capture changes due to pulsatile secretion every 90-minutes (117). Additionally, it is useful to note that circulating cortisol is mainly protein bound and therefore fluctuations in cortisol binding globulin and albumin may influence the assays (117).

Articles were predominantly observational, and causality is difficult to establish, particularly due to the bi-directional relationship existing between cancers and circadian rhythm disorders, and influence from external factors. Evidence suggests that CRDs impact on several neuroendocrine-immune functions, including inflammatory responses and hormonal secretion, and predispose individuals to developing cancer (191). Cancer patients have increased circulating cytokines which in turn can influence circadian rhythms (191). Anticancer therapies, such as chemotherapy, can disrupt melatonin rhythms and melatonin disruption has been linked to an abundance of oestrogen receptors in breast cancer patients (184).

Rest-activity patterns are influenced by several factors, including age, sex, race, education and voluntary behaviour (119, 190). This review highlighted that cancer patients with CRDs are more likely to experience disease progression and a shortened survival. Actigraphy defined CRDs may represent reduced daytime activity and increased night-time activity. Exercise plays a role in circadian rhythm regulation and has been associated with improved anticancer treatment efficacy and anticancer side effects (191). Cortisol values are also susceptible to change by gender, age, BMI, menstrual cycle, sleep disturbances, renal disease and acute illness, for example (117). The review highlights heterogeneity in the patient sample, with research including inpatients and outpatients prior to, during, and after anticancer therapies. These factors can influence circadian rhythmicity (192).

Actigraphy data can report the timing of events, duration of events, or relationship between events. Although studies may focus on “sleep-wake” or “rest-activity” periods, they are similar in nature. Diagnostic criteria have been formulated for circadian rhythm sleep-wake disorders by American Academy of Sleep Medicine

(89). The diagnosis considers the timing of sleep onset and offset, and the presence of jet lag or shift work, to categorise patients into 7 different diagnoses. Many studies of advanced cancer patients reported actigraphy measures across the 24-hour period rather than focussing on this timing of sleep onset-offset. The circadian rest-activity rhythm disorders in cancer patients are likely separate to intrinsic circadian sleep-wake rhythm disorders. Diagnostic criteria of other forms of CRDs do not currently exist.

Actigraphy data can be analysed to produce several parameters. In this review, actigraphy parameters were associated with physical and psychological symptoms, quality of life, survival, or a combination. Only four parameters ($I<O$, r_{24} , mean activity, and SE) were associated with at least 3 of these areas. Future studies should consider the overall study objectives and align these with appropriate actigraphy parameters. Although a wealth of information can be obtained using actigraphy, the reporting parameters should be targeted, and limited, to allow a clear message in the literature.

The scoping review was strengthened by using independent authors at multiple stages of the review process. Additional evidence was actively sought through hand searching review papers and reference lists and placed minimal limitations in the search strategy. It made no attempt to critically analyse the quality of evidence. Although the review aimed to focus on advanced cancer patients, several studies included non-advanced cancer patients. This may have dampened associations, but it was felt to be more inclusive and to provide a broader insight of the topic. Furthermore, the review did not exclude several confounding factors within studies, such as medications and chemotherapy. This information was not available in several studies and through exclusion, it would have limited the generalisability of the findings.

2.6. CONCLUSION

Cancer patients, particularly those with advanced disease, are at risk of circadian rhythm disorders and there are significant clinical associations. It remains unclear which subset of patients are most susceptible to experiencing circadian disruption.

Conflicting results within the review highlight the need for further study to identify patient populations that are most impacted by circadian rhythm disorders. Current investigative approaches require a multiple sampling approach (blood, urine, saliva) or a prolonged period of activity monitoring. In the clinical setting, this may not be feasible or appropriate, particularly in the advanced cancer population. Attempts need to be made to identify a more clinically appropriate means of identifying patients with circadian rhythm disorders. There also need to be an attempt to standardise research approaches and reporting practice within circadian rhythm research. Research standardisation and targeted approaches may help in future research aimed at developing management approaches to circadian rhythm disorders.

2.7. Questions remaining unanswered

1. What is the optimal approach to assess and report circadian rest-activity rhythms in patients with cancer?

CHAPTER 3. GENERATING CONSENSUS RECOMMENDATIONS FOR THE INVESTIGATION AND DIAGNOSIS OF CIRCADIAN REST-ACTIVITY RHYTHM DISORDERS IN PATIENTS WITH CANCER – AN INTERNATIONAL E-DELPHI STUDY

3.1. INTRODUCTION

Circadian rest-activity rhythm disruption, in advanced cancer, is associated with increased symptomatology, poorer quality of life and shorter survival. These rhythms have primarily been investigated using wrist accelerometry (actigraphy). As highlighted in chapter 2, approaches to the investigation and reporting of circadian rest-activity rhythms, when using actigraphy, vary significantly between studies. Uncertainty also exists around the threshold values of normal, and abnormal, actigraphy parameters. It therefore remains unclear when using actigraphy, which parameters should be focussed on and what values are abnormal. Clinical trials commonly use outcome measures and the selected measures should be important to the researcher, clinician and patient (193). Within research, the use of several outcomes, and heterogeneity in their measurement, limits the ability to synthesise the results of individual studies and, without a predefined core set of outcomes, authors may focus on favourable results (193). Clear diagnostic criteria for a circadian rest-activity rhythm disorder are missing. Accelerometry in a clinical setting requires a period of monitoring (typically at least 7 days) alongside technical expertise in analysing the data. Therefore, despite the benefits of using accelerometry within research, it may be less applicable to a clinical setting. This chapter aims to resolve some of these uncertainties by drawing on the knowledge and experiences of key researchers identified in the earlier literature review.

3.2. Chapter aims

1. To discuss the potential approaches to developing consensus opinion
2. To provide a detailed overview of the Delphi process
3. To generate consensus expert opinion on the following:
 - a. Circadian rest-activity rhythm disorders as a concept

- b. Relevant assessment methods and patient-related factors to consider for patients with a circadian rest-activity rhythm disorder
- c. Diagnostic criteria for circadian rest-activity rhythm disorders in patients with cancer

3.3. Research methodology options

Methodologies aimed at creating a consensus statement include brain-storming, the nominal group technique (NGT) and the Delphi technique (194). These approaches attempt to use a team of experts to generate a group, or consensus, opinion on a complex issue, which provides additional information and strength when compared to relying solely on individual opinion (195, 196).

3.3.1. The nominal group technique (NGT)

The NGT, created in 1968, uses a structured, experienced facilitator-led, face-to-face group discussion (197). Each meeting, lasting up to 2 hours, involves participants writing down, presenting and elaborating on ideas within group discussion, prior to individuals voting on the proposed ideas (197). The group responses are then fed back to the group for further discussion prior to re-voting (197). Face-to-face studies are challenging and costly (when including geographically diverse participants in several time zones), which may as a result limit the included sample (196). As we aimed to include researchers from an international background, the NGT was not an appropriate option.

3.3.2. The Delphi process

Delphi studies, created in the 1950s, provide a structured, iterative process to creating consensus opinion amongst experts on a complex issue (195, 197, 198). Delphi studies are increasingly being used within healthcare research, including in the formulation of guidelines, evaluation of knowledge and the development of diagnostic criteria or assessment tools (195, 198). Within palliative care, Delphi studies have predominantly focused on clinical interventions, particularly symptom management (198). Although Delphi studies are a low level evidence source, they

may be appropriate in select cases where other research methodology may be ethically, economically or practically inappropriate (199).

Rather than face-to-face discussion, Delphi studies utilise questionnaires which help overcome geographical barriers, promotes inclusivity and diversity, allows for larger sample sizes and allows participants to be flexible in their participation (196, 200, 201). However, this approach can limit a participant's ability to elaborate on answers and although electronically delivered (e-Delphi) studies allow for faster responses, there is a higher participant dropout rate (195, 196, 200).

Important elements of a Delphi study include the use of repeated rounds, or an iterative process, the anonymity of participant responses, statistical analysis of responses, and controlled feedback to participants (195, 198, 202). The quality of the Delphi studies can also be enhanced by a clear 'consensus' definition and the targeted selection of 'experts' (195, 198, 199).

3.3.2.1. Delphi rounds

Traditionally, the Delphi process involves an iterative approach whereby participants complete several rounds of questionnaires (195, 196). Ideally, at least 2 questionnaire rounds should be used, and up to 5 rounds is acceptable (199). Within palliative care research, studies have used between 1-5 rounds and lasted 2-18 months (198).

The research focus, and items for review, may be developed through focus groups or literature reviews (195). The process often begins with open-ended questions aimed at generating ideas, statements, or questions, that participants will then rank, or rate their level of agreement with, in the subsequent rounds (195, 196). This qualitative data can also be collected using focus groups and interviews (194). The open-ended nature reduces any influence from researchers and improves the validity of the study (193). As rounds progress, participants re-assess their level of agreement whilst being presented with anonymised responses from the group (195, 196). Although the removal of statements in subsequent rounds reduces participant burden, it also reduces the range of opinions available and can

introduce a degree of bias (194). Free-text boxes may be used throughout the Delphi process, to add further depth to answers (195).

When using the Delphi process, qualitative or quantitative data may be collected in each round (196). Collection methods may include rating scales, selection of items or a ranking system (198). Owing to flexibility in the process, the term 'modified' Delphi is often used, but details of modifications are often lacking (198). Questionnaires, particularly if delivered online, are cost-effective alternatives to face-to-face meetings, and allow participants flexibility in their participation (196). Workshops to share, contextualise and identify opinions may be utilised and can be particularly important if deviating opinions are identified (199).

3.3.2.2. 'Expert' definition

The term 'expert' is flexible but needs to be clearly defined. 'Experts' may include individuals or organisations with clinical, academic or social knowledge and expertise, and may include service users or patients (198, 199). Although expert opinion may be a low level evidence source, their opinion incorporates several sources, including existing research, and improves the validity of findings compared to individual opinion (199). The size of the 'expert' cohort will depend on the research topic and availability, with 30-50 being optimum and 10-100 being seen in existing research (195, 199). The use of multiple 'experts' increases the validity of the findings (199). Diversity and geographical distribution of panel members is encouraged to ensure innovation, creative discussion and generalisable results (195, 199). In the case of a niche research area, a more homogenous sample may be preferred (195).

3.3.2.3. 'Expert' identification

Quantitative research often focuses on generalisable findings, utilising random sampling techniques, whereas qualitative research focuses on gaining in-depth understanding of research topics through purposive sampling (203). 'Expert' selection often uses purposive sampling, of which there are several strategies (Table 3) (194, 204). This includes recruiting participants that are easily accessible

(convenience sampling), highlighted through existing participants (“snowballing”), representative of diverse subgroups (stratified sampling), identified following initial data analysis and theoretical formation (theoretical sampling), or from particular events or issues (criterion sampling) (203). Purposive sampling may utilise a single strategy or, in the context of multi-stage research, combine several strategies (204). Purposive sampling may introduce bias in participant selection, including non-selection of hard to reach groups, and confounding factors which may influence the generalisability of the results (203, 204).

Table 3. Purposive sampling strategies (204).

Sampling strategy	Description
Focused on similarity within the sample	
Criterion	Participants that meet or exceed a specified criterion
Extreme case	Participants that are typical and atypical
Homogeneity	Participants of a particular subgroup
Snowball	Participants highlighted by other participants with similar characteristics
Typical case	Participants that are typical
Focused on variation within the sample	
Confirming-disconfirming case	Participants that fit with and rival with emerging patterns
Critical case	Participants of an isolated group
Intensity	Participants that are typical and atypical but to a lesser extreme than ‘Extreme case’
Stratified purposeful	Participants within a particular subgroup ordered into strata
Purposeful random	Participants within a particular subgroup selected at random
Theory-based	Participants manifesting theoretical constructs
Non-focused	
Convenience	Participants who are easily accessible
Opportunistic	Participants highlighted as circumstances / opportunities arise

Delphi studies can be delivered to two similar, but independent, groups to improve the reliability of the study processes, and the validity of the results can also be improved by interviewing the participants (197). Sub-groups may be noted within an expert group and, if not equally represented, dominant responses from the larger group, or more authoritative groups, may result in the subgroups not being represented (193).

3.3.2.4. 'Expert' recruitment and retention in Delphi studies

A Delphi study may be advertised through notices, emails, the internet, the media or social spaces (203). Widely advertising the study and using key organisations, or networks, to identify relevant participants may improve the sample size (201). Any advertisements should be attractive and inform viewers on the scope of the study and provide relevant contact details (203). Recruitment and retention may be aided by using pre-study invitations to identify motivated participants, and by listing participants who complete all rounds or agree on the final statement in research outputs (193, 197). Participants are most likely to engage in the Delphi process if their practice will be impacted by the findings (194). Purposive, versus random, sampling is also associated with higher retention (197).

Clear communication is key to the success of a Delphi study. Time commitments and expectations should be clear from the outset, as should the wording in communications and the tasks throughout the study (201). Follow up discussions after recruitment should be considered (205). Regular personalised updates and repeatedly approaching non-responders can improve response rates and retention (197, 201, 206). A dedicated study website and social media may improve participant-research relationships, communication and dissemination of information (201).

Long gaps between rounds are associated with higher attrition, but participants should be provided with time to reflect on the study material and not feel rushed (201). Attrition should be considered in the analysis. Participants with minority views are more likely to drop out of the study and the findings may therefore overestimate consensus (193).

3.3.2.5. Anonymity

Anonymous, or pseudoanonymised responses, add to the study's quality for several reasons. Anonymity reduces bias from social pressure and dominant participants, and it provides a level of comfort for participants when responding to uncertain and complex areas (193, 195, 198).

3.3.2.6. Controlled feedback

By providing feedback in a controlled fashion, the researchers can analyse and convert responses into easily understood formats (195). Alternatively, if using an electronic format, feedback can be released in real-time (199).

3.3.2.7. Defining consensus and determining an endpoint

The aim of the Delphi process is to achieve a consensus opinion. There are various definitions of 'consensus' within Delphi studies, with many studies failing to outline how consensus has been achieved (195, 199). Studies may focus on cut-off values or central tendencies and, as a percentage, consensus has ranged from 50-97% (195). Once consensus, or non-consensus, is achieved for a given item it may remain or be removed in subsequent rounds (195). Although consensus may be achieved in a round, this may not persist in successive rounds, and therefore consensus and stability may be more appropriate as criteria to end the study (195, 197). As rounds proceed, participant motivation decreases and response bias increases, but using the number of rounds as an end-point defeats the purpose of the NGT and Delphi studies (197).

Due to disparities in the methodology and reporting practices of Delphi studies, recommendations have been generated (Table 4) (195, 198). Clarity in the study design, including data analysis, allows the reader to appraise, interpret and consider the applicability of the presented evidence (193).

Table 4. Recommendations for Conducting and REporting of DElphi Studies (CREDES) (198).

Recommendation	Explanation
Rationale for the choice of the Delphi technique	The choice of the Delphi technique as a method of systematically collating expert consultation and building consensus needs to be well justified. When selecting the method to answer a particular research question, it is important to keep in mind its constructivist nature
Planning and design	The Delphi technique is a flexible method and can be adjusted to the respective research aims and purposes. Any modifications should be justified by a rationale and be applied systematically and rigorously. Definition of consensus. Unless not reasonable due to the explorative nature of the study, an a priori criterion for consensus should be defined. This includes a clear and transparent guide for action on (a) how to proceed with certain items or topics in the next survey round, (b) the required threshold to terminate the Delphi process and (c) procedures to be followed when consensus is (not) reached after one or more iterations
Study conduct	Informational input. All material provided to the expert panel at the outset of the project and throughout the Delphi process should be carefully reviewed and piloted in advance in order to examine the effect on experts' judgements and to prevent bias Prevention of bias. Researchers need to take measures to avoid directly or indirectly influencing the experts' judgements. If one or more members of the research team have a conflict of interest, entrusting an independent researcher with the main coordination of the Delphi study is advisable Interpretation and processing of results. Consensus does not necessarily imply the 'correct' answer or judgement; (non)consensus and stable disagreement provide informative insights and highlight differences in perspectives concerning the topic in question External validation. It is recommended to have the final draft of the resulting guidance on best practice in palliative care reviewed and approved by an external board or authority before publication and dissemination

Reporting	Purpose and rationale. The purpose of the study should be clearly defined and demonstrate the appropriateness of the use of the Delphi technique as a method to achieve the research aim. A rationale for the choice of the Delphi technique as the most suitable method needs to be provided Expert panel. Criteria for the selection of experts and transparent information on recruitment of the expert panel, sociodemographic details including information on expertise regarding the topic in question, (non)response and response rates over the ongoing iterations should be reported Description of the methods. The methods employed need to be comprehensible; this includes information on preparatory steps (How was available evidence on the topic in question synthesised?), piloting of material and survey instruments, design of the survey instrument(s), the number and design of survey rounds, methods of data analysis, processing and synthesis of experts' responses to inform the subsequent survey round and methodological decisions taken by the research team throughout the process Procedure. Flow chart to illustrate the stages of the Delphi process, including a preparatory phase, the actual 'Delphi rounds', interim steps of data processing and analysis, and concluding steps Definition and attainment of consensus. It needs to be comprehensible to the reader how consensus was achieved throughout the process, including strategies to deal with non-consensus Results. Reporting of results for each round separately is highly advisable in order to make the evolving of consensus over the rounds transparent. This includes figures showing the average group response, changes between rounds, as well as any modifications of the survey instrument such as deletion, addition or modification of survey items based on previous rounds Discussion of limitations. Reporting should include a critical reflection of potential limitations and their impact of the resulting guidance Adequacy of conclusions. The conclusions should adequately reflect the outcomes of the Delphi study with a view to the scope and applicability of the resulting practice guidance

	Publication and dissemination. The resulting guidance on good practice in palliative care should be clearly identifiable from the publication, including recommendations for transfer into practice and implementation. If the publication does not allow for a detailed presentation of either the resulting practice guidance or the methodological features of the applied Delphi technique, or both, reference to a more detailed presentation elsewhere should be made (e.g. availability of the full guideline from the authors or online; publication of a separate paper reporting on methodological details and particularities of the process (e.g. persistent disagreement and controversy on certain issues)). A dissemination plan should include endorsement of the guidance by professional associations and health care authorities to facilitate implementation

3.3.2.8 Generating the Delphi survey

Questionnaire development will be needed for the Delphi study. Well-designed questionnaires can collect information about people's knowledge, attitudes, beliefs and behaviour (206). Questionnaires should be valid, in capturing information it aims to, and reliable, with consistent results when repeated with the same respondents or different researchers (206). They should also be standardised in its delivery with each respondent being provided the same material in the same format (206). Question design will impact on the responses provided, data quality and conclusions drawn (207). Once generated, questionnaires should undergo pilot testing (194).

Open-ended questions allow participants free expression and creativity in their answer, which may lead to responses researcher have not considered (206). However, they require respondents to articulate their thoughts and commit more time and effort (206). There is also additional burden for researchers in the analysis of qualitative data (206). Closed-ended questions are quicker and easier for participant to complete and for researchers to analyse, but provide less rich data (206). Richness of the data can be increased by including free-text boxes (206). Questionnaires should be clear on what is being asked (206). Vague words in questions should be avoided, particularly around frequency of events, as these can be open to interpretation (206). Response options should reflect the question stem wording and, for both open-ended and closed-ended questions, instructions or use of examples may aid in completing the questionnaire (206). Questions should generally be up to 12 words, unless the focus is of a sensitive nature (206).

With closed-ended questions, the response options must be considered. Participants should be provided with several options, including the option of "unsure" or "don't know" to assure quality (207). Scaling responses are an option and are easy to construct (207). Scales can be unipolar, in one direction, or bipolar, with a negative-positive continuum and a central neutral zone (207). Options range from participants offering their own value to being provided with a fixed scale (207). In general, increasing response options is beneficial, but in excess adds complexity in discerning the difference between options (207). A two-point scale provides a

direction of response, a three-point scale allows for neutrality, and additional points highlight the intensity of a response (207). The ideal number of points remains unclear but there is some evidence to suggest that more than 5 provides no additional benefit (207). Clearly labelling scale responses may improve the validity of the responses but increases the cognitive effort (207). Care must be taken in analysing scaling responses, as participants are often biased in their responses towards agreement options and away from negative options (207). When delivered electronically, a slider tool appears more engaging and drag-and-drop options more burdensome (207).

3.3.2.9. Analysing Delphi findings

Delphi studies may use an open-ended initial round followed by rating or ranking responses in subsequent rounds. Qualitative and quantitative data may therefore be collected, requiring different analytical approaches. Including qualitative responses, and subsequent analysis of this data, reduces the need for repeated rounds (197).

Several methods of qualitative analysis exist, including phenomenology, grounded theory, ethnography and content analysis (200). Each approach aims to identify and understand categories within the data (200). The end-point is often when saturation, the point at which additional data provides no further information, is achieved (203).

Content analysis describes “a systematic and objective means to make valid inferences from verbal, visual, or written data in order to describe and quantify specific phenomena” (208). Content analysis can be performed on data from interviews, questionnaires or observations and can take a qualitative or quantitative approach (200). Qualitative analysis will consider the words and themes within the data, whereas quantitative analysis will consider the frequency of ideas (200).

Qualitative analysis should begin by reviewing the entire data set to establish the overall response before decontextualising the data by highlighting meaning units, or codes, within the text (200). Descriptions of code meanings should be

documented to ensure consistency in the analysis and any deviations from the approach should be noted (200). The coding process may use inductive or deductive reasoning. Inductive reasoning involves weaving new information into theories, whilst deductive reasoning focuses on testing existing hypotheses or principles (200). Focus may be placed on what is actually stated within the text, manifest analysis, or on assumptions about what is meant by the text, latent analysis (200). Latent analysis may allow misinterpretation of the data (200). Stability and reliability of the coding process can be improved by repeating the coding process (200). After codes have been developed, codes should be recontextualised to ensure that only data relevant to the research aims is included (200). Uncoded data should be reviewed in the context of the study aims and either included or removed (200). Similar codes are finally grouped together or categorised before compiling objective conclusions in the context of existing literature (200). Validity is strengthened by independent researchers analysing the data separately and discussing findings to achieve consensus (200).

Quantitative data from the ranking of items may be presented using descriptive statistics, inferential statistics or by a visual analysis (205). Results from the final round should include the distribution of scores, particularly if there are a mixture of participants within the group (193). This may highlight disagreement within the group and further analysis, such as outlier or bipolar analysis, may describe the data in further detail (193, 205). If participant characteristics are gathered, it is also possible to explore differing opinions between subgroups, e.g. by profession (197).

When considering terminating the Delphi process, common endpoints include achieving consensus for the statements and having stable participant responses between rounds. Although consensus is important, fluctuating opinions between rounds may indicate a lack of consensus. Consensus and stability are therefore relevant. As noted, the definition of consensus varies between studies with no agreed value. Consensus may be supported by a reducing number of comments, an increase in agreement, or convergence of opinion, in subsequent rounds (209). Various methods for assessing stability exist with no agreed method. For example, stability may be demonstrated by an increase in the weighted Kappa (κ) statistic,

which considers a participant's response between rounds (209). Various statistical methods exist, and the size of the group should be considered. For example, if the study includes 30 or more participants, the coefficient of variation difference, or the Pearson correlation coefficient, for items between rounds may be assessed (210). However, if the group has less than 30 participants, the McNemar Change test between rounds, for dichotomous responses, or the Spearman's Rank Correlation Coefficient for items between rounds, may be considered (210).

3.4. AIMS

The aims of our electronic Delphi (e-Delphi) study are to gain systematic consensus 'expert' opinion on three areas of uncertainty:

1. Characteristics of circadian rest-activity rhythms
2. Diagnostic criteria for circadian rest-activity rhythm disorders
3. Assessment methods to investigate for circadian rest-activity rhythm disorders

An e-Delphi approach was chosen due to the international nature of the study and to allow participants to engage in the study alongside other commitments.

3.5. METHODOLOGY

The e-Delphi, consisting of three rounds, used the online Welphi platform and took place between 30th August 2022 and 19th December 2022. The study was registered at <http://www.comet-initiative.org/studies/searchresults?guid=dd7711a4-4991-4931-972c-c539a641ce1a>.

3.5.1. Inclusion criteria

Inclusion criteria included participants being actively involved in research into circadian activity rhythms in cancer patients, and English proficiency. The

approached authors included previous researchers of 'sleep-wake' and/or 'rest-activity' as it was felt that authors in each category may provide useful information.

3.5.2. Recruitment

Criterion and snowball sampling was used to identify 'Experts'. First, last, and frequent authors, identified from a scoping review of circadian activity rhythm disorders in advanced cancer, were contacted via email to register interest. Where a contact email was not available, other research outputs and academic websites were reviewed for contact information. This initial cohort was also invited to recommend additional relevant participants, who were then reviewed for appropriateness. Potential participants received an email invite and a follow up reminder email.

3.5.3. Study procedures

Study processes are shown in Figure 4. Interested respondents were provided with further study information (Appendix 3) and asked to complete a consent form (Appendix 4). Participants were allocated a pseudonymised code. Participant's country, job title and specialty, and the number of years investigating activity rhythms in cancer patients were collected.

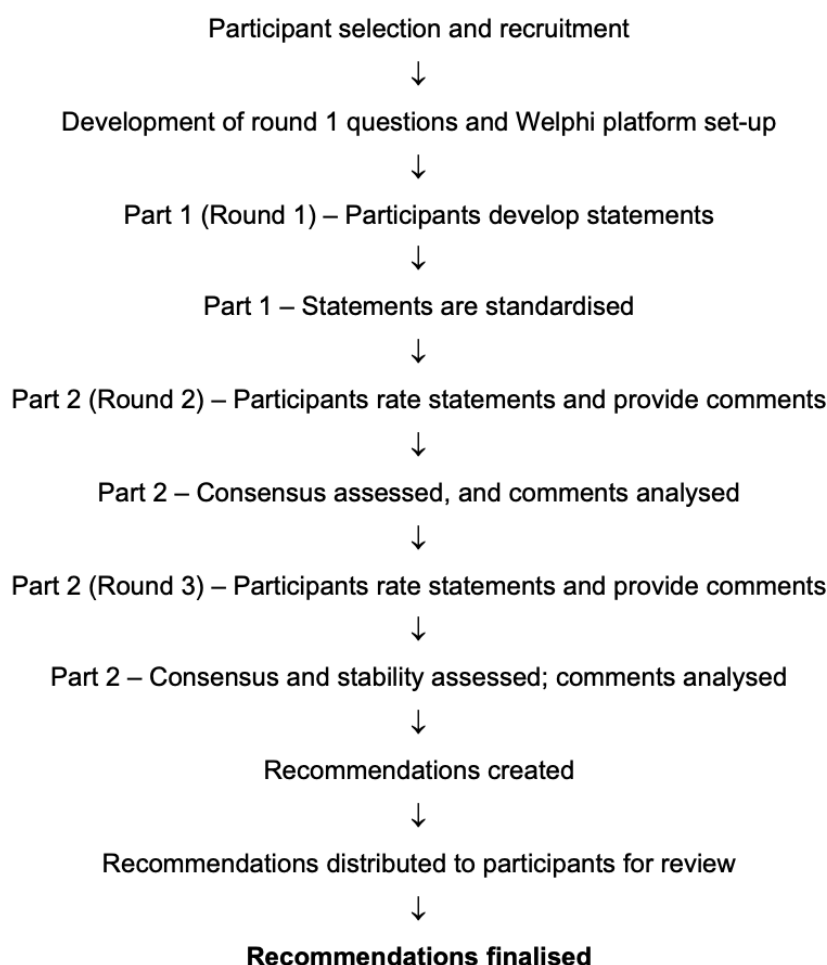


Figure 4. A flow chart of e-Delphi process and creation of recommendations.

This e-Delphi study, using the ‘Welphi’ platform, was performed in two parts. Part 1 focussed on generating statements in three areas (rest-activity rhythm disorders, diagnostic criteria, and the assessment of rest-activity rhythms). This included free text boxes, allowing participants to express their own responses to open-ended questions. It also included closed-ended questions. Yes / No / Unsure options were used when providing opinions on rest-activity rhythms. Yes / No – but it is supportive / No – it is not needed / Unsure were used when providing opinions on assessment techniques. Questions in round 1 (Table 5) were reviewed by 3 members of the research team prior to conducting the Delphi, with the first round being open for 3 weeks.

Table 5. Questions used within round 1 of the e-Delphi study.

Round 1 questions
Part 1 – Rest-activity rhythm disorders This section aims to establish if disordered activity rhythms occur in specific populations, and if there are existing definitions or diagnostic criteria
1. Which serious diseases are associated with circadian rest-activity rhythm disorders? (Free text box) 2. Are circadian rest-activity rhythm disorders different from primary circadian sleep-wake disorders? (Yes / No / Unsure) 3. If circadian rest-activity rhythm disorders are different from primary circadian sleep-wake disorders, please comment on how they are different. (Free text box) 4. Do circadian rest-activity rhythm disorders exist in patients with cancer? (Yes / No / Unsure) 5. If circadian rest-activity rhythm disorders exist in patients with cancer, do they disorders differ from those seen in other serious diseases? (Yes / No / Unsure) 6. If you feel that circadian rest-activity rhythm disorders in patients with cancer are different from those in other serious diseases, please comment on how they are different. (Free text box) 7. Are you aware of any published definitions of circadian rest-activity rhythm disorders? (Yes / No) 8. Are you aware of any published definitions of cancer-related circadian rest-activity rhythm disorders? (Yes / No) 9. If you are aware of any published definitions, please provide reference (Free text box) 10. Are you aware of any published diagnostic criteria for circadian rest-activity rhythm disorders? (Yes / No) 11. Are you aware of any published diagnostic criteria for cancer-related circadian rest-activity rhythm disorders? (Yes / No) 12. If you are aware of any published diagnostic criteria, please provide reference. (Free text box)

13. Do you have any other comments on existing definitions and/or diagnostic criteria? (Free text box)
Part 2 – Diagnostic criteria This section aims to establish diagnostic criteria
1. What do you think are essential criteria for diagnosing a circadian rest-activity rhythm disorder? 2. What criteria are suggestive (not essential) for diagnosing a circadian rest-activity rhythm disorder? 3. What criteria are suggestive of a different cause of a rest-activity rhythm disturbance? 4. Do you have any other comments about diagnostic criteria?
Part 3 – Assessment of rest-activity rhythm This section aims to establish circadian rest-activity rhythm assessment methods
1. Is a clinical history needed to identify a circadian rest-activity rhythm disorder? (Yes / No – but it is supportive / No – it is not needed / Unsure) 2. If a clinical history is taken, what questions are important to identify a circadian rest-activity rhythm disorder? (Free text box) 3. If a clinical history is taken, what questions are important to identify other causes of rest-activity disturbance? (Free text box) 4. Is a physical examination needed to identify a circadian rest-activity rhythm disorder? (Yes / No – but it is supportive / No – it is not needed / Unsure) 5. If a physical examination is performed, what physical signs are important to identify a circadian rest-activity rhythm disorder? (Free text box) 6. Is actigraphy essential to identify a circadian rest-activity rhythm disorder? (Yes / No – but it is supportive / No – it is not needed / Unsure) 7. If actigraphy is used, what is the minimum period a patient should be monitored? (days) (Free text box) 8. If actigraphy is used, what is the maximum period a patient should be monitored? (days) (Free text box)

9. If actigraphy is used, what parameters should be measured? Please include a description of the parameter and the normal values (Free text box)
10. Is a sleep diary essential to identify a rest-activity rhythm disorder? (Yes / No – but it is supportive / No – it is not needed / Unsure)
11. If a sleep diary is used, how many days should be completed? (Free text box)
12. If a sleep diary is used, what time points or events should be documented? (Free text box)
13. Is an activity diary essential to identify a rest-activity rhythm disorder? (Yes / No – but it is supportive / No – it is not needed / Unsure)
14. If an activity diary is used, how many days should be completed? (Free text box)
15. If an activity diary is used, what time points or events should be documented? (Free text box)
16. Are there any investigations that are useful to identify a circadian rest-activity rhythm disorder? (Free text box)
17. Do you have any other comments about assessment? (Free text box)

The lead researcher did not participate in the e-Delphi process and reviewed answers with an independent member of the research team to formulate statements. Similar participant responses were combined, and statements were standardised to align with any existing statements. Where a clear majority view was present, in the case of Yes / No / Unsure options, the statement wording aligned with the majority. Any additional findings from an earlier scoping review of the topic, which were not raised in the initial e-Delphi round, were added to the group of statements (211). The statements generated for round 2 of the Delphi were agreed by two members of the research team. Findings from the scoping review were not presented to participants prior to starting round 1 to avoid any influence on participant responses. Rounds were open for a 3-week period, unless all respondents completed the round at an earlier stage. Personalised opening and closing emails were used at the start and end of each round, along with reminder emails during the round for non-responders. Participants were also encouraged to raise any questions or concerns throughout the process.

Part 2, and subsequent rounds, focussed on assessing 'experts' level of agreement with the statements generated in part 1. Statements were provided to participants, and they were asked to rate their level of agreement using a 5-point Likert scale (Strongly Disagree, Disagree, Unsure, Agree, Strongly Agree). Due to the novel nature of the research area, 'unsure' was added. There was also the option to make comments, suggest modifications and suggest new statements in each round. With subsequent rounds, the same statements were re-presented with group responses from the previous round and any new or modified statements were added to an additional section towards the end of the Delphi round.

We aimed to perform repeated rounds of questionnaires until consensus, and stability in responses between rounds, were achieved. Consensus was defined as 67% agreement (majority agree, majority disagree, majority unsure) between participants about a statement. Due to the novel area and diverse participant group, we accepted that consensus would not be achieved for all statements.

3.5.4. Data analysis

Overall response, recruitment and completion rates were reported throughout the e-Delphi process using crude figures and percentages. Group ratings were reviewed during each round to assess for consensus and were presented for each round to provide transparency. Content analysis was used for comments made during each round. Prior to analysing comments, two researchers agreed that the data would be coded as an explanation for their response, a suggested modification, or a suggested new statement. The two researchers also agreed that following a review of a comment, the outcomes may be to take no action, incorporate the comment into research outputs, create a modified statement, or create a new statement. The team were open to creating new themes as the comments were reviewed. Comments were reviewed by two independent researchers to determine if any new or modified statements were required. Stability of responses between rounds was then assessed using Spearman's Rank Correlation Coefficient.

3.5.5. Forming recommendations

The Delphi findings were then used to create recommendations on the assessment and diagnosis of circadian rest-activity rhythm disorders. The recommendations were fed back to participants for comments and adjustments. Separately, a screening tool, based on the diagnostic criteria, was created.

3.5.6. Ethical approval

Ethical approval for the study was granted by the joint St James' Hospital-Tallaght University Hospital Research Ethics Committee (see appendix 2).

3.6. RESULTS

60 researchers were identified in a scoping review and sent an email invite to participate in the e-Delphi study, and 16 participants completed consent forms and entered the e-Delphi study (Figure 5). Participant demographics and completion rates can be seen in tables 6 and 7. Participants not completing the e-Delphi included a medical consultant and a professor from Canada and Norway. No information was provided by the third participant who did not complete the study.

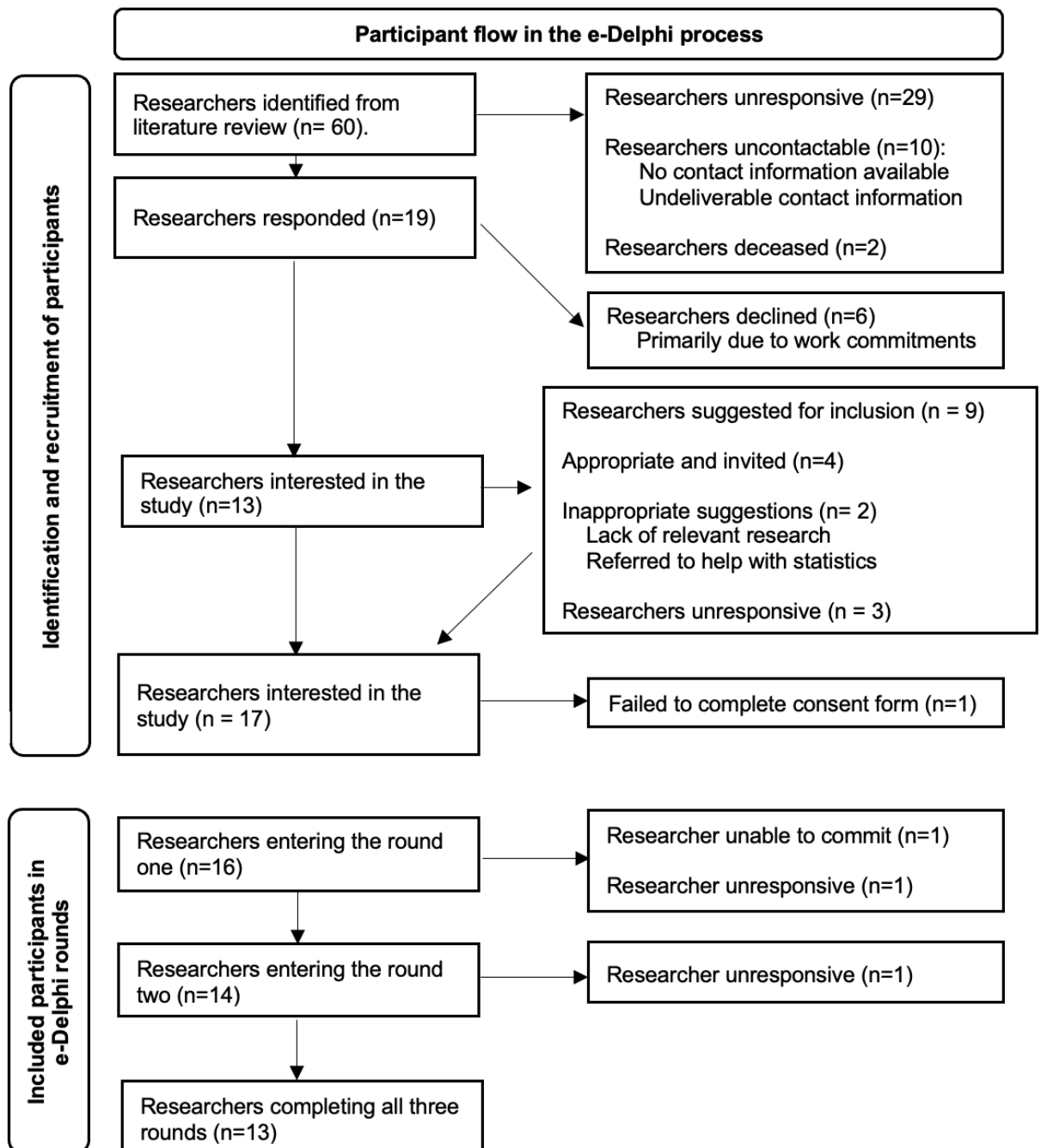


Figure 5. A participant flow chart through the Delphi process (212).

Table 6. e-Delphi participant demographics.

Participant demographics (n = 16)		
Time spent researching activity rhythms in cancer patients		5-35 years
Job Title	Specialism	Location
Professor (n = 7)	Oncology (n = 3)	United States (n = 5)
Associate Professor (n = 3)	Biosciences (n = 2)	India (n = 2)
Medical Consultant (n = 2)	Psychiatry (n = 2)	Norway (n = 2)
Clinical Psychologist (n = 1)	Psychology (n = 2)	UK (n = 3)
Senior Lecturer (n = 1)	Sleep and Physiology (n = 2)	Canada (n = 1)
No response (n = 1)	Anaesthesiology (n = 1)	France (n = 1)
	Nursing (n = 1)	Ireland (n = 1)
	Oncology, Palliative Medicine and Sleep (n = 1)	No response (n = 1)
	Palliative Medicine (n = 1)	
	No response (n = 1)	

Table 7. e-Delphi completion rates by round.

Completion rate			
	Round 1	Round 2	Round 3
Of recruited participants	14/16 87.5%	13/16 81.3%	13/16 81.3%
Of participants entering the round	14/16 87.5%	13/14 92.9%	13/13 100%
Reason for drop-out (if suggested)	Unable to commit (1), No response (1)	IT problems / no response (1)	n/a

Round 1 generated 155 statements which were combined with 6 statements from a literature review, totalling 161 statements. Statements related to circadian rest-activity rhythms (n = 27), diagnostic criteria for a circadian rest-activity rhythm disorder (n = 35), history and physical examination (n = 20), and investigations (n = 79). Following round 2, consensus was achieved for 91 statements (rest-activity rhythms (n = 17), diagnostic criteria (n = 17), clinical history and examination (n = 14), and investigations (n = 43)). Round 2 also generated 43 comments about 37

statements. This identified explanations for a participant's response (n = 25), suggested modifications to an existing statement (n = 13), suggested new statements (n = 3) or an explanation and suggested modification (n = 1). Response to the comments included taking no action (n = 38), creating new statements (n = 2), considering comments in the write up (n = 2) and modifying a statement (n = 1).

Following round 3, consensus and stability were considered (see tables 8a-8e). Consensus was achieved for 106 of the original 161 statements (rest-activity rhythms (n = 19), diagnostic criteria (n = 24), clinical history and examination (n = 14), and investigations (n = 49)). Consensus was also achieved for 1 modified statement and 1 new statement. Of the remaining 55 statements, 3 statements had a majority response (>50%) for unsure but this did not reach consensus. Remaining statements were categorised into opposing disagree and agree responses (n = 22), a spread of opinions across options (n = 15), or a skewedness towards agree or disagree (n = 15).

Considering the stability of responses for each statement between round 2 and 3, statistically significant associations were seen with 129 (80%) statement responses being very strongly associated, and 27 (17%) statement responses being strongly associated. The remaining 5 statement responses were moderately correlated with no statistical significance. Due to consensus being achieved for 66% of statements and strong correlations between responses in rounds 2 and 3, no further e-Delphi rounds took place.

Table 8a. Circadian rest-activity rhythms - group responses for individual statements and stability between rounds.

Statement	Round 2					Round 3					Spearman's rank correlation coefficient R2 and R3	Sig.
	SD	D	U	A	SA	SD	D	U	A	SA		
Circadian rest-activity rhythm disorders ARE different from primary circadian sleep-wake disorders differ	0%	8%	31%	23%	38%	0%	0%	23%	15%	62%	0.647	p=0.017
	8%		31%	61%		0%		23%	77%			
The pathophysiology, clinical features, and consequences between circadian rest-activity and sleep-wake rhythm disorders differ	0%	15%	38%	23%	23%	0%	8%	31%	31%	31%	0.895	p<0.001
	15%		38%	46%		8%		31%	62%			
Circadian rest-activity rhythm considers the relationship between peak and trough activity levels	0%	15%	0%	62%	23%	0%	15%	0%	54%	31%	0.593	p=0.033
	15%		0%	85%		15%		0%	85%			
Circadian rest-activity rhythm considers physical activity across the 24-hour period	0%	0%	8%	38%	54%	0%	0%	8%	23%	69%	0.776	p=0.002
	0%		8%	92%		0%		8%	92%			
Circadian rest-activity rhythm considers the strength, or regularity, of rest and activity periods between days	0%	8%	8%	46%	38%	0%	8%	0%	38%	54%	0.442	p=0.130
	8%		8%	84%		8%		0%	92%			
Circadian rest-activity rhythm disorders do not focus on the timing of the sleep period	0%	54%	23%	15%	8%	0%	54%	23%	15%	8%	0.629	p=0.021
	54%		23%	23%		54%		23%	23%			
Patients with rest-activity rhythm disorders have dampened and disrupted circadian rhythms, rather than phase shifts or lengthening/shortening of the period	8%	0%	15%	69%	8%	8%	0%	15%	69%	8%	1.000	p = 0.01
	8%		15%	77%		8%		15%	77%			
Circadian rest-activity rhythm disorders are related to rest e.g. sleep fragmentation	8%	8%	0%	77%	8%	8%	8%	0%	77%	8%	1.000	p = 0.01
	16%		0%	85%		16%		0%	85%			

Circadian rest-activity disorders are related to activity e.g. reduced daytime activity levels	8%	8%	8%	46%	31%	8%	8%	8%	46%	31%	1.000	p = 0.01
	16%		8%	77%		16%		8%	77%			
Circadian rest-activity rhythm disorders are related to reduced amplitude of activity levels (the difference between peak and trough levels)	0%	15%	8%	46%	31%	0%	15%	0%	54%	31%	0.966	p<0.001
	15%		8%	77%		15%		0%	85%			
Circadian rest-activity rhythm disorders exist in patients with cancer and those receiving anticancer therapies	0%	0%	0%	54%	46%	0%	0%	0%	38%	62%	0.732	p=0.004
	0%		0%	100%		0%		0%	100%			
Circadian rest-activity rhythm disorders in patients with cancer ARE NOT different to circadian rest-activity rhythm disorders in patients with other serious diseases	0%	8%	62%	31%	0%	0%	8%	85%	8%	0%	0.639	p=0.019
	8%		62%	31%		8%		85%	8%			
There is not enough data to know if circadian rest-activity rhythm disorders are different between patients with cancer and other serious diseases	0%	23%	0%	54%	23%	0%	0%	23%	62%	15%	0.857	P<0.001
	23%		0%	77%		0%		23%	77%			
Circadian rest-activity rhythm disorders exist in patients with neurological disorders (e.g. Alzheimer's, Parkinson's, Delirium, Epilepsy, Traumatic brain injury)	0%	0%	0%	62%	38%	0%	0%	0%	54%	46%	0.854	p<0.001
	0%		0%	100%		0%		0%	100%			
Circadian rest-activity rhythm disorders exist in patients with sleep disorders (e.g. insomnia)	0%	8%	8%	77%	8%	0%	8%	8%	77%	8%	1.000	p = 0.01
	8%		8%	85%		8%		8%	85%			
Circadian rest-activity rhythm disorders exist in patients with respiratory disorders (e.g. obstructive sleep apnoea)	0%	8%	15%	69%	8%	0%	8%	15%	69%	8%	1.000	p = 0.01
	8%		15%	77%		8%		15%	77%			

Circadian rest-activity rhythm disorders exist in patients with psychiatric disorders (e.g. mood disorders, schizophrenia, eating disorders)	0%	0%	15%	77%	8%	0%	0%	0%	92%	8%	0.628	p=0.022
	0%		15%	85%		0%		0%	100%			
Circadian rest-activity rhythm disorders exist in patients with musculoskeletal disorders (e.g. osteoarthritis, inflammatory disorders)	0%	8%	38%	46%	8%	0%	8%	31%	54%	8%	0.910	p<0.001
	8%		38%	54%		8%		31%	62%			
Circadian rest-activity rhythm disorders exist in patients with acute illness (e.g. infection, hospitalisation)	0%	0%	8%	85%	8%	0%	0%	0%	85%	15%	0.544	p=0.055
	0%		8%	93%		0%		0%	100%			
Circadian rest-activity rhythm disorders exist in patients with ocular disorders (e.g. blindness)	0%	15%	38%	23%	23%	0%	15%	31%	31%	23%	0.958	p<0.001
	15%		38%	46%		15%		31%	54%			
Circadian rest-activity rhythm disorders exist in patients with endocrine disorders (e.g. diabetes, adrenal insufficiency)	0%	15%	38%	38%	8%	0%	15%	31%	38%	15%	0.916	p<0.001
	15%		38%	46%		15%		31%	53%			
Circadian rest-activity rhythm disorders exist in patients with gastrointestinal disorders (e.g. liver cirrhosis)	0%	8%	46%	46%	0%	0%	8%	38%	54%	0%	0.887	p<0.001
	8%		46%	46%		8%		38%	54%			
Circadian rest-activity rhythm disorders exist in patients with fibromyalgia and chronic fatigue syndrome	0%	8%	31%	54%	8%	0%	8%	31%	54%	8%	1.000	p = 0.01
	8%		31%	62%		8%		31%	62%			
Circadian rest-activity rhythm disorders exist in patients with cardiovascular disorders	0%	8%	31%	54%	8%	0%	8%	31%	46%	15%	0.955	p<0.001
	8%		31%	62%		8%		31%	61%			
Circadian rest-activity rhythm disorders exist in patients with fertility disorders	0%	8%	85%	8%	0%	0%	8%	85%	8%	0%	1.000	p = 0.01
	8%		85%	8%		8%		85%	8%			

Altered rest-activity rhythms can be a phenotype of other problems e.g. nocturia	0%	0%	23%	62%	15%	0%	0%	23%	62%	15%	1.000	p = 0.01
	0%		23%	77%		0%		23%	77%			
There are NO published diagnostic criteria for circadian rest-activity rhythm disorders, including cancer-related circadian rest-activity rhythm disorders	0%	8%	0%	54%	38%	0%	8%	0%	54%	38%	1.000	p = 0.01
	8%		0%	92%		8%		0%	92%			
Number of statements with consensus	17/27 (63%)					19/27 (70%)						

Blue shaded area represents reaching the agreed consensus level. SD: Strongly disagree, D: Disagree, U: Unsure, A: Agree, SA: Strongly agree. R2 and R3: round 2 and round 3, Sig.: significance

Table 8b. Diagnostic criteria for circadian rest-activity rhythm disorders (CARDs) - group responses for individual statements and stability between rounds.

Statement	Round 2					Round 3					Spearman's rank correlation coefficient R2 and R3	Sig.
	SD	D	U	A	SA	SD	D	U	A	SA		
Essential clinical criteria												
Evidence of a decreased daytime activity and increased night-time activity (e.g. daytime sedentariness and nocturnal restlessness)	0%	8%	0%	69%	23%	0%	8%	0%	69%	23%	1.000	p = 0.01
	8%		0%	92%		8%		0%	92%			
Evidence of fluctuating patterns of rest and activity between days	0%	15%	15%	54%	15%	0%	15%	8%	62%	15%	0.939	p<0.001
	15%		15%	69%		15%		8%	77%			
Evidence of physical activity spread across the 24-hour period, rather than focussed periods of rest and activity	0%	15%	15%	38%	31%	0%	0%	23%	46%	31%	0.960	p<0.001
	15%		15%	69%		0%		23%	77%			
Evidence of rest and activity periods that are not aligned with the 24-hour clock	0%	15%	8%	54%	23%	0%	15%	15%	54%	15%	0.737	p=0.004
	15%		8%	77%		15%		15%	69%			
The change in rest-activity rhythm occurred after the diagnosis of cancer or other serious disease	15%	23%	31%	23%	8%	15%	23%	31%	31%	0%	0.991	p<0.001
	38%		31%	31%		38%		31%	31%			
Essential time duration criteria												
The circadian rest-activity rhythm disorder should be present for 2 weeks or more	15%	31%	8%	31%	15%	15%	31%	0%	31%	23%	0.965	p<0.001
	46%		8%	46%		46%		0%	54%			
The circadian rest-activity rhythm disorder should be present for 1 month or more	15%	0%	31%	38%	15%	15%	0%	15%	62%	8%	0.834	p<0.001
	15%		31%	53%		15%		15%	70%			
Essential impact criteria												
The circadian rest-activity rhythm should have a clinical impact on the individual (i.e. fatigue, drowsiness, poor appetite)	0%	0%	15%	46%	38%	0%	0%	15%	46%	38%	1.000	p = 0.01
	0%		15%	84%		0%		15%	84%			
The circadian rest-activity rhythm should have an impact on family members or carer	23%	54%	15%	8%	0%	23%	62%	8%	8%	0%	0.939	p<0.001
	77%		15%	8%		85%		8%	8%			

Essential criteria												
There should be objective evidence of physical activity to diagnose a circadian rest-activity rhythm disorder (e.g. actigraphy)	0%	8%	0%	54%	38%	0%	8%	0%	54%	38%	1.000	p = 0.01
	8%		0%	92%		8%		0%	92%			
There should be objective evidence of biomarkers to diagnose a circadian rest-activity rhythm disorder (e.g. melatonin)	8%	46%	0%	46%	0%	8%	54%	0%	38%	0%	0.887	p<0.001
	52%		0%	46%		62%		0%	38%			
There should be subjective evidence of physical activity to diagnose a circadian rest-activity rhythm disorder (e.g. self-reported measures)	8%	23%	8%	54%	8%	8%	23%	0%	69%	0%	0.889	p<0.001
	31%		8%	62%		31%		0%	69%			
Suggestive criteria												
There should be subjective evidence of physical activity to diagnose a circadian rest-activity rhythm disorder (e.g. self-reported measures)	8%	15%	15%	54%	8%	8%	8%	15%	62%	8%	0.864	p<0.001
	23%		15%	62%		16%		15%	70%			
The individual has difficulty getting up and out of bed in the morning	8%	54%	15%	15%	8%	8%	62%	8%	23%	0%	0.778	p=0.002
	62%		15%	23%		70%		8%	23%			
The individual experiences fatigue that is not alleviated by rest	0%	38%	23%	31%	8%	0%	46%	8%	46%	0%	0.629	p=0.021
	38%		23%	39%		46%		8%	46%			
The individual naps in the day	0%	23%	31%	46%	0%	0%	15%	23%	62%	0%	0.712	p=0.006
	23%		31%	46%		15%		23%	62%			
The individual has disrupted sleep	0%	8%	15%	46%	31%	0%	0%	15%	54%	31%	0.908	p<0.001
	8%		15%	77%		0%		15%	85%			
The individual has low levels of physical activity	0%	23%	31%	23%	23%	0%	23%	38%	23%	15%	0.880	p<0.001
	23%		31%	46%		23%		38%	38%			
Alternative causes of rest-activity rhythm disturbance												
The use of sedatives	0%	8%	31%	54%	8%	0%	0%	31%	62%	8%	0.888	p<0.001
	8%		31%	62%		0%		31%	70%			
The use of stimulants	0%	8%	38%	46%	8%	0%	0%	38%	54%	8%	0.885	p<0.001
	8%		38%	54%		0%		38%	62%			
The use of steroids	0%	15%	54%	15%	15%	0%	15%	54%	15%	15%	0.867	p<0.001
	15%		54%	30%		15%		54%	30%			

The use of chemotherapy	8%	0%	8%	46%	38%	8%	0%	0%	62%	31%	0.852	p<0.001
	8%		8%	84%		8%		0%	93%			
The use of alcohol	0%	0%	31%	62%	8%	0%	0%	15%	77%	8%	0.753	p=0.003
	0%		31%	70%		0%		15%	85%			
Substance misuse / illicit drug use	0%	0%	54%	31%	15%	0%	0%	54%	38%	8%	0.974	p<0.001
	0%		54%	46%		0%		54%	46%			
Experiencing pain	0%	15%	8%	54%	23%	0%	15%	0%	62%	23%	0.953	p<0.001
	15%		8%	77%		15%		0%	85%			
Experiencing fatigue	0%	8%	31%	46%	15%	0%	8%	23%	54%	15%	0.928	p<0.001
	8%		31%	61%		8%		23%	71%			
Experiencing poor sleep	0%	0%	8%	77%	15%	0%	0%	8%	69%	23%	0.853	p<0.001
	0%		8%	92%		0%		8%	92%			
Experiencing urinary symptoms e.g. nocturia	0%	0%	31%	62%	8%	0%	0%	15%	77%	8%	0.753	p=0.003
	0%		31%	70%		0%		15%	85%			
Acute illness	8%	0%	15%	54%	23%	8%	0%	8%	62%	23%	0.939	p<0.001
	8%		15%	77%		8%		8%	85%			
Comorbid illness	0%	0%	15%	69%	15%	0%	0%	15%	69%	15%	1.000	p = 0.01
	0%		15%	84%		0%		15%	84%			
Diet	15%	8%	38%	38%	0%	15%	8%	38%	38%	0%	1.000	p = 0.01
	23%		38%	38%		23%		38%	38%			
Genetic evidence of short or long sleep times	8%	23%	46%	23%	0%	8%	23%	46%	23%	0%	1.000	p = 0.01
	31%		46%	23%		31%		46%	23%			
Hormonal imbalance	0%	8%	62%	15%	15%	0%	8%	62%	15%	15%	1.000	p = 0.01
	8%		62%	30%		8%		62%	30%			
Shift work	0%	0%	8%	38%	54%	0%	0%	0%	46%	54%	0.974	p<0.001
	0%		8%	92%		0%		0%	100%			
Jet lag	8%	8%	8%	54%	23%	8%	0%	0%	69%	23%	0.666	p=0.013
	16%		8%	77%		8%		0%	92%			
Number of statements with consensus	17/35 (49%)					24/35 (69%)						

Blue shaded area represents reaching the agreed consensus level. SD: Strongly disagree, D: Disagree, U: Unsure, A: Agree, SA: Strongly agree. R2 and R3: round 2 and round 3, Sig.: significance

Table 8c. A clinical assessment for circadian rest-activity rhythm disorders (CARDs) - group responses for individual statements and stability between rounds.

Statement	Round 2					Round 3					Spearman's rank correlation coefficient	Sig
	SD	D	U	A	SA	SD	D	U	A	SA		
A clinical history IS needed to identify a circadian rest-activity rhythm disorder and to consider alternative causes of a rest-activity rhythm disturbance	0%	0%	8%	38%	54%	0%	0%	8%	15%	77%	0.678	p=0.011
	0%		8%	92%		0%		8%	92%			
A clinical history should include an oncological history (cancer site, stage, site of metastases, and cancer treatments)	0%	0%	8%	46%	46%	0%	0%	8%	23%	69%	0.700 1.000	p=0.008
	0%		8%	92%		0%		8%	92%			
A clinical history should include medical, surgical and psychiatric comorbidities	0%	0%	0%	54%	46%	0%	0%	0%	46%	54%	0.857	p<0.001
	0%		0%	100%		0%		0%	100%			
A clinical history should include the use of medications (e.g. melatonin, beta blockers, steroids, stimulants, sedatives)	0%	0%	0%	46%	54%	0%	0%	0%	23%	77%	0.592	p=0.033
	0%		0%	100%		0%		0%	100%			
A clinical history should include daily routine and physical activity (e.g. duration and type of exercise)	0%	0%	0%	69%	31%	0%	0%	0%	62%	38%	0.843	p<0.001
	0%		0%	100%		0%		0%	100%			
A clinical history should include how long the individual has struggled with their rest / activity levels	0%	0%	0%	46%	54%	0%	0%	0%	31%	69%	0.720	p=0.006
	0%		0%	100%		0%		0%	100%			
A clinical history should include a sleep history	0%	0%	0%	38%	62%	0%	0%	0%	23%	77%	0.693	p=0.009
	0%		0%	100%		0%		0%	100%			
A clinical history should include an assessment of their chronotype (own sleep time preference)	0%	0%	23%	38%	38%	0%	0%	8%	54%	38%	0.922	p<0.001
	0%		23%	76%		0%		8%	92%			
A clinical history should include an assessment of their greatest alertness (morning or evening person)	0%	15%	15%	46%	23%	0%	8%	8%	62%	23%	0.861	p<0.001
	15%		15%	69%		8%		8%	85%			
A clinical history should include sleep patterns of immediate family members (for genetic cause)	0%	31%	31%	38%	0%	0%	31%	15%	54%	0%	0.899	p<0.001
	31%		31%	38%		31%		15%	54%			

A clinical history should include assessing for symptoms (e.g. fatigue, daytime sleepiness, pain) and the timing of symptoms	0%	0%	0%	54%	46%	0%	0%	0%	46%	54%	0.857	p<0.001
	0%		0%	100%		0%		0%	100%			
A clinical history should include symptoms of hormonal imbalances or treatment for hormonal imbalances in family members	8%	23%	46%	15%	8%	8%	23%	46%	23%	0%	0.995	p<0.001
	31%		46%	23%		31%		46%	23%			
A clinical history should include the individual's environment (e.g. family, newborns, occupation and shift work, long haul travel, light and noise exposure)	0%	8%	0%	54%	38%	0%	0%	0%	54%	46%	0.835	p<0.001
	8%		0%	92%		0%		0%	100%			
A clinical history should include tobacco, alcohol, caffeine and illicit drug use	0%	8%	8%	62%	23%	0%	0%	0%	62%	38%	0.461	p=0.113
	8%		8%	85%		0%		0%	100%			
A clinical history should include daytime sunlight / bright light exposure	0%	8%	8%	62%	23%	0%	8%	8%	62%	23%	1.000	p = 0.01
	8%		8%	85%		8%		8%	85%			
A clinical history should include health behaviour history	0%	0%	31%	46%	23%	0%	0%	23%	46%	31%	0.878	p<0.001
	0%		31%	69%		0%		23%	77%			
A physical examination is NOT needed to identify a circadian rest-activity rhythm disorder	23%	23%	23%	23%	8%	23%	23%	23%	31%	0%	0.991	p<0.001
	46%		23%	31%		46%		23%	31%			
A physical examination should consider a musculoskeletal examination	0%	23%	38%	38%	0%	0%	23%	38%	38%	0%	1.000	p = 0.01
	23%		38%	38%		23%		38%	38%			
A physical examination should include an eye examination (e.g. visual impairment)	0%	31%	38%	31%	0%	0%	31%	38%	31%	0%	1.000	p = 0.01
	31%		38%	31%		31%		38%	31%			
A physical examination should include assessing body mass index	8%	23%	23%	46%	0%	8%	23%	8%	62%	0%	0.897	p<0.001
	31%		23%	46%		31%		8%	62%			
Number of statements with consensus	14/20 (70%)					14/20 (70%)						

Blue shaded area represents reaching the agreed consensus level. SD: Strongly disagree, D: Disagree, U: Unsure, A: Agree, SA: Strongly agree. R2 and R3: round 2 and round 3, Sig.: significance

Table 8d. The use of actigraphy and other investigations - group responses for individual statements and stability between rounds.

Statement	Round 2					Round 3					Spearman's rank correlation coefficient	Sig.
	SD	D	U	A	SA	SD	D	U	A	SA		
Actigraphy is ESSENTIAL to identify a circadian rest-activity rhythm disorder	8%	0%	8%	23%	62%	8%	0%	0%	15%	77%	0.796	p=0.001
	8%		8%	85%		8%		0%	92%			
Actigraphy is SUPPORTIVE in identifying a circadian rest-activity rhythm disorder	8%	31%	0%	15%	46%	8%	31%	0%	8%	54%	0.955	p<0.001
	39%		0%	61%		39%		0%	62%			
The MINIMUM period actigraphy should be used for is 3 days	8%	38%	8%	23%	23%	8%	46%	8%	23%	15%	0.812	p<0.001
	46%		8%	46%		54%		8%	38%			
The MINIMUM period actigraphy should be used for is 5 days	8%	69%	8%	8%	8%	8%	69%	8%	8%	8%	1.000	p = 0.01
	77%		8%	16%		77%		8%	16%			
The MINIMUM period actigraphy should be used for is 14 days	15%	38%	15%	31%	0%	15%	38%	15%	31%	0%	1.000	p = 0.01
	53%		15%	31%		53%		15%	31%			
The MAXIMUM period actigraphy should be used for is 7 days	15%	38%	15%	15%	15%	15%	38%	15%	15%	15%	1.000	p = 0.01
	53%		15%	30%		53%		15%	30%			
The MAXIMUM period actigraphy should be used for is 14 days	8%	38%	8%	38%	8%	8%	38%	8%	46%	0%	0.977	p<0.001
	46%		8%	46%		46%		8%	46%			
The MAXIMUM period actigraphy should be used for is 30 days	23%	62%	15%	0%	0%	23%	62%	15%	0%	0%	1.000	p = 0.01
	85%		15%	0%		85%		15%	0%			
The MAXIMUM period actigraphy should be used for is 56 days	31%	54%	8%	8%	0%	31%	62%	8%	0%	0%	0.920	p<0.001
	85%		8%	8%		93%		8%	0%			
There is no maximum period actigraphy should be used	15%	38%	15%	23%	8%	15%	31%	15%	31%	8%	0.900	p<0.001
	53%		15%	31%		46%		15%	39%			
When using actigraphy, the watch should be worn on the DOMINANT wrist	23%	62%	0%	0%	15%	23%	69%	0%	0%	8%	0.915	p<0.001
	85%		0%	15%		92%		0%	8%			
When using actigraphy, the watch should be worn on the NON-DOMINANT wrist	0%	8%	0%	62%	31%	0%	0%	0%	69%	31%	0.931	p<0.001
	8%		0%	93%		0%		0%	100%			
Important and clinically relevant rest-activity parameter												
Physical activity mesor (rhythm adjusted average activity level of the day)	15%	8%	0%	69%	8%	15%	8%	0%	69%	8%	1.000	p = 0.01
	23%		0%	77%		23%		0%	77%			

Physical activity amplitude (the different between peak and trough activity levels)	0%	8%	8%	54%	31%	0%	8%	8%	54%	31%	1.000	p = 0.01
	8%		8%	85%		8%		8%	85%			
Physical activity acrophase (timing of peak activity)	8%	8%	15%	46%	23%	8%	0%	23%	54%	15%	0.619	p=0.024
	16%		15%	69%		8%		23%	69%			
Peak activity level	8%	23%	8%	46%	15%	8%	8%	8%	69%	8%	0.736	p=0.004
	31%		8%	61%		16%		8%	77%			
Physical activity period (time period of physical activity)	0%	8%	0%	85%	8%	0%	8%	0%	92%	0%	0.736	p=0.004
	8%		0%	93%		8%		0%	92%			
Interdaily stability (a measure of rhythm stability between days)	0%	0%	0%	69%	31%	0%	0%	0%	77%	23%	0.822	p<0.001
	0%		0%	100%		0%		0%	100%			
Intra-daily variability (a measure of rhythm fragmentation)	0%	0%	15%	69%	15%	0%	0%	8%	77%	15%	0.879	p<0.001
	0%		15%	84%		0%		8%	92%			
Dichotomy index (percentage of in bed activity counts less than median out of bed activity counts)	0%	0%	15%	31%	54%	0%	0%	15%	31%	54%	1.000	p = 0.01
	0%		15%	85%		0%		15%	85%			
Daytime sedentariness (percentage of activity out of bed which falls below the median activity in bed)	8%	0%	15%	38%	38%	8%	0%	0%	54%	38%	0.944	p<0.001
	8%		15%	76%		8%		0%	92%			
24-hour autocorrelation coefficient (r24) (a measure of assessing regularity of activity between 24 hour periods)	0%	8%	15%	38%	38%	0%	8%	15%	31%	46%	0.930	p<0.001
	8%		15%	76%		8%		15%	77%			
M10 (mean timing of 10 most active hours)	8%	23%	8%	54%	8%	8%	23%	0%	62%	8%	0.953	p<0.001
	31%		8%	62%		31%		0%	70%			
L5 (mean timing of 5 least active hours)	8%	23%	15%	54%	0%	8%	31%	0%	62%	0%	0.923	p<0.001
	31%		15%	54%		39%		0%	62%			
Rhythm quotient (a measure of activity and sleep consolidation, considering amplitudes at 4-, 8-, 12-, and 24-hour periods)	0%	15%	31%	54%	0%	0%	15%	31%	54%	0%	1.000	p = 0.01
	15%		31%	54%		15%		31%	54%			
Circadian quotient (a measure of circadian rhythm strength, ratio of amplitude to mesor)	0%	15%	23%	38%	23%	0%	15%	23%	46%	15%	0.958	p<0.001
	15%		23%	61%		15%		23%	61%			
Time spent in bed (time between getting in and out of bed)	0%	15%	0%	69%	15%	0%	15%	0%	69%	15%	1.000	p = 0.01
	15%			84%		15%		0%	84%			
Sleep onset (beginning of sleep period)	8%	8%	15%	46%	23%	8%	8%	8%	54%	23%	0.956	p<0.001

	16%	15%	69%	16%	8%	77%		
Sleep offset (end of sleep period)	8% 8%	15%	46% 23%	8% 8%	8%	54% 23%	0.956	p<0.001
	16%	15%	69%	16%	8%	77%		
Total sleep time (total time asleep between in and out of bed time)	0% 15%	8%	62% 15%	0% 15%	0%	69% 15%	0.933	p<0.001
	15%	8%	77%	15%	0%	84%		
Sleep duration (time between sleep onset and offset)	0% 23%	8%	62% 8%	0% 15%	0%	77% 8%	0.796	p=0.001
	23%	8%	70%	15%	0%	85%		
Sleep efficiency (percentage of time asleep between sleep onset and offset)	0% 15%	23%	38% 23%	0% 8%	15%	46% 31%	0.823	p<0.001
	15%	23%	61%	8%	15%	77%		
Sleep fragmentation index (number of awakenings to total sleep time)	0% 15%	15%	31% 38%	0% 15%	0%	38% 46%	0.912	p<0.001
	15%	15%	69%	15%	0%	84%		
Wake after sleep onset (number of minutes awake between sleep onset and offset)	0% 23%	23%	38% 15%	0% 23%	15%	38% 23%	0.931	p<0.001
	23%	23%	53%	23%	15%	61%		
Sleep onset latency (the number of minutes from getting into bed and falling to sleep)	8% 23%	15%	38% 15%	8% 23%	8%	46% 15%	0.968	p<0.001
	31%	15%	53%	31%	8%	61%		
Number of night-time awakenings	0% 15%	8%	54% 23%	0% 15%	8%	54% 23%	1.000	p = 0.01
	15%	8%	77%	15%	8%	77%		
Duration of night-time awakenings	0% 15%	8%	62% 15%	0% 15%	8%	62% 15%	1.000	p = 0.01
	15%	8%	77%	15%	8%	77%		
Number of daytime naps	0% 15%	0%	62% 23%	0% 15%	0%	62% 23%	1.000	p = 0.01
	15%	0%	85%	15%	0%	85%		
Duration of daytime naps	8% 0%	8%	54% 31%	8% 0%	8%	46% 38%	0.910	p<0.001
	8%	8%	85%	8%	8%	84%		
Patient diary								
A patient diary is ESSENTIAL to identifying a circadian rest-activity disorder	8% 31%	23%	8% 31%	8% 31%	38%	0% 23%	0.949	p<0.001
	39%	23%	39%	39%	38%	23%		
A patient diary is SUPPORTIVE in identifying a circadian rest-activity rhythm disorder	0% 15%	0%	77% 8%	0% 15%	0%	77% 8%	1.000	p = 0.01
	15%	0%	79%	15%	0%	85%		
A patient diary supports the use of actigraphy in identifying a circadian rest-activity rhythm disorder	8% 0%	0%	62% 31%	8% 0%	0%	62% 31%	1.000	p = 0.01
	8%	0%	93%	8%	0%	93%		
Without actigraphy, a patient diary is not necessary to identify a circadian rest-activity rhythm disorder	8% 31%	38%	15% 8%	8% 38%	31%	15% 8%	0.946	p<0.001
	39%	38%	23%	46%	31%	23%		

To help identify a circadian rest-activity rhythm disorder, a patient diary should be used for 5 days	0%	62%	23%	15%	0%	0%	69%	15%	15%	0%	0.895	p<0.001
	62%		23%	15%		69%		15%	15%			
To help identify a circadian rest-activity rhythm disorder, a patient diary should be used for 7 days	0%	38%	15%	31%	15%	0%	38%	15%	31%	15%	0.946	p<0.001
	38%		15%	46%		38%		15%	46%			
To help identify a circadian rest-activity rhythm disorder, a patient diary should be used for 14 days	8%	31%	8%	46%	8%	8%	31%	8%	46%	8%	1.000	p = 0.01
	39%		8%	54%		39%		8%	54%			
To help identify a circadian rest-activity rhythm disorder, a patient diary should be used for the duration of actigraphy monitoring	0%	0%	0%	46%	54%	0%	0%	0%	31%	69%	0.720	p=0.006
	0%		0%	100%		0%	0%	0%	100%			
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's bedtime	8%	0%	8%	54%	31%	8%	0%	8%	46%	38%	0.910	p<0.001
	8%		8%	85%		8%		8%	84%			
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's time to lights out	8%	8%	0%	54%	31%	8%	8%	0%	46%	38%	0.910	p<0.001
	16%		0%	85%		16%		0%	84%			
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's sleep onset time	8%	15%	8%	38%	31%	8%	8%	8%	38%	38%	0.895	p<0.001
	23%		8%	69%		16%		8%	76%			
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's sleep latency (time from getting into bed and falling asleep)	8%	15%	8%	38%	31%	8%	8%	8%	38%	38%	0.895	p<0.001
	23%		8%	69%		16%		8%	76%			
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's time and duration of awakenings from sleep	8%	15%	0%	54%	23%	8%	8%	0%	62%	23%	0.939	p<0.001
	23%		0%	77%		16%		0%	85%			
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's wake up time	0%	8%	0%	54%	38%	0%	8%	0%	54%	38%	1.000	p = 0.01
	8%		0%	92%		8%		0%	92%			
	0%	0%	0%	62%	38%	0%	0%	0%	62%	38%	1.000	p = 0.01

To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's get out of bed time	0%	0%	100%	0%	0%	100%		
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's pain level at bed and wake time	8% 15%	23%	31% 23%	8% 15%	23%	31% 23%	1.000	p = 0.01
	23%	23%	54%	23%	23%	54%		
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's fatigue level at bed and wake time	8% 8%	23%	46% 15%	8% 8%	23%	46% 15%	1.000	p = 0.01
	16%	23%	61%	16%	23%	61%		
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's nap time and duration	8% 0%	8%	54% 31%	8% 0%	0%	62% 31%	0.952	p<0.001
	8%	8%	85%	8%	0%	93%		
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's level of daytime sleepiness	8% 8%	0%	62% 23%	8% 8%	0%	62% 23%	1.000	p = 0.01
	16%	0%	85%	16%	0%	85%		
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's time of meals	0% 31%	38%	23% 8%	0% 38%	31%	31% 0%	0.728	p=0.005
	31%	38%	31%	38%	31%	31%		
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's time of physical activity	0% 8%	15%	69% 8%	0% 0%	8%	77% 15%	0.609	p=0.027
	8%	15%	77%	0%	8%	92%		
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's description and duration of physical activity	0% 8%	15%	69% 8%	0% 8%	8%	69% 15%	0.798	p=0.001
	8%	15%	77%	8%	8%	84%		
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's perceived level of exertion during activity	8% 23%	15%	46% 8%	8% 23%	0%	62% 8%	0.923	p<0.001
	31%	15%	54%	31%	0%	70%		
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's symptoms during activity (e.g. fatigue or pain)	8% 23%	23%	38% 8%	8% 15%	8%	69% 0%	0.735	p=0.004
	31%	23%	46%	23%	8%	69%		
	8% 0%	0%	62% 31%	8% 0%	0%	62% 31%	1.000	p = 0.01

To help identify a circadian rest-activity rhythm disorder, a patient diary should include the times the device was removed or replaced	8%	0%	93%	8%	0%	93%		
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's time spent in a dark room resting e.g. watching a movie	8% 23% 31%	31%	23% 15% 38%	8% 23% 31%	31%	31% 8% 39%	0.985	p<0.001
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's time spent indoors and outdoors	8% 31% 39%	15%	38% 8% 46%	8% 31% 39%	8%	46% 8% 54%	0.968	p<0.001
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's mood	8% 31% 39%	31%	15% 15% 30%	8% 31% 39%	31%	15% 15% 30%	1.000	p = 0.01
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's acute stressful events	8% 23% 31%	38%	23% 8% 31%	8% 23% 31%	38%	23% 8% 31%	1.000	p = 0.01
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's subjective sleep quality	8% 0% 8%	15%	54% 23% 77%	8% 0% 8%	15%	54% 23% 77%	1.000	p = 0.01
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's pre-bedtime activities	8% 31% 39%	23%	31% 8% 39%	8% 31% 39%	8%	46% 8% 54%	0.947	p<0.001
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's use of alcohol, caffeine, and smoking	0% 8% 8%	0%	85% 8% 93%	0% 15% 15%	0%	77% 8% 85%	0.817	p<0.001
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's use of medications	0% 15% 15%	0%	69% 15% 84%	0% 15% 15%	0%	69% 15% 84%	1.000	p = 0.01
To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's most active time period	8% 31% 39%	31%	23% 8% 31%	8% 38% 46%	31%	15% 8% 13%	0.838	p<0.001
	8% 31%	31%	23% 8%	8% 38%	31%	15% 8%	0.838	p<0.001

To help identify a circadian rest-activity rhythm disorder, a patient diary should include the patient's most restful time period	39%		31%	31%		46%		31%	13%			
Additional investigations to identify a circadian rest-activity rhythm disorder include the circadian melatonin measures	8%	23%	8%	62%	0%	8%	23%	8%	62%	0%	1.000	p = 0.01
	31%		8%	62%		31%		8%	62%			
Additional investigations to identify a circadian rest-activity rhythm disorder include blood tests (full blood count, thyroid function, metabolic panel)	8%	31%	31%	23%	8%	8%	31%	31%	23%	8%	1.000	p = 0.01
	39%		31%	31%		39%		31%	31%			
Additional investigations to identify a circadian rest-activity rhythm disorder include circadian body temperature	8%	23%	15%	38%	15%	8%	23%	15%	46%	8%	0.968	p<0.001
	31%		15%	53%		31%		15%	52%			
Additional investigations to identify a circadian rest-activity rhythm disorder include measures of bedroom environment (e.g. light, temperature, sound)	8%	23%	23%	38%	8%	8%	23%	8%	54%	8%	0.926	p<0.001
	31%		23%	46%		31%		8%	64%			
Additional investigations to identify a circadian rest-activity rhythm disorder include measures of daytime environment (e.g. light, temperature, sound)	8%	23%	31%	31%	8%	8%	23%	31%	31%	8%	1.000	p = 0.01
	31%		31%	39%		31%		31%	39%			
Number of statements with consensus	43/79 (54%)					49/79 (62%)						

Blue shaded area represents reaching the agreed consensus level. SD: Strongly disagree, D: Disagree, U: Unsure, A: Agree, SA: Strongly agree. R2 and R3: round 2 and round 3, Sig.: significance

Table 8e. Additional statements - group responses for individual statements and stability between rounds.

Round 3 modified statement				SD	D	U	A	SA
When using actigraphy, the watch should be worn on the non-dominant wrist unless there is a medical reason not to do so				0%	0%	0%	31%	69%
				0%		0%	100%	
Round 3 new statements				SD	D	U	A	SA
				15%	15%	15%	46%	8%

Devices that measure rest and activity, including accelerometry, are essential to identifying a circadian rest-activity rhythm disorder				30%		15%	54%	
Rest-activity rhythms can be assess using accelerometry at multiple sites, including wrist, chest, hip or leg				0%	0%	0%	62%	38%
				0%	0%	0%	100%	

Blue shaded area represents reaching the agreed consensus level. SD: Strongly disagree, D: Disagree, U: Unsure, A: Agree, SA: Strongly agree. R2 and R3: round 2 and round 3, Sig.: significance

The consensus statements, final round comments and formulated recommendations were distributed to the participants for comments and suggested adjustments. Recommendations on diagnostic criteria and assessment methods were then finalised. Based on the diagnostic criteria, a screening questionnaire, aimed at identifying patients with a circadian rest-activity rhythm disorder, was developed.

3.6.1. Recommendations for assessing and diagnosing circadian rest-activity rhythm disorders in patients with cancer

- **Circadian rest-activity rhythm disorder definition**

Cancer patients may develop a circadian rest-activity rhythm disorder (CaRD), which involves an ongoing change in physical activity over a 24-hour period (day and night) and which is associated with increased morbidity and/or decreased quality of life.

Box 2. Diagnostic criteria for a circadian rest-activity rhythm disorder in people with cancer

- A.** Patients exhibit relatively less daytime physical activity and more night-time physical activity; **OR** Rest and physical activity spread across the 24-hour period, rather than distinct rest and active periods; **OR** A lack of regularity in rest and active periods between days
- B.** The altered physical activity pattern
- A. has been present for at least 1 month
 - B. has a clinical impact on the patient
 - C. is demonstrable by objective and subjective measures
- C.** The altered rest-activity rhythm is not primarily due to another cause

CARDs can occur in patients with cancer. However, they also occur in other serious diseases including neurological, respiratory, and psychiatric conditions,

primary sleep disorders and acute illness. It is unknown whether the circadian rest-activity rhythm disruption differs significantly between diagnoses. Other causes of disturbed rest-activity rhythms include chemotherapy, alcohol, sedatives, stimulants, uncontrolled symptoms, shift work, and jet lag.

A clinical history (essential), accelerometry (essential) and patient diary (suggested) are recommended to assess a CARD in people with cancer.

- **Clinical history**

A clinical history should consider:

- An oncological history (cancer site, stage, site of metastases, and cancer treatments)
- The presence and timing of symptoms e.g. fatigue, daytime sleepiness, pain
- Medical, surgical and psychiatric comorbidities
- Daily routine, type and duration of physical activity
- If daytime sedentariness and/or nighttime restlessness is noted, the duration should be considered
- Sleep history, assessment of chronotype, and peak alertness
- Medication history (e.g. melatonin, beta blockers, steroids, stimulants and sedatives)
- The use of tobacco, alcohol, caffeine, and illicit drug use
- Environmental factors e.g. shift work, jet lag, noise and light exposure

- **Accelerometry**

Accelerometry should take place for at least 72 consecutive hours. The location of an accelerometry device should be documented, and when using wrist actigraphy, the non-dominant wrist should be used unless contraindicated. Removal of the device should be documented. Relevant parameters to identifying a CARD include:

A. Evidence of nighttime restlessness

- Sleep efficiency, number and duration of nighttime awakenings

B. Evidence of daytime sedentariness

- Daytime sedentariness, number and duration of daytime naps

C. Evidence of daytime sedentariness and nighttime restlessness

- The dichotomy index, physical activity relative amplitude, intra-daily variability

D. Evidence of a lack of regularity in rest and active periods between days

- The 24-hour autocorrelation coefficient, interdaily stability

E. Phase markers

- M10, acrophase, L5

- **Patient diary**

A sleep and activity diary supports accelerometry and the diagnosis of a CARD. A diary should consider day and night-time events and be used for the duration of accelerometry monitoring. Information to capture in a sleep and activity diary includes:

A. Daytime events

- Time, description, duration and perceived level of exertion of physical activity
- Nap time and duration
- Subjective level of daytime sleepiness
- Presence of symptoms during physical activity (e.g. pain or fatigue)
- Medication use
- Alcohol, smoking, caffeine, and substance use

B. Night-time events

- Bedtime
- Time to lights out
- Sleep onset
- Time and duration of awakenings from sleep
- Wake up time
- Get out of bedtime

- Subjective sleep quality

3.6.2. A screening tool to identify CARDs in people with cancer

Questions were created aiming to identify diagnostic features of a CARD (Table 9). Due to overlap between ‘rest-activity’ and ‘sleep-wake’ rhythms, questions were also developed aiming to identify circadian sleep-wake rhythm disorders (Table 10).

Table 9. A circadian rest-activity rhythm disorder screening tool.

Since your cancer diagnosis...	Yes	No
1. Have you been aware that you are more restless during some of the nights each week? (e.g. moving around in bed, getting out of bed)		
2. Have those that you live with been aware that you are more restless during some of the nights each week?		
3. Have you spent more time being less active or napping in the daytime each week? (e.g. spending long periods sitting down or lying in bed)		
4. Have you noticed that the amount of time that you are active or resting varies from day to day? (e.g. some days you spend more time being physical active, and other days you spend more time resting)		
5. Do you feel that your quality of life or any of your symptoms relate to your rest and activity levels?		
Time to complete	min	s

Table 10. A circadian rhythm sleep-wake disorder screening tool.

Since your cancer diagnosis...	Yes	No
1. Has your sleep pattern changed?		
2. Are you going to bed and waking up earlier some days of the week?		
3. Are you going to bed and waking up later, some days of the week?		
4. Does your sleep pattern vary from day to day?		
Time to complete	min	s

3.7. DISCUSSION

The e-Delphi study led to recommendations for the assessment and diagnosis of circadian rest-activity rhythm disorders (CARDs) in patients with cancer. The recommendations provide a defined and standardised method to approach CARDs in academic research and, potentially, in future clinical practice. The e-Delphi focussed on experts within cancer research and the recommendations cannot be directly extrapolated to other clinical conditions. Further research is required to characterise circadian rest-activity rhythms in different patient populations, including cancer subgroups, to identify similarities, differences, and their significance.

Diagnostic criteria include evidence of less daytime activity with more night-time activity, rest and activity spread across a 24-hour period or a lack of rest-activity regularity between days. This is supported objectively by disordered I_{CO} and r_{24} in patients with cancer, which are associated with shorter survival, increase physical and psychological symptoms, and poorer quality of life (112, 113).

Accelerometry has been validated against polysomnography-measures, such as total sleep time and sleep efficiency, when investigating sleep-wake rhythms, and accelerometry parameters such as sleep interruptions, sleep latency and mean daily activity are strongly correlated with Pittsburgh Sleep Quality Index (PSQI) self-reported sleep quality (48, 213). Hip and wrist sited devices correlate well with

moderate-to-vigorous activity but are less able to detect sedentary activity or static exercise (45, 51). This may be a limitation of wrist-worn actigraphy in detailing all levels of activity. Thigh accelerometers are more capable of detecting postural changes and sedentary behaviour and, although combined wrist and thigh monitoring may provide more detail, any additional patient burden should be considered (68).

The recommendations highlight that CARs occur in patients with several clinical conditions other than cancer. Research highlights, for example, rest-activity rhythm fragmentation occurs in patients with chronic obstructive pulmonary disease and bipolar disorder (214, 215). Fragmented rest-activity rhythms have also been demonstrated in early stage Alzheimer's disease, which contrasts with cancer diagnoses where measures, such as the dichotomy index, appear more pronounced with advanced disease (114, 216). Worse cognitive performance has also been associated with disordered rest-activity rhythms in those with early Parkinson's disease, post-acute respiratory failure and older men with osteoporotic fractures (217-219).

Assessment of circadian rest-activity rhythms requires measurement of activity across the 24-hour period. Continuous monitoring is therefore required. We recommend a minimum 72-hour monitoring despite no consensus being achieved for the minimum recording period. A minimum duration was felt necessary to guide practice. Existing recommendations for actigraphy monitoring, within sleep-wake studies, suggests 7-14 days monitoring, with longer monitoring periods providing additional detail, such as weekday and weekend activity (220). Patients with advanced cancer however, demonstrate similar activity counts and rest-activity rhythm measures on mid-week and weekend days (180, 221). Prolonged periods of monitoring may therefore be unnecessary. Reviews of activity monitoring, in patients with cancer, highlight a wide range of monitoring periods (72 hours up to 270 days) with 72-hours / 3 days, being commonly used (222, 223). Device placement is mainly the wrist, as recommended, but research has included the hip, waist, thigh, and ankle (222, 223). Studies of wearable devices have included a range of cancer diagnoses, including cancer survivors and those with advanced disease (222, 223). Adherence rates have ranged between 73% and 97% (222).

Several factors modify circadian rhythmicity, including chemotherapy and surgery (224, 225). Chemotherapy has significant effects on rest-activity rhythms (RARs), including loss of day-night activity distinction, and worsening of I/O and r24, with progressive cycles (225). Patients with endometrial cancer undergoing surgery and, for the majority of cases, adjuvant chemotherapy, have demonstrated less variation in their RAR at 1- and 4-week post-surgery (224). RAR recovery was demonstrated 4 months after treatment (224). It remains unclear if RARs in this instance recover from the surgery and chemotherapy, or from the reduced disease burden of anticancer treatments. Considering environmental factors, long-haul travel can also influence circadian rhythmicity. A review demonstrated that there is significant interindividual variation in the impact of travel on circadian rhythms and the subsequent recovery periods (226). Circadian disturbance may be evident for psychometric markers (up to 3 days), perceived jet lag (up to 7 days), and physiological disturbance, such as grip strength, body temperature, melatonin and cortisol (up to 11 days) (226). The time to recover from transient modifiers of circadian rhythmicity likely varies depending on the influence, e.g. hospitalisation, jet lag, chemotherapy, surgery, and the circadian measure being considered, e.g. melatonin profiles or RARs. The e-Delphi recommendations include the RAR disturbance being present for at least 1 month. This timing considers recovery from temporary modifiers of circadian rest-activity rhythms. It remains unclear at which stage in the cancer process circadian rest-activity rhythm disorders occur, and they may pre-date the diagnosis.

An 81% completion rate of our e-Delphi study is comparable to other e-Delphi studies of core outcome measures, typically at least 80% (ranging 45-100%) (227). Similar to our study, the majority of Delphi studies used 2 or 3 rounds which ranged from 10 days to 10 weeks (198). Higher completion rates occur with 2 rounds, compared to 3-4 rounds, and lower completion rates occur with larger groups and a larger number of statements within the Delphi (227). Similar to our study, a third of previous Delphi studies within palliative care used the Delphi alone to answer the research question and had an international scope (198). Including participants from several countries and clinical specialties, whilst combining academics and clinicians researching 'rest-activity' and 'sleep-wake' strengthens the validity of the

recommendations. Similar to this study, Delphi expert selection methods have included being part of a profession, research field, or having relevant academic and/or clinical experience (198). A 5-point rating scale has also been commonly used, along with 9-point scales (198). Reporting of completion and attrition rates within Delphi studies varies and may be considered in relation to participants within the previous round or those who entered the study initially. Figures for both were included for completeness.

There is a lack of agreement on adequate consensus levels and the method to assess for stability within Delphi studies. A consensus threshold of 67% was chosen and indicated a majority view. Delphi studies have used consensus thresholds of 50-97% and within e-Delphi, 75% or 80% is often used (195, 198). When taking this into account, 89% of statements reaching the pre-determined 67% consensus threshold, were also over the 75% threshold used in other studies. Due to the small sample size, the Spearman's rank correlation coefficient was felt an appropriate measure and agreed by our statistician (209). Due to consensus being present for most statements, and stability between rounds, it was felt that recommendations could be created without the need for additional methods, such as face-to-face meetings. Participants were engaged in the Delphi process and provided qualitative feedback throughout, including in reviewing the final recommendations. Further e-Delphi rounds may have led to consensus for additional statements, but at the risk of higher attrition rates with reduced validity of the final recommendations. Due to the heterogeneity of the participant sample and novel research area, it was accepted prior to starting the e-Delphi that consensus for all statements was unlikely.

The recommendations have not been reviewed externally. The sample included international academics and clinicians to provide unique and generalisable insights into the research topic. Further validation of the diagnostic criteria is required. Following study completion, the recommendations were presented at the International Networking Workshop for Personalized Cancer Chronotherapy (Paris, April 2023).

3.8. CONCLUSION, IMPLICATIONS, AND FUTURE RESEARCH DIRECTIONS

Circadian rest-activity rhythm disorders are prevalent and have significant associations in patients with cancer. The e-Delphi study led to recommendations for the assessment and diagnosis of the disorder in patients with cancer. This aims to standardise and focus future research and reporting practice. Several areas require further investigation. This includes the validation of the newly formed diagnostic criteria, further characterisation of rest-activity rhythms and disorders between patient populations and within cancer subgroups, and to identify high-risk characteristics. Additionally, research should investigate alternative methods to identify patients at high-risk of a circadian rest-activity rhythm disorder. Research investigating management approaches to improve rest-activity rhythm disorders is required and, in the event of improved rhythms, to further assess the impact of improved rhythmicity on clinically relevant outcomes.

3.9. Questions remaining unanswered

1. How are circadian rest-activity rhythms characterised in patients with advanced cancer?
2. What is the role of a patient sleep and activity diary in assessing circadian rest-activity rhythms in patients with advanced cancer?
3. What is the prevalence and associations of circadian rest-activity rhythm disorders in patients with advanced cancer using the newly formed recommendations?
4. What are the risk factors for developing a circadian rest-activity rhythm disorder for a patient with advanced cancer?
5. Is there an easy way to identify, or screen, for patients with cancer and a circadian rest-activity rhythm disorder?

CHAPTER 4. IDENTIFYING AND CHARACTERISING CIRCADIAN REST-ACTIVITY RHYTHM DISORDERS (CARDs) IN PATIENTS WITH ADVANCED CANCER

4.1. INTRODUCTION

This chapter focuses on assessing circadian rest-activity rhythms (RARs) of patients with advanced cancer. A comprehensive assessment, using wrist and thigh accelerometry, a novel screening tool and a patient sleep and activity diary, will be used to assess circadian RARs and will aim to identify those who have a circadian rest-activity rhythm disorder (CARD) according to the newly formed diagnostic criteria. CARDs will then be considered in relation to demographics, symptom burden, past medical history, lifestyle factors, chronotype, quality of life (QoL) and prognosis. Modifiers of circadian rest-activity rhythm disorders will also be considered. Methods of capturing said factors will be discussed initially.

Assessment of functional status, symptoms and QoL are of paramount importance in palliative care, allowing for earlier appreciation of changing needs and an improvement in clinical outcomes. Self-reporting of such factors, as opposed to clinician reported, is often undertaken. Amongst patients with solid tumours receiving chemotherapy, those who completed self-reports of symptoms versus routine monitoring, had significant improvement in health-related QoL measures, less hospitalisation and received longer periods of chemotherapy (228). Due to the clear benefits of patient-reported measures, they will be prioritised within patient assessments.

4.1.1. Assessing performance status in patients with cancer

Assessment of performance status (PS), an individual's ability to carry out daily activities and a measure of independence, can highlight changes in a patient's clinical state over time and can aid treatment decisions. A commonly used tool is the Eastern Cooperative Oncology Group (ECOG) score (see table 11), whereby lower ECOG scores reflect increasing independence and performance ability (229).

Table 11. The Eastern Cooperative Oncology Group score.

Eastern Cooperative Oncology Group (ECOG) score	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Similar ECOG scores, when assessed by a range of oncology professionals, including consultants, specialty trainees and nurse specialists are reported (230). PS scores may also differ between clinician- and patient-completed assessments, and assessments tend to be more accurate in those with a better PS (229). Better PS scores correlate with improved effectiveness and reduced side effects of chemotherapy, improved QoL and prolonged survival (229). However, assessing PS alone provides a limited picture of a patient's functional status and alternative tools, such as the Comprehensive Geriatrics Assessment (CGA), which considers several domains, may provide a more complete picture (229). The Timed Get Up and Go Test or Short Physical Performance Battery also provide additional information when assessing PS (229). Furthermore, objective measures, such as accelerometers, may aid PS assessment, but their use is limited by cost and a lack of technical expertise (229).

4.1.2. Assessing symptoms in patients with cancer

Completing symptom assessment tools allows for greater identification of symptoms compared to patient reporting alone (231). A commonly used tool, the

Memorial Symptom Assessment Scale (MSAS), is validated in patients with cancer, and involves the assessment of frequency, severity and associated distress of common symptoms over the preceding week (231). To reduce participant burden, the shorter form (MSAS-SF), consisting of 32 symptoms covering global distress, physical symptoms and psychological symptoms, was created (232). MSAS-SF demonstrates validity, test-retest reliability and internal reliability for the global distress index (0.80), physical symptom distress (0.82), psychological symptom distress (0.76), and total symptom distress (0.87) (232). Anxiety and depression, identified using the Hospital Anxiety and Depression Scale (HADS) in patients with advanced cancer, is also associated with the MSAS-SF GDI and psychological subscale (233). The MSAS-SF may therefore reduce participant and researcher burden by avoiding the need for two separate tools.

4.1.3. Assessing sleep quality in patients with cancer

Sleep disorders are common in the general population, including obstructive sleep apnoea (up to 38%), periodic limb movement (up to 30%), insomnia (up to 20%), and restless leg syndrome (up to 11.6%) (234). Sleep disorders impact nighttime restfulness, daytime sleepiness and fatigue levels, and are therefore relevant to circadian RARs. Poor sleep quality is common in patients with cancer and may result from cancer itself, anticancer therapies, or the side effects of anticancer therapies. Cancer results in a pro-inflammatory state with increased cytokine production, such as interleukin-1, which reduces rapid eye movement sleep (234). Indeed, higher levels of pro-inflammatory cytokines are found in patients undergoing anticancer therapy who report poor sleep quality compared to those with improved sleep quality (235). Slow-wave sleep, sleep latency, and sleep efficiency (SE) are poorer in patients with cancer (236). Up to 63% of patients with cancer experience insomnia, with higher rates in males and particular associations with breast, lung and head and neck cancers (234). Insomnia is also associated with symptoms of depression, anxiety, pain and fatigue (234). Patients experiencing insomnia often self-perpetuate the condition with cognitive and behavioural processes, such as a belief of being unable to fall asleep, resulting in hyperarousal in bed (237). Poor subjective sleep quality is associated with a shorter time to disease progression (hazard ratio = 1.74) and shorter overall

survival (hazard ratio = 1.40), a finding reflected in the association between objective evidence of sleep disruption and shorter overall survival (hazard ratio = 1.74) (238).

Measures of sleep quality and its impact may be objective (polysomnography (PSG), accelerometry, and bispectral index monitoring (BIS)) or subjective (Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Insomnia Severity Index (ISI), and Consensus Sleep Diary (CSD)) (239). PSG, as highlighted in chapter 1, is the gold standard for investigating sleep and wake. BIS, reflecting electroencephalogram (EEG) activity alone, correlates well with PSG and scores below 80 out of 100 indicate sleep (239).

The PSQI considers subjective sleep quality over the past month using a 19-item, self-reported, questionnaire (239). Lower scores relate to improved sleep quality and a threshold total score of 5 or more demonstrates good sensitivity and specificity at detecting sleep impairment (239). The PSQI is a valid and reliable measure of sleep disturbance and sleep quality in cancer patients (>0.8 for global sleep score >0.7 for sleep disturbance component) (240). For cancer patients, mean PSQI scores were higher in those with sleep problems and so a threshold of 8 may be more appropriate (240). When compared to the PSQI, the brief PSQI (bPSQI) (Table 12), comprised of 6 of the original 18 PSQI questions, demonstrated similar sensitivity (75.82%) and specificity (76.99%) for identifying poor sleepers when using a cut off value of >5 (241). The bPSQI may therefore be more appropriate in studies that use several questionnaires to reduce participant burden.

Table 12. The brief Pittsburgh Sleep Quality Index (bPSQI).

5 components from 6-item questions	Score			
	0	1	2	3
1. Sleep latency (minutes)	≤15	16-30	31-60	>60
2. Sleep quality	Very good	Fairly good	Fairly bad	Very bad
3. Nighttime awakenings and early morning waking	Not in the past month	Less than once a week	Once or twice a week	Three or more nights a week
4. Sleep duration (hours)	>7	6-7	5-6	<5
5. Sleep efficiency (sleep duration / time in bed)	>85%	75-84%	65-74%	<65%

The ISI assesses insomnia symptoms over the past 2 or 4 weeks using a 7-item questionnaire and leads to four classifications of insomnia (no insomnia, slight insomnia, moderate insomnia, and severe insomnia). It is a reliable and valid tool, but uncertainty remains over threshold scores for insomnia (239). The ESS assesses daytime sleepiness, commonly noted in patients with sleep disorders, during 8 different situations using an 8-item, self-reported questionnaire (239). Higher scores correlate with worse daytime sleepiness (239). The CSD uses 9 questions in those with a sleep disturbance to capture sleep habits. The tool is able to detect sleep disturbance when compared to ISI and accelerometry (239).

4.1.4. Assessing quality of life in patients with cancer

The use of 39 different quality of life (QoL) assessment tools in advanced cancer has been highlighted in a recent review (242). QoL tools often include symptom assessment, associated distress and impact on daily functioning (242). As with many assessment tools, patient-completed QoL assessments are more accurate than clinician-completed assessments (242). The most commonly used, and

widely validated, tool is the European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) (242). Although many tools lack a complete psychometric assessment, the EORTC-QLQ-C30 and EORTC-QLQ-C15-PAL, a shorter version for use within palliative care, demonstrate good content and construct validity, and good measurement error (242). EORTC-QLQ-C15-PAL focuses on symptoms at the end of life and may not be appropriate across the cancer trajectory (242). The EORTC-QLQ-C30 in this case may be more appropriate and better reflects health-related QoL (242).

4.1.5. Assessing prognosis in patients with cancer

An accurate prognosis may help patients, and those important to them, to access support and services, and to prepare them for the future (243). It may also aid researchers in classifying research participants (243). Clinician Predicted Survival (CPS) is commonly used for patients with advanced cancer and any prognostic tool needs to be as good as CPS, if not better (244). Several prognostic tools exist and may include subjective measures, objective measures, clinical factors (i.e. anorexia and performance status) and biomarkers (i.e. C-reactive protein and albumin) (245). A review highlights that although several prognostic tools exist, there is limited evaluation of specific tools (i.e. the B12/C-Reactive Protein Index (BCI) and Prognosis in Palliative Care Study (PiPS)), and there is a lack of direct comparison between prognostic tools (245).

The Palliative Prognostic Score (PaP) and delirium-PaP (D-PaP) include objective and subjective measures and can similarly predict 30-day survival in patients with advanced cancer (244, 245). Professionals lacking experience in prognostication may be reluctant to use the tool due to the inclusion of the CPS (243, 245). Although the BCI scores correlate with shorter survival and incorporates objective measures, the inclusion of vitamin B12 levels, which may not be routinely measured, limits its use (245).

The Performance Scale (PPS) tool captures functional status, is accurate in estimating prognosis for scores of 40% or less, and scores of 50% or more are associated with lower hazard ratios (244, 245). The PPS has been extensively

investigated and uses subjective measures with a particular focus on performance status.(245) The Palliative Prognostic Index (PPI) considers survival as less than 3 weeks, less than 6 weeks or more than 6 weeks.(244) The PPI incorporates the PPS and, due to and increased use of subjective measures, opens to tool to bias and additional complexity.(245) The PPI is less accurate than CPS at predicting 3- and a 6-week survival (244). Furthermore, the Glasgow Prognostic Score (GPS) tool is also available, is quick and easy to use, and focuses on objective measures (245). All tools have been validated in patients with cancer (245).

The PiPS tool considers survival measured in days, weeks, or months (243). PiPS can be equally as predictive as CPS and may include solely subjective measures (PiPS-A) or incorporate objective measures (PiPS-B) (245). Despite the use of subjective measures within PiPS, there is a focus on specific parameters included in the European Association for Palliative Care's prognostic factors (245). Compared to agreed multi-professional estimates of survival (AMPES), including experienced doctors and nurses, PiPS-B was as accurate at estimating survival, whereas PiPS-A was less accurate (243). In the case of limited resources, where AMPES may not be easy or viable, or prognostication is required by inexperienced professionals, PiPS-B may support individual professionals in estimating prognosis (243).

4.1.6. Modifiers of circadian rest-activity rhythms

Circadian RARs can be disordered when daytime physical activity is reduced and nighttime physical activity is increased, rest and activity periods are poorly differentiated, or variability in rest and active periods exists between days. Considering factors which can influence activity across and between 24-hour periods, may identify reversible modifiers of rest-activity rhythm disturbance and be a target for intervention.

4.1.6.1. Symptoms

Circadian rhythm disorders are associated with increased symptom burden. This association can be considered bidirectional with specific symptoms impacting on

sleep and restfulness, as well as energy and physical activity. Pain, breathlessness, and fatigue are common in patients with advanced cancer and impact on daily activities such as walking, working and sleep (246). Fatigue, a multidimensional subjective physical and mental experience of exhaustion, with associated loss of motivation and need to reduce physical activity, has several underlying mechanisms (247). This includes serotonin, hypothalamic-pituitary-adrenal, circadian rhythm, muscle metabolism and cytokine dysregulation (247). Common contributors include anaemia, weight loss, mood disorders and sleep disorders (247). Fatigue, anxiety and depression are also associated with insomnia which impacts on sleep and daytime sleepiness (248). The presence and severity of symptoms may fluctuate during the day and between days with varying impact on RARs. Uncontrolled symptoms are known to impact physical activity and should be assessed in patients with circadian rest-activity rhythm disorders (246).

4.1.6.2. Sleep-related disorders

Sleep disturbances are common in patients with cancer and include insomnia (30-50%), excessive daytime sleepiness (28%) and restless legs (41%) (248). The prevalence of disorders varies by cancer type, with patients with lung cancer experiencing more sleep problems in general, and patients with breast cancer experiencing more insomnia and fatigue (248). Symptoms of insomnia correlate with objective sleep measures including longer time to fall asleep (sleep latency), shorter sleep time, and lower sleep efficiency (248). Poor sleep quality impacts daytime and nighttime activity, and should therefore also be considered in patients with circadian rest-activity rhythm disorders (248).

Sleep disordered breathing (SDB), an increasingly recognised condition, can result in hypertension, diabetes, cardio- and cerebrovascular disease, and circadian disruption (249). SDB impacts several circadian rhythms including body temperature, sleep-wake, and rest-activity (249). When compared to healthy controls, patients with SDB have reduced intradaily stability and increased relative amplitude, with increased disruption associated with SDB severity (249). More severe SDB is associated with increased nighttime activity and less stable activity patterns (249). When SDB is treated with continuous positive airway pressure

(CPAP), circadian rhythms become less fragmented with improved day-night distinction and less nocturnal activity (249). Obstructive sleep apnoea (OSA), a form of sleep disordered breathing, is common in the general population (10-30%) and often remains undiagnosed (250). Within cancer, OSA rates are likely higher (27-67%) and, due to the impact on circadian rhythms, it is worthwhile considering in the assessment of patients with circadian rest-activity rhythm disorders (250). The STOP-Bang questionnaire (Table 13) is an easy and valid tool to detect OSA across populations (251). Increasing sensitivity of the tool is demonstrated for higher apnoea-hypopnoea index scores which correlate with moderate-to-severe OSA (251).

Table 13. The STOP-Bang Questionnaire (251).

	Question
Snoring	Do you snore loudly (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?
Tiredness	Do you often feel tired, fatigued, or sleepy during the daytime (such as falling asleep during driving or talking to someone)?
Observed apnoea	Has anyone observed you stop breathing or choking/gasping during your sleep?
Pressure	Do you have or are being treated for high blood pressure?
BMI	Body mass index more than 35 kg/m ² ?
Age	Age older than 50?
Neck	Neck size 40cm or larger?
Gender	Gender = Male?
Scoring	
Low risk	Yes to 0-2 questions
Intermediate risk	Yes to 3-4 questions
High risk	Yes to 5-8 questions OR Yes to 2 or more of STOP questions + male OR BMI >35 OR neck circumference >40cm

Restless leg syndrome (RLS) is characterised by an unpleasant urge to move limbs, is associated with restlessness and involuntary movements, and may occur during sleeping and waking periods (252, 253). RLS may be idiopathic (primary) or secondary to disorders such as end-stage renal disease, iron deficiency and neuropathies (254). RLS is associated with cortical iron deficiency, which in turn may be associated with a hypo-adenosinergic state (255). Interestingly, increasing extracellular adenosine levels, through the blockade of adenosine reuptake, has been shown to improve periodic limb movements and sleep parameters (sleep onset latency (SOL), SE) (255). Circadian rhythms of restlessness have been established with peaks after midnight and troughs in the morning (252). RLS prevalence rates are significantly higher in patients with cancer undergoing chemotherapy compared to the general population (18% vs. 2-4%) (254). Higher rates of RLS are also noted in “poor sleepers” compared to “good sleepers” (28.8% vs. 15.8%) and higher PSQI scores, reflecting poorer sleep quality, correlate with RLS severity (254). Due to the prevalence and potential impact on circadian RARs, it may be useful to assess for RLS using the International RLS Study Group criteria (Table 14) for patients with a CARD.

Table 14. Criteria for diagnosing Restless Leg Syndrome (253).

Five essential diagnostic criteria (all must be met)	
1.	An urge to move the legs usually, but not always, accompanied by or caused by uncomfortable or unpleasant sensations in the legs
2.	The urge to move the legs and any accompanying unpleasant sensation a. Begin or worsen during periods of rest or inactivity, such as lying down or sitting b. Are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues c. During rest or inactivity only occur, or are worse, in the evening or night than during the day
3.	The occurrence of the above features is not solely accounted for as symptoms primary to another medical or behavioural condition

4.1.6.3. Blood and electrolyte abnormalities

Electrolyte disturbances are common in patients receiving anticancer therapies, including hyponatraemia (62%), hypokalaemia (40%), hypophosphataemia (32%), hypomagnesaemia (17%), and hypocalcaemia (12%) (256). Disturbances, such as hyponatraemia, are a poor prognostic feature and are associated with increased symptomatology (256). Baseline electrolyte disturbance increases the risk of developing additional disturbances during anticancer treatment (256).

Due to its antagonistic N-methyl-D-aspartate (NMDA) receptor activity, and agonistic gamma-aminobutyric acid (GABA) receptor activity, magnesium plays a likely role in sleep regulation (257). During a double-blind, randomised, placebo-controlled trial, magnesium supplementation led to significantly improved day time physical activity, night-time sleep time, SE, and SOL (257). ISI scores also significantly improved (257).

Vitamin deficiencies are common in patients with cancer. Between 40-70% of patients with cancer have a vitamin D insufficiency (30-50 nmol/L) or deficiency (<30 nmol/L) (258, 259). Higher rates are seen in those with more advanced disease and a vitamin D deficiency is associated with cancer-related mortality (258, 259). A meta-analysis highlighted vitamin D deficiency is also associated with sleep disorders, poor sleep quality, shorter sleep duration, and daytime sleepiness (259).

Anaemia affects up to 90% of patients with cancer and is often multifactorial, including bone marrow infiltration, systemic inflammation, bleeding, nutritional deficiencies (predominantly iron, vitamin B12, folate), and anticancer therapies (260). Anaemia can result in fatigue, potentially resulting from hypoxia-related organ dysfunction, and therefore impact on daytime physical activity (247, 260). As mentioned above, in addition to anaemia, iron deficiency may contribute to RLS and disturbed sleep (260).

Furthermore, interactions exist between endocrine systems and circadian rhythmicity. Thyroid stimulating hormone (TSH) levels follow a circadian pattern, with peaks between 2200-0500 and troughs at 1500-1900, and a reduced

amplitude between this peak and trough is present for those with poor sleep (261). Patients with hypothyroidism, low levels of circulating thyroid hormones, experience less non-rapid eye movement (NREM) stages 1 and 2, and increased NREM stage 3 and REM sleep (261). Patients with hypothyroidism often suffer with fatigue, are at increased risk of sleep-related breathing disorders, and also experience less slow wave sleep and more nighttime awakenings (261). There is conflicting evidence of impact on sleep for patients with hyperthyroidism (261). There is some evidence associating hyperthyroidism with sleep disruption, including prolonged SOL, reduced total sleep time, reduced SE, and increased body movements, including tremors (261).

4.1.6.4. Medication

Patients with advanced cancer may receive medication for comorbid disease, symptom management or as anticancer therapy. Various prescribed medications, and their abrupt discontinuation, can influence sleep, physical activity, or other components of circadian rhythmicity, such as melatonin (Appendix 6). This may be a drug class effect or specific to the individual drug. Examples of commonly used medications are discussed.

Several medications may be used to manage pain in patients with advanced cancer, including non-steroidal anti-inflammatory drugs (NSAIDs), opioids and gabapentinoids. NSAIDs, such as aspirin and ibuprofen, increase night-time awakenings and reduce SE (262). NSAIDs likely impact sleep by reducing evening melatonin and prostaglandin D2 levels, or altering body temperature (262). NSAIDs can also lead to gastric irritation, which may impact on sleep (263). Unfortunately, medications protecting from gastric irritation, such as histamin-2-receptor antagonists, are also associated with insomnia (263). Opioids reduce slow wave and rapid eye movement (REM) sleep, sleep duration and continuity, and may be associated with daytime sedation (263, 264). Gabapentin conversely increases slow wave sleep whilst maintaining REM sleep (263).

Anti-emetics are also commonly used in advanced cancer to manage nausea and vomiting. Prokinetics, such as domperidone and metoclopramide can cause sleep

disturbance (263). Antipsychotics, such as haloperidol, may be used as an antiemetic, or to manage agitation and psychosis, and have been associated with sleep disturbance in a minority of patients (263). Several other antipsychotics also cause sedation, reduce SOL and increase sleep quantity and sleep continuity (264).

Antidepressants, used to manage symptoms of depression and anxiety, can have sedative effects (263). Sedating tricyclic antidepressants (TCAs) reduce REM sleep but prolong slow wave sleep (263). Selective serotonin reuptake inhibitors (SSRIs) have a more temporary impact with associated reduced SE, REM sleep and total sleep time (263). Benzodiazepines, used for symptoms including anxiety and agitation, do increase total sleep time but reduce REM sleep and slow wave sleep (263). Paradoxically, benzodiazepines can also lead to agitation and insomnia in a minority of patients (263). Tolerance to the sedative effect of benzodiazepine often builds over time and may lead to escalating doses (263).

Anticonvulsant drugs, such as phenobarbital, phenytoin, and carbamazepine impact sleep in different ways. Phenobarbital reduces sleep latency and increases SE whilst carbamazepine, in the short-term, increases nighttime awakenings and reduces REM sleep (263).

Drugs which may be used for non-cancer conditions are also important contributors to sleep and activity disruption. Beta-blockers for example, used for hypertension, arrhythmias, and ischaemic heart disease, are known to lower evening melatonin levels, reduce REM sleep, and are associated with poor sleep and fatigue (263, 265). Beta-blocker users taking supplemental melatonin experience reduced sleep latency and increased total sleep time (265). The effects of beta-blockers on sleep appear related to the lipid solubility of the drug rather than pharmacological class, with sleep quality worsening with metoprolol but improving with nebivolol, for example (263, 266). For those with hypercholesterolaemia or ischaemic heart disease, cholesterol lowering drugs (statins) can be associated with muscle aches and cramps with a subsequent disturbance of sleep (263).

The abrupt cessation of many drugs and substances may also impact sleep. Withdrawal of histamine-2 receptor antagonists, TCAs, SSRIs and opioids can result in insomnia and increased REM sleep (263).

Of note, several drugs are associated with sleep-related behaviours including sleep driving, sleep eating, and sleepwalking, including antipsychotics, Z-drugs (e.g. zopiclone), SSRIs, serotonin-noradrenergic reuptake inhibitors (SNRIs), antiepileptics and beta blockers (264).

4.1.6.5. Lifestyle

An individual's chronotype, a measure of sleep-wake timing or preference of the sleep-wake timing, can impact on the level and timing of daily activities. Of note, morning-types (MTs), who have a preference for activities earlier in the 24-hour period, are more likely to have higher physical activity levels and engage in more vigorous activities than evening-types (ETs) (267). "Eveningness" is also associated with higher rates of use, or misuse, of several illicit substances, nicotine, alcohol and caffeine (268). Poor sleepers are more likely to misuse alcohol and other substances, and resulting from such use, substance misusers often have irregular sleep patterns and experience daytime sleepiness (268). The use of, and withdrawal from, psychoactive substances can have detrimental effects on sleep and circadian rhythmicity and this impact will depend on the substance involved (268). Stimulating substances often lead to the sensation of restlessness causing problems with sleep continuity (268). Conversely, although opiates, alcohol and benzodiazepines can initially improve sleep latency, withdrawal during the night results in increased nighttime awakenings (268). Substance withdrawal can also lead to prolonged sleep latency and reduce the total sleep time (268). Substance use may impact other circadian rhythms, with chronic alcohol use being associated with an inverse of the usual melatonin rhythm and delayed dim-light melatonin onsets (DLMOs) (268).

A bi-directional relationship exists between alcohol intake and sleep. Insomnia symptoms may lead to an individual self-medicating with alcohol (237). Unfortunately, alcohol has several detrimental effects on sleep including prolonged

sleep latency, reduced REM sleep, SE and total sleep time, and increased night-time awakenings (237). Alcohol cessation then often leads to improvements in insomnia symptoms (237). Alcohol has also been shown to impact circadian rhythms in body temperature and melatonin (237). High alcohol use is associated with “Eveningness” which in turn may also be associated with ‘social jetlag’ (237). Furthermore, alcohol increases the risk of sleep-related breathing disorders which can further impact on sleep-wake and rest-activity rhythms (237).

Both ‘short’ and ‘long’ duration sleepers engage in more sedentary activities than ‘adequate’ sleepers (267). Those who sleep for shorter or longer periods, rather than adequate periods, and those with an “Eveningness” preference are also more likely to smoke (267). Smoking is associated with shorter total sleep times and increased daytime sleepiness, which appears related to early morning awakening rather than reduced SE or prolonged sleep latency (269).

Caffeine, an adenosine receptor antagonist, may be used to manage symptoms such as daytime sleepiness (255). This impact depends on the chronicity of intake, the level of sleep pressure, and adenosine receptor genetic polymorphism (255). For example, greater reductions in subjective sleepiness are seen following caffeine ingestion if sleep pressure is high, as is more the case in the evening (255). Following acute ingestion alertness and mood typically improve and, if used in the late evening, it may impact on sleep latency and SE (255). Following chronic ingestion, the body appears to adapt and this response is dampened (255). Although caffeine itself has minimal effects on circadian phase shifts, it augments the impact of light on rhythmicity (255).

The term social jetlag refers to a socially or occupationally influenced shift in behaviours, such as physical activity and sleep, relevant to the 24-hour clock (236). Noise and light pollution, which can relate to social jetlag, also impact circadian rhythmicity (236). Social jetlag is associated with a later sleep preference, or “eveningness”, which in turn is associated with reduced daytime physical activity, and increased alcohol and nicotine use (237, 267).

4.1.7. Objective measures of circadian rest-activity rhythms

Although several accelerometry parameters can indicate RAR disruption, significant inter-individual variability exists and thresholds for normal and abnormal accelerometry parameter values has not been established. Sedentary activities are also increasing amongst the general population. Previous research has focused on median values within a cohort or considered the accelerometry parameter on an overall scale of lower and higher values to define abnormal rhythms. Threshold values aid in diagnosing abnormalities; however, a scale of values will also be considered in relation to the severity of abnormalities.

4.1.7.1. Evidence of daytime sedentariness

Sedentary behaviour describes a “waking behavior characterized by an energy expenditure ≤ 1.5 METs while in a sitting or reclining posture” and daytime sedentariness was highlighted as behaviour of concern within the e-Delphi recommendations (270). Daytime sedentariness increases with advancing age and has been associated with poorer clinical outcomes across patient groups (271). Although daytime sedentariness will be considered, it is important to remember that significant variation exists, and it is increasingly found amongst “healthy” adults. When compared to healthy controls, daytime sleep percentages are higher (19.11% vs. 3.24%) and median daytime activity is lower (128.61 minutes versus 200.33 minutes) in patients with cancer (50). In a cohort of healthy young adults, time spent in various activities have been reported as around 10.5 hours sedentary, 4.5 hours in low intensity physical activity (LPA), and less than 30 minutes in moderate-to-vigorous physical activity (MVPA) per day (272). In a large population sample of 1122 participants undergoing four days of accelerometry, considering 24-hour time periods, time was spent in sedentary activities (51%), sleeping (32%), LPA (11%) and MVPA (6%) (273). For this population sample, sedentary activities lasted an average 32 minutes with 5.6 sedentary episodes each day (273).

Although cancer may affect all ages, increasing rates are seen with increasing age. In a cohort of older adults, accelerometry highlighted daytime activity was

predominantly spent being sedentary (60.2%), followed by engaging in LPA (36.1%) and finally engaging in MVPA (3.6%) (271). Females spent more time in low-level activities and less time in sedentary activities than males (271). Less MVPA is associated with increasing age and weight, higher levels of education, poorer self-reported health and motor vehicle use (273). When considering older adults with care needs, sedentary time per day and steps per day was higher for those in intermediate care facilities compared with those in high level care facilities (7.6-12.8 hours vs. 9.6-12.7 hours sedentary time per day, and 4556 steps vs. 729 steps per day) (274). For cancer survivors, around 9.5 hours daily sitting time and 3.9 hours of sedentary bouts has been reported (275). Studies suggest that 8 hours or more of sedentary behaviour daily is associated with an increased all-cause mortality for cancer survivors and that such behaviours are associated with increased symptomatology and poorer QoL (275). Patients with cancer who are engaged in higher levels of physical activity, pre- and post-diagnosis, have improved cancer-related, cardiovascular-related and overall survival (275). Post-diagnosis activity appears to be most important (275). Sedentary behaviour may be captured within accelerometry software as sedentary bouts or “nap” frequency and duration. Although sedentary behaviours can be captured subjectively in the form of diaries, it is often inaccurate due to recall bias and preferential behaviour reporting (271). It will be considered prospectively as a marker, but threshold levels are not currently available and will be considered retrospectively.

4.1.7.2. Evidence of nighttime restlessness

Nighttime restlessness can be investigated by considering the number and duration of nighttime awakenings, SE and nighttime physical activity, for example. SE, measured on a scale of 0-100%, reflects the time asleep whilst in bed. Normal values are generally considered to be >92%, whilst abnormal values are considered to be <85.75% (50, 276). <86% will be used to indicate abnormal sleep efficiency in this study. A normal wake after sleep onset (WASO) has included up to 25 minutes and in cancer patients may be up to 68 minutes (50, 276). Nighttime activity of around 31 minutes has been seen in patients with cancer and around 16 minutes in healthy controls (50). WASO lasting >30 minutes will be considered as abnormal in this study.

4.1.7.3. Evidence of daytime sedentariness and nighttime restlessness

Variability of the RAR across a 24-hour period can be measured using the dichotomy index (I<O), intradaily variability (IV) and the relative amplitude (RA). The dichotomy index provides values from 0-100% with higher values suggesting a more robust circadian rhythm. I<O values deemed “good” or “normal” have included 98.45% and 99.5% (35, 154). “Bad” or “abnormal” values have included 91.36 and <97.5% (35, 154). Due to significant associations with poorer clinical outcomes below the 97.5% level, this will be used as the abnormal value in this study. The IV reflects fragmentation of the rhythm on a scale of 0-2 (127). Lower values suggest healthier and less fragmented rhythms and a value <1 is suggested as normal (276). Values >1 will be used to indicate abnormal and fragmented rhythms in this study. Lower RA also suggests less variability in the rhythm (127).

4.1.7.4. Evidence of lack of regularity in the RAR between days

Regularity between days can be measured using the 24-hour autocorrelation coefficient (r_{24}) and the interdaily stability (IS). The r_{24} provides a measure of regularity between days in the RAR, with values ranging from -1 to 1, and increasing values suggesting greater regularity (127). “Good” or “normal” values include 0.46 and >0.47 (50, 154). “Bad” or “abnormal” values have been cited as 0.28 or <0.35 (50, 154). Of note, many parameters are associated and patients with a “bad” r_{24} also demonstrate abnormal I<O values (154). <0.35 will be used as an abnormal values in this study. The IS is measured from 0-1 with increasing values suggesting regularity in the rhythm (127). A value of 0.6 or higher has been highlighted in healthy individuals and will be used as a reference point in this study (276).

4.2. AIMS

4.2.1. Primary study aim

1. To assess the preliminary validity of a screening tool to highlight patients with advanced cancer with a Circadian rest-Activity Rhythm Disorder

4.2.2. Secondary study aims

1. To identify the prevalence of Circadian rest-Activity Rhythm Disorders in patients with advanced cancer according to diagnostic criteria
2. To characterise Circadian rest-Activity Rhythm Disorders in patients with advanced cancer, including different phenotypes and identify the relevance of different intensities of physical activity
3. To identify associations between patient characteristics and Circadian rest-Activity Rhythm Disorders
4. To identify associations between symptom measures, quality of life measures and prognostic tools with Circadian rest-Activity Rhythm Disorders
5. To assess the role of combined measures (patient sleep and activity diary, wrist and thigh accelerometry) in the characterising rest-activity rhythms and diagnosing Circadian rest-Activity Rhythm Disorders

4.3. METHODOLOGY

4.3.1. Study design and setting

A prospective, observational, outpatient study. The study was registered at <https://clinicaltrials.gov/study/NCT06023654?term=circadian%20cancer&sort=StudyFirstPostDate&page=3&rank=22> (NCT06023654).

4.3.2. Participant selection and recruitment

Initially, outpatients were identified by Oncology and Palliative care teams across two organisations (St James' Hospital and Our Lady's Hospice & Care Services) and provided with information of the study. If the patient was interested in the study, consent was gained for the patient to be contacted by the research team and a patient information leaflet provided (Appendix 3). Referred patients were then contacted by the research team, provided with details of the study, and screened for eligibility. They were also provided the opportunity to ask questions. Due to low referral rates, alternative methods of recruitment were explored. Subsequently, in addition to the original method, a single researcher (CG) could pre-screen and approach patients directly.

4.3.3. Inclusion and exclusion criteria

Inclusion criteria

- i. ≥ 18 years old
- ii. Outpatient
- iii. Diagnosis of advanced cancer (locally advanced, incurable, metastatic)
- iv. Ambulatory
- v. Estimated prognosis ≥ 3 months

Exclusion criteria

- i. Inpatient^a
- ii. Engaged in shift work^a
- iii. Long-haul travel in the last 14 days^a
- iv. Cognitive impairment limiting the ability to complete the assessment tool and/or patient diary

^a as an identified modifier of circadian rhythmicity

4.3.4. Sample size

The study aimed to recruit 100 patients. The sample size was pragmatic, since there was no previous data to guide a formal sample size calculation. A sample size of 100 was deemed realistic (given the timeframe), and appropriate for testing a tool in a population with an expected prevalence of CARD of 40-50%.

4.3.5. Consent

Potentially eligible patients were provided with a patient information leaflet, verbal information about the study and an opportunity to ask questions. Initially, there was a minimum cooling off period of 24 hours before the patient provided consent (Appendix 4) and was enrolled in the study. However, due to the potential infrequency or irregularity of outpatient visits, and the observational nature of the study, this cooling off period was subsequently removed.

4.3.6. Confidentiality

Baseline participant details were kept to a minimum and based on the international recommendations created in the e-Delphi study. Data was collected on paper case report forms and participants were allocated a pseudonymised code. Personal identifiable information was not recorded within the case report form.

Patient data was stored securely and only accessible by the research team. All members of the research team are trained in Good Clinical Practice and Caldicott principles was re-iterated prior to the start of the study.

4.3.7. Patient assessments

4.3.7.1. Baseline assessments

Patients attended to meet the research team at a convenient clinical location and completed a consent form and baseline assessments. A venous blood sample was taken at the beginning or end of the study.

Baseline assessments included:

- a. Demographics: age, sex, race, level of education, employment, living situation, bedroom situation
- b. Clinical history: cancer history (date of diagnosis, type and stage of cancer, and oncology treatment), past medical history, medication, weight loss
- c. Lifestyle: smoking, caffeinated drink, and alcohol use
- d. Examination: manual heart rate, neck size, weight, and height
- e. ECOG performance status scale¹⁶, symptoms assessed by Memorial Symptom Assessment Scale – Short Form (MSAS-SF)¹⁷, quality of life assessed by EORTC QLQ-C30¹⁸, cognition assessed by Abbreviated Mental Test Score (AMTS), a global health score, chronotype using Morningness-Eveningness Questionnaire (MEQ)¹⁹, Circadian rest-Activity Rhythm Disorder (CARD) screening tool
- f. A venous blood sample

The Circadian rest-Activity Rhythm Disorder (CARD) screening tool was developed using the diagnostic criteria identified within the e-Delphi study and the Circadian Sleep-Wake Screening Tool developed considering the Circadian Rhythm Sleep Wake Disorder (CRSWD) criteria (Tables 15a, 15b, 16a, 16b). The tools were adjusted during the study after considering the utility of the tool and feedback from participants.

Table 15a. Rest-Activity Screening Tool (Version 1.0).

Since your cancer diagnosis...		Yes	No
1. Have you been aware that you are more restless during some of the nights each week? (e.g. moving around in bed, getting out of bed)			
2. Have those that you live with been aware that you are more restless during some of the nights each week?			
3. Have you spent more time being less active, or napping, in the daytime each week? (e.g. spending long periods sitting down or lying in bed)			
4. Have you noticed that the amount of time that you are active or resting varies from day to day? (e.g. some days you spend more time being physically active, and other days you spend more time resting)			
5. Do you feel that your quality of life or any of your symptoms relate to your rest and activity levels?			
During the last month...			
1. Has your level of daytime physical activity	Worsened	Stayed the same	Improved
2. Has your night-time restlessness	Worsened	Stayed the same	Improved
Time to complete		min	s

Min: minutes, s: seconds

Table 15b. Rest-Activity Screening Tool (Version 2.0).

Since your cancer diagnosis...		Yes	No
1. Have you been aware that you are more restless during some of the nights each week? (e.g. moving around in bed, getting out of bed)			
2. Have those that you live with been aware that you are more restless during some of the nights each week?			
3. Have you spent more time being less active, or napping, in the daytime each week? (e.g. spending long periods sitting down or lying in bed)			
4. Have you noticed that the amount of time that you are active or resting varies from day to day? (e.g. some days you spend more time being physically active, and other days you spend more time resting)			
5. Do you feel that your symptoms or quality of life relate to how much time you have spent being active or resting?			
During the last month...			
1. Has your level of daytime physical activity	Worsened	Stayed the same	Improved
2. Has your night-time restlessness	Worsened	Stayed the same	Improved
Time to complete		min	s

Table 16a. Circadian Sleep-Wake Screening Tool (v1.0).

Since your cancer diagnosis...	Yes	No
1. Has your sleep pattern changed?		
2. Are you going to bed and waking up earlier some days of the week?		
3. Are you going to bed and waking up later, some days of the week?		
4. Does your sleep pattern vary from day to day?		
Time to complete	min	s

Min: minutes, s: seconds

Table 16b. Circadian Sleep-Wake Screening Tool (v2.0).

Since your cancer diagnosis...	Earlier	At the same	Later
1. Do you get into bed			
2. Do you go to sleep			
3. Do you wake up			
4. Do you get out of bed			
5. Does the time that you get in and out of bed change day to day?	Yes		No
6. Does the time that you fall asleep and wake up change day to day?	Yes		No
Time to complete	min		s

A wrist-accelerometer (Figure 6) was securely applied to the non-dominant wrist, unless contraindicated, to ensure no excess movements of the watch would occur. A thigh accelerometry (Figure 6) was applied to the middle and anterior aspect of the right thigh. The ActivPAL was placed in a nitrile sleeve and placed with the device upright and facing forwards, before being secured with a Tegaderm™ film to ensure secure placement. The Micro Motionlogger has an alternating marker in the lower right screen, and the ActivPAL has a flashing green light, to indicate that the devices are actively collecting data. These features were checked when placing the devices.



Figure 6. Accelerometry devices used within the study. Left: The Ambulatory Monitoring Inc. Micro Motionlogger wrist accelerometry device with event button on the left below the time. Middle: Micro Motionlogger in situ. Right: activPAL3™ thigh accelerometry device.

Participants were provided with instructions on how to use the devices (i.e. recording time in and out of bed, bathing, general care) and advised to wear the devices continuously. Accelerometers detect movement and therefore activity levels. Wrist-accelerometers better detect MVPA, whilst thigh accelerometry better detects LPA and sedentary behaviour. The patient wore the devices continuously for at least 72 hours (including 3 nights). Participants were advised to use the event button to mark any non-wear time and the time they got into and out of bed for their primary sleep period.

Participants were also provided with a sleep and activity diary (Appendix 5) and instructed on how to use it. The sleep and activity diary was developed considering key elements identified within the e-Delphi study alongside input from physiotherapy colleagues and patient and public involvement. The original diary was amended after considering its utility and participant feedback (Appendix 5).

If uncontrolled symptoms or abnormal blood results were identified, and with the patient's verbal consent, the clinical team (general practitioner, oncologist, or palliative team) were made aware of the findings to review further.

4.3.7.2. Day 4 assessments

After a 72-hour period, including 3 nights, the participant was advised to return to a convenient clinical location. The accelerometry devices and diary were retrieved and the data downloaded. The patient then completed the CARD assessment tool for a second time and a patient acceptability questionnaires of completing the tool and the use of the diary. They also completed the brief Pittsburgh sleep quality index (bPSQI) tool for sleep quality, Epworth Sleepiness Scale (ESS) for daytime sleepiness, STOP-Bang questionnaire for obstructive sleep apnoea, and were assessed for restless leg syndrome using the diagnostic criteria.

Patient-related factors and clinical outcomes being considered through this observational study are outlined in Figure 7.

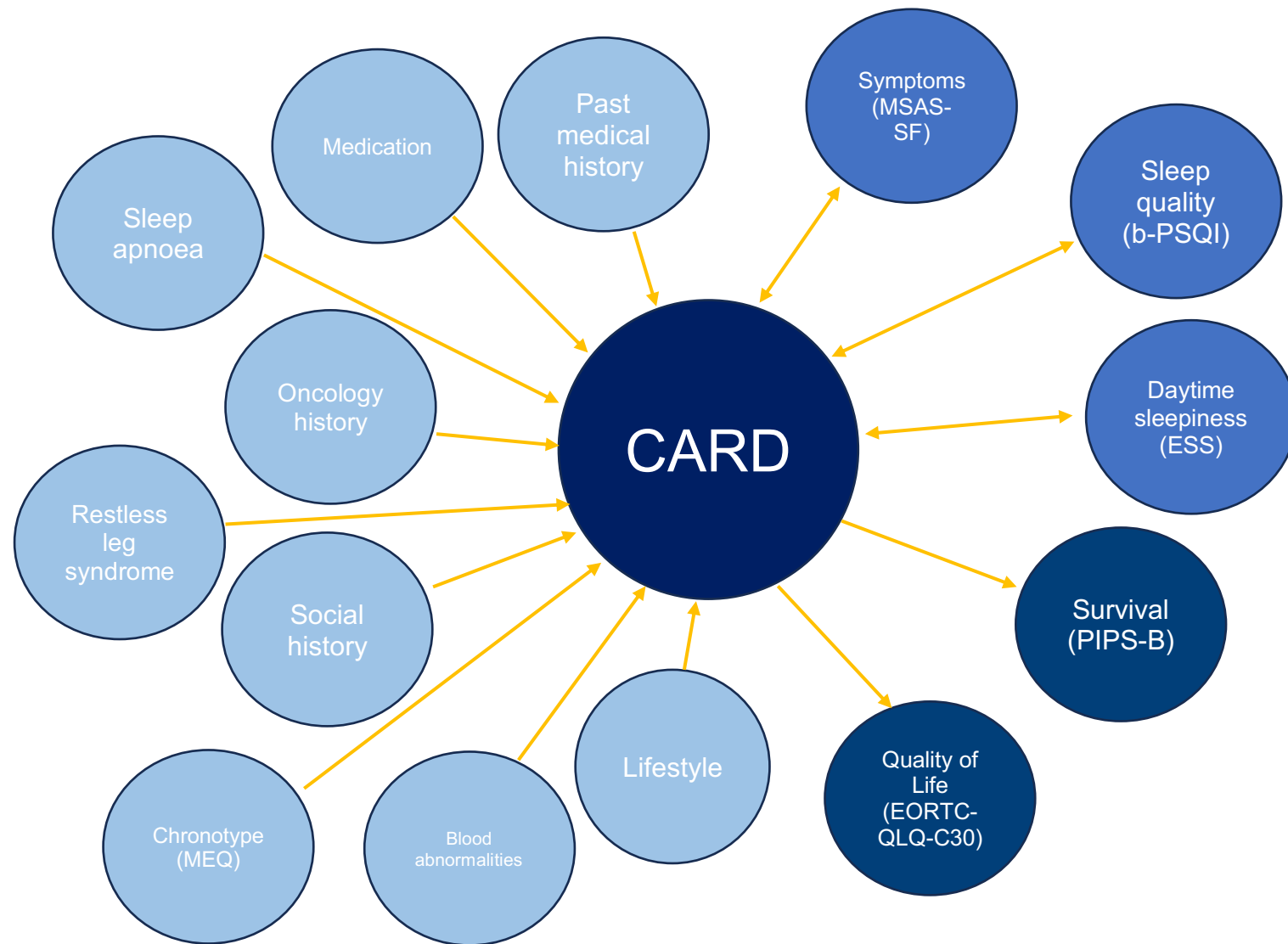


Figure 7. Factors to be considered in association with a CARD. Patient-related factors which may contribute towards a CARD (light blue), factors which likely interact bidirectionally with a CARD (middle blue), and factors thought to be a result of a CARD (dark blue) are demonstrated.

4.3.8. Outcome measures

4.3.8.1. Primary outcome measures

- i. The predictive validity and reliability of the screening tool to identify a patient with a circadian rest-activity rhythm disorder
 - a. The specificity, sensitivity, positive predictive value, and negative predictive value of the screening tool against diagnostic criteria
 - b. The Test-retest reliability of the screening tool to identify a patient with a circadian rest-activity rhythm disorder
- ii. The acceptability, ease of use and understandability of the screening test

4.3.8.2. Secondary outcome measures

- i. To identify the incidence of Circadian rest-Activity Rhythm Disorders in patients with advanced cancer
- ii. To assess rest and physical activity patterns in patients with advanced cancer
- iii. To assess patient characteristics and risk factors for Circadian rest-Activity Rhythm Disorders in patients with advanced cancer
- iv. To assess associations between Circadian rest-Activity Rhythm Disorders in patients with advanced cancer and symptoms, quality of life, sleep quality, daytime sleepiness, and prognostic factors

4.3.9. Accelerometry data preparation and analysis

The study benefited from the use of waterproof devices and continuous monitoring of at least 72 hours. Data was initially checked for any “bad” or missing data suggesting off-wrist use. Such data was removed. The data was then trimmed at the start and end of the recording to allow for a 72-hour period of analysis. This focussed on the final 72 hours of the recording prior to the final morning out of bedtime. In most instances this allowed for the removal of the first day and night.

For calculation of several circadian RAR parameters, the time that the participant physically got into bed (DOWN time) and out of bed (UP time) is required. This can be established from the patient diary, wrist event marker and positional changes from thigh accelerometry. For patient-reported methods, patient diaries provide less accurate DOWN and UP timings. Event marker timings were therefore treated as superior to patient diary entries. Thigh accelerometry can also provide an objective measure of moving from an upright to sedentary position and vice versa. The accuracy of patient-reported timings can therefore be improved by reviewing and adjusted according to the thigh accelerometry data. Furthermore, the DOWN and UP times can also be estimated using automated software (Action-W2 for wrist accelerometry and ActivPAL for thigh accelerometry). Independent software (MATLAB R2018b) was also considered, which can estimate DOWN and UP times from thigh accelerometry. The approach to determining DOWN and UP times, along with analysis of accelerometry data, has yet to be standardised. Due to a breadth of mechanisms to interpret DOWN and UP times, these were all considered along with a novel approach.

1. Patient diary
2. Watch event marker
3. Patient diary or event marker time considered alongside thigh accelerometry data. In the event of significantly different diary and event marker timings, visual inspection of the data was considered to assume the most likely correct timing
 - a. Time adjusted to the nearest sedentary to upright (objective UP), or upright to sedentary (objective DOWN) transition point
 - b. Time adjusted to beginning or end of the current activity period without a preceding or subsequent repeat positional change within a 15-minute period
4. Combined event marker and patient diary in the event of incomplete data with a presumed superiority of event marker entries
 - a. Time adjusted to the nearest sedentary to upright (objective UP), or upright to sedentary (objective DOWN), transition point
 - b. Time adjusted to beginning or end of the current activity period without a preceding or subsequent repeat positional change within a 15-minute period

5. Automated Matlab timing
6. ActivPal thigh accelerometry automated timing
7. Automated ActionW2 timing

The MicroMotionlogger watch accelerometry data was initially analysed using dedicated software (Action-W 2.7.3401 and Action-4 Version 1.16) using the zero-crossing mode and considering 1-minute epochs (time interval). The zero-crossing mode assesses frequency of a movement above a threshold, often close to zero (277). Action software can automatically score sleep and deduce the sleep and wake period. Sleep and wake periods can be manually adjusted and was done so based on activPAL data and/or patient diary and event marker. Similarly, the activPAL thigh accelerometry data was initially analysed automatically using PALanalysis v18.11.8.75 [VANE algorithm v0.1].

Prevalence of the circadian rest-activity rhythm disorder will be calculated. Diagnostic criteria have been established through an e-Delphi study (Box 3).

Box 3. Diagnostic criteria for a circadian rest-activity rhythm disorder in people with cancer.

1. Patients exhibit relatively less daytime physical activity and more night-time physical activity; **OR** Rest and physical activity spread across the 24-hour period, rather than distinct rest and active periods; **OR** A lack of regularity in rest and active periods between days
2. The altered physical activity pattern
 - A. has been present for at least 1 month
 - B. has a clinical impact on the patient
 - C. is demonstrable by objective and subjective measures
3. The altered rest-activity rhythm is not primarily due to another cause

Validation of the screening tool will consider the specificity, sensitivity, Positive Predictive Value, Negative Predictive Value and accuracy against diagnostic criteria (Box 4) for a circadian rest-activity rhythm disorder.

Box 4. Criteria for screening positive using the CARD screening tool.

A combination of daytime sedentariness and nighttime restlessness

(Yes to question 1 or 2 AND question 3)

OR

A lack of regularity in their rest-activity rhythm between days (Yes to question 4)

AND

An associated clinical impact (Yes to question 5)

Correlation coefficients between the screening tool at two points were used to assess test-retest reliability. Descriptive statistics were used to report the ease of understanding, ease of completion and acceptability of the screening tool.

Descriptive statistics were used to describe the data, normality of the data was assessed using Kolmogorov-Smirnov statistic, Mann-Whitney and Spearman's rho correlation were used to consider correlations and differences between groups for non-normally distributed data and independent T-tests and Pearson's correlation were used to consider correlations and difference between groups for normally distributed data.

4.3.10. Ethical approval

Ethical approval for the study was granted by the joint St James' Hospital-Tallaght University Hospital Research Ethics Committee (Appendix 2).

4.3.11. Patient and Public Involvement

The study protocol and participant facing information were reviewed by the Voices4Care team, made up of people with palliative care needs, carers and volunteers. Suggested changes were then implemented prior to starting the study.

4.4. RESULTS

134 patients were deemed appropriate and approached to take part in the study over a 12-month period. 72 patients (Table 17) were subsequently recruited from St James's Hospital ((Oncology outpatients (n = 33, 46%), Palliative Care outpatients (n = 5, 7%)) and Our Lady's Hospice & Care Services ((Palliative Care outpatients (n = 20, 28%), Community Palliative Care Teams (n = 14, 19%)). See Figure 8 for a flow of potential participants.

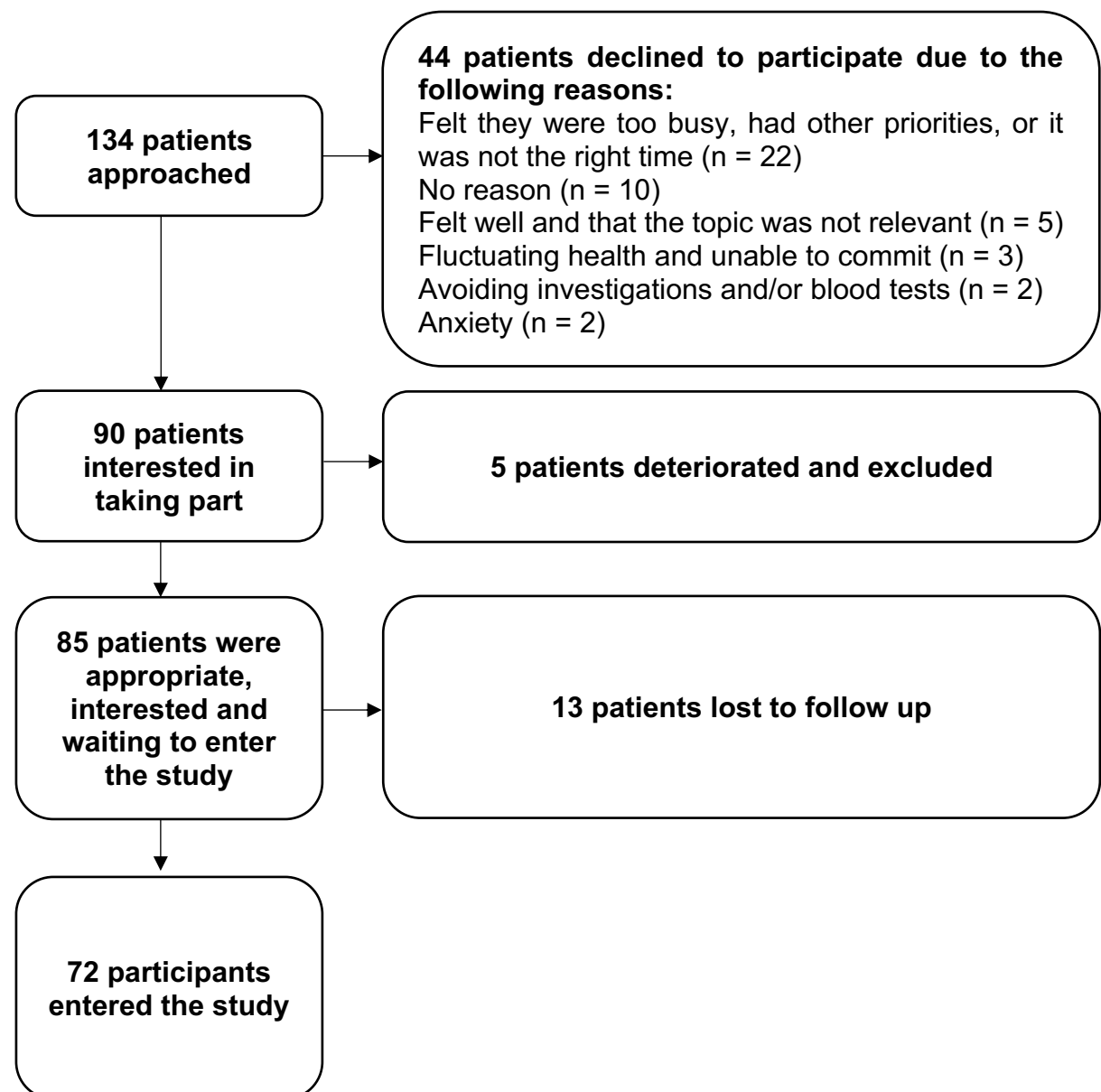


Figure 8. Flow diagram of potential participants to the screening study. The figure demonstrates those approached, interested and entering the study alone with reasons for declining or exiting the recruitment process.

Table 17. Screening study participant characteristics.

Demographics	Age	Mean: 62 years old (38-86)
	Sex	Female (n = 35, 54%) Male (n = 30, 46%)
	Ethnicity	White Irish (n = 60, 92.3%) White British (n = 2, 3.1%) White Romanian (n = 1, 1.5%) White Other (n = 1, 1.5%) Asian (n = 1, 1.5%)
Medical characteristics	Cancer diagnosis	Gastrointestinal (n = 18, 27.7%)
		Breast (n = 14, 21.5%)
		Lung (n = 13, 20%)
		Prostate (n = 9, 13.8%)
		Renal (n = 4, 6.2%)
		Gynaecological (n = 4, 6.2%)
		Skin (n = 2, 3.1%)
		Synchronous thyroid / breast (n = 1, 1.5%)
	European Cooperative Oncology Grade (ECOG)	ECOG 0 (n = 12, 18%) ECOG 1 (n = 40, 62%) ECOG 2 (n = 11, 17%) ECOG 3 (n = 2, 3%)
	Primary tumour in situ	Yes (n = 33, 51%) No (n = 32, 49%)
	Location of metastatic sites	Organ involvement (n = 44, 68%) Bony involvement (n = 29, 45%) Lymph node involvement (n = 30, 46%) Cerebral involvement (n = 7, 11%) Adrenal involvement (n = 3, 5%)
	Radiological disease status	Improving (n = 20, 31%) Stable (n = 17, 26%) Progressive (n = 20, 31%) Not applicable (n = 8, 12%)

Medical characteristics	Biochemical disease status	Improving (n = 8, 12%) Stable (n = 14, 22%) Progressive (n = 12, 18%) Not applicable (n = 31, 48%)
	Current anticancer therapy	Receiving anti-cancer therapies (n = 54, 83%) Hormonal therapy (n = 11) Hormonal therapy and kinase inhibitor (n = 5) Hormonal therapy and monoclonal antibody (n = 1) Chemotherapy and monoclonal antibody (n = 10) Chemotherapy (n = 9) Chemotherapy and radiotherapy (n = 2) Chemotherapy and hormonal therapy (n = 1) Monoclonal antibody alone (n = 8) Kinase inhibitor (n = 7) Off anti-cancer therapies (n = 11, 17%)
	Time since last anticancer treatment	Continuous (n = 20, 31%) <1 week (n = 19, 29%) 1-2 weeks (n = 9, 14%) 2-4 weeks (n = 6, 9%) Off treatment (10, 15%) Unknown (n = 1, 2%)
	Previous treatments	Chemotherapy (n = 45, 69%) Radiotherapy (n = 41, 63%) Surgery (n = 34, 52%) Immunotherapy (n = 30, 46%) Hormonal therapy (n = 24, 37%) Targeted therapy (n = 19, 29%)
	Comorbidities	Median no. 2 (0-9)
	Medication	Median no. 5 (0-15)
	Perceived weight loss in the last month	Yes (n = 22, 34%) No (n = 43, 66%)
Socioeconomic characteristics	Employment status	Unemployed (n = 25, 38%) Retired (n = 26, 40%) Employed (n = 14, 22%)
	Educational attainment	Third degree level (n = 21, 32%) Junior cycle (12-15 years old) (n = 17, 26%) Post-senior cycle certificate (n = 12, 19%) Senior cycle (16-18 years old) (n = 11, 17%) Apprenticeship (n = 2, 3%) Primary school (<12 years old) (n = 2, 3%)
	Caring role	Yes (n = 13, 20%) No (n = 52, 80%)

Socioeconomic characteristics	Living	Alone (n = 12, 18%) With others (n = 53, 82%)
	Young children in the home	Yes (n = 11, 17%) No (n = 54, 83%)
	Bedroom	Own bedroom (n = 34, 52%) Shared bedroom (n = 31, 48%)
Lifestyle characteristics	Smoking status	Smoker (n = 10, 15%) Non-smoker (n = 55, 85%) Median time of last cigarette of the day = 22:50
	Caffeine status	Caffeine drinker (n = 61, 94%) Non-caffeine drinker (n = 4, 6%) Median time of last caffeinated drink of the day = 18:00
	Alcohol status	Alcohol drinker (n = 25, 38%) Non-alcohol drinker (n = 40, 62%) Median timing of last alcoholic drink of the day = 21:30
Examination	Body mass index (kg / m²)	Underweight (<18.5) (n = 3, 5%) Healthy weight (18.5-24.9) (n = 20, 31%) Overweight (25.0-30) (n = 23, 35%) Obesity (>30.0) (n = 19, 29%)
	Neck size (cm)	Mean = 38.18 (30-49)
	Heart rate (beats per minute)	Mean = 80 (48-120)
Baseline assessments	STOP-Bang	High risk (n = 8, 12%) Intermediate risk (n = 25, 39%) Low risk (n = 32, 49%)
	Restless Leg Syndrome criteria	Met (n = 11, 17%) Not met (n = 54, 83%)
	Chronotype	Definite morning (n = 6, 9%) Moderate morning (n = 24, 37%) Intermediate (n = 33, 51%) Moderate evening (n = 2, 3%)
	PIPS-B (n = 62)	Prognosis measured in months (n = 62, 95%) and weeks (n = 3, 5%) Median 14-day survival = 99% (89-100%) Median 56-day survival = 86.5% (43-99%)

4.4.1. Blood results

Blood results for the participants cohort have been summarised (Table 18).

Table 18. A summary of blood results for participants.

	Average	Reference value
Haemoglobin (g/dl)	12.5	13.0 – 17.0
Mean corpuscular volume (MCV) (fl)	91	80 – 100
Platelet ($10^9/l$)	236	150 – 400
White cell count ($10^9/l$)	6.0	3.5 – 11.0
Neutrophils ($10^9/l$)	3.8	2.0 – 8.0
Lymphocytes ($10^9/l$)	1.3	1.0 – 4.0
Total bilirubin (umol/L)	7.0	0 – 21
Alanine transaminase (ALT) (IU/L)	20	9 – 59
Alkaline phosphatase (ALP) (IU/L)	101	30 – 130
Urea (mmol/L)	5.1	2.5 - 7.8
Creatinine (umol/L)	68.0	59 – 104
Estimated glomerular filtration rate (eGFR) (mL/min/1.73m ²)	88	
Thyroid stimulating hormone (TSH) (mIU/L)	1.81	0.27 – 4.2
Free triiodothyronine (FT3) (pmol/L)	4.7	3.1 – 6.8
Free thyroxine (FT4) (pmol/L)	16.6	11.9 – 21.6
Albumin (g/L)	35.2	35 – 50
Iron (umol/L)	16.8	5.8 – 34.5
Transferrin (g/L)	2.5	2.00 – 3.60
Total iron binding capacity (TIBC) (umol/L)	57.7	44.8 – 71.6
Transferrin saturation (%)	29.3	
Vitamin B12 (ng/L)	454	197 - 771
Folate (ug/L)	11.1	
Vitamin D (nmol/L)	57	30 – 125
Magnesium (mmol/L)	0.84	0.70 – 1.00
C-reactive protein (CRP) (mg/L)	4.7	0 – 5.0
Ferritin (ug/L)	206	30 – 400

NB: Vitamin B12 >2000 adjusted to 2000, CRP <1.0 adjusted to 0,

53% (n = 37) of participants had a mild anaemia (Hb 10-12.9g/dl), 7% (n = 5) had a moderate anaemia (Hb 8.0 – 9.9g/dl) and 1% (n = 1) had a severe anaemia (Hb <7.9g/dl). Of 43 participants with an anaemia, 86% (n = 37) had a normocytic anaemia, 12% (n = 5) participants had a macrocytic anaemia, and 2% (n = 1) participant had a microcytic anaemia. Of 43 participants with anaemia, two samples were haemolysed limiting the interpretation of iron, folate and vitamin B12 status. Of the 41 remaining participants, 5% (n = 2) were vitamin B12 deficient (<192 ng/L) and 39% (n = 16) had supranormal levels, including 22% (n = 9) participants with a vitamin B12 level >2000 ng/L. 24% (n = 10) of participants with anaemia had a folate level <7.0 ug/L and 35% (n = 15) had a folate level >12 ug/L. 16% (n = 7) of participants with anaemia had a low serum iron (<8.0 umol/L), 47% (n = 20) had a low transferrin saturation (<20%). 7% (n = 5) of participants with anaemia had an elevated transferrin saturation (>45%).

Considering inflammatory status, 26% (n = 18) had a ferritin >400 ug/L and 49% (n = 33) had a CRP >5.0 mg/L. 43% (n = 30) of participants had a low albumin (<35 g/L). 5% (n = 4) of participants had hypomagnesaemia (<0.7 mmol/L), 5% (n = 4) of participants had vitamin D deficiency (<30 nmol/L) and 33% (n = 23) had vitamin D insufficiency (30-50 nmol/L).

3% (n = 2) of participants had a low TSH (<0.27 mIU/L) and 19% (n = 13) participants had a raised TSH (>4.2 mIU/L). 1% (n = 1) had a low FT4 and 4% (n = 3) had a raised FT4. 3% (n = 2) had a FT3 and 3% (n = 2) participants had a raised FT3.

4.4.2. Symptom burden, distress and participant functioning

The median number of overall symptoms, physical symptoms and psychological symptoms reported using the MSAS-SF was 11 (range 2-27), 9 (range 2-23) and 1 (range 0-4), respectively. The most frequent physical symptoms were lack of energy (86%), pain (69%), difficulty sleeping (60%), feeling drowsy (57%) and dry mouth (52%). The mean physical distress score was 0.85 (SD 0.70-1.00). The mean Global Distress Index was 1.07 (SD 0.92-1.24). The most common psychological symptoms were sadness (48%) and worry (48%), followed by

irritability (45%) and nervousness (25%). The median psychological distress score was 0.98 (SD 0.78-1.18).

The EORTC-QLQ-C30 indicated the highest symptom scores, reflecting worse symptom burden, for fatigue (98%), pain (62%) and insomnia (57%). The EORTC-QLQ-C30 found the highest scoring functioning subscales were emotional functioning (83.3) and cognitive functioning (83.3), followed by physical functioning (73.3) and finally social functioning (66.7) and role functioning (66.7).

48% of participants were deemed poor sleepers with a bPSQI score above 5 (median score 5, range 0-15) and the distribution of scores can be seen in Figure 9.

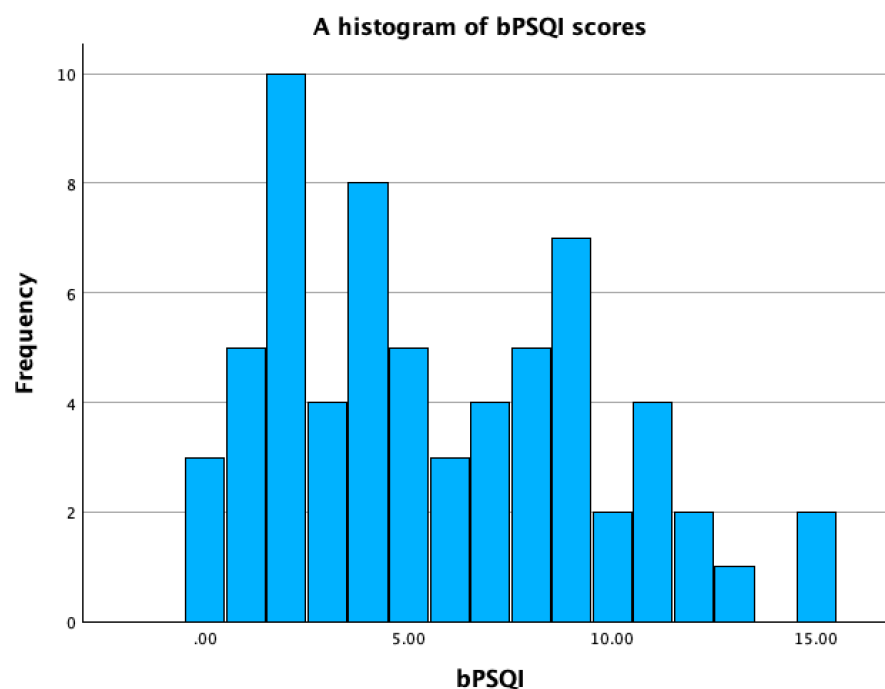


Figure 9. A histogram demonstrating the frequency of bPSQI scores. The histogram demonstrates the frequency of bPSQI scores ranging from 0-15, with a skewness of data towards lower values.

The Epworth Daytime Sleepiness Scale demonstrated a median score of 4 (0-21) (Figure 10) and most participants (60%) were categorised as having lower normal levels of daytime sleepiness. The remaining participants had higher normal levels

(28%), mild excessive levels (8%), moderate excessive levels (1%) and severe levels of daytime sleepiness (3%).

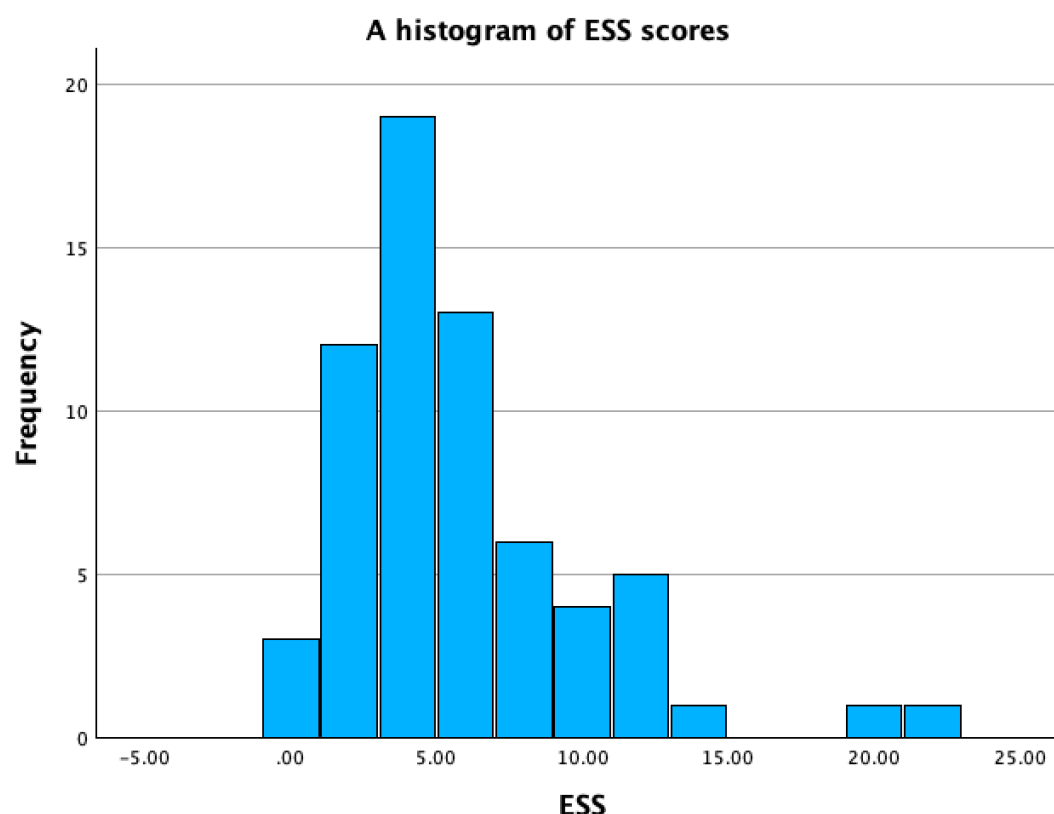


Figure 10. A histogram demonstrating the frequency of ESS scores. The histogram demonstrates the frequency ESS scores ranging from 0 to 21, with a skewness of data towards lower values.

4.4.3. Methodological considerations

4.4.3.1. Assessing DOWN and UP times

During the study period, there were four DOWN and four UP times. The most consistent methods of obtaining these times were automated programmes followed by the patient diary and then the event marker. With this considered for all participants, 8 time points were generated for all participants using the automated action-W2 software, 83% using the patient diary and 48% using the event diary. As the devices are removed on the final day of monitoring, Matlab was unable to generate the final UP time, and the remaining 7 time points were generated for 93% of participants.

4.4.3.2. Patient reported methods

Patient reported methods of recording DOWN and UP times consisted of patient diary entries and use of the Micromotionlogger watch event marker. More DOWN times were generated by the patient diary than event marker (267 vs. 221). More UP times were also generated by the patient diary than event marker (263 vs. 221).

The median time difference between a patient reported DOWN and the nearest objective upright to sedentary transition (DOWN) was shorter for the event marker than patient diary (1 vs. 5 minutes). Similarly, the range in disparity between a patient reported time and nearest objective marker time was smaller for the event marker (0-296 minutes) than the patient diary (0-574 minutes). The median time difference from patient reported DOWN to the end of an activity period was also shorter for the event marker than patient diary record (2 vs. 10 minutes).

The median time difference between a patient reported UP and the nearest sedentary to upright transition was shorter for the event marker than patient diary reports (2 vs. 4 minutes). Conversely, the range in disparity between a patient reported time and objective marker was smaller for patient diary entries (0-240 minutes) than event marker (0-250 minutes). Similarly, the median time difference between a patient reported UP to the beginning of an activity period was shorter for the event marker than patient diary record (2 vs. 3 minutes).

4.4.3.3. Adjusted patient reported methods using objective evidence

For the DOWN time, 279 time points were considered for their proximity to the nearest transition from an upright to sedentary position and their proximity to the end of the current activity period. The most “likely” DOWN time used the event marker entry in 133 cases (47.7%) and the patient diary entry in 59 cases (21.1%). 69 cases (24.7%) had a single patient diary or event marker entry, and 18 cases (6.5%) had the same time for both patient diary and event marker.

For the UP time, 274 time point were considered for their proximity to the nearest transition from a sedentary to upright position, and their proximity to the beginning

of the activity period. The most likely UP time used the event marker entry in 122 cases (44.5%) and the patient diary entry in 76 cases (27.7%). 61 cases (22.3%) had solely a patient diary or event marker time, and 15 cases (5.5%) had the same UP time for both patient diary and event marker. The adjusted patient reported times were used to reflect the varied accuracy of the patient-reported timings between subjects.

4.4.4. Circadian rest-activity rhythm patterns in patients with advanced cancer

65 participants had 72 hours of wrist accelerometry data and reported sufficient DOWN and UP times to allow for data analysis. Four of the 72 had incomplete wrist accelerometry data due to technical issues with the devices, and three did not have self-reported measures of DOWN and UP times.

4.4.4.1. Daytime sedentariness and nighttime restlessness

When determining the dichotomy index (I<O), the median dichotomy index for this patient cohort was 95.05% (range 78.51-99.87, Figure 11). 46 participants (70.8%) had an I<O below 97.5. The median intradaily variability (IV) was 0.54 (0.26-1.09), and two participants (3.1%) had an IV >1.0. The median relative amplitude (RA) was 0.84 (0.44-0.94), with no previous set threshold of significance.

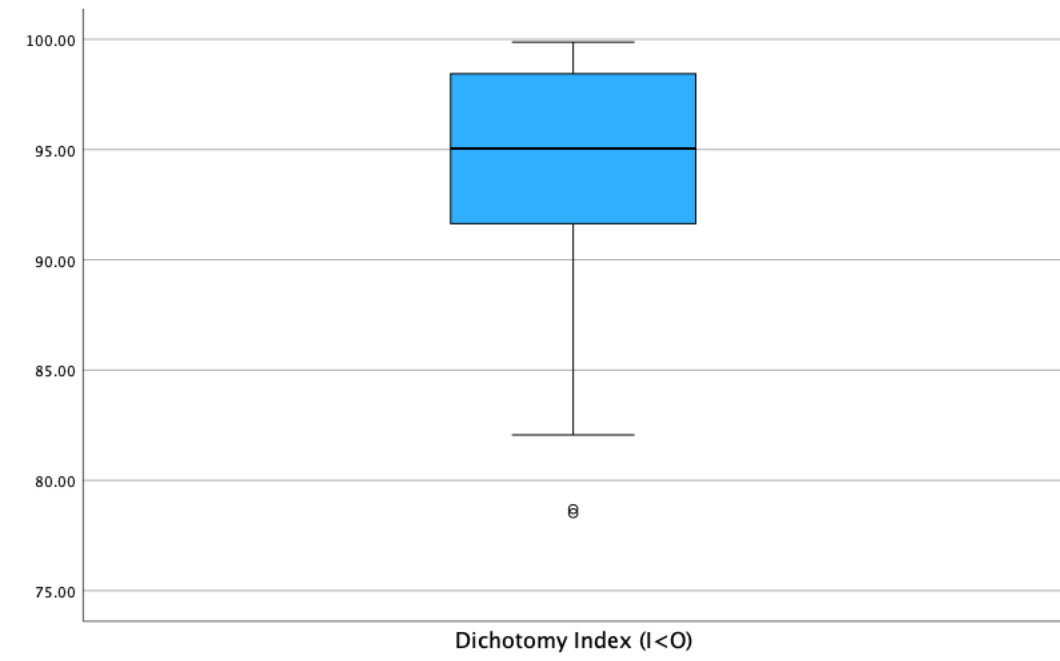


Figure 11. A boxplot of dichotomy index values. The boxplot demonstrates a skewedness towards higher I<O values, and a median I<O of 95.05% (interquartile range (IQR) 6.94). Two outliers are also demonstrated <80%.

IN bed activity was significantly lower in participants with an above average dichotomy index compared to participants with a below average dichotomy index (median = 21.93 vs. 33.07, $U = 254$, $p < 0.001$). OUT of bed activity was significantly higher in participants with an above average dichotomy index compared to participants with a below average dichotomy index (median = 195.41 vs. 134.73, $U = 902$, $p < 0.001$). A combination of higher in-bed activity and lower out-of-bed activity was seen in participants with a poorer dichotomy index. Actigrams can illustrate the difference between a participant with a ‘good’ (Figure 12) and ‘bad’ (Figure 13) I<O.

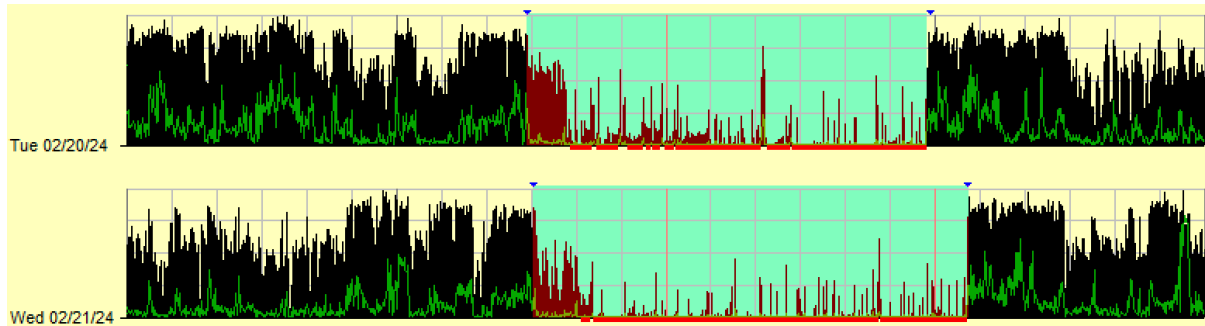


Figure 12. A linear actigram illustrating a ‘good’ dichotomy index ($I < O$). The black lines represent activity levels per minute. There is a clear distinction between IN bed (blue zone) and OUT of bed activity, with proportional higher activity levels OUT of bed.

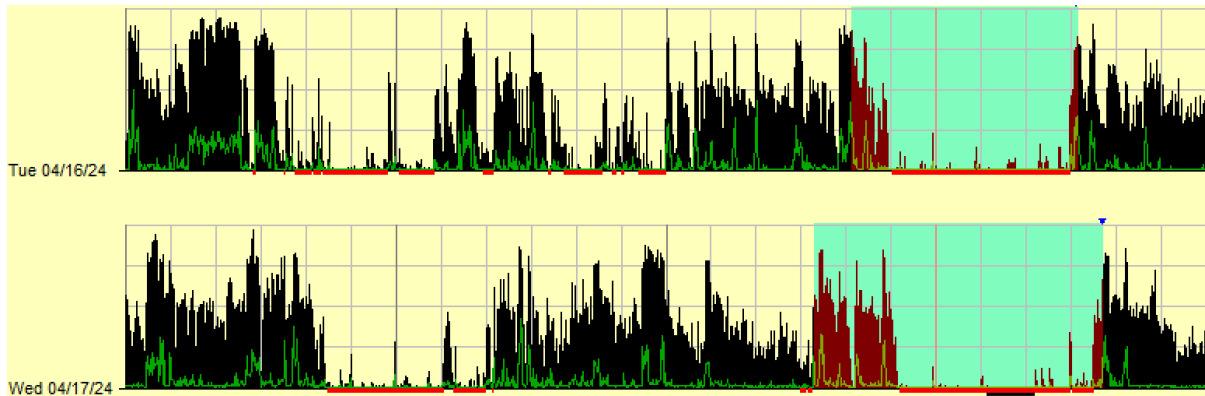


Figure 13. A linear actigram demonstrating a ‘bad’ dichotomy index ($I < O$). In contrast to figure 12, there is a lack of distinction between rest and activity levels IN (blue zone) and OUT of bed.

Lower (poorer) dichotomy index values were seen in patients with metastatic organ involvement ($p = 0.038$), not receiving active anticancer therapy ($p = 0.08$), a higher CRP (>5.0 , $p = 0.018$), an ECOG score 2 compared to ECOG score 0 ($p = 0.018$), who did not drink alcohol ($p = 0.037$) and who did not share a bedroom ($p = 0.009$). There was also a significant correlation between the dichotomy index and bilirubin level ($r = 0.251$, $p = 0.045$) and albumin ($r = 0.274$, $p = 0.028$). There were no significant associations with other patient-related factors.

4.4.4.2. Nighttime restlessness

Median sleep efficiency (SE) ((sleep minutes / sleep onset-sleep offset) x 100) was 90.35% (51.00-98.36%, Figure 14), with 51 participants (78%) having a SE >80% and 45 participants (69%) having a SE ≥86%. Median percent sleep ((sleep minutes / time in bed) x 100) was 80.10% (20.81-94.62%), with 33 participants (51%) having a percent sleep >80%. The median sleep onset latency (SOL) was 23.33 minutes (7.33-299.33), with 28 participants (43%) having a SOL of <20 minutes. Median wake after sleep onset (WASO) was 49.00 minutes (4.33-246.67 minutes), with 20 participants (31%) having a WASO <30 minutes.

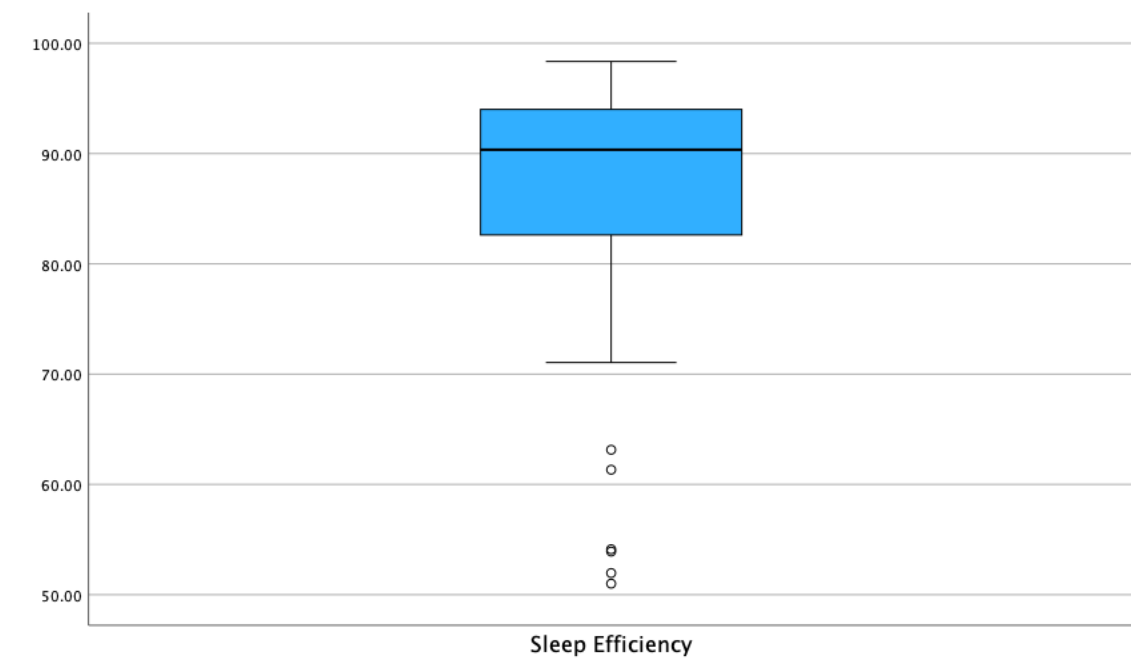


Figure 14. A boxplot of sleep efficiency (SE) values. The boxplot demonstrates skewness towards higher SE values and several outliers with low SE values. The median SE is 90.35% (interquartile range (IQR) 12.55).

SE was significantly worse in those receiving hormonal and chemotherapy treatments compared to combination anticancer therapies ($p = 0.018$ and $p = 0.043$, respectively). Higher SE was associated with higher haemoglobin levels ($p = 0.04$), higher bilirubin levels ($p = 0.02$) and lower ALT levels ($p = 0.03$). There were no other patient-related factors that were significantly associated with sleep efficiency.

Participants with poor sleep quality (bPSQI) or sleep complaints (MSAS-SF and EORTC-QLQ-C30) had no objective differences in values for SE, percent sleep, SOL or WASO when compared to those with good sleep quality or the absence of sleep complaints (all $p > 0.05$).

4.4.4.3. Day-to-day irregularity

The mean 24-hour autocorrelation coefficient (r_{24}) was 0.405 (range 0.13-0.72, Figure 15). 28 participants (43.1%) had an r_{24} below 0.35. The median interdaily stability (IS) was 0.80 (range 0.53-0.92). 9 participants (13%) had an IS below 0.6.

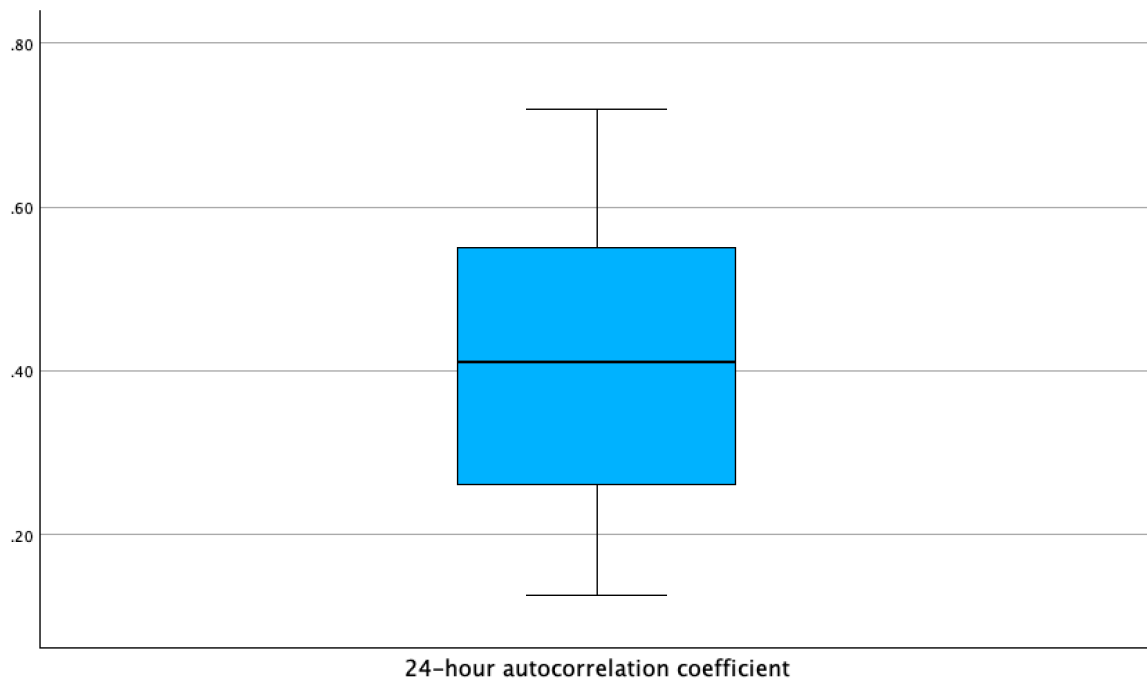


Figure 15. A boxplot of 24-hour autocorrelation coefficient values. The boxplot suggests normality of the data, with a mean value of 0.41 (95% CI 0.36-0.45), and no outliers.

Actimeters can illustrate the difference between participants with a 'good' (Figure 16) and 'bad' (Figure 17) r_{24} .

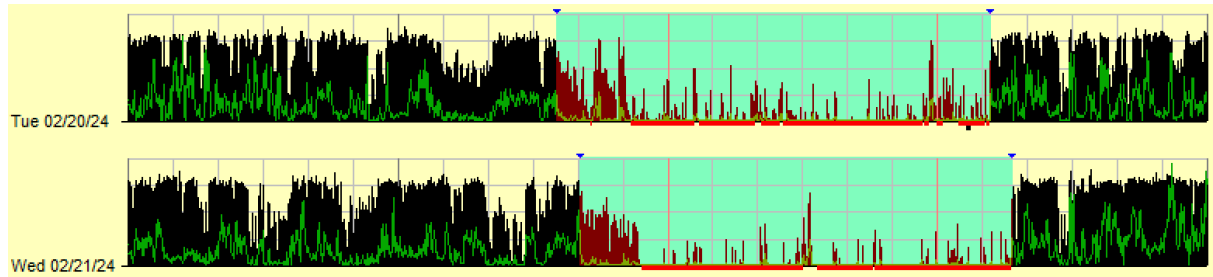


Figure 16. A linear actigram demonstrating a ‘good’ 24-hour autocorrelation coefficient (r_{24}). Day-to-day regularity in rest and activity levels is demonstrated whereby similar time frames between days are similar in their active (black bars) and rest (absence of black bar) states. The blue zone represents the patient’s IN bed time.

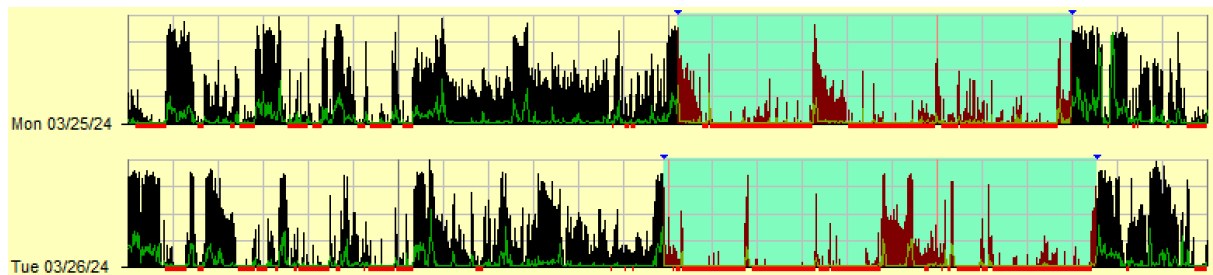


Figure 17. A linear actigram demonstrating a ‘bad’ 24-hour autocorrelation coefficient (r_{24}). In comparison to figure 16, this figure demonstrates a more irregular day-to-day pattern in rest and activity. The blue zone again represents the patient’s IN bed time.

Participants with a lower (poorer) r_{24} included those who did not share a bedroom ($p = 0.041$), had a raised CRP (>5 , $p = 0.002$), or were smokers ($p = 0.025$). r_{24} values were correlated with haemoglobin ($r = 0.34$, $p = 0.007$), iron levels ($r = 0.38$, $p = 0.002$), transferrin saturation ($r = 0.36$, $p = 0.003$), sodium ($r = 0.35$, $p = 0.005$), ALT ($r = 0.271$, $p = 0.03$), folate levels ($r = 0.29$, $p = 0.019$), WCC ($r = -0.33$, $p = 0.008$), CRP ($r = -0.36$, $p = 0.004$) and ALP ($r = -0.25$, $p = 0.043$). A significant difference was also seen between time since treatment groups (2-4 weeks (0.58), continuous (0.44), < 1 week (0.40), 1-2 weeks (0.32), and off treatment (0.30), $p = 0.012$). There was also a significant difference between ECOG groups (0 (0.53), 1 (0.40), 2 (0.28), 3 (0.35), $p = 0.002$). There were no other significant patient-related associations.

4.4.4.4. Associations between circadian parameters

Correlations were considered between the main circadian parameters (Figure 18). A large positive correlation was demonstrated between the I<O and r24 ($r = 0.703$, $p < 0.001$) and the I<O and sleep efficiency ($r = 0.515$, $p < 0.001$). Higher I<O, representing proportionally less in bed to out of bed activity, was associated with more day-to-day regularity in the rest-activity rhythms and more time spent sleeping between sleep onset and sleep offset. A small correlation was demonstrated between the r24 and sleep efficiency ($r = 0.284$, $p = 0.022$).



Figure 18. A scatterplot demonstrating the correlation between the dichotomy index, sleep efficiency and 24-hour autocorrelation coefficient. A positive correlation can be seen between the I<O and SE, and the I<O and r24. This suggests patients with a higher (better) I<O, have a higher (better) SE and r24. A similar relationship is seen between SE and r24 (higher SE is associated with a higher r24), but to a lesser degree.

4.4.4.5. Physical activity and inactivity over 24-hour periods

Thigh accelerometry provided data for all 72 participants. The median daily step count was 4206 (258-20924). The median daily sit to stands was 45 (11-184).

Across the 24-hour period, median time was spent in sedentary behaviours for 19.9 hours (12.7-23.4), standing for 3 hours (0.4-8.9 hours) and stepping for 1 hour (0.1-4.4 hours).

Considering the time spent in sedentary bouts, most time was spent in sedentary bouts lasting more than 4 hours (5.69 hours), followed by <0.5-hour bouts (3.89 hours), 1–2-hour bouts (3.05 hours), 2–4-hour bouts (2.82 hours) and lastly 1–2-hour bouts (2.52 hours).

4.4.5. Diagnostic criteria and the use of a screening tool

4.4.5.1. CARD prevalence

The e-Delphi defined CARD diagnostic criteria requires a patient to demonstrate objective (primarily an abnormal $I<O$ and/or r_{24}) and subjective (patient diary) evidence of circadian rest-activity rhythm disruption with a related clinical impact that is not primarily due to an alternative cause.

Of the 72 participants, 46 participants (70%) had evidence of an abnormal $I<O$ (<97.5%) and/or r_{24} (<0.35). 45 participants (69%) had evidence of an abnormal $I<O$, 28 participants (43%) had evidence of day-to-day irregularity and 27 participants (42%) had evidence of both. Therefore, almost all patients with an abnormal r_{24} (96%) had an abnormal $I<O$, yet a significant minority of patients with an abnormal $I<O$ (40%) had a normal r_{24} . 42 participants (65%) had objective and subjective evidence of circadian rest-activity rhythm disruption.

61 participants (94%), including all participants with evidence of circadian rest-activity rhythm disruption, demonstrated a 'clinical impact' which primarily

considered distressing or frequent fatigue, sleep disturbance or difficulty engaging in daily activities.

Of the 42 participants with evidence of circadian rest-activity rhythm disruption and a clinical impact, 3 participants (5%) had a likely primary alternative cause of their altered rest-activity rhythm (acute diarrhoea secondary to chemotherapy, nighttime disruption from a pet, significant nocturia) and therefore could not meet the diagnostic criteria.

39 participants (60%) were therefore diagnosed with a circadian rest-activity rhythm disorder.

4.4.5.2. CARD Screening Tool Version 1.0

48 participants completed the CARD screening tool version 1.0, with a summary of responses provided in (Table 19). On average, it took 57 seconds (range 18-140 seconds) to complete the first section of the tool, and 25 seconds (range 6-103 seconds) to complete the second section of the tool.

Of the 48 participants, 31 screened positive (65%). Of the 31 participants who screened positive, 19 (61%) were diagnosed with a CARD.

Table 19. Results from the CARD screening tool version 1.0.

	Test-retest reliability
Since your cancer diagnosis...	
1. Have you been aware that you are more restless during some of the nights each week? (e.g. moving around in bed, getting out of bed) Yes (n = 34, 71%) No (n = 14, 29%)	Good κ 0.639 (95% CI 0.396 to 0.882) p<0.001
2. Have those that you live with been aware that you are more restless during some of the nights each week? Yes (n = 20, 42%) No (n = 21, 44%) NA (n = 7, 14%)	Good κ 0.667 (95% CI 0.475 to 0.859) p<0.001
3. Have you spent more time being less active or napping in the daytime each week? (e.g. spending long periods sitting down or lying in bed) Yes (n = 40, 83%) No (n = 8, 17%)	Moderate κ 0.447 (95% CI 0.102 to 0.792) p=0.002
4. Have you noticed that the amount of time that you are active or resting varies from day to day? (e.g. some days you spend more time being physical active, and other days you spend more time resting) Yes (n = 30, 63%) No (n = 18, 37%)	ns
5. Do you feel that your quality of life or any of your symptoms relate to your rest and activity levels? Yes (n = 35, 73%) No (n = 13, 27%)	Moderate κ 0.416 (95% CI 0.120 to 0.712) (p =0.003)

During the last month...	
Has your level of daytime physical activity Worsened (n = 7, 14%) Stayed the same (n = 33, 69%) Improved (n = 8, 17%)	Fair κ 0.240 (95% CI 0.024 to 0.456) p=0.011
Has your night-time restlessness Worsened (n = 5, 11%) Stayed the same (n = 39, 81%) Improved (n = 4, 8%)	Fair κ 0.234 (95% CI -0.048 to 0.516) p=0.031

Kappa value interpretation: Good (0.81-1.00), moderate (0.41-0.60), fair (0.21-0.40), none to slight (0.01-0.20). ns: non-significant, CI: confidence interval, κ : kappa

Most participants reported finding themselves more restless on a nighttime, less active in the day, and with more variability in rest and activity levels between days, since their cancer diagnosis. The majority also reported similar levels of day and nighttime activity during the last month.

31 participants screened positive ((Q1 or Q2 AND Q3) OR Q4) AND Q5): 24 screened positive based on day and night activity, 25 screened positive based on irregularity between days, and 18 screened positive based on both. A comparison of the screening tool and diagnostic criteria results are outlined (Table 20).

Table 20. A cross-tabulation of findings from screening tool 1.0 and diagnostic criteria.

n = 48	Positive using screening tool	Negative using screening tool
Positive using e-Delphi derived diagnostic criteria	n = 19	n = 9
Negative using e-Delphi derived diagnostic criteria	n = 12	n = 8

The sensitivity and specificity of the tool was 67.86% and 40%, respectively. The positive and negative predictive values were 61.29% and 47.06% respectively.

Of the 48 participants completing the circadian sleep-wake screening tool version 1.0, 65% reported that their sleep pattern had changed since their cancer diagnosis, with 31% reporting going to bed and waking up earlier some days of the week, 23% reporting going to bed and waking up later some days of the week, and 42% reporting that their sleep pattern varies from day to day.

100% of participants reported that the tool was easy to complete, easy to understand and acceptable to complete. Comments on the tool were limited to two participants who highlighted that their change in activity patterns relate to no longer being employed and that sleep patterns have changed over time. One participant noted that their sleep patterns were more disrupted after the initial diagnosis and whilst receiving chemotherapy but are better now.

4.4.5.3. CARD Screening Tool Version 2.0

17 participants completed and repeated the CARD version 2.0, with a summary of responses provided below (Table 21). On average, this version of the tool took 64.5 seconds (range 43-109 seconds) to complete the first section, and 41.5 seconds (range 28-128 seconds) to complete the second section.

Similarly, most participants reported finding themselves more restless on a nighttime, less active in the day, and with more variability in rest and activity levels between days, since their cancer diagnosis. The majority also reported similar levels of day and nighttime activity during the last month.

Table 21. Results from the CARD screening tool version 2.0.

	Test-retest reliability
Since your cancer diagnosis...	
1. Have you been aware that you are more restless during some of the nights each week? (e.g. moving around in bed, getting out of bed) Yes (n = 11, 65%) No (n = 6, 35%)	ns
2. Have those that you live with been aware that you are more restless during some of the nights each week? Yes (n = 11, 65%) No (n = 6, 35%)	Good κ 0.622 (95% CI 0.305 to 0.939) p < 0.001
3. Have you spent more time being less active or napping in the daytime each week? (e.g. spending long periods sitting down or lying in bed) Yes (n = 15, 88%) No (n = 2, 12%)	Good κ 0.767 (95% CI 0.336 to 1.198) p = 0.001
4. Have you noticed that the amount of time that you are active or resting varies from day to day? (e.g. some days you spend more time being physically active, and other days you spend more time resting) Yes (n = 12, 71%) No (n = 5, 29%)	ns

5. Do you feel that your symptoms or quality of life relate to how much time you have spent being active or resting? Yes (n = 12, 71%) No (n = 5, 29%)	ns
During the last month...	
a. Has your level of daytime physical activity Worsened (n = 5, 39%) Stayed the same (n = 10, 59%) Improved (n = 2, 12%)	ns
b. Has your night-time restlessness Worsened (n = 5, 39%) Stayed the same (n = 10, 59%) Improved (n = 2, 12%)	Good κ 0.691 (95% CI 0.381 to 1.001) $p < 0.001$

Kappa value interpretation: Good (0.81-1.00), moderate (0.41-0.60), fair (0.21-0.40), none to slight (0.01-0.20). ns: non-significant, CI: confidence interval, κ : kappa

There were variable responses to getting into bed and going to sleep, but most participants reported that they wake up and get out of bed at the same time (65%). Participants were more likely to get into bed earlier rather than later since their cancer diagnosis (53% vs. 6%). Participants were also more likely to get out of bed later rather than earlier since their cancer diagnosis (47% vs. 0%).

Of the 11 participants who screened positive with version 2.0 of the screening tool, 8 (72%) were subsequently diagnosed with a CARD. A cross-tabulation of the screening tool and diagnostic criteria results are outlined (Table 22).

Table 22. A cross-tabulation of findings from screening tool version 2.0 and diagnostic criteria.

n = 17	Positive using screening tool	Negative using screening tool
Positive using the e-Delphi defined diagnostic criteria	n = 8	n = 3
Negative using the e-Delphi defined diagnostic criteria	n = 3	n = 3

Compared to version 1.0, improvements were seen with version 2.0 for sensitivity (72.72 % vs. 67.86%), specificity (50% vs. 40%), PPV (72.27% vs. 61.29%) and NPV (50% vs. 47.06%).

17 participants completed the circadian sleep-wake screening tool version 2.0 which considered changes since their cancer diagnosis. Most participants reported getting into bed 'earlier' (53%) followed by 'at the same time' (41%) and 'later' (6%). Most participants also reported going to sleep 'at the same time' (41%), followed by 'earlier' (30%) and 'later' (29%). Most participants reported waking up 'at the same time' (52%), followed equally by 'earlier' (24%) and 'later' (24%). Furthermore, participants reported getting out of bed either 'at the same time' (53%) or 'later' (47%).

Finally, most participants (65%) reported that the time they get in and out of bed does not change between days, but most participants (52%) reported that the time they fall asleep and wake up does change between days.

100% of participants reported the tool was easy and acceptable to complete. One participant reported that the tool was not easy to understand. Comments on the tool were limited to two participants. One participant highlighted that changes to their sleep and symptoms pre-dated the cancer diagnosis. One participant highlighted further clarification was needed to answer question 5 (symptoms and quality of life).

4.4.6. Associations between circadian parameters, a CARD diagnosis and clinical outcomes

4.4.6.1. MSAS-SF symptomatology

There were no significant correlations between I<O, r24 and SE values and the MSAS Global Distress Index, MSAS Physical Distress or MSAS Psychological Distress scores.

MSAS-SF GDI, Physical Distress and Psychological Distress scores were considered by circadian parameter, with participants being categorised as below or above average values. The GDI scores were not different between I<O groups (1.05 vs. 1.1, $p = 0.789$), but were significantly different between SE groups (1.40 vs. 0.98, $p = 0.028$) and r24 groups (1.24 vs. 0.92, $p = 0.043$). This suggests that participants with lower (poorer) sleep efficiency and r24 values have higher global distress. MSAS Physical Distress Scores were significantly different between r24 groups (0.73 vs. 0.50, $p = 0.016$). This suggests participants with poorer r24 values report higher physical distress. MSAS Physical and Psychological Distress Scores were not significantly different between I<O or SE groups (all $p > 0.05$).

A CARD diagnosis was significantly associated with more MSAS-identified symptoms (9 vs. 12, $p = 0.018$), including more loss of energy ($p = 0.003$), feeling drowsy ($p = 0.005$), shortness of breath ($p = 0.028$), change in taste ($p = 0.013$), and constipation ($p = 0.028$). A CARD diagnosis was also significantly associated with higher MSAS-SF Global Distress Index (1.31 vs. 0.73, $p = <0.001$), higher Psychological Distress Scores (1.21 vs. 0.65, $p = 0.005$) and higher Physical Distress Scores ($U = 729$, $p = 0.003$).

4.4.6.2. EORTC-QLQ-C30 symptomatology and quality of life

The dichotomy index was significantly correlated with the EORTC-Physical Function Score ($r = 0.425$, $p < 0.001$). The r24 was significantly correlated with the EORTC-Global Health Status ($r = 0.292$, $r = 0.018$), EORTC-Physical functioning ($r = 0.407$, $p < 0.001$), EORTC-Social Functioning ($r = 0.250$, $p = 0.044$) and

EORTC-Fatigue ($r = -0.299$, $p = 0.015$) scores. Sleep efficiency was significantly associated with EORTC-Diarrhoea scores ($r = -0.274$, $p = 0.027$).

When considering participants above and below average I<O, SE, and r24 values, EORTC-Physical Functioning scores were higher in those with a higher I<O ($p = 0.006$) and r24 ($p = <0.001$). Those with in the higher r24 group also had higher EORTC-Global Health Status ($p = 0.012$), and lower EORTC-Fatigue ($p = 0.001$) and EORTC-Dyspnoea ($p = 0.037$) scores. There were no significant differences in EORTC-QLQ-C30 scores between those below and above the average SE.

Compared to participants without a CARD diagnosis, participants with a CARD diagnosis had poorer EORTC Global Health Status (Md 58.33 vs Md 79.17, $p = 0.005$), poorer EORTC Physical Functioning scores (Md 66.67 vs. Md 86.67, $p = <0.001$), poorer EORTC Role Functioning scores (Md 100 vs. Md 66.67, $p = 0.014$). Participants with a CARD diagnosis also had higher scores for EORTC Fatigue (Md 55.56 vs. Md 22.22, $p <0.001$), EORTC Dyspnoea (Md 33.33 vs. Md 0.00, $p = 0.005$), and EORTC Constipation (Md 33.33 vs Md 0.00, $p = 0.026$).

4.4.6.3. Subjective sleep quality and daytime sleepiness

Participants with and without bPSQI-identified poor sleep quality did not have different I<O ($p = 0.948$), r24 ($p = 0.627$), or SE ($p = 0.698$) values. Participants with a CARD diagnosis did not have significantly different bPSQI scores (5.62 vs 5.84, $p <0.816$).

The mean bPSQI score differed for those with and without subjective sleep complaints (MSAS-SF 7.44 vs. 3.23 ($p <0.001$), EORTC-QLQ-C30 7.59 vs. 3.32 ($p < 0.001$)). However, bPSQI scores did not differ for those with and without objective sleep disturbance based on SE (5.79 vs. 5.74 ($p = 0.963$)). Linear regression modelling demonstrated that SE plays a small role in predicting bPSQI scores ($\text{bPSQI} = 4.436 + 0.0153 \text{ (SE)}$). Linear regression modelling also demonstrated that the sleep disturbance identified by MSAS-SF and EORTC-QLQ-C30 is more predictive of bPSQI scores ($\text{bPSQI} = 3.231 + 4.205 \text{ (MSA-SF Sleep)}$), or ($\text{bPSQI} = 3.321 + 4.273 \text{ (EORTC-QLQ-C30 Sleep)}$). This suggests that a

baseline score of 3 or less is found in those without sleep complaints and a score of 8 or more found in those with MSAS or EORTC sleep disturbance. Scores of 4-7 may be indeterminate. When reconsidered at a cut-off score of 8, the median SE was not significantly different between those with a bPSQI <8 (n = 42, 67%) than those with a bPSQI ≥8 (n = 23, 35%) (90.64 vs. 90.32, p = 0.927).

Higher ESS scores, representing increased daytime sleepiness, were associated with a poorer dichotomy index (r = -0.470, p<0.001), day-to-day irregularity (r = -0.346, p = 0.005) and poorer sleep efficiency (r = -0.368, p = 0.003). ESS scores were significantly higher in those with a CARD diagnosis (6.54 vs. 3.65, p = 0.003).

4.4.6.4. Blood results and a CARD diagnosis

Those with a CARD diagnosis has significantly lower haemoglobin (11.69 vs. 12.78, p = 0.010), albumin (34.28 vs. 36.64, p = 0.019), iron (13.79 vs. 20.96, p = 0.002), and transferrin saturation levels (24.86 vs. 34.87, p = 0.011). Those with a CARD diagnosis also had lower sodium (139 vs. 140, p = 0.034) and bilirubin levels (6.00 vs. 8.50, p = 0.024), and higher CRP levels (8.8 vs. 3.9, p = 0.009).

4.4.6.5. Survival

There were small positive correlations between the dichotomy index and both the 14-day and 56-day predicted survival using PIPS-B (r = 0.267, p = 0.036 and r = 0.292, p = 0.021, respectively). There was a large positive correlation between the 14-day and 56-day survival using PIPS-B (r = 0.658, p <0.001).

There was no significant correlation between r24 values, and the 14-day or 56-day predicted survival using PIPS-B (r = 0.273, p = 0.038 and r = 0.244, p = 0.065). Nor was there a significant correlation between SE values and the 14-day or 56-day predicted survival using PIPS-B (r = 0.203, p = 0.127 and r = 0.062, p = 0.641).

There was no significant difference in median PIPS-14 day or PIPS-56 day predicted survival between those with and without a CARD diagnosis ($p = 0.261$ and $p = 0.157$).

4.5. DISCUSSION

The study assessed the utility of a novel screening tool for identifying patients at risk of a circadian rest-activity rhythm disorder (CARD). The study also characterised the circadian rest-activity rhythms in 65 patients with advanced cancer, alongside potential risk factors and important clinical associations.

4.5.1. Key findings

This is the first study to assess a screening tool to identify CARDs in patients with advanced cancer. The tool was found to be quick to complete, easy to use, and acceptable to participants. The sensitivity, specificity, PPV and NPV all improved with the second version of the tool. Although the tool can identify patients with a CARD diagnosis, it is a poor predictor of those without a CARD and may not be feasible as a screening tool. Of note, the study has highlighted discrepancies in objective and subjective measures, particularly when considering sleep. Most participants reported restless nights, sedentary days and fluctuations in their rest-activity rhythms between days. This subjective experience may not correlate with objective findings used within the diagnostic criteria. The study utilised a small sample of participants with advanced cancer and ongoing research assessing CARD screening tools in larger cohorts is required. Of note, the tool asked participants to consider how their rest-activity patterns have changed since their cancer diagnosis. Research has highlighted that circadian disruption is a risk factor for cancer development and therefore may occur prior to a formal diagnosis (278). A future tool may benefit from assessing participants current rest and activity patterns irrespective of the timing of diagnosis. Anticancer therapies change during the disease trajectory and study participants noted that different anticancer therapies had varying impact on their sleep, activity and wellbeing.

This is also the first study to diagnose CARDs as a clinical entity. CARDs were found to be common (60%) in patients with advanced cancer, with more

participants demonstrating abnormal I<O than abnormal r24. Participants with evidence of circadian disruption (from individual circadian parameters or a CARD diagnosis) were noted to have increased symptom burden, particularly fatigue and drowsiness, and higher symptom-related distress. Participants with disruption also reported poorer Global Health Status and Functioning subscales when using the EORTC-QLQ-C30. These findings are supported by previous reports whereby symptoms such as pain, sleep disturbance and fatigue were associated with abnormal I<O and r24 values (211). Disordered circadian rest-activity rhythm parameters, which are required for a CARD diagnosis, have been linked to additional functioning sub-scales, such as social functioning, which were not significantly associated with the diagnosis (211).

Although this study is yet to report on prognosis, a predictor of prognosis (PIPS-B) was used. Previous work has demonstrated a link between the I<O, r24 and several sleep markers, including SE, with prognosis (211). This study failed to demonstrate a significant association between the r24, SE, or CARD diagnosis and PIPS-B 14-day or 56-day predicted survival. However, the study did demonstrate a small, yet significant, association with I<O and PIPS-B outcomes.

A CARD diagnosis is supported by objective evidence of circadian rest-activity rhythm disruption, predominantly the dichotomy index (I<O) and 24-hour autocorrelation coefficient (r24). The average I<O within this study (95.05%) resembled, but was lower, than that in previous work, which reported the average I<O to be 97-97.5%; albeit some previous work has focused solely on patients with metastatic colorectal cancer (35, 113, 154). Although this study reported an average r24 of 0.41, it is important to note that previous reports have highlighted significant variation of group-level circadian parameters, which was seen in this study (r24 (0.13-0.72), I<O (78.51-99.87%) and SE (51.00-98.36%)), and with no agreed threshold level, it is difficult to make an adequate comparison between studies (211). Differences in circadian parameter values may be expected due to variable methods of assessing DOWN and UP, the use of several devices and variable data processing and analysis methods.

Previous work has considered potential risk factors for circadian disruption in patients with cancer and has included male sex, more advanced disease, chest wall disease, hormone use, radiotherapy, and African-American ethnicity in females (211). Similarities were noted within this study which found more circadian disruption in those with more advanced disease (particularly metastatic organ involvement), poorer performance status, higher inflammatory status (raised CRP), anaemia and iron deficiency, and in those off systemic anticancer therapy. Interestingly, sharing a bed was also associated with better day-night distinction and day-to-day regularity.

The top three patient reported physical symptoms were lack of energy, pain and difficulty sleeping in this cohort of patients with advanced cancer. In comparison to the top symptoms in a study of the MSAS-SF in advanced cancer, the patients in this study reported less lack of energy (86% vs. 92%), less feeling drowsy (57% vs. 88%) and less pain (69% vs. 86%) (233). Psychological symptoms also differed with the participants in this study reporting less sadness (48% vs. 63%), worry (48% vs. 68%), and irritability (45% vs. 47%). The prevalence of a CARD diagnosis may differ in other cohorts of patients with advanced cancer experiencing higher symptom burden.

Subjective sleep disturbance was found in between 48-60% of participants depending on the assessment tool used (60% MSAS-SF, 57% EORTC-QLQ-C30, 48% bPSQI > 5). This is, as expected, higher than that of patients with cancer generally (40%), as patients with more advanced cancer tend to experience more sleep disturbance, but lower than previous reports of patients with advanced cancer (70%) (279-281). Objective sleep disturbance varied on the measure used but was highest for WASO >30 minutes (69%), followed by a prolonged SOL >20 minutes (57%), and finally for reduced SE <80% (22%).

Interestingly, although a relationship was noted between subjective measures of sleep disturbance, the bPSQI scores were not significantly associated with objective accelerometry evidence. This finding is supported by a study of patients with breast cancer that found several objective sleep parameters (SOL, TST, SE, WASO) were not significantly different between those identified as good or poor

sleepers using the PSQI (282). Self-reported and accelerometry-derived measures of sleep duration, SOL and WASO have also been found to have poor to moderate levels of agreement in a cohort of patients with colorectal cancer (283). Furthermore, in patients with advanced lung cancer, actigraphy defined SE and SOL was not significantly associated with the PSQI global score or PSQI defined sleep disturbance for inpatients or outpatients, but conversely, the PSQI global score was significantly associated with WASO in the outpatient setting (48). Due to discrepancies in subjective and objective measures of sleep, future studies should ensure the outcome measures are appropriately matched with the aims of the study. This study highlights a bPSQI cut-off score of 8, rather than 5, is more accurate at detecting subjective sleep disturbance in patients with advanced cancer. This finding is similar to previous work which evaluated the psychometric properties of the full PSQI and noted a cut-off of 8, rather than 5, being more accurate in cancer patients (240).

Varied practice remains in the identification of DOWN and UP times across research, and identification of these times may consider a sleep diary, event marker, device light levels or activity levels (284). Automated software can determine DOWN and UP times but studies may also adjust these timings based on the self-reported times (283). This study has highlighted that the most consistent measure of DOWN and UP times was achieved from automated software, followed by patient diaries and event markers. Event markers may be a more accurate patient-reported measure, compared to patient diaries, as event marker timings were closer to objective measures of DOWN and UP transitions. The study also highlighted a large variation in the timing between patient reported DOWN and UP times and the beginning or end of a physical activity period, which is often used for calculating the time in and out of bed using automated software. These findings support a recent study which considered actigraphy, and patient-reported, sleep measures in cancer survivors (285). Compared to actigraphy measures, sleep diary entries tended to report longer time in bed, SOL and WASO, and shorter total sleep time and SE (285). As several circadian parameters require accurate detection of DOWN and UP times, future research should consider standardising the assessment practice further and define the optimum approach for DOWN and UP time detection.

4.5.2. Strength and limitations

External validity was strengthened by utilising an array of cancer diagnoses but the small sample sizes for individual cancer groups limits the ability to detect significant intergroup findings. Most participants also had an ECOG status of 0 or 1, which limits generalising the findings to those with a poorer performance status. Previous studies have highlighted how those with more advanced disease, and thus poorer performance status, have more disordered circadian rhythms than may be evident in the study results (211). Furthermore, ethnicity is known to contribute to circadian rest-activity rhythms and, as 92% of participants were white Irish, the findings of this study cannot be generalised to other ethnic groups (67).

Circadian rhythms are complex and are influenced by several external factors. The study provides a comprehensive assessments of patient-related factors and potential contributing factors. However, not all known confounding factors have been captured and unknown confounding factors are still likely. This includes not capturing diet and feeding patterns, which are known entrainers of several circadian rhythms, including sleep and endocrine function (286). Although prescribed medication was considered, previous use of recreational drug use, or drug use during the study, was not captured and may, if present, have impacted daytime sleepiness, sleep quality, and sleep disruptions (268). Furthermore, although participant's living situation was considered, it did not capture the presence of domestic animals. People with co-sleeping arrangements with their pets, for example, report longer SOL, more tiredness on waking and, being more likely to wake during the night due to animal noises (287). Pet ownership is also associated with more frequent daytime physical activity and positive psychological effects which may influence clinical outcomes of interest (288).

Although the screening tool considered a participant's perception of their daytime activity and sleep over the preceding month, their pre-morbid levels of sleep and activity were not assessed. Some participants have highlighted that disruption in their own sleep and activity became disordered prior to their formal cancer diagnosis and differed with changing anticancer therapies. The screening tool focussed on a change after diagnosis and may therefore not identify those with

pre-existing changes. Most patients who receive a cancer diagnosis reduce their physical activity levels and reports suggest that this can relate to the person's beliefs in their own ability to exercise, beliefs around the impact of cancer on physical activity and a feeling of loss of control (289). Assessing for, and addressing, pre-existing beliefs may also be important when considering any intervention aimed at improving physical activity.

There is also a lack of agreed standards on the optimum device, data processing and data analysis with regards to accelerometry, circadian rest-activity rhythm assessment, and their use in patients with cancer. It remains unclear how to accurately assess their DOWN and UP times and the study highlights variation between patient-reported and objective measures of these time points. Previous research has highlighted inconsistency in the reporting of sleep parameters, with attribution from a lack of consensus for sleep onset and offset (277). A participant's time in bed may be defined from the time they have physically got into bed, turned off the lights or attempted to fall asleep and, similarly, time out of bed defined by the waking up time, the time lights were turned on or the time that they have physically got out of bed (277).

The study assessed participants for a 72-hour window mid-week. Although similar dichotomy index values have been reported when captured midweek or on weekend, the reporting study did not detail the employment status of participants (221). 22% of participants in this study were employed and it is unknown if their circadian parameters differ significantly between midweek and weekend days in this group of participants.

4.6. CONCLUSION

CARDs are prevalent in patients with advanced cancer, and most commonly relate to daytime sedentariness and nighttime restlessness. A CARD diagnosis has implications with regards to symptomatology and quality of life. A comprehensive assessment has provided insight into potential risk factors for a CARD and, by including patient diary, event marker and automated tools, has aided in identifying more accurate in-bed and out-of-bed timings. Although the screening tool failed to

adequately identify patients at risk of a CARD, further understanding of CARDS in this patient group, including patient-related risk factors, may aid in strengthening the tool. Future research is required to assess optimum approaches to circadian rest-activity rhythm assessment in patients with advanced cancer.

CHAPTER 5. AN 8-WEEK, SINGLE ARM, MULTI-MODAL, NON-PHARMACOLOGICAL, INTERVENTIONAL FEASIBILITY STUDY AIMED AT IMPROVING CIRCADIAN REST-ACTIVITY RHYTHMS IN PATIENTS WITH ADVANCED CANCER

5.1. INTRODUCTION

Circadian rest-activity rhythms can be altered in several ways. Patients may demonstrate increased nighttime activity levels and reduced daytime activity, poorly discriminated rest and activity periods, or a lack of regularity in their rest and activity levels between days. Interventions aimed at improving circadian rest-activity rhythms therefore need to strengthen inter-daily regularity, increase daytime activity, and reduce night-time activity. Although pharmacological options may improve circadian rest-activity rhythms, effective and acceptable non-pharmacological options should be considered first-line to reduce patient burden and medication-related complications. This chapter will highlight the evidence for several non-pharmacological options, before discussing a multi-modal feasibility trial. Potentially reversible causes of circadian rest-activity rhythm disturbance have also been discussed in chapter 4. A multi-modal approach is being considered as previous circadian rhythm disorder trials highlight the additive effects of combining treatments (290). More pronounced circadian rhythm disruption occurs in those with more advanced disease and improving rhythmicity may require a multi-modal approach.

5.1.1. Bright light therapy

The presence and absence of light over a 24-hour period is the strongest zeitgeber in synchronising internal circadian rhythms to the environment, primarily due to its effect on the SCN, ability to inhibit melatonin synthesis and by activating the ascending arousal system (291). The timing of light exposure, along with wavelength and lux should be considered. Natural visible light has a wavelength of 380-760nm, which is similar to artificial bright light, and blue light, which has a wavelength of 460nm, appears to have the greatest ability to cause phase shifts (292). When considering lux, dawn sunlight (7,000-12,000 lux) can affect circadian

rhythms and is significantly less than midday sunlight (100,000 lux) (292). The effects of increasing lux lessen once over 550 lux, and 9000 lux results in only a double effect when compared to 100 lux (292).

Bright light therapy (BLT) is a simple, easy to use, and inexpensive intervention that does not lead to tolerance and demonstrates small to medium size effects (291). BLT has traditionally been investigated in the treatment of circadian rhythm sleep-wake disorders, with attempts to re-aligning the timing of sleep-wake with the environment (291). For example, morning light exposure can advance (bring forward) circadian rhythms and evening exposure can delay circadian rhythms (291). When BLT is used for seasonal affective disorder, rhythm advancement is seen following exposure at a rate of 5000 lux/hour, or 10,000 lux/30 minutes (292).

BLT appears to have larger effects on sleep architecture than sleep complaints and, for insomnia, increased light intensity is associated with a larger effect size (291). When BLT is added to sleep hygiene, insomnia symptoms improve significantly and greater effects are seen for durations of BLT lasting more than 45 minutes when compared to 20 minutes (292). Morning exposure, particularly if delivered 8.5 hours after the dim light melatonin onset (DLMO), is most effective (292). In healthy volunteers, improved activity and exertional levels have been achieved following BLT versus dim light exposure (293). Effects are seen for circadian rhythm sleep-wake disorders, insomnia, dementia-related sleep problems, and other sleep problems (all $p < 0.01$) (291). Improvements are also seen for the time in bed spent sleeping (sleep efficiency (SE)) and sleep quality (291). For patients with dementia, BLT leads to less rest-activity rhythm variability, a more stable acrophase (timing of peak activity), and more consolidated sleep (292, 294). A review highlights variation in the duration of exposure, lux used and the distance that the light is placed from the patient in BLT trials (292).

Effects of BLT has been reported across cancer groups. In patients with breast cancer undergoing chemotherapy, those exposed to dim-red light (DRL) displayed increased sleep activity, reduced SE, more daytime naps and less daytime activity (295). Although such parameters did not improve with BLT, no such deterioration was experienced, and patients exposed to BLT had longer total sleep times (295).

In cancer survivors, 30 minutes of BLT versus dim light led to improved SE persisting for up to 3 weeks after the intervention, and improvements have been reported in cancer-related fatigue (296, 297). In patients with breast cancer undergoing chemotherapy, a known modifier of circadian rhythms, light therapy led to shorter time to fall asleep (sleep onset latency (SOL)), SE and total sleep time, and reduced depression scores (298).

5.1.2. Cognitive behavioural therapy for insomnia (CBT-I)

Insomnia describes a difficulty in initiating or maintaining sleep (299). Those with insomnia have cognitive and physical hyperarousal, and detrimental sleep-related beliefs (300). Primary insomnia occurs with no identifiably underlying cause, whereas secondary insomnia may result, for example, from chronic pain, mood disorders, and comorbid disease (301). Cognitive behavioural therapy for insomnia (CBT-I) utilises five approaches to improve symptoms of insomnia and sleep disturbance (299). This includes limiting exposure to stimuli prior to bed (stimulus control), restricting time in bed not asleep (sleep restriction), sleep hygiene advice, addressing maladaptive sleep beliefs (cognitive restructuring) and relaxation training (299, 302). CBT-I has long-lasting effects, minimal side effects and is as effective as sedative medications in the short- and long-term management of primary and secondary insomnia (300, 301). Larger treatment effects are seen in the general population when compared to pharmacological treatment, relaxation and sleep hygiene alone (300). CBT-I was traditionally delivered face-to-face but telephone, virtual, online and self-help delivery has been developed (299). The alternative delivery approaches have helped overcome the lack of experience and training amongst healthcare professionals and the geographical and financial barriers associated with face-to-face delivery.

Insomnia is common amongst patients with cancer, with up to 69% of patients experiencing sleep difficulties, up to 29% satisfying insomnia criteria, and up to 25% using medication to manage sleep difficulties (299). Insomnia in patients with cancer is multifactorial in nature and is associated with depression, pain, fatigue, and reduced quality of life (QoL) (299). CBT-I is as effective as medication use, and is preferred by patients (299). Significant improvements in sleep quality, SOL,

wake after sleep onset (WASO) and SE have been seen in cancer survivors and across cancer groups for up to 6 months, with comparable efficacy for face-to-face and online delivery in (299, 300, 302).

5.1.3. Physical activity

Physical activity plays a significant role in health and disease, with sedentary behaviours associated with several diagnoses including metabolic, neurodegenerative and cardiovascular disease, as well as cancer (303, 304). Increased exercise is associated with reduced cancer occurrence, cancer-related mortality, overall mortality and anticancer treatment side effects (305). This includes up to a 48% reduction in cancer incidence and 27% reduction in cancer mortality (306). Fatigue, depression, sleep quality and QoL are all improved with higher exercise levels (305). Significant improvements have been seen in anxiety, depression, cancer-related fatigue, health-related QoL, and physical function with aerobic and resistance training, and larger effects are seen with supervised elements to exercise programmes (307). However, benefits have also been seen with supervised and unsupervised home activity (306). There is mixed evidence for the effect of exercise on bone health and sleep (307). Trials have often focused on single cancer diagnoses and therefore limit the generalisability of results (307).

The American College of Sports Medicine (ACSM) guidelines for cancer survivors, of 150 minutes of moderate or 75 minutes of vigorous activity across the week, are not generalisable to all patients with cancer (308). Up to 70% of cancer survivors adhere to such guidelines (306). Higher rates of activity, amongst cancer survivors, are associated with higher socioeconomic status and higher levels of education (303). Conversely, lower rates of activity are associated with female sex, increasing age and higher body mass index (BMI) (303). Research has often focused on more vigorous activities and patients may be unable to reach generic goals, especially if they have low pre-existing activity levels (273). As a minimum, sedentary activity should be avoided and low-level physical activity (LPA) encouraged (273, 275). LPA makes up a significant proportion of daytime activity and may be perceived as more achievable and therefore easier to encourage patients to engage with (273).

To be effective, physical activity as a management strategy needs to be individualised. Breast cancer survivors have highlighted the importance of remaining independent, that physical activity should be convenient to engage with, that any fears or barriers are addressed, and that social elements are incorporated into a plan (309). Barriers may include physical factors, such as comorbid disease, cancer-related effects, and anticancer treatment side effects (275). Psychosocial barriers may include poor motivation and low self-efficacy (275). Plans should progress steadily over time and consider an individual's physical ability, psychological and physiological state, readiness to engage in activity, and symptoms such as fatigue and poor sleep (308). Cancer-related fatigue, common in advanced disease, can last for several hours following physical activity, and impact adherence with current exercise plans and any long-term behavioural change (310). This reinforces the idea of an individualised approach and the need to incorporate pacing of activities.

Initial screening can take place, using tools such as the Physical Activity Readiness Questionnaire or PARmed-X, which consider the suitability and safety of activities for each individual (311). Assessment might consider comorbidities, contraindications, toxicities from systemic anticancer therapies, symptom burden, bony metastases and any balance or mobility concerns (307). The presence of anaemia, infection and bleeding risk should be considered, along with exercise induced symptoms such as chest or limb pain, dizziness or syncope (306). No assessments are required for most cancer survivors engaging in low-intensity activity, gradually progressive resistance training or flexibility training (307). At a minimum, patients should be advised to avoid sedentary activity and be as active as possible (307).

Personalised goal setting and an activity plan should be developed alongside the patient and consider the intensity, frequency, duration and modality of activity (308, 311). Improved adherence is seen where activities are enjoyed or paired with an enjoyable activity, where the plan includes short- and long-term goals using the Specific, Measurable, Achievable, Realistic and Timely (SMART) framework, where patients can self-monitor their activities and where social support exists for

engagement in activity (305). An individualised plan allows for better engagement, increased activity frequency and improved recovery (308).

Wearable activity trackers allow users to monitor their own physical activity and to set activity goals (312). Benefits have been seen in several conditions including cardiovascular, musculoskeletal, and metabolic diseases (312). Amongst the general population, regular exercise is associated with small effects on total sleep time and SE, small-to-medium size effects on SOL, and large effects on overall sleep quality (313). Research, predominantly amongst breast cancer survivors, demonstrates moderate-to-large size effects of improving moderate and total physical activity, and step count amongst cancer survivors (312).

Long-term physical activity acts as an important synchroniser of circadian rhythms, including sleep-wake and rest-activity rhythms, and may reduce elevated cortisol levels (304). With acute changes in the sleep-wake rhythm, such as jetlag, exercise may also allow for earlier resynchronisation with the 24-hour clock (314). A combination of bright light therapy and exercise acts as a strong synchroniser of rhythmicity (314). Several circadian measures, including r_{24} , I_{CO} , activity amplitude and activity MESOR, are significantly associated with daytime activity levels and light exposure in patients with oesophageal and gastric cancer (315). Low level interventions, such as home based walking, have also proven effective in patients with lung cancer at improving sleep quality and total sleep time, but did not impact on objective measures such as r_{24} and I_{CO} (42). Furthermore, improved SE, WASO, number of awakenings, and total Pittsburgh Sleep Quality Index (PSQI) has been demonstrated with the use of wearable activity trackers in breast cancer survivors, with larger effects for those identified as poor sleepers (316). Adverse events associated with physical activity are uncommon and often relate to musculoskeletal complaints (312). Wearable activity trackers are acceptable to patients with cancer, with up to 87% retention over prolonged periods (24 weeks) and are found to be useful for goal setting (312, 316).

5.1.4. Alternative approaches

Of note, several additional management strategies to synchronise and strengthen circadian rhythms exist. This includes manipulating the diet and dietary intake pattern, although most of the research is pre-clinical. Ad hoc eating disrupts several metabolic process and interplays predominantly with the peripheral, rather than central, circadian clocks (317). The approach aims to deliver more controlled feeding-fasting schedules, with time-restricted periods of feeding (317). In mice models, the approach has improved cognitive function and reduced inflammation (317). Cancer patients often experience weight loss and reduced appetite, and a palliative approach focuses on maintaining adequate dietary intake. Although this management approach has potential, there is limited evidence at present and the associated risks within the patients with advanced cancer are unknown.

5.1.5. Defining feasibility

The terms ‘feasibility’ and ‘pilot’ studies have been used interchangeably in clinical research and may be used in preparation for a definitive study. Feasibility is an overarching concept, considering how a research question could be answered, whether it is possible to address this question and to support whether a definitive trial should take place or not. Feasibility work may include randomised and non-randomised pilot studies, in addition to other types of studies (318). Early feasibility work tends to have a broader focus, more flexibility and may consider aspects relating to both intervention implementation and running the study (318). Feasibility work primarily considers research processes (i.e. recruitment, retention, randomisation processes and time to collect and analyse data) and participant related factors (i.e. acceptability, safety and adherence in relation to interventions) (319).

If minor issues are identified within early feasibility work, a pilot trial may take place which more closely resembles the definitive trial, albeit of a smaller sample size, and focuses predominantly on recruitment and randomisation (318, 320). This pilot study may be incorporated into the beginning of the definitive trial (internal pilot) or be carried out as a separate study (external pilot) depending on whether minor or

major issues have been identified (320). Pilot studies demonstrating feasibility support proceeding to the definitive trial.

5.2. AIMS

5.2.1. Primary aim

To assess the feasibility and acceptability of a multi-modal, non-pharmacological intervention to improve circadian rest-activity rhythm disorders in patients with advanced cancer.

5.2.2. Secondary aims

To assess the impact of a multi-modal non-pharmacological intervention on patient-reported symptoms and associated distress, quality of life, sleep quality, daytime sleepiness.

To assess the impact of a multi-modal non-pharmacological intervention on objectively measured circadian accelerometry parameters.

5.3. METHODOLOGY

5.3.1. Study design and setting

A prospective, single armed, outpatient feasibility study of a multi-modal, non-pharmacological, intervention. The study was registered at <https://clinicaltrials.gov/study/NCT06329479?term=circadian%20cancer&sort=StudyFirstPostDate&page=2&rank=13> (NCT06329479).

5.3.2. Participant selection and recruitment

Participants with locally advanced or metastatic cancer and a circadian rest-activity rhythm disorder, identified in an earlier study and recruited from two sites (Our Lady's Hospice & Care Services and St James's Hospital, Dublin), were invited to

take part in a follow-on feasibility study which was conducted from Our Lady's Hospice & Care Services, Dublin.

5.3.3. Sample size

The feasibility study aimed to recruit 30 patients over the course of 1 year. Several justifications exist for determining the sample size in feasibility studies (321). This includes using a minimum of 12-50 participants per arm or using 3% of the definitive study sample size, and a review of feasibility and pilot studies has determined the median sample size for each arm is 30 (321).

5.3.4. Inclusion and exclusion criteria

Inclusion criteria

1. Age ≥ 18 years old
2. Outpatient
3. Diagnosis of advanced cancer (locally advanced, metastatic)
4. Ambulatory
5. Estimated prognosis ≥ 3 months
6. Evidence of a circadian rest-activity rhythm disorder

Exclusion criteria

1. Inpatient^a
2. Engaged in shift work^a
3. Long-haul travel in the last 14 days^a
4. Physical impairment limiting movement of the non-dominant arm
5. Cognitive impairment limiting the ability to complete the assessment tool and/or patient diary
6. Uncontrolled high blood pressure or tachycardia^b
7. Exercise-related symptoms and signs (e.g. chest pain, syncope, limb claudication, hypoxia at rest)^b
8. Participant has a history of uncontrolled mania or bipolar disorder^c
9. Participant has a recent change in antidepressant medication^{c,d}
10. Participant has a recent history or current thoughts of self-harm or suicided^d

11. Participant has an eye disorder (e.g. glaucoma, cataracts, retinopathy)^e

^a due to being a known modifier of circadian rhythms

^b due to potential adverse events when engaging in increased physical activity

^c due to the potential for bright light therapy to precipitate mania

^d due to the rare occurrence of increased suicidality with bright light therapy

^e due to the reduce effect of bright light therapy

5.3.5. Consent

Patients were provided with a patient information sheet (Appendix 3) and provided with the opportunity to ask questions about the study. They were then required to complete and sign a consent form.

5.3.6. Study interventions

The study involved four main interventions: 1) a clinical review; 2) an online cognitive behavioural therapy for insomnia (CBT-I) course; 3) daily bright light therapy; and 4) a personalised activity plan. Participants were provided with information sheets for each intervention (Appendix 7).

The clinical assessment was carried out by the lead researcher (CG) who considered the presence and reversibility of uncontrolled symptoms, blood abnormalities, and medication, which may contribute to circadian disruption. Where present, clinical teams were updated, and a plan put in place. The clinical assessment was carried out at two time points (baseline and at the end of week 2).

Patients received an information sheet on sleep hygiene and were provided with access to THIS WAY UP's CBT-I self-guided online program (THIS WAY UP, St Vincent's Hospital, Sydney). The program combines psychoeducation with evidence-based skills and strategies delivered over four lessons (Table 23). Participants also completed the Kessler Psychological Distress Scale (K-10, Table 24) (322), which assesses psychological distress over the past 2 weeks, and the

Insomnia Severity Index (ISI, Table 25) (323), which assesses sleep quality, distress from sleep loss and functional impairment over the past 2 weeks, prior to completing each lesson (322, 323). The course incorporates a mandatory 5-day waiting period between each lesson, with action plans and workbooks for use between lessons. Participants were advised to complete the CBT-I course by the end of week 6 to allow for time to reflect on the course and put the course material into practice.

Table 23. Psychoeducation and evidence-based skills and strategies delivered by the CBT-I course.

Psychoeducation	Evidence-based skills and strategies
- What insomnia is and how it works - Factors that regulate sleep - Sleep hygiene - Sleep efficiency - Sleep medications - Unhelpful thinking styles - Cognitive behavioural therapy - Sleep effort - How anxiety works - How worry interacts with sleep - Rumination and negative thoughts - Lapses and relapses	- Using diet and exercise to improve sleep - Changing the sleep environment - Sleep diaries - Sleep routines - Stimulus control - Worry time - Time-in-bed restriction - Thought challenging - Accepting worries - Activity scheduling - Slow breathing - Structure problem solving - Relapse prevention planning

Table 24. Kessler Psychological Distress Scale (K-10)(322).

During the last 30 days, about how often did...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
1...you feel depressed? that nothing could cheer you up?					
2...you feel so depressed					
3...you feel hopeless?					
4...you feel restless or fidgety?					
5...you feel so restless that you could not sit still?					
6...you feel tired out for no good reason?					
7...you feel that everything was an effort?					
8...you feel worthless?					
9...you feel nervous?					
10...you feel so nervous that nothing could calm you down?					

Table 25. Insomnia Severity Index (ISI)(323).

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).					
Insomnia problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep					
2. Difficulty staying asleep					
3. Problems waking up too early					
4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?					
Very satisfied (0)	Satisfied (1)	Moderately satisfied (2)	Dissatisfied (3)	Very Dissatisfied (4)	
5. How NOTICEABLE to others do you think your sleep problems are in terms of impairing your quality of life?					
Not at all Noticeable (0)	A little (1)	Somewhat (2)	Much (3)	Very Much Noticeable (4)	
6. How WORRIED/DISTRESSED are you about your current sleep problem?					
Not at all Worried (0)	A Little (1)	Somewhat (2)	Much (3)	Very Much Worried (4)	
7. To what extent do you consider your sleep problems to INTEFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?					
Not at all Interfering (0)	A Little (1)	Somewhat (2)	Much (3)	Very Much Interfering (4)	
Scoring					
0-7 = No clinically significant insomnia					
8-14 = Subthreshold insomnia					
15-21 = Clinical insomnia (moderate severity)					
22-28 = Clinical insomnia (severe)					

Participants were also provided with an information sheet on the role of bright light therapy. Bright light therapy was delivered using the Lumie L[®] light box (Figure 19) which provides 10,000 lux at 20cm and 2500 lux at 50cm. Participants were advised to place the light box within arm's reach and in a direction whereby light reached the face and eyes. Participants were informed that the aim was to use the light box every morning on waking for at least 30 minutes. The first week allowed for a trial of the light box and for participants to progressively increase their duration of exposure. The device was demonstrated during the first visit. Utility of the light box and any technical challenges were addressed weekly.



Figure 19. The Lumie-L lightbox with stand. Use of the Lumie, Cambridge UK, class IIa ISO 13485 Medical Device is demonstrated.

Finally, participants were provided with an information sheet on the role of physical activity in patients with cancer. Participants were provided with a Polar Unite watch (Figure 20) to wear on their non-dominant wrist, unless contraindicated, and the watches functions were demonstrated.



Figure 20. Polar Unite watch. Polar Electro OY (ISO 9001:2015) demonstrated the workout watch face (top left) and heart rate monitoring watch face (bottom).

The Polar Unite can provide real-time feedback on steps, daily activity, heart rate, sleep, and heart rate variability. The watch also alerts the wearer to prolonged sedentary activity. The watch can be personalised based on previous activity levels and activity goals, which can be adjusted over time. At the initial meeting, personalised interests, barriers to physical activity, and short- and long-term goals were established. These were reviewed weekly and adjusted, where able, with the

aim of gradually increasing physical activity levels and reducing sedentary behaviour. Any technical issues with the Polar watch were also addressed weekly. The importance of having regular activity patterns was encouraged. Importantly, the activity goal was individualised, and co-created with the participant, rather than using pre-determined exercises. The Polar Unite watch was reviewed at face-to-face meetings to establish activity patterns in the preceding weeks and to increase, maintain or reduce activity goals as needed.

During the final week of the study, participants repeated accelerometry monitoring using the Micro Motionlogger wrist accelerometer and ActivPal thigh accelerometer. They also completed the sleep and activity diary (Appendix 5).

The study involved 4 face-to-face meetings at baseline and at the end of weeks 2, 4 and 8 with a set agenda (Box 5). These could occur in healthcare settings or in the community, depending on participant preference. Weekly virtual meetings were also arranged which, based on participant preference, could take place over the telephone, via text or email.

Box 5. Areas to be considered during weekly researcher-participant contact.

1. Assess for adverse events or development of new symptoms
2. Assess for technical difficulties
3. Assess for adherence with CBT-I
4. Assess for adherence with bright light therapy
5. Assess activity levels and compliance with pre-agreed activity plan
6. Set goals for the upcoming week

In the related screening study, enrolled participants had completed assessments on symptoms (MSAS-SF), quality of life (EORTC CQC-C30), sleep quality (bPSQI) and daytime sleepiness (ESS). These were repeated at the end of week 4 and 8 of the feasibility study. Through the CBT-I platform, participants also completed the K-10 and ISI prior to each of the four sleep lessons.

5.3.7. Outcome measures

5.3.7.1. Primary outcome measures

The feasibility and acceptability of the multi-modal intervention considering:

- i. Recruitment and retention rates
- ii. Completion of research assessments
- iii. Engagement with each intervention
- iv. Acceptability and usability of the interventions
- v. Adverse events

5.3.7.2. Secondary outcome measures

- i. Participant reported interests in, and barriers to, physical activity
- ii. Potentially reversible factors contributing to circadian rest-activity rhythm disruption

Preliminary analysis of the impact of the intervention on:

- i. Patient reported outcomes (symptoms, quality of life, psychological distress, sleep quality and daytime sleepiness)
- ii. Objective accelerometry-derived circadian parameters
- iii. Objective accelerometry-derived daytime physical activity

5.3.8. Statistical analysis

Descriptive statistics were used for participant characteristics, recruitment rates, retention rates, engagement with interventions, completion of research reviews and assessments, adverse events and clinical outcomes. Content analysis was used for participant reported interests and barriers to physical activity. One-way repeated measures ANOVA and the Friedman test was used to consider the significance of change in clinical outcomes over time.

5.3.9. Ethical approval

Ethical approval for the study was granted by the joint St James' Hospital-Tallaght University Hospital Research Ethics Committee (Appendix 2).

5.3.10. Patient and public involvement

The study protocol and participant facing information was reviewed by the Voices4Care team, made up of people with palliative care needs, carers and, with implementation of suggested changes prior to starting the study.

5.4. RESULTS

5.4.1. Primary outcomes

5.4.1.1. Participant recruitment and retention

39 participants were identified to have a circadian rest-activity rhythm disorder. 8 were excluded from the feasibility study due to a subsequent clinical deterioration (n = 3), short prognosis (n = 2), lost to follow up (n = 2) or the end of feasibility study being reached (n = 1). 11 declined to enter the feasibility study and reasons included being too busy (n = 3), would not engage with the interventions (n = 2), information technology literacy problems (n = 2), the study would be “too much” (n = 2), had since been approached about a separate research study (n = 1), and no reason provided (n = 1). Hence, 20 participants (Table 26) were eligible and recruited to the feasibility study.

Table 26. Feasibility study participant characteristics (n = 20).

Age	59 years old (47 – 77 years old)
Gender	Female (n = 16, 80%) Male (n = 4, 20%)
Cancer	Gastrointestinal (n = 7, 35%) Breast (n = 5, 25%) Lung (n = 5, 25%) Renal (n = 1, 5%) Prostate (n = 1, 5%) Melanoma (n = 1, 5%)
Treatment status	Receiving anticancer treatment (n = 19, 95%) Not receiving anticancer treatment (n = 1, 5%)
ECOG	1 (n = 15, 75%) 2 (n = 5, 25%)

ECOG: Eastern Cooperative Oncology Group performance status.

All participants underwent the initial meeting which included providing equipment, a clinical review and the creation of the personalised activity plan. Repeat thigh accelerometry monitoring was subsequently achieved for 15 participants. Repeat accelerometry monitoring was not possible for 5 participants due to clinical deterioration with a subsequent dropout (n = 4) and loss of contact during the trial (n = 1). Repeat wrist accelerometry was not achieved for one of the 15 participants due to incorrect wear. This led to 14 participants having repeat wrist and thigh accelerometry data at baseline and at the end of the trial for comparison.

Participants who experienced a clinical deterioration were allowed to continue where able. Of the four patients who deteriorated and subsequently dropped out, one deteriorated during the 1st week of the study and dropped out at the end of week 3, a second deteriorated at the end of the 2nd week and dropped out at the end of week 6, a third deteriorated at the end of the 3rd week and dropped out at the end of week 5, and the final deteriorated during the 8th week and was excluded.

5.4.1.2. Completion of research reviews and assessments

MSAS-SF, EORTC-QLQ-C30, bPSQI and ESS questionnaires, along with face-to-face reviews, were completed at baseline (n = 20, 100%), at the end of week 4 (n = 18, 90%), and at the end of week 8 (n = 16, 80%). 15 participants (75%) repeated wrist and thigh accelerometry. Comparison accelerometry data, between baseline and repeat monitoring periods, was available for 14 participants (70%).

Bi-directional contact was possible each week for 6 of the participants (32%), with 13 of the remaining participants (68%) missing between 1 and 3 contacts. In this instance, goals were re-iterated, and any potential further improvements suggested over an email or text. Contact was completely lost with one participant after the 1st week.

5.4.1.3. Engagement with interventions

The four lessons of the CBT-I course, along with completion of the ISI and KPS questionnaires prior to each lesson, were achieved for 15 participants (75%). The course was completed during week 4 (n = 5), week 5 (n = 3), week 6 (n = 2), week 7 (n = 3), and week 8 (n = 2).

Engagement with light therapy and the activity plan was self-reported, with objective evidence of physical activity captured during face-to-face reviews. Engagement with the CBT-I course was possible through the THIS WAY UP website.

15 participants (79%) reported engaging daily with bright light therapy, except whilst an inpatient or on holiday. 3 participants (16%) reported using bright light therapy intermittently, and one participant (5%) reported not using the bright light therapy.

17 participants reported engaging with the activity plan and the majority made progress from reviewing watch data. Participants reported struggling with the

activity plan intermittently due to anticancer side effects (n = 2), an inpatient admission (n = 1), lack of motivation (n = 1), and the weather (n = 1).

5.4.1.4. Participant acceptability, ease of use and feedback

Participant views on usability and acceptability were achieved for 16 participants. Both clinical reviews and the weekly researcher reviews were reported to be easy and acceptable to all 16 participants.

Most participants reported that the CBT-I course was easy to use (n = 15, 94%) and acceptable (n = 16, 100%). One participant had repeated difficulty logging in to the website, whilst several others reported some difficulty with this task. Positive feedback of the CBT-I course primarily related to its use as an educational tool, particularly in relation to sleep hygiene, setting a routine and learning new techniques. Participants noted the information and summaries were helpful. The material was delivered concisely, and they liked the visual displays. Two participants felt the course did not relate to their situation and one participant felt they already knew most of the course material. One participant noted the course to be repetitive, one felt there were too many questions following each lesson and another felt the summary sheet alone would have been sufficient. The Australian nature of the course was highlighted as a negative for two participants, including a participant with high levels of distress.

All participants reported that the bright light therapy was easy to use and acceptable.

Participants noted that it was helpful when it became part of a daily routine, and reported the light box to be relaxing, energising and that it improved mood. Participants also noted it increased alertness and helped with motivation. Two participants reported buying their own devices for use after the study. “Negative” aspects included two participants noting that it was easy to forget to use the light box. One participant and a family member felt that the light was very bright. Two participants noted not feeling any instant benefit from the light box. One participant noted that the weather was likely to impact the use of light therapy and its

effectiveness. During sunny mornings, one participant opted to be outdoors as opposed to use the light box.

Most participants found the physical activity plan and Polar watch easy to use (n = 15, 94%) and acceptable (n = 16, 100%). Many participants noted that the watch was motivating, helped with goal setting and planning their days, particularly during bad weather. Participants noted that goal setting was helpful in providing a focus and motivation. One participant noted that it gave increased awareness of their current sleep and activity levels. Three participants found it difficult to engage with the activity plan due to fluctuating health. One participant was concerned with watch off-time during charging and the watch not capturing their activities. One participant noted increased sweating around the watch, and another noted skin irritation. One participant felt that the watch activity did not always match up to actual activity and another felt the watch had too many functions making it a busy visual display.

If participants were to be involved in design of the study, suggested changes included a more tailored CBT-I course, incorporating cognitive activity as well as physical activity into a plan, to consider a daily diary or tick box, and to reduce research involvement over time with increasing responsibility for the participant.

Other feedback:

- A weekly check in was needed
- A partner was useful in encouraging activity
- The charger for the polar watch is very small and easy to lose
- One participant felt they could have completed tasks in a timelier fashion and that they struggled with motivation
- One participant struggled to remember to use the event marker and found the patient diary difficult to follow
- One participant felt they struggled to engage with the study due to clinical deteriorations
- One participant felt the study was great and could have useful earlier in the cancer journey, neuropathy during the study had been a big set back

5.4.1.5. Adverse events and changes to patient factors

During the feasibility study, three participants had progression of disease. This led to discontinuation of anticancer therapy (n = 2), and a change in anticancer therapy (n = 1). One participant had their anticancer therapy dose reduced due to side effects and one participant received radiotherapy for a known progression of disease prior to starting the study. Several participants noted recurring side effects of anticancer therapy during the study which they felt impacted on sleep and daytime activity.

6 participants developed an infection during the feasibility study (presumed viral n = 3, presumed bacterial n = 3). This resulted in the prescription of antibiotics for 3 participants. 4 participants were admitted to hospital during the study bowel obstruction (n = 1), constipation (n = 1), diarrhoea (n = 1), infection (n = 1). One participant had a fall which did not require a medical review. No adverse events were felt to be related to the intervention.

5.4.2. Secondary outcomes

5.4.2.1. Participant's interests and perceived barriers to physical activity

Varied interests were noted by participants and were divided into physical and social activities (Table 27). Reported barriers to engaging with physical activity included physical, psychological and social factors (Table 28).

Table 27. Participant reported interests in physical and social activities.

Physical	Social
Walking (n = 16)	Meeting up with friends (n = 5)
Cooking / baking (n = 4)	Going out for a meal / coffee (n = 4)
Gardening (n = 4)	Going shopping (n = 3)
Reading (n = 4)	Going to the cinema, gallery, museum or theatre (n = 3)
Housework (n = 3)	Spending time with partner
Yoga (n = 3)	

Biking, incl. indoor biking (n = 2) Swimming, incl. sea swimming (n = 2) Dancing DIY Drawing Dress making Jigsaws Knitting Light jogging Listening to music Model airplanes Physiotherapy Playing the piano	

Table 28. Participant reported barriers to physical activity.

Physical	Psychological	Social
Physical fatigue / energy levels (n = 16) Pain (n = 5) Being unwell (n = 2) Breathlessness (n = 2) Chemotherapy symptoms Constipation Diarrhoea Low immune system Numbness in feet Sweats / hot flushes Vaginal discharge	Motivation (n = 5) Fear of falling (n = 3) Cognitive fatigue (n = 2) Anxiety Poor concentration	Social isolation The weather Unable to drive Work-related e.g. having to take equipment to work

5.4.2.2. Outcome of the clinical review

Potentially reversible factors which may have contributed to rest-activity rhythm disruption were discussed during the clinical review and resulted in patient education focussed on symptom management (n = 18, 90%), medication management (n = 14, 70%), or lifestyle factors such as caffeine and alcohol intake (n = 8, 40%). It also led to the prescription of a new medication (n = 6, 30%), or the advice for ongoing monitoring/further investigation by the clinical team (n = 3, 15%).

5.4.2.3. Patient reported clinical outcomes

5.4.2.3.1. MSAS-SF

The average number of symptoms, and number of psychological symptoms alone, improved significantly over time ($p = 0.04$ and $p = 0.03$) (Table 29).

Table 29. Change in MSAS-SF reported symptoms over time.

	Total Symptom	Physical Symptoms	Psychological Symptoms
Mean number of symptoms at baseline (SD)	13.53 (5.17)	11.13 (4.70)	2.33 (1.29)
Mean no. of symptoms at week 4 (SD)	11.87 (6.36)	10.00 (5.45)	2.00 (1.69)
Mean number of symptoms at week 8 (SD)	9.67 (5.77)	8.53 (5.03)	1.33 (1.40)
Significance	$p = 0.04$	0.103	$P = 0.026$

SD: standard deviation

Changes in the frequency of symptoms over time are reported (Table 30). Notable improvements include less difficulty concentrating, lack of energy, feeling drowsy and difficulty sleeping.

Table 30. Frequency of symptoms in the last week at baseline and week 8.

Symptom	Frequency (baseline vs. week 8)
Physical	
Difficulty concentration	60% vs. 33%
Lack of energy	100% vs. 80%
Pain	60% vs. 60%
Cough	33% vs. 27%
Changes in skin	20% vs. 20%
Dry mouth	67% vs. 53%
Nausea	40% vs. 27%
Vomiting	20% vs. 7%
Feeling drowsy	73% vs. 47%
Numbness in hands and feet	53% vs. 47%
Difficulty sleeping	67% vs. 27%
Feeling bloated	40% vs. 40%
Problems with urination	13% vs. 0%
Shortness of breath	67% vs. 53%
Diarrhoea	40% vs. 20%
Sweats	47% vs. 40%
Mouth sores	27% vs. 20%
Problems with sexual interest or activity	13% vs. 13%
Itch	20% vs. 20%
Loss of appetite	47% vs. 33%
Dizziness	27% vs. 27%
Difficulty swallowing	13% vs. 7%
Change in taste	33% vs. 27%
Weight loss	13% vs. 0%
Hair loss	27% vs. 33%
Constipation	53% vs. 47%
Swelling of arms or legs	13% vs. 20%
Look like self	33% vs. 40%
Psychological	

Sadness	53% vs. 33%
Worry	80% vs. 53%
Irritable	67% vs. 27%
Nervousness	40% vs. 20%

There was a significant improvement in GDI scores between baseline and week 8 GDI (1.52 vs. 0.85, $p = 0.023$, Table 31, Figure 21).

Table 31. Change in global distress index (GDI) scores over time.

	Mean Global Distress Index scores (standard deviation)
Baseline	1.52 (0.72)
End of week 4	1.17 (0.78)
End of week 8	0.85 (0.46)

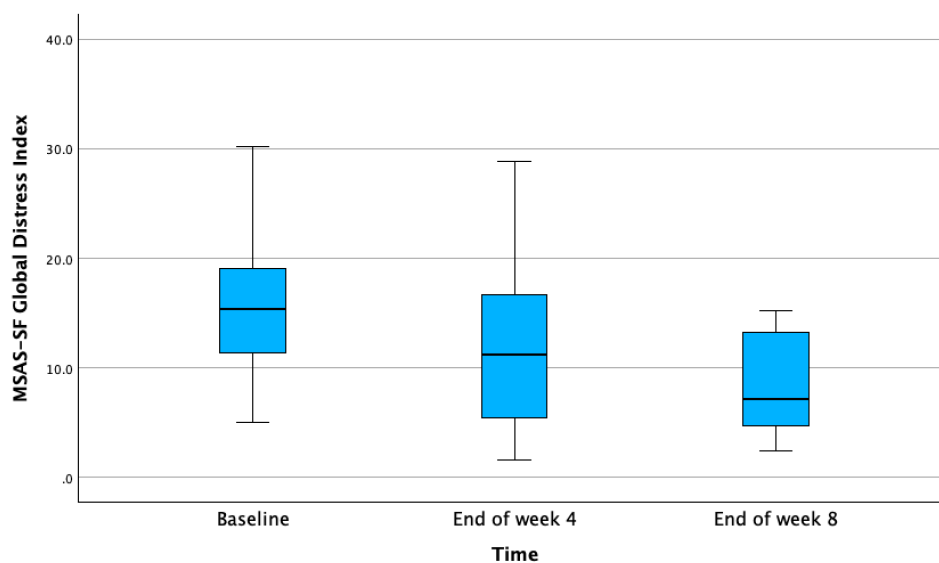


Figure 21. A boxplot demonstrating global distress index (GDI) scores over time. Average GDI scores reduced from baseline to week 4 and to week 8. The spread of data also reduced over time towards more participants reporting lower GDI scores.

There was also a significant improvement in Physical Distress Scores (0.73 vs. 0.60, $p = 0.011$, Figure 22) and Psychological Distress Scores (1.37 vs. 0.4, $p < 0.001$, Figure 23) over time. By the end of week 8 median distress scores had reduced from baseline and week 4.

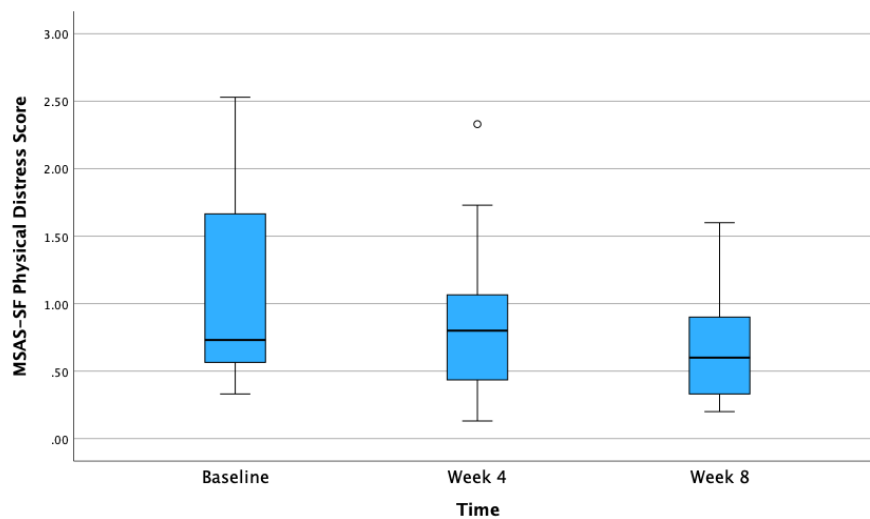


Figure 22. Boxplots of MSAS-SF Physical Distress Scores at baseline, the end of week 4 and the end of week 8. The boxplot shows an initial increase in the average physical distress scores between baseline and week 4, before a further reduction in the physical distress score by week 8. The interquartile range, demonstrating spread of the data, narrows over time with more patients having lower physical distress scores.

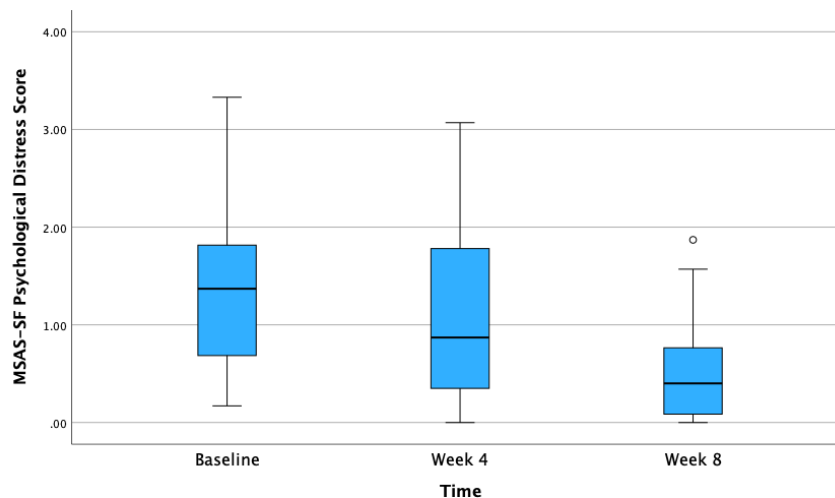


Figure 23. Boxplots of MSAS-SF Psychological Distress Scores at baseline, the end of week 4 and the end of week 8. The average psychological distress scores are shown to reduce progressively between baseline, week 4 and week 8 assessments. The interquartile range, a measure of spread of the data, narrows over time with more patients having lower psychological distress scores.

5.4.2.3.2. EORTC-QLQ-C30

Fatigue and insomnia scores significantly improved over time ($p = 0.003$ and $p = 0.021$ respectively, Figures 24 and 25).

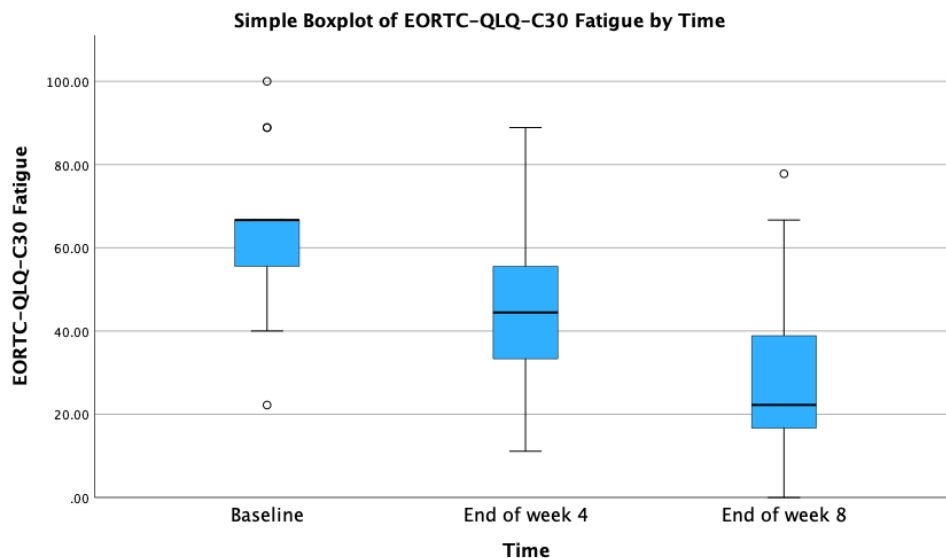


Figure 24. Boxplot of EORTC-QLQ-C30 Fatigue scores at baseline, the end of week 4 and the end of week 8. Average scores for fatigue are shown to reduce between baseline, week 4 and week 8 assessments. Data also becomes more skewed to lower fatigue scores.

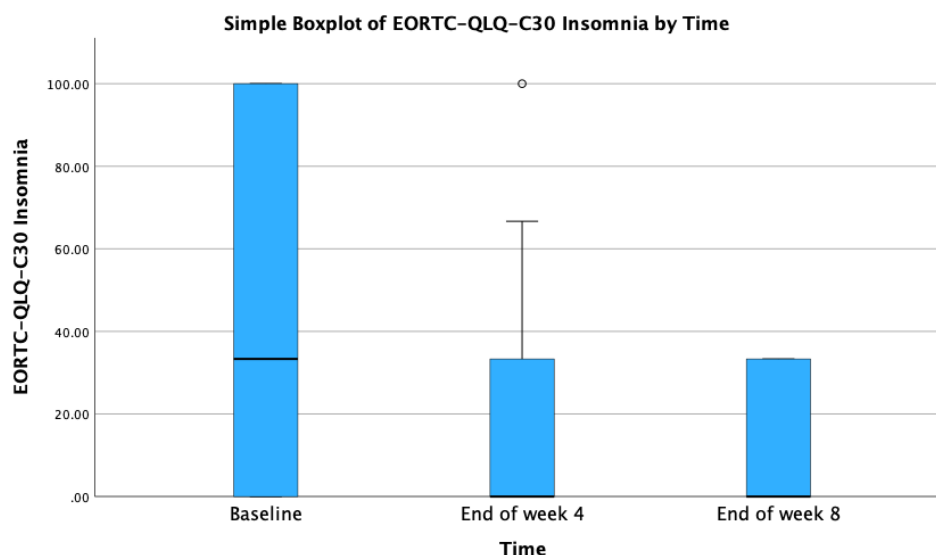


Figure 25. Boxplot of EORTC-QLQ-C30 Insomnia scores at baseline, the end of week 4 and the end of week 8. Average scores for insomnia reduce from baseline to week 4 and remain at the same level between weeks 4 and 8. The spread of the data also reduced between baseline and weeks 4 and 8, with more patients having lower scores.

There were no significant differences in other symptom scores or financial difficulties scores (Table 32).

Table 32. Changes in EORTC-QLQ-C30 symptom scores over time.

	F	NV	P	D	I	AL	C	D	FD
Baseline	Md 66.67 IQR 11.12	Md 0.00 IQR 16.67	Md 16.67 IQR 83.33	Md 33.33 IQR 66.67	Md 33.33 IQR 100	Md 0.00 IQR 66.67	Md 33.33 IQR 66.67	Md 0.00 IQR 33.33	Md 0.00 IQR 66.67
Week 4	Md 44.44 IQR 22.23	Md 0.00 IQR 0.00	Md 0.00 IQR 33.33	Md 0.00 IQR 66.67	Md 0.00 IQR 33.33	Md 0.00 IQR 66.67	Md 0.00 IQR 33.33	Md 0.00 IQR 33.33	Md 0.00 IQR 33.33
Week 8	Md 22.22 IQR 33.33	Md 0.00 IQR 0.00	Md 16.67 IQR 33.33	Md 33.33 IQR 33.33	Md 0.00 IQR 33.33	Md 0.00 IQR 33.33	Md 0.00 IQR 66.67	Md 0.00 IQR 0.00	Md 0.00 IQR 33.33
p value	0.003*	0.961	0.245	0.254	0.021*	0.368	0.296	0.527	0.430

F: Fatigue, NV: Nausea and Vomiting, P: Pain, D: Dyspnoea, I: Insomnia, AL: Appetite Loss, C: Constipation, D: Diarrhoea, FD: Financial Difficulties, Md: Median, IQR: interquartile range, Median (IQR). * represents a significant difference between assessments.

EORTC-QLQ-C30 GHS and functioning subscales scores were considered between assessment periods (Table 33). Significant large effect improvements over time were seen for Physical Functioning (Partial Eta Squared 0.377, $p = 0.046$), Emotional Functioning (Partial Eta Squared 0.496, $p = 0.012$), Cognitive Functioning (Partial Eta Squared 0.541, $p = 0.006$), and Social Functioning (Partial Eta Squared 0.757, $p < 0.001$) subscale scores. Non-significant improvements over time were seen for Global Health Status ($p = 0.234$) and Role Function Subscale ($p = 0.307$).

Table 33. Changes in EORTC-QLQ-C30 global health status and functioning subscales over time.

	GHS	PFS	RFS	EFS	CFS	SFS
Baseline	57.22 (SD 21.10)	65.78 (SD 14.45)	58.89 (SD 37.20)	77.22 (SD 17.39)	77.78 (SD 26.48)	38.89 (SD 36.00)
End of week 4	59.44 (SD 21.10)	73.78 (SD 15.01)	64.44 (SD 32.65)	76.11 (SD 19.64)	72.22 (SD 26.48)	66.67 (SD 30.86)
End of week 8	64.45 (SD 19.02)	75.11 (SD 13.21)	76.67 (SD 31.37)	87.22 (SD 10.85)	84.44 (SD 17.21)	83.33 (SD 21.82)
p value	0.234	0.046*	0.307	0.012*	0.006*	<0.001*

GHS: global health status, PFS: physical functioning scale, RFS: role functioning scale, EFS: emotional functioning scale, CFS: cognitive functioning scale, SFS: social functioning scale. SD: standard deviation. * represents a significance difference between assessments.

5.4.2.3.3. Psychological distress (Kessler Psychological Distress Scale K-10)

15 participants completed the KPS on four occasions. The KPS score improved for 73% of participants and there was a significant reduction in the distress scores over time (Mean 20.80 vs. 16.01, $p = 0.013$, Eta squared 0.524). The KPS category also improved for 60% of participants.

5.4.2.3.4. Sleep quality (brief Pittsburgh Sleep Quality Index (bPSQI) and Insomnia Severity Index (ISI))

bPSQI scores reduced over time but were not significantly different ($p = 0.169$). Between the initial and final ISI assessments, the ISI score improved for 87% and there was a significant reduction in ISI scores between baseline and week 8 (Mean 12.93 vs. 8.133, $p = 0.001$). The ISI category improved for 7 participants (47%).

5.4.2.3.5. Daytime sleepiness (Epworth Sleepiness Scale (ESS))

ESS scores between the baseline and final assessments improved for 87% of participants. The change in the baseline and week 8 ESS was significant (mean 7.00 vs. 3.67, $p = 0.03$). The ESS category improved for 60% participants.

5.4.2.4. Objective outcomes

5.4.2.4.1. Accelerometry-derived circadian parameters

Changes in the I/O, r24 and SE values for each participant between the initial and final assessment can be seen in Figures 26-28. Dichotomy index values improved for 11 participants (79%), with improvement of the mean IN bed activity for 7 participants (50%) and improvement of the mean OUT of bed activity for 11 participants (79%). r24 values improved for 9 participants (64%). SE values improved for 7 participants (50%). At a group level, non-significant improvements were seen for the dichotomy index, IN bed activity, r24, and sleep onset latency (Table 34). Significant improvements were seen in OUT of bed activity ($p = 0.045$).

Table 34. Changes to accelerometry-derived circadian parameters between the initial and final assessment

	Initial assessment	Final assessment	Trend	Sig.
I<O	89.67 (5.19)	91.17 (5.71)		p = 0.407
In bed activity	44.45 (25.96)	43.18 (18.36)		p = 0.773
Out of bed activity	149.55 (36.00)	162.88 (40.15)		p = 0.045
r24	0.30 (0.12)	0.31 (0.16)		p = 0.664
SE	80.84 (13.38)	79.02 (12.57)		p = 0.557
PSLP	68.24 (18.88)	67.78 (13.88)		p = 0.891
SOL	66.43 (83.29)	45.64 (41.88)		p = 0.198
WASO	92.26 (65.02)	101.83 (54.28)		p = 0.571

The green dot represents improving values between the initial and final assessment, whilst the red dot represents worsening values between the initial and final assessment. I<O: dichotomy index, r24: 24-hour autocorrelation coefficient, SE: sleep efficiency, PSLP: percentage sleep, SOL: sleep onset latency, WASO: wake after sleep onset, Sig.: significance

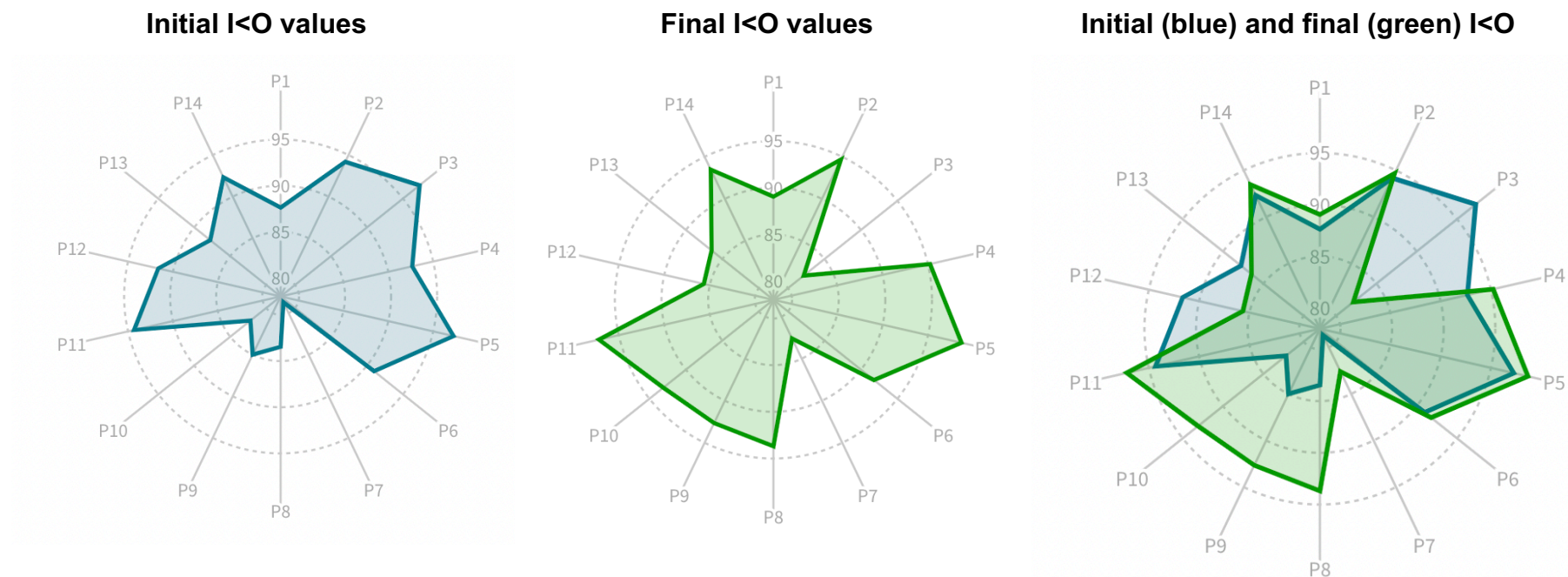


Figure 26. A comparison of dichotomy index (I<O) values for individual participants between the initial and final assessment. Blue represents I<O values from the initial assessment (left), green represents I<O values from the final assessment (middle), and green superimposed on blue represents I<O values from both assessment points (right).

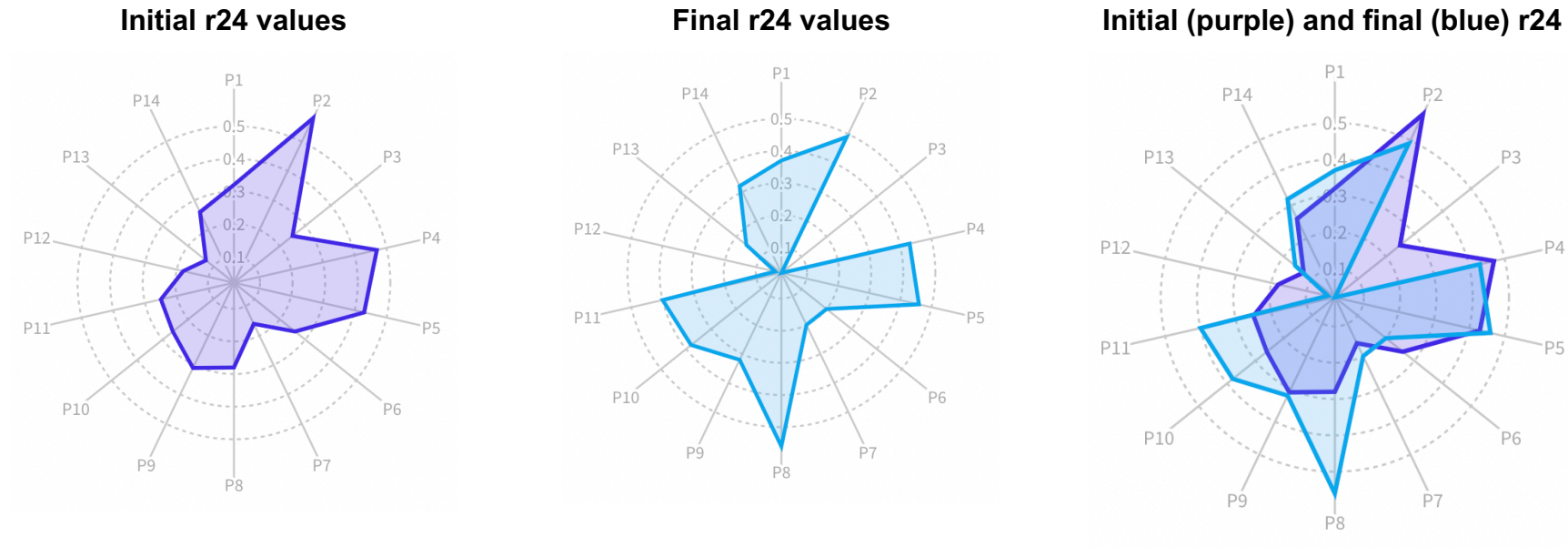


Figure 27. A comparison of 24-hour autocorrelation coefficient (r24) values for individual participants between the initial and final assessment. Purple represents r24 values from the initial assessment (left), blue represents r24 values from the final assessment (middle), and blue superimposed on purple demonstrates r24 values from both assessment points (right).

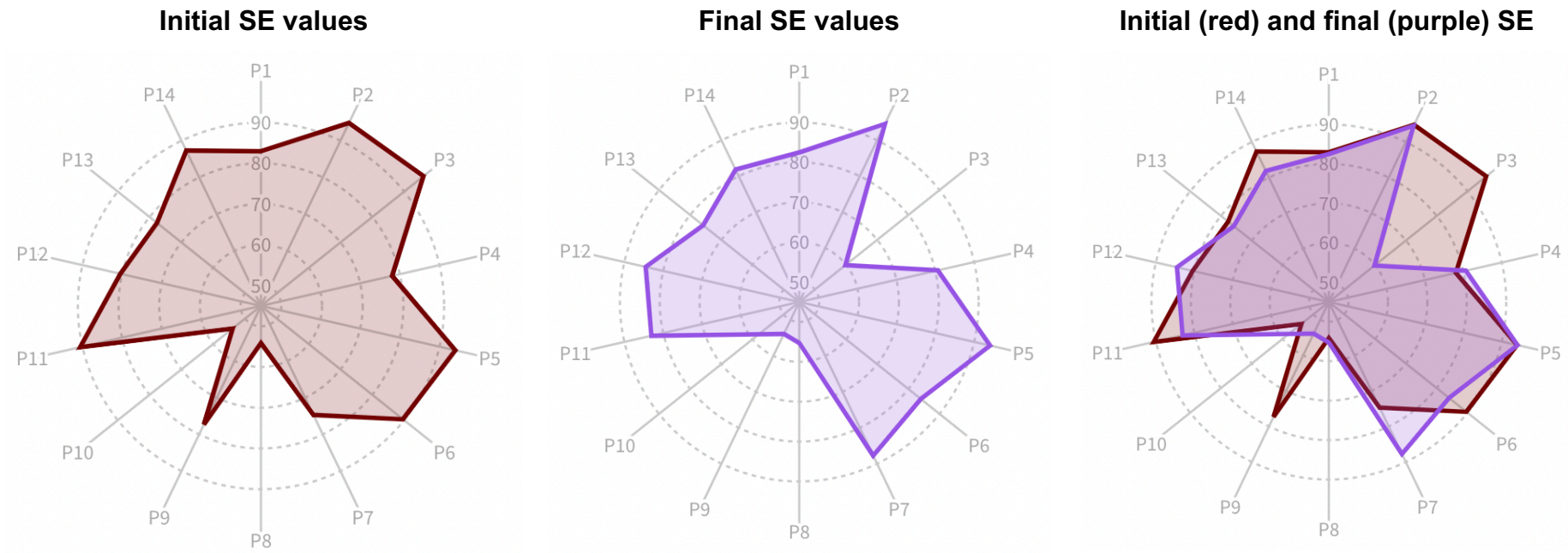


Figure 28. A comparison of sleep efficiency (SE) values for individual participants between the initial and final assessment. Red represents SE values from the initial assessment (left), purple represents SE values from the final assessment (middle), and purple imposed on red represents SE values from both assessment points (right).

5.4.2.4.2. Daytime physical activity

At a group level several measures of interest improved by varying degrees, although changes were not statistically significant (Table 35).

Table 35. Changes to daytime physical activity parameters between the initial and final assessment periods

	Initial assessment	Final assessment	Trend	Sig.
Average daily steps (SD)	4301 (2562.20)	4984 (3553.03)		0.157
min – max	508 – 13102	146 – 16092		
Average sum of steps over 3 days (SD)	12890 (7667.42)	14950 (10659.10)		0.155
Average daily sit to stands (SD)	41.06 (18.67)	41.11 (15.21)		0.984
min - max	11 - 99	8 – 91		
Average daily sitting time (SD)	20.79 (1.48)	20.27 (1.62)		0.069
min - max	17.00 – 23.40	15.10 – 23.80		
Average daily standing time (SD)	2.28 (1.09)	2.61 (1.17)		0.102
min - max	0.40 – 5.00	0.10 – 6.50		
Average daily active time (SD)	1.00 (0.54)	1.07 (0.61)		0.521
min - max	0.10 – 3.70	0.00 – 3.00		

The green dot represents improving values between the initial and final assessment, whilst the red dot represents worsening values between the initial and final assessment. SD: standard deviation, Sig.: significance, min-max represents the daily minimum and maximum values across all participants during that assessment period.

5.5. DISCUSSION

This study assessed the feasibility of a multimodal intervention for circadian rest-activity rhythm disorders. The study considered the recruitment and retention ability, and the completion of study procedures and assessments. It also gained preliminary clinical outcome data with regards to patient reported symptoms and quality of life, and objective measures of circadian rest-activity rhythm parameters alongside daytime physical activity. Furthermore, the study outlined patient interests in, and barriers to, physical activity.

5.5.1. Key findings

The intervention was not feasible in reaching the target of 30 participants over a one-year period. Recruitment to the trial was limited by patient-related factors (predominantly clinical deteriorations or patient's having other priorities) and researcher-related factors (single researcher performing all study procedures across sites). Although chapter 4 highlighted a prevalence of 60% in those with advanced cancer, the identification of eligible participants is protracted, requiring a 1-week assessment period followed by data analysis to identify a CARD. The recruitment rate (51%) is similar to exercise interventional studies in patients with advanced cancer (51% vs. 49%) and interestingly time constraints, as noted in this study, have been reported as a barrier to engagement in similar studies (324). An attrition rate of 20% was largely unavoidable due to the clinical deterioration often seen in this patient cohort, which occurred at various stages in the trial, rather than patient preference or resulting from the intervention. Similar attrition rates (24%), primarily due to progression of disease, in other exercise interventional studies has been reported (324).

Individual interventions and the study procedures were deemed acceptable and usable by participants, and an adequate completion of research assessments was seen for patient reported outcomes (80%) and objective measures (70%). However, consistent weekly contact between these assessments was not possible for most. Such intensive engagement may also not be feasible on a larger scale and requires additional resources. Participant feedback noted an increasing need

for independence and self-motivation as the study progresses, this would reduce researcher burden.

Participant feedback also highlighted a range of individual interests and barriers to physical activity. Although most patients identified walking as a physical activity of interest, when developing a physical activity goal, the majority did not choose walking as a focus. Instead, most patients chose to use the Polar watch's activity goal and incorporated several activities to reach this. Additionally, most participants identified social activities as a source of physical activity. This re-iterates the need for behavioural interventions to be tailored, rather than being standardised, where previous work has suggested personalising activities based on intensity, frequency, duration and modality of activity (308, 311). This study incorporated indirect supervision of general physical activity with preliminary data noting improvements in physical function and quality of life measures. This has also been reported in more formal exercise programmes and, during such trials, superior improvement has been reported if supervised exercise is incorporated (325).

The study was not adequately powered to detect significant changes in clinical outcomes. However, preliminary data demonstrates clinical improvements across the study for patient-reported and objective measures. This included improvements in daytime sleepiness (ESS), all distress scores (MSAS-SF) and the number of symptoms identified by MSAS-SF. Similarly, all symptoms improved when assessed using the EORT-QLQ-C30. This was most marked for fatigue and insomnia, and less so for nausea and vomiting and diarrhoea. Furthermore, the Global Health Status and all functioning subscales improved. When considering circadian participants in the study, the I<O was most likely to improve, followed by the r24 and finally the SE. OUT of bed activity improved more than IN bed activity. At a group level, the I<O and r24 improved, but the most sleep parameters (SE, PSLP and WASO) worsened. Average daily steps, time spent sitting, standing and being active also improved at a group level. Chapter 4 highlighted that subjective sleep disturbance, or poor sleep quality, did not relate to objective measures of sleep and interestingly, the multimodal intervention improved subjective measures more markedly than objective measures.

Similar findings are noted when considering individual interventions. Bright light therapy positively impacts sleep quality and fatigue, whilst having limited impact on SE and SOL (326). However, additional improvements in WASO were not noted in this study (326). The r24 did improve for 64% of participants receiving BLT and previous work has demonstrated improved rest-activity rhythm variability, which can be reflected by the r24, with the use of BLT (292, 294). The use of BLT has also been shown to stabilise, rather than improve, sleep parameters which without intervention otherwise deteriorate (295). This study, using a multimodal approach, may suggest superiority compared to single interventions as, for some patients with advanced cancer, improvements rather than stability, were possible for several parameters.

Similarly, research has shown that CBT-I can improve sleep quality, but also SE, SOL and WASO in patients with cancer (299, 300, 302). Although this study showed a positive effect at reducing SOL, this was not significant, and no improvements were noted in SE or WASO. When considering changes in activity, this study demonstrated a significant improvement in out of bed activity and non-significant improvements in steps, time standing and time being active. Research has shown how those with improved activity levels tend to have lower symptom burden and better QoL measures (305, 307). The impact of activity on circadian rest-activity rhythm parameters has been varied in previous research, but reports of improved r24 and I<O are supported by this study (42, 315). Research suggests positive effects of exercise on clinical outcomes lasting at least 8-12 weeks (307). Long-term exercise is a strong entrainer of circadian rhythms and it is unclear if 8-weeks is a sufficient period, or indeed if more prolonged interventions have any additive effects. As research has shown the beneficial effect of the included interventions on the clinical outcomes of interest, it remains unknown if this is a direct effect or is mediated by improved circadian rhythmicity. Recent work following patients for 5-years after treatment for colorectal cancer demonstrated that improved circadian rhythm consistency (r24) and a marked difference in day and night activity (I<O) was associated with improved quality of life, less fatigue and less insomnia (25).

Several entrainers are noted in this thesis, particularly light and physical activity. Although participants were advised to use bright light therapy upon waking, a time restriction was not placed on physical activity and several participants spread their activity across the waking day. Patients with advanced cancer often experience fatigue, as seen in this study, and pace their activities across the day. In this study participants often chose to combine several activities when using the Polar watch activity goal as a target or measure of activity, rather than performing a single exercise at a prescribed time. It is useful to therefore recall that timing of exercise has the potential to advance, delay, increase or decrease markers of circadian rhythmicity and this time-related information should be considered in both the delivery of interventions and in data collection (327). It remains unclear what the optimal timing of physical activity is to re-synchronise circadian rhythmicity.

Of note, previous work has demonstrated the benefit of individual interventions. As this was a single arm trial, an understanding of the contribution from each intervention is not possible. A recent study compared multimodal therapy (primarily sleep education and psychoeducation), multimodal therapy combined with aerobic exercise, and aerobic exercise alone in breast cancer survivors experiencing cancer-related fatigue, and supports the concept of superiority for multimodal and multimodal-combined groups with respect to sleep quality, but not to fatigue (328). Future work should consider multiple arm trials with randomisation to explore the contribution of individual interventions further.

This study was carried out in a group of patients with advanced cancer. It remains unknown how susceptible patients with CARDs are to different circadian entrainers, and how this may change across the cancer trajectory. Future research should consider the impact of individual and multi-modal interventions, across cancer groups, at various stages, to assess susceptibility to intervention and if CARDs may become refractory to intervention.

5.5.2. Strengths and limitations

The feasibility study recruited predominantly participants that were female, receiving anticancer therapy, and had an ECOG performance status of 1. This

limits the findings of the study to the wider population of patients with advanced cancer.

Research has demonstrated the varied impact of anticancer therapies on symptoms, quality of life and circadian rhythms (225). Such clinical outcomes are also subject to influence from an array of factors which undoubtedly change during an individual's time within a study, particular with regards to clinical deterioration and acute illness. Their treatment plans also change over time and are individualised, in frequency and duration, particularly between cancer groups. When assessing participants in a standardised manner during a clinical trial, it is therefore difficult to capture participants at a similar timepoint in relation to their anticancer therapy for separate research assessments (i.e. monitoring a participant 1-week after chemotherapy at baseline and again during the repeat monitoring) when the study has a fixed timing schedule for all. Capturing patients at different time points, in relation to anticancer therapy delivery or acute deteriorations for example, has the potential to be more impactful on outcomes of interest than the interventions themselves and may mask any significant change.

This study took place over a 1-year period and thus several seasons. Timing of the year is a potential bias to be mindful of, particularly in any future study, and equal representation between sub-intervention groups across seasons should be considered or accounted for in the analysis. Sunlight exposure, along with the ability and psychological willingness to engage in physical activity, is likely to differ depending on the weather and timing of year. The engagement with interventions such as bright light therapy is also likely to differ, as shown in this study, depending on the outdoor weather, with participants potentially opting for authentic light exposure during warm, sunny days instead. A degree of flexibility and pragmatism was allowed for participants but capturing the frequency of light box versus natural sunlight exposure would be helpful in future research. Research has demonstrated that the weather, and temperature changes seen during the year, impact the timing of sleep and wake times, alongside the duration of sleep periods (329). Time in sedentary activities and bed have also been shown to be significantly higher during winter months, whereas low-level physical activity tends to be higher during the

spring and summer months (330). This information should be captured and considered in future circadian rest-activity rhythm studies.

A limitation of the study is the reliance on self-reported measures of engagement with light therapy and lack of standardisation in its delivery. Objective measures of engagement with the CBT-I course and physical activity were possible within the study, but there were no objective measures of engagement with light therapy. Although participants were provided with the same instructions for use, it is unknown how similar participants were with regards to distance from the light source, or the duration and frequency of bright light therapy. This is perhaps more pragmatic and reflective of real-life conditions, but when considering impact on outcomes of interest, there is perhaps a lack of standardisation in its use. Several approaches to bright light therapy in patients with cancer have been trialled with varying light intensity and wavelength, duration and delivery form, and the optimum approach remains unknown (326). It is also unclear how different cancer groups or underlying circadian pathologies respond to bright light therapy (326). Standardised sleep hygiene advice was also provided through patient information leaflets, regular reviews and the CBT-I course. Regular sleep-wake timing was encouraged but strict enforcement may not be possible in this patient group.

Participants noted a lack of motivation to be a barrier to physical activity. Similarly, a recent study on patients with advanced cancer noted that motivation and pre-existing physical activity levels were within the top 6 patient-reported barriers (331). This study did not assess premorbid physical activity or motivation levels, and this may be an important factor when considering retention rates, engagement with the intervention, and the scope for improvement in activity levels.

The study included baseline and repeat assessments at the beginning and end of the study. It did not include a third assessment after the study, and this would need to be considered in a future study to consider the longevity of any effect. As thigh accelerometry allows for an objective measure of DOWN and UP times, as well as a prolonged period of monitoring, this could be carried out as a more continuous process throughout the intervention, rather than isolated assessment periods and

may reduce participant burden compared to wrist accelerometry, event marker operations and patient diary completion.

The study has also relied on the accurate identification of patients with a CARD. Although a standardised assessment approach and diagnostic criteria exist, there is still a lack of uncertainty as to the optimum accelerometry devices and data analytical software to be used.

5.5.3. Conclusion

This study demonstrated how a multi-modal intervention, consisting of a CBT-I course, bright light therapy and personalised physical activity plan, was usable and acceptable to participants with advanced cancer. Recruitment and retention rates were similar to other related studies. Promising results were found on the clinical impact of the multi-modal intervention with respect to symptoms, symptom distress, sleep and daytime activity. Future studies should delineate the contribution of individual interventions when used within a multi-modal approach.

CHAPTER 6: DISCUSSION OF THE ASSESSMENT, IDENTIFICATION AND MANAGEMENT OF CIRCADIAN REST-ACTIVITY RHYTHM DISORDERS IN PATIENTS WITH ADVANCED CANCER

6.1. SUMMARY OF INDIVIDUAL CHAPTERS

Chapter 1 outlined the physiology and assessment of circadian rhythms, particularly in relation to patients with cancer, and outlined their relevance to this patient group.

Chapter 2 discussed circadian rhythms in patients with advanced cancer, and through a comprehensive scoping review, highlighted significant variation in both the investigational approach and reporting of sleep-wake, rest-activity, cortisol and melatonin rhythms across cancer diagnoses. Studies mainly included, rather than focused on, patients with advanced cancer. Several circadian parameters exist, and a range of parameters have been used within the literature. Disordered circadian rhythms were more apparent in patients with advanced disease and significant associations with symptomatology, quality of life and survival were identified. Several non-invasive measurements of circadian rhythmicity (dichotomy index, 24-hour autocorrelation coefficient and sleep efficiency) appeared to be important.

Chapter 3 detailed approaches to developing consensus, including the Delphi process, and addressed the lack of standardisation in the assessment and reporting of circadian rest-activity rhythms in patients with advanced cancer. Through a 3-round e-Delphi study, several international experts were brought together and developed a consensus on the definition of a circadian rest-activity rhythm disorder, assessment methods and diagnostic criteria. A novel screening tool, based on this newly formed diagnostic criteria was also generated.

Chapter 4 assessed a novel screening tool and the circadian rest-activity rhythms in patients with advanced cancer using subjective and objective tools. An observational study of 65 patients highlighted CARDs to be highly prevalent in this patient group, along with potential risk factors and important clinical associations.

The study found that the diagnosis of a CARD was more significantly associated to clinical outcomes than individual accelerometry-defined circadian parameters. The study failed to demonstrate validity of the novel screening tool. The study generated a wealth of data, with several areas yet to be assessed.

Chapter 5 assessed the feasibility and acceptability of a multi-modal non-pharmacological intervention to improve circadian rest-activity rhythm disorders in 20 patients who were identified to have the CARD diagnosis in the earlier study. The study failed to demonstrate recruitment feasibility but demonstrated acceptability and usability of the intervention. The study also demonstrated preliminary evidence of clinical benefit, perhaps more so for subjective rather than objective measures.

6.2. STRENGTHS AND LIMITATIONS OF THE APPROACHES USED WITHIN THE THESIS

The strengths and limitations of research approaches in this thesis have been addressed in detail within each chapter. However, there are overlapping features which require consideration for the thesis. These mainly include utilising a range of methodological approaches, issues of generalisability, patient and public involvement and knowledge and skill gaps in the field of circadian rest-activity rhythm research.

The thesis is strengthened by using a range of methodical approaches and study designs (scoping review, e-Delphi study, observational study, feasibility study) to further understand circadian rest-activity rhythms in patients with advanced cancer. Observational approaches have provided an insight into the topic area and despite the study highlighting several significant associations with CARDs, the study design is unable to determine causation. It remains unknown whether a cancer diagnosis or CARD precedes the other, further confounding the understanding of causation. The thesis also lacks a qualitative approach which would have provided more understanding of the patient perspective in those at risk of, or who are currently experiencing, circadian rest-activity disruption. A qualitative approach

should be considered in a future study, which may focus on eliciting the patient's beliefs, drivers and barriers to sleep, rest and physical activity.

Despite an array of approaches, each study had a relatively small final sample size (e-Delph (n = 13), observational study (n = 65), feasibility study (n = 20). Subgroups (i.e. cancer diagnoses) were even smaller and it is therefore difficult to fully extrapolate the findings within this thesis to all patients with advanced cancer. The work within this thesis could be strengthened by: 1) externally validating the recommendations arising from the e-Delphi study; 2) carrying out a larger observational study of patients with a range of advanced cancers, considering risk factors and associations with a CARD diagnosis; and 3) carrying out a larger more definitive feasibility study with randomisation of several arms to allow for confounding variables and to elicit the contribution of each intervention compared to the standard of care.

The inclusion and exclusion criteria in the observational study ultimately impacted, and was expanded upon for, the feasibility study. The criteria were appropriately defined and justified with rationale focus on safety for participants and suitability in clinical practice. The criteria aimed to be broad to allow more generalisable findings from the observational and feasibility studies. However, it has been noted that most recruited participants were of a white Irish background and had a performance status of 1-2. A larger study with a more diverse cohort of patients with advanced cancer is required to further understand the contribution of a range of patient-related factors. It should also be noted that there is an inherent bias in recruiting participants to studies that involve physical activity, whereby those who are interested, willing and able to participate in studies, of either an observational or interventional nature, likely display different behaviours to those who do not.

Circadian rhythms are complex and multifactorial in nature which makes it difficult to fully control for confounding variables. This thesis has used a comprehensive approach to patient assessment considering a vast range of potential confounding factors before making preliminary conclusions. Research within circadian rhythms is rapidly progressing and will hopefully identify any additional significant confounding factors to consider in future research studies. This approach needs to

be balanced against a pragmatic and flexible approach, particularly in this patient cohort, to reduce burden to participants and to allow for a real-life picture. The use of multi-arm interventional studies, whilst employing randomisation, will allow for confounding variables, known and unknown, to be considered. There is also an inherent risk of bias in the observational and interventional studies of a behavioural aspect (i.e. rest-activity rhythms). Participants may display more desirable behaviours whilst being knowingly observed and indeed those who are recruited to behavioural trials may be habitually different to those who feel uninterested or unable to take part. Blinding is also inherently difficult in any behavioural intervention such as physical activity. Researcher bias is also possible in the observational and feasibility study as all study procedures, data processing and analysis has been completed by a single, unblinded researcher. Future studies should consider incorporating a blinded assessor.

The thesis received input from outside of the primary research team at several points. Patient and Public involvement (PPI) was achieved through the Voices4Care team (of All Ireland Institute for Hospice and Palliative Care), who reviewed and provided feedback on study protocols and patient information documentation, ensuring the material was accessible and understandable. It also provided insight into the appropriateness of planned study procedures. Their feedback was valued, considered and taken onboard. Furthermore, feedback was encouraged from participants within the feasibility study on their perception of acceptability and usability of interventions, alongside the strengths and weaknesses of the interventions and study procedures. Participants also proposed adjustments to the study design, which will help to shape a future definitive study. This feedback could have been strengthened by carrying out interviews or focus groups with included participants. The thesis did not include PPI in the original design of the studies, including in the generation of research topics and key questions to address.

The e-Delphi also allowed for a collaborative approach and engaged several leaders in this research field. Patients were not involved in e-Delphi study as it focused on specialist and technical processes. However, the resulting

recommendations may have benefited from PPI in relation to the acceptability of proposed assessments and additional areas for consideration.

PPI should be embedded within research institutions and follow appropriate standards (332). In the event of a larger definitive study, PPI will be encouraged and incorporated through all research stages, in a collaborative manner with shared decision-making. PPI involvement should be inclusive, ensuring representation of underrepresented groups, and aim for transparency and clear communication amongst key stakeholders, including members of the public. In the event of complex processes or concepts, PPI members should be supported and provided with adequate training and resources to meaningfully engage with processes.

A significant gap within the research, noted throughout the thesis, is a lack of standardisation. This was initially highlighted in a lack of standardisation in the assessment and reporting practices with regards to circadian rest-activity rhythms. Although the thesis has tackled an area of this (the definition, assessment approach, and diagnosis), it has not addressed the issue of standardising the devices, data processing and data analysis, which is of importance when trying to further understand circadian rest-activity rhythms. As a final example, when assessing time in sedentary, light, moderate and vigorous physical activity, a recent study found correlations of 0.317 and 0.995 between different data processing packages (333). The study then demonstrated the impact different processes can have on calculating parameters where, as an example, time in sedentary activity ranged from 633 to 1147 minutes per day (333). Without standardisation, it is difficult to correctly identify normal and abnormal rhythms, and their associations. It is also difficult to accurately assess circadian rest-activity rhythms pre- and post-interventions.

6.3. GAPS WITHIN THE EXISTING LITERATURE AND IMPLICATIONS OF THE THESIS

The observational study has generated a wealth of data, and several areas are yet to be addressed. This includes:

1. The predictive validity of a sleep and physical activity diary compared to objective accelerometry
2. The acceptability, ease of use and understandability of the sleep and physical activity diary
3. The assessment of the most accurate and feasible method to determine DOWN and UP times in patients
4. The assessment of the impact of varying DOWN and UP times on the calculation of circadian parameters
5. The comparison of wrist and thigh accelerometry in the assessment of circadian rest-activity rhythms
6. The assessment of predictive models of an objective circadian rest-activity rhythm disruption and a CARD diagnosis

The thesis has also identified several areas for ongoing research, this includes:

CARDs:

1. What role does ethnicity play in determining circadian rest-activity rhythms in patients with advanced cancer?
2. What role does different cancer diagnoses play in determining circadian rest-activity rhythms in patients with advanced cancer?
3. What are the risk factors for patients with cancer in developing a CARD?
3. Is there a simpler way to identify CARDs, allowing easier recruitment to clinical trials and easier identification in clinical practice?
4. What are the similarities and differences in circadian rest-activity rhythms and disturbances between patients with cancer and other life-limiting illnesses?

Methodology:

1. What is the most accurate, and most feasible, way to detect in-bed and out-of-bed timing?

2. What is the optimum method of processing accelerometry data when assessing circadian rest-activity rhythms?
3. What are the threshold normal and abnormal values for circadian parameters when assessing circadian rest-activity rhythms?
4. How do these threshold values vary between different forms of accelerometry (i.e. wrist and thigh accelerometry)?

Intervention:

1. Do patients with cancer demonstrate varying susceptibility to circadian entrainers at different stages of the cancer trajectory?
2. What is the optimum way to manipulate light when improving circadian rest-activity rhythms (i.e. bright light therapy vs. light blocking glasses)?
3. Are alternative non-pharmacological approaches effective at improving circadian rest-activity rhythm disorders (i.e. controlled feeding-fasting)?
4. How do non-pharmacological approaches compared to pharmacological approaches and standard of care in improving CARDs?

6.4. CONCLUSION

The thesis has advanced the understanding of circadian rest-activity rhythm disorders in patients with cancer, devised a standardised method to assess, diagnose and report circadian rest-activity rhythms in this patient group and assessed a novel screening tool. The thesis has also demonstrated an acceptable and usable non-pharmacological multi-modal intervention with preliminary evidence of positive effect on important clinical outcomes. Furthermore, the thesis has highlighted several areas for future consideration regarding ongoing research, education and training.

PUBLICATIONS ARISING FROM THESIS

Gouldthorpe C, Power J, Davies A. Circadian rhythm disorders in patients with advanced cancer: a scoping review. *Frontiers in Oncology*. 2023;13:1240284.

Gouldthorpe C, Ancoli-Israel S, Cash ED, Innominato P, Jakobsen G, Lévi F, Miaskowski C, Parganiha A, Pati AK, Pereira D, Revell V, Zeitzer J, Davies A. International e-Delphi Consensus Recommendations for the Assessment and Diagnosis of Circadian rest-Activity Rhythm Disorders (CARDs) in Patients with Cancer. *Cancers*. 2023;15(15):3784.

PRESENTATIONS ARISING FROM THESIS

Gouldthorpe C. Overview of circadian rhythm disorders (oral presentation). Moving Points in Palliative Care Conference ('Innovation not stagnation: making the evidence count'). March 2023, Dublin (Ireland).

Gouldthorpe C, Davies A. Circadian disruption in cancer: diagnostic criteria recommendations from the Delphi study (oral presentation). Building an International Multidisciplinary Network Towards Personalized Cancer Chronotherapy Workshop. April 2023, Paris (France).

Gouldthorpe C, Davies A. Recommendations for assessing and diagnosing a circadian rest-activity rhythm disorder in people with advanced cancer: an international delphi process (e-Poster presentation). Multinational Association of Supportive Care in Cancer. June 2023, Nara (Japan).

Gouldthorpe C. Circadian rhythm disorders (lectures x 3). Guildford Advanced Pain and Symptom Management Courses. September & December 2023 (Manchester, London, Dublin).

Gouldthorpe C. Circadian Rhythms in Cancer (oral presentation). Trinity St James's Cancer Institute Christmas Research Blitz. December 2023, Dublin (Ireland).

Appendix 1. Findings from the scoping review

Table 1a. Melatonin circadian rhythms and their associations in patients with advanced cancer

STUDIES WITH A CONTROL GROUP			
Article	Participants	Circadian measures	Outcomes relevant to review
Levi et al, 2020 (35)	“IDEAs” study: 25 (21 M) locally advanced or metastatic gastrointestinal cancer patients, median age 66yr “PicaPill” study: 33 (15 M) control subjects, median age 35yr	6-hour salivary melatonin levels (1900, 2000, 2100, 2200, 2300, 0000) and the dim-light melatonin onset (DLMO), which represents the time melatonin levels rise above a threshold.	Melatonin levels rose from baseline in all participants between 1800 and 2300. Patients with cancer had higher baseline melatonin levels. The rise in melatonin was higher in controls and patients with cancer with relatively less in-bed to out-of-bed physical activity (3-fold low I<O group, 5-fold high I<O group, and 6-fold in control subjects). Patients with cancer and relatively less daytime to night-time activity had earlier DLMOs (1948 vs. 2144, $p=0.08$). Significant inter-individual variation was noted.
Mazzoccoli et al, 2012 (148)	9 (M) stage 2-4 non-small cell lung cancer patients, mean age 51yr 11 (M) control subjects, mean age 44yr	24-hour rhythm of serum melatonin: (0600, 1000, 1400, 1800, 2200, 0200)	A 24-hour rhythm was found in all subjects with a peak concentration at night, and a trough concentration near waking. Mean values did not differ between the groups at any time points.
Hu et al, 2009 (160)	30 (26 M) “advanced” non-small cell lung cancer patients, mean age 60yr 63 (53 M) control subjects, mean age 67yr	Serum melatonin levels and 24-hour rhythm (1200, 0000) and urine 6-sulfatoxymelatonin levels (major metabolite of melatonin) (0700, 1600)	A 24-hour rhythm of melatonin and 6-sulfatoxymelatonin were present in all subjects. Serum melatonin at 0000 was lower in patients than in control subjects ($p<0.05$). Urine 6-sulfatoxymelatonin at 0700 and 1600 was lower in patients than in control subjects ($p<0.05$)
Karasek et al, 2005 (164)	31 (F) stage 0-4 cervical cancer patients, mean age 53yr 14 (F) control subjects, mean age 54yr	Serum melatonin levels and area under the curve (AUC) (0800, 1200, 1600, 2000, 2400, 0200, 0400, 0800)	Cancer patients had significantly lower melatonin levels and area under the curve (AUC) than control subjects ($p<0.05$). “Nocturnal” melatonin levels and the AUC were significantly lower in patients with stage 3-4 cancer compared to patients with stage 0-1 cancer ($p<0.05$).
Mazzoccoli et al, 2005 (107)	17 stage 1-2 non-small cell lung cancer patients, mean age 67yr 17 stage 3-4 non-small cell lung cancer patients, mean age 70yr 17 control subjects, mean age 69yr	24-hour rhythm of serum melatonin and AUC (0600, 1000, 1400, 1800, 2200, 0200, 0600)	A 24-hour rhythm was present in all three groups. AUC levels were lower in cancer patients ($p<0.05$) and lower in cancer patients with a higher cancer stage ($p=ns$)

Muc-Wierzgon et al, 2003 (161)	42 (25 M) "advanced" (metastatic) gastrointestinal cancer patients, mean age 61yr 30 (25 M) control subjects, mean age 57yr	Serum melatonin levels, 24-hour rhythm (0800, 1400, 1800, 2200, 0200, 0800), amplitude (difference between peak and trough levels) and acrophase (time of peak level)	A 24-hour rhythm was noted in all subjects. The maximal peak levels were higher for control subjects, but the minimal trough levels were similar for control subjects and patients. The mean amplitude was higher for control subjects. The acrophase occurred earlier for control subjects (0435 vs. 0850).
Ermachenkov et al, 2013 (167)	89 (49 M) gastric cancer patients (8 metastatic) 86 (31 M) colorectal cancer patients (5 metastatic) Mean age 62yr	Diurnal urinary 6-sulfatoxymelatonin levels	Gastric cancer patients with distant metastases had lower diurnal excretion than patients without distant metastases (231 ± 27 ng/h vs. 422 ± 36 ng/h, $p < 0.001$). Colorectal cancer patients with metastatic disease had lower diurnal excretion than patients without metastatic disease (176 ± 44 ng/h vs. 422 ± 36 ng/h, $p < 0.001$).
Karasek et al, 2000 (163)	23 (F) mixed gynaecological cancer, mean age 50yr, included "invasive ovarian" 16 (F) control subjects, mean age 51yr 7 (F) myomatous uterus patients, mean age 46yr	24-hour rhythms and AUC of serum melatonin (0800, 1200, 1600, 2000, 2200, 2400, 0200, 0400, 0600, 0800)	There was no significant difference in the 24-hour rhythm and AUC between the three groups.
Baranowski et al, 1999 (29)	30 (17 M) stage 4 gastrointestinal cancer patients, mean age 64yr 29 age-matched healthy control subjects (gender not defined)	Serum melatonin: 0800, 1400, 1800, 2200, 0200, 0800	A 24-hour rhythm was present for all subjects. Compared to controls, patients with cancer had similar minimum levels (12.1pg/ml vs. 12pg/ml), lower maximum levels (34.3pg/ml vs. 65pg/ml), and lower average levels (MESOR) (23.1pg/ml vs. 48.2pg/ml)
Tarquini et al, 1999 (165)	39 (17 M) mixed cancer patients (21 metastatic), mean age 72yr 28 (11 M), control subjects, mean age 65yr	24-hour serum melatonin levels and amplitude (0000, 0400, 0800, 1200, 1600, 2000, 2400)	A 24-hour rhythm was present for all subjects. The amplitude was smaller in cancer patients than control subjects ($p = 0.003$) with higher daytime levels and lower night-time levels. No difference in amplitude was found in relation to cancer stage.
Dogliotti et al, 1990 (168)	Study 1: 132 (90 F), stage 1-4 mixed cancer patients, median age 63yr. 58 (32 M) control subjects, median age 35yr Study 2: 20 stage 1-3 breast cancer patients, median age 60yr	Study 1: Serum melatonin (0800, 2400) Study 2: Serum melatonin (0800, 2400)	Study 1: Melatonin levels were higher at both time points in patients than controls ($p < 0.0001$). Stage 4 breast cancer patients had higher mean melatonin concentration than controls ($p < 0.0001$) and higher levels at 2400 ($p < 0.002$) and 0800 ($p < 0.0001$) than stage 1-2 breast cancer patients. Advanced lung cancer patients had higher mean melatonin levels than control at both time-points ($p < 0.001$ at 2400, $p < 0.0001$ at 0800). Highest levels were in patients with SCLC.

	Study 3: 18 mixed cancer patients, age and gender not defined, Control subjects age, gender and number not defined	Study 3: 24-hour serum melatonin (0800, 1200, 1600, 2000, 0000, 0400, 0800)	Advanced GI cancer patients had higher mean melatonin levels than control ($p<0.005$ at 2400, $p<0.001$ at 0800). Increased melatonin levels at 0800 were associated with lower performance status ($r=-37$, $p<0.01$). Study 2: Melatonin levels did not differ in breast cancer patients pre- and post-surgical removal of the primary tumour Study 3: The circadian melatonin rhythm was similar between patients and controls.
Bartsch et al, 1981 (166)	10 (F) stage 1-4 breast cancer patients, mean age 57yr 10 (F) control subjects, mean age 53yr	24-hour urinary melatonin (0600-1000, 1000-1400, 1400-1800, 1800-2200, 2200-0600)	Cancer patients had a lower average melatonin urinary excretion and elevated levels between 0600-1000 than controls. The differences were not statistically significant. A more synchronised excretion pattern was found in controls
STUDIES WITHOUT A CONTROL GROUP			
Mormont et al, 2002 (129)	18 (14 M) metastatic colorectal cancer patients, mean age 58yr	24-hour rhythms for serum melatonin and serum 6-alpha-sulfatoxymelatonin on 3-6 hours apart for 10-13 times points	15 /18 (83%) patients had a 24-hour serum melatonin rhythm and 6/18 (33%) had a 24-hour 6-alpha-sulfatoxymelatonin rhythm.
Mormont et al, 1998 (159)	18 (14 M) metastatic colorectal cancer patients, age 35-72yr	24-hour rhythm of blood melatonin	A group 24-hour rhythm was evident for melatonin ($p<0.00001$) and significant circadian melatonin rhythm for 15 patients ($p<0.05$). Wide interindividual variation was noted.
Vivani et al, 1992 (162)	7 (6 M) small cell lung cancer patients, median age 51yr Patients administered IL-2	Baseline and weekly serum melatonin (0800, 1600 and 2400)	Abnormal melatonin 24-hour rhythms were found in all patients at baseline which was absent in 5 patients and had an earlier acrophase in 2 patients. The mean values were not significantly higher than those at 0800 or 1600.

M = male; F = female; AUC = area under curve; ns = not significant

Table 1b. Cortisol circadian rhythms and their associations in patients with advanced cancer

STUDIES WITH A CONTROL GROUP			
Article	Participants	Circadian measures	Outcomes relevant to review
Levi et al, 2020 (35)	IDEAs study: 25 (21 M) locally advanced or metastatic gastrointestinal cancer patients, median age 66 PicaPill study: 33 (15 M), control subjects, median age 35	2-day salivary cortisol (3-hourly) & 7-day wrist actigraphy and chest accelerometry and 1-day melatonin samples hourly at 1900	A consistent diurnal change in cortisol levels was seen in most controls and patients, irrespective of their dichotomy index (I<O) which represents the relative difference between in-bed and out-of-bed physical activity. Those with a high I<O (i.e. relatively less in-bed to out-of-bed activity) had a larger circadian cortisol amplitude. No significant difference was found in other cortisol parameters between I<O groups.
Zeitzer et al, 2016 (149)	97 (F) recurrent or metastatic breast cancer patients, age 57.6 24, health age-matched controls, age 57.1 (Gender not identified)	Combination: 28-hour plasma cortisol (20-60-minute intervals) and polysomnography & 2-week actigraphy (Actiwatch 2) and sleep diary	There were no differences in the cortisol amplitude, MESOR (mean value) or absolute/relative timing between groups ($p>0.09$). There were no differences in the diurnal cortisol rhythm between groups ($p>0.11$). Abnormal cortisol peaks, midway through the sleep episode, were seen in a subset of patients and were associated with increased wake episodes ($p=0.004$), metastases to bone or organs rather than local recurrence ($r=-0.37$, $p=0.002$), use of steroids ($r=0.26$, $p=0.03$), ER negative status ($r=-0.25$, $p=0.04$) and higher a stage of initial diagnosis ($r=0.31$, $p=0.009$). In a multivariate analysis, metastases to bone ($p=0.02$) and ER negative status ($p=0.048$) continued to be associated with the abnormal cortisol peaks. Abnormal cortisol peaks were not related to psychological traits ($p>0.018$). Larger abnormal peaks were associated with a shorter disease-free interval ($r=-0.30$, $p=0.004$). The disease-free interval (DFI) and the diurnal cortisol rhythm were not associated ($p>0.10$).

Du et al, 2013 (155)	25 (15 M) stage 2-4 lung cancer patient with depression, mean age 55.1 39 (23 M) stage 2-4 lung cancer patients without depression, mean age 57.0 21 (8 M) patients with depression, mean age 53.8 41 (21 M) control subjects, mean age 55.9	24-hour salivary cortisol (0800, 1600, 0000, 0600)	Lung cancer patients with depression had a flattened circadian cortisol pattern (less diurnal variation) compared to other groups. Lung cancer patients also had higher salivary cortisol at 0000 compared to lung cancer patients without depression ($p<0.001$). The salivary cortisol area under the curve (AUC) was significantly higher in patients with depression only than the other groups ($p = 0.021$). Salivary cortisol diurnal variation (VAR) was significantly lower in lung cancer patients with depression than other groups ($p<0.001$).
Kim et al, 2012 (33)	52 (37 M) stage 3a-4 lung cancer patients, mean age 60.8 56 (32 M), control subjects, mean age 60.7	2-day salivary cortisol (waking, +30 min, +60 min, 2100)	The cortisol awakening rise (CAR) represents the rapid rise in cortisol on awakening, and levels at 0, +30 min and +60 minute were significantly higher in controls than in patients ($p<0.05$). CARauci and CARi were higher in controls than in patients ($p<0.05$). Cortisol levels at 2100 were similar between patients and controls. Flatter diurnal cortisol slopes were seen in patients compared to controls ($p<0.001$). Decreased cortisol levels and abnormal secretory patterns were seen in patients with an ECOG PS of 3 and 4 compared to controls ($p<0.001$). A positive correlation was seen between the diurnal cortisol slope and clinical disease stage ($p<0.01$). CARi and CARauci were not associated with clinical disease stage. For patients, gender, number of metastatic sites, chemotherapy status, body mass index and smoking status were independent of the cortisol profile ($p>0.05$).
Mazzoccoli et al, 2012 (148)	9 (M) stage 2-4 non-small cell lung cancer patients, mean age 51.0 11 (M) control subjects, mean age 43.6	Combination: serum cortisol and melatonin (0600, 1000, 1400, 1800, 2200, 0200)	Prominent 24-hour cortisol rhythms were seen in all subjects with peaks at night for melatonin and near waking for cortisol. Mean cortisol values did not differ between groups at any time points. The overall 24-h mean for cortisol was higher in cancer patients than controls ($p=0.001$). An increased cortisol slope was associated with increasing disease severity ($p<0.001$).

Weinrib et al, 2010 (140)	100 (F) stage 1-4 ovarian cancer patients, mean age 58.19 77 (F) benign disease, mean age 51.04 33 (F) control subjects, mean age 52.79	Salivary cortisol (waking, 1600-1830, bedtime)	Mean afternoon cortisol for ovarian cancer patients was 55% higher than for healthy females ($p<0.0001$) and similar to patients with benign disease ($p=0.07$). Nocturnal cortisol levels for ovarian cancer were 41.5% higher than benign disease ($p=0.02$) and 103% higher than healthy females ($p=0.0001$). Cortisol variability of ovarian cancer patients was lower than for benign disease ($p=0.023$) and healthy females ($p<0.0001$). Adjusted for age and disease stage in the ovarian group, a higher nocturnal cortisol and lower cortisol variability was associated with greater fatigue ($p=0.005$ and $p = 0.01$). Lower cortisol variability also associated with poorer physical well-being ($p=0.007$). Depression scores were associated with a higher nocturnal cortisol ($p=0.059$) and lower cortisol variability ($p=0.028$). A more advanced cancer stage was associated with a higher morning ($r=0.23$, $p=0.02$) and afternoon ($r=0.32$, $p=0.002$) cortisol, but not nocturnal cortisol ($r=0.13$, $p=0.33$). Adjusted for age and disease stage in ovarian cancer group: higher nocturnal cortisol associated with poorer physician-rated PS (rated on a 0-4 scale) ($p=0.043$) and patient-related PS ($p=0.035$). Lower cortisol variability was also associated with poorer physician-rated PS ($p=0.01$) and poorer patient-rated PS ($p=0.004$).
Wu et al, 2008 (138)	13 (9 M) stage 2-4 nasopharyngeal cancer, median age 41 14 (8 M) healthy control subjects, mean age 24.5	24-hour plasma cortisol (4 hourly sampling)	Patients had a lower cortisol MESOR compared to control (200.31 ± 14.38 nmol/L vs. 243.77 ± 14.96 nmol/L, $p=0.30$) The acrophase was later for patients than controls (0914 vs. 0841) The amplitude was higher for patients than controls (64.01 vs. 61.94) A clear cortisol circadian rhythm with peaks in the morning was seen in both groups
Mazzocchi et al, 2005 (107)	17 healthy subjects, mean age 68.8 17 stage 1-2 non-small cell lung cancer patients, mean age 67.2 17 stage 3-4 non-small cell lung cancer patients, mean age 69.5	Combination: 24-hour serum cortisol and melatonin (4 hourly)	No significant different in cortisol levels was seen amongst groups. Cancer patients did not show a clear rhythm of cortisol secretion.

Abercrombie et al, 2004 (30)	17 (gender not defined) metastatic breast cancer patients, mean age 57.6 31 (F) control subjects, mean age 56.0	3-day salivary cortisol at waking (mean collection time 0717), 1200, 1700, and 2100	Patients had significantly flatter diurnal cortisol slopes than controls ($p<0.05$). Disease severity was associated with flatter diurnal cortisol slopes ($p=0.07$) and higher mean cortisol levels ($p<0.05$). Mean cortisol levels between groups were not significantly different at different time points. Diurnal cortisol slopes and mean cortisol levels did not correlate with psychological measures ($p>0.32$).
Baranowski et al, 1999 (334)	30 (17 M), "advanced" gastric, pancreatic, or colorectal cancer patients, mean age 63.5 20 control subjects (gender not defined), mean age 59.5	Serum cortisol (0800, 1400, 1800, 2000, 0200, 0800)	A "well defined circadian rhythm" was seen in control subjects, with a MESOR of 116.8pg/ml, amplitude of 85.5pg/ml and acrophase of 0720. In patients, a later acrophase of 0808 at 520 ± 11.8 ng/ml was noted, and the trough occurred at 1800 at 279.7 ± 3.7 ng/ml.
Mormont et al, 1998 (27)	3 study cohorts 1. 19 (7 M) control subjects, 7 young (mean age 24), 6 elderly females (mean age 74.7), 6 elderly males (mean age 71.7) 2. 19 (F) advanced ovarian cancer patients, mean age 59 3. 18 (14 M) advanced metastatic colorectal cancer patients, mean age 58	Serum cortisol Retrospective studies – 4 circadian time series at 3-monthly intervals Prospective study – 5-6 samples in 1 st and 4 th day of chemotherapy	The mean cortisol peak occurred at 0800. The cortisol trough occurred earlier in controls (2000) than in ovarian and colorectal cancer patients (0000 or 0100). Mean serum cortisol amplitude was 30% lower in cancer patients compared to controls (ovarian $p=0.01$, colorectal cancer $p=0.002$). There was no significant influence of age, gender, performance status, percentage of liver replacement or number of metastatic sites on the mean estimate of circadian amplitude in the colorectal cancer patients. Ovarian cancer patients with a WHO PS 3-4 had a significantly lower MAX-MIN and lower mean H8-16 cortisol than those with a performance status of 2 or less.
Singh et al, 1998 (335)	25 (F), early (TNM B-1) and advanced (TNM B-2) breast cancer patients, aged 25-60 years 15(F), control subjects, aged 25-40 years	24-hour urine 17-ketogenic steroid (17-KGS) and 17-ketosteroid (17-KS) at 6 hourly collections 17-KGS and 17-KS are metabolites that may be derived from adrenal steroids and androgens from the gonads	A significant circadian rhythm of urinary 17-KGS in controls and early-stage breast cancer (all $p<0.001$) with an acrophase of 1814 in controls and 1855 in early-stage breast cancer. In advanced-stage breast cancer the acrophase occurred at 1626 with elevated values at almost all time points compared to controls and early-stage breast cancer patients. A significant circadian rhythm of urinary 17-KS was noted in controls. The acrophase was 2118. A circadian rhythm of urinary 17-KS was also found in early-stage breast cancer with an acrophase around 2059. An irregular circadian rhythm of urinary 17-KS was noted in patients with advanced breast cancer with an acrophase of

			2016, when compared to controls and early-stage breast cancer
Payer et al, 1997 (141)	11 (8 M), bowel cancer patients (4 metastatic) median age 65 17 (13 M), ulcerative colitis patients, median age 32.5, 28 (15 M) patients with large bowel polyps, median age 32.5 13 (10 M) health controls, median age 21	Serum cortisol (0800, 1200, 1600, 2000, 0400, 0800)	Cancer patients had a lower cortisol amplitude ($p<0.05$) and shorter 12-hour acrophase ($p<0.05$) than other groups.
Singh et al, 1995 (137)	25 (F) early and advanced breast cancer patients, aged 25-60 15 (F) control subjects, aged 25-40	Serum 17-hydroxycorticosteroid (OHCS) (0600, 1200, 1800, 0000)	Control subjects had a mean 17-OHCS of 19.21μg/dl at 0600 which reduced throughout the day to minimum concentrations at 0000. A significant difference at time points was found ($p<0.001$). The MESOR was 13.2$\pm$0.55μg/dl and amplitude was 5.43μg/dl. The amplitude was significantly different from zero. The acrophase occurred at 0856. Patients with advanced breast cancer had higher 17-OHCS at 0600 than controls (34.56μg/dl), and an earlier acrophase of 0438. Breast cancer patients have a higher MESOR than controls ($p<0.001$).
Singh et al, 1987 (132)	10 (F) advanced breast cancer patients, aged 35-60 Patient group split into two groups according to their circadian pattern (not further defined) 10 (F) control subjects, aged 25-40	24-hours serum cortisol at 8-hourly intervals from 0800	Control subjects had a mean 17-OHCS at 0800 of 18.03μg/dl with a minimum level at 0000. The amplitude was significant from baseline ($p=0.001$) suggesting a marked circadian rhythm. Group 2 (6 patients) had deranged circadian rhythms with no significant difference in mean values between time points or in the change in cortisol level from baseline. Group 3 (4 patients) had a mean 17-OHCS at 0800 of 25.20μg/dl with a minimum at 0000. A normal circadian rhythm was seen with a significant amplitude from baseline ($p=0.05$).

DeMeester et al, 1979 (134)	76 stage 1-3 non-oat-cell bronchogenic carcinoma 15 control subjects with suspected carcinoma but found to have benign disease Age and gender not defined	Serum cortisol (0800, 16000, 0000)	Stage 1 patients' cortisol levels at all time points did not significantly differ from controls. Stage 2-3 patients had higher 0800 and 1600 levels than control subjects and stage 1 ($p<0.05$). Stage 3 metastatic patients had similar 0000 levels to 0800 peak of controls. 66 patients maintained a normal diurnal rhythm with significantly higher 0800 levels to 0000. 2 patients lost their diurnal variation and in 8 patients the rhythm was reversed with 0000 levels higher than 08000. Elevated cortisol at 0000 was associated with progressive disease but not length of survival.
Bishop et al, 1970 (139)	80 inoperable lung cancer patients admitted for radiotherapy/chemotherapy, 45 inoperable or metastatic cancer patients (not lung) 35 control subjects admitted for minor surgery Age and gender not defined	Serum cortisol (basal 0830-0930, midnight 2300-2400, 0830-0930 the morning after 2mg dexamethasone)	Cancer patients had significantly higher 8am cortisol than controls. A reduction in the diurnal cortisol variation was seen in cancer patients. All cancer patients showed less cortisol suppression following dexamethasone than control. No significant correlation was found between TNF-alpha and cortisol. Significance levels not reported
STUDIES WITHOUT A CONTROL GROUP			
Cheung et al, 2021 (28)	30 (16 M) stage 3b-4 non-small cell lung cancer patients Group 1 – Aerobic exercise, mean age 61.00 Group 2 – Tai-Chi, mean age 61.11 Group 3 – Self-management group, mean age 58.36	Combination: Salivary cortisol rhythms (0.5, 4, 8 and 12 hours after waking) & 3-day actigraphy (AMI)	The diurnal cortisol slope (representing the decline in cortisol levels during the day following the morning peak) and the cortisol area under the curve values at baseline were identified but no correlations reported. No control group was included for comparison.

Allende et al, 2020 (145)	99 (F) metastatic or recurrent breast cancer patients, median age 54	3-day salivary cortisol at waking, +30, 1200, 1700, and 2100	The diurnal cortisol slope data was split at the median point to distinguish flat and steep slopes. Flat and steep diurnal cortisol slopes had significantly different salivary cortisol levels at 1200 ($p=0.0086$), 1700 ($p<0.0001$), and 2100 ($p<0.0001$), but not at waking ($p=0.4795$) or waking +30 minutes ($p=0.1364$). This suggests that the differences between flat and steep cortisol slopes occur at 1200 or later. Flatter diurnal cortisol slopes were associated with an escape from dexamethasone suppression ($p=0.0042$).
Oh et al, 2019 (142)	46 (39 M), stage 2-4 small cell lung cancer and non-small cell lung cancer patients (15 patients had metastatic disease), 23 $\leq$ 65 years old, 23 >65 years old	24-hour salivary cortisol (waking, +30 min, +60 min, 2100-22000)	Cortisol concentrations differed between patient and controls ($p<0.001$). The cortisol awakening response (CAR) represents changes in cortisol levels within given time periods. CARi (the cortisol increase in the first 30 minutes after waking) and CARauc (the cortisol increase in the first 60 minutes from waking) were both significantly smaller in the patients compared to controls ($p<0.01$). A flatter diurnal cortisol slope was seen in the patients compared to controls ($p<0.001$). Patients with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 3-4 had a small CAR ($p<0.001$) and flatter diurnal cortisol slope ($p<0.001$) compared to than patients with an ECOG PS of 1-2. Patients with metastatic disease had a small CARauc than those without metastatic disease ($p=0.003$). Total MD Anderson Symptom Inventory scores, fatigue and interference with general activity, work and walking were all significant associated with a reduced CAR and a flatter diurnal cortisol slope ($p<0.05$).
Rebholz et al, 2018 (158)	57 (F) stage 0-5 breast cancer patients, mean age 52.32	Combination: 3-day salivary cortisol (waking, +30 min, 1600, bedtime) & 3-day actigraphy (AMI)	The diurnal cortisol slope was not significantly correlated with QoL.
Cash et al, 2015 (31)	43 (F), stage 0-4 breast cancer patients, mean age 52.49	Combination: 3-day salivary cortisol (waking, +30 min, 1600, "prior to going to bed") & 3-day actigraphy (Micro Mini-Motionlogger) and sleep diary	A higher CAR was associated with elevated levels of VEGF, TGF-beta, and MMP-9 (markers associated with angiogenesis, immunosuppression, epithelial-mesenchymal transition, tumour invasion and metastasis).

Hsiao et al, 2015 (146)	62 (F) stage 0-3 breast cancer patients, 25.8% had metastatic disease, mean age 35.3	24-hour salivary cortisol (waking, +30 min, +45 min, 1200, 1700, 2100)	A flatter diurnal cortisol slope was associated with greater tumour size ($p=0.01$) an increase of body mass index over 8 months ($p<0.001$) and a persistently later waking time over 8 months ($p=0.006$). Factors that were not significantly associated with the cortisol slope included metastatic status, physical activity levels, time of going to bed, sleep problem index and depressive symptoms.
Schrepf et al, 2015 (36)	113 (F) stage 1-4 ovarian, primary peritoneal or fallopian tube cancer patients, mean age 57.99	Salivary cortisol (waking, 1700 and bedtime)	Increasing age was associated with a higher evening cortisol ($p=0.004$) but not cortisol variability or slope. “High grade” disease, and poorer physical well-being were associated with a higher night cortisol, a flattened diurnal cortisol slope, and reduced cortisol variability (all $p<0.05$). “Late” stage disease was also associated with higher evening cortisol ($p=0.05$). Shorter survival was seen with elevated night cortisol prior to surgery (HR1.802, $p<0.001$), and the diurnal cortisol slope (HR1.633, $p=0.001$). Longer survival was seen with cortisol variability (HR 0.644, $p<0.001$). Estimated median survival for low evening cortisol was 7.3 years compared to 3.3 years in those with a high evening cortisol. Elevated night cortisol, a flattened diurnal cortisol slope, and reduced cortisol variability were associated with higher levels of inflammation indicated by ascitic and plasma IL-6 (all <0.05). The diurnal cortisol slope was associated to cortisol variability ($r = 0.88$, $p<0.001$). Night cortisol was correlated with cortisol variability ($r=-0.727$, $p<0.001$) and the diurnal cortisol slope ($r=0.758$, $p<0.001$).
Zeitzer et al, 2015 (34)	97 (F) recurrent or metastatic breast cancer patient, “age” 57.4	Combination: 27-hour inpatient serum cortisol (20–60-minute intervals from 3 hours prior to bedtime to 1 hour after wake time), salivary cortisol 0900 on day 1, awakening and 30 minutes on day 2 & 2-week outpatient actigraphy (actiwatch 2) and sleep diary logs	The cortisol diurnal slope varied depending on the analytical method used. 10/91 (11%) had a “positive” slope from 0600. A flatter diurnal cortisol slope was associated with a lower morning peak and elevated evening trough. Plasma and salivary cortisol concentrations were correlated ($p<0.001$).

Diaz et al, 2014 (157)	99 (F) metastatic breast cancer patients, median age 54	2-day salivary cortisol (waking, +30 min, 1200, 1700 and 2100)	Post-traumatic growth (positive psychological change following cancer diagnosis or treatment) was associated with a steeper cortisol slope ($p=0.039$). 'Relating to others' subscale was also associated with a steeper cortisol slope ($p=0.039$). Income, education, marital status, age, time since recurrence, PR status and metastatic sites were unrelated to cortisol slope ($p>0.05$).
Palesh et al, 2014 (153)	97 (F) metastatic or locally advanced breast cancer patients, mean age 54.6	Combination: 2-day salivary cortisol (waking, +30 minutes, 1200, 1700 and 2100) & 3-day actigraphy (micro mini-motionlogger) and sleep diary	Salivary diurnal cortisol was associated with survival (HR 1.03, $p=0.85$) (character of the slope was not noted).
Sephton et al, 2013 (111)	62 (34 F) stage 1-4 non-small cell lung cancer and small cell lung cancer patients, mean age 64	2-day salivary cortisol (waking, +45 min, 1600, 2100) Single serum cortisol (time not defined)	A lack of normal diurnal variation was associated with shortened survival (HR 68052.8, $p=0.009$). The cortisol AUC and CAR were not associated with survival time. Flattened cortisol rhythms were associated with more advanced lung cancer ($r=0.35$, $p=0.003$), poor performance status ($r=-0.29$, $p=0.012$), being male ($p=0.028$), low total lymphocytes ($r=-0.39$, $p=0.002$) and low cytotoxic T lymphocyte count ($r=-0.030$, $p=0.017$). The diurnal cortisol slope was not significantly associated with CAR, age at diagnosis, cancer type, time since radio- or chemotherapy, socioeconomic status, prior marital disruption, depressive symptoms, fatigue, or sleep difficulties. The diurnal salivary cortisol slope was not associated with serum cortisol levels.
Cohen et al, 2012 (152)	202 (156 M), metastatic renal cell cancer patients, mean age 59	3-day salivary cortisol at waking +45 minutes, 8 hours, 12 hours, and bedtime)	The cortisol slope was significantly associated with survival (HR 1.88, $p=0.002$). The cortisol slope was not associated with psychosocial variables or CES-D scores.
Dedert et al, 2012 (171)	57 (F) stage 1-4 breast cancer patients, mean age 52	Combination: 3-day salivary cortisol (3 days – waking, 30 minutes after, 1600 and bedtime) & actigraphy and sleep diary	Intrusion and avoidant coping were not related to cortisol measures. A higher autocorrelation co-efficient (a measure of physical activity circadian consistency between days) was associated with a steeper diurnal cortisol slope ($r=-0.41$, $p=0.003$).

Brivio et al, 2010 (143)	14 (10 M) metastatic non-small cell lung cancer, pancreatic cancer, prostate cancer and malignant melanoma patients, median age 67	Serum cortisol (0800 and 1600) at baseline and following melatonin treatment	Patients had abnormal cortisol circadian rhythms (defined as a lack of decline of 30% in the cortisol level from the morning to the afternoon). No significant difference was reported in morning or afternoon mean cortisol levels between stable and progressive disease (significance levels not reported).
Sephton et al, 2009 (156)	72 (F), stage 4 metastatic breast cancer, mean age 54.5	3-day salivary cortisol (0800, 1200, 1700, 2100)	Greater depression symptoms were associated with higher morning cortisol ($p < 0.02$) and accentuated diurnal cortisol rhythms ($p \leq 0.05$). Depression scores were uncorrelated with mean cortisol levels.
Lutgendorf et al, 2008 (147)	25 (F) low malignant potential patients, mean age 51.24 26 (F) early-stage ovarian cancer patients, mean age 55.6 86 (F) advanced ovarian cancer patients, mean age 60.22	Salivary cortisol (waking, +30 min, 1500-1800, 2000-2400)	Salivary cortisol was increased for all patients with advanced cancer patients having approximately 3 times the healthy population normal values. Cortisol AUC was significantly higher in advanced-stage patients compared to the low malignant potential patients ($p = 0.047$). Diurnal cortisol levels did not significantly differ between groups or over the day ($p > 0.06$ and $p > 0.73$). Higher evening cortisol levels were associated with higher total depression ($p = 0.026$) and vegetative depression ($p = 0.005$).
Palesh et al, 2008 (150)	99 (F), metastatic breast cancer patients, mean age 54.65	Combination: 2-day salivary cortisol (waking, +30 min, 1200, 1700, 2100) & 3-day actigraphy (micro mini-motionlogger)	A flatter cortisol slope was associated with longer average wake episodes at night ($r = 0.21$, $p = 0.04$). No significant relationship was found between mean waking cortisol or cortisol rise and other sleep measures.
Giese-Davis et al, 2006 (32)	29 (F) stage 4 breast cancer patients, mean age 53.21 All received supportive-expressive group therapy (SET)	3-day salivary cortisol (0800, 1200, 1700, 2100)	Steeper diurnal cortisol slopes were associated with shorter duration of negative affect ($p = 0.02$). 0800 and mean cortisol levels were not associated.
Jehn et al, 2006 (37)	114 (38 M), mixed stage 4 cancer patients, (71 had "progressive" disease, 43 had "stable" disease) Mean age of patients with depression 62.7 Mean age of patients without depression 59.4	Serum cortisol (0800 and 2000)	Cortisol concentrations were significantly higher in patient with depression at 0800 ($p = 0.003$) and 2000 ($p < 0.001$). Cortisol diurnal variation (VAR) was significantly decreased in cancer patients with depression compared to those without depression (11.7% vs. 60.6%, $p = 0.001$).

Mussi et al, 2006 (131)	40 (22 F), colorectal cancer patients (13 patient had nodal disease, 10 had liver metastases), median age 66	Serum cortisol (2300 and 0800)	Patients with liver involvement had a higher evening cortisol ($p<0.0005$). Nodal involvement did not impact on cortisol levels. 28% had an altered circadian rhythm defined as 2300 level $>50\%$ of 0800 level. This was more frequent if there was nodal involvement and metastatic spread ($p<0.005$). Cortisol levels and circadian rhythm were unrelated to CD4+ lymphocyte count (a prognostic marker).
Spiegel et al, 2006 (144)	99 (F) metastatic breast cancer patients, median age 54	2-day salivary cortisol (waking, +30, 1200, 1700, 2100)	The cortisol slope was correlated with cortisol rise within 30 minutes of waking ($r=0.29$, $p=0.004$), but not with the waking level ($p=0.19$). A flatter slope was associated with a higher 2100 level ($r=0.85$, $p<0.0001$) and escape from cortisol suppression ($r=0.30$, $p=0.005$). No significant associated were reported between the cortisol slope and CRF administration or social stress. Antidepressant use was associated with higher waking cortisol ($r=0.21$, $p=0.04$) and lower cortisol rise ($r=-0.32$, $p=0.001$). Lower income status was associated with flatter cortisol slope ($r=-0.28$, $p=0.008$). Patients with progesterone receptor positive breast cancer had a lower waking cortisol rise ($r=0.22$, $p=0.04$). The cortisol slope was unrelated to demographics, disease-free interval or treatment. Patients with progesterone receptor positivity had lower waking cortisol rise ($p=0.04$).
Rich et al, 2005 (154)	80 (52 M) metastatic colorectal cancer patients Group 1 - 40 patients with a "good" rhythm ($r_{24} >0.47 <0.77$), median age 59.6 Group 2 - 40 patients with a "dampened" rhythm ($r_{24} >0.03$, <0.35), median age 60	Combination: 2-day serum cortisol (0800 and 1600) & 3-day actigraphy (Actigraph)	Patients with a "good" activity rhythm had higher cortisol ratios (between 0800 and 1600) compared to those with a "dampened" activity rhythm. Mean cortisol levels did not differ significantly between groups Mean cortisol was prognostic ($p<0.0001$). IL-6 and TGF-α was positively correlated with mean serum cortisol ($p=0.0001$). IL-6 was negatively correlated with circadian cortisol ratio ($p = 0.042$). .

Giese-Davis et al, 2004 (133)	91 (F) metastatic breast cancer patients, mean age at diagnosis of metastatic disease 49.08-55.93	3-day salivary cortisol (mean times 0806, 1226, 1725, 2026)	40% patients displayed the usual morning cortisol peak with a decline across the day. 56% had peaks later in the day and 4% had flattened rhythms. Patient's demonstrating psychological repression had flatter slopes than the self-assured ($p=0.01$) and non-extreme groups ($p=0.02$). Mean cortisol levels were not significantly different between groups.
Mormont et al, 2002 (151)	Round the clock study (RTCS): 18 (14 M) metastatic colorectal cancer patients, mean age 58 Two-time point study (TTPS): 192 (128 M) metastatic colorectal cancer patients, mean age 58	RTCS: Cortisol (13 blood and salivary samples 1 st and 4 th day of 4-day chemotherapy) TTPS: Cortisol (2 day – blood and saliva 0800 and 1600, + saliva 2300 all before chemotherapy)	A significant circadian rhythm was seen in the serum of 8/18 (44.4%) patients and in the saliva of 6/16 patients (37.5%). Patients with marked circadian rhythms had lower 0800 and 1600 levels. Marked cortisol rhythms were not associated with longer survival than those with altered rhythms and cortisol did not predict the clinical outcome. A higher performance status and percent of liver replacement was associated with higher cortisol concentrations at 0800 and 1600. Salivary and serum cortisol were correlated, particularly for those with stronger circadian rhythms.
Mormont et al, 2002 (129)	18 (14 M) metastatic colorectal cancer patients, mean age 58	Combination: salivary cortisol and serum cortisol, melatonin and 6-alphasulfatoxymelatonin (3-6 hourly over 10-13 time points on day 1 and 4) & 3-day actigraphy (Actigraph)	A circadian cortisol rhythm was seen in serum cortisol for 8 patients, and 6 patients had a significant salivary cortisol rhythm. Interindividual variation in markers of circadian rhythm.
Mormont et al, 2000 (113)	192 (128 M) metastatic colorectal cancer patients, mean age 58	Combination: 2-day blood cortisol (0800 and 1600) & 3-day actigraphy (actigraphy) and sleep diary	Mean cortisol was higher in patients with a low r24 (a measure of physical activity circadian consistency) ($r=-0.17$, $p=0.04$), low I<O (a measure of activity in and out of bed) ($r=-0.24$, $p=0.07$), poor performance status ($p=0.0005$) or severe liver involvement ($p=0.0001$). The estimate of cortisol circadian rhythm (difference in cortisol values) was correlated with r24 ($r=0.16$, $p=0.04$) but not I<O or mean activity. Cortisol was not prognostic, and the circadian rhythm did not estimate treatment response.

Sephton et al, 2000 (110)	104 (F), metastatic breast cancer patients, mean age 53.2	3-day salivary cortisol (0800, 1200, 1700, 2100)	Flatter diurnal cortisol slopes were associated with shorter survival (HR464.9, $p = 0.0036$). The change in survival between slopes was seen up to 7 years later. The diurnal cortisol slopes were split at the median value, 77% with “flat” rhythms averaged 3.2 years survival, whereas 60% with “steep” rhythms averaged 4.5 years survival. The diurnal cortisol slope remained prognostic after adjusting for age at initial diagnosis, disease free interval, and oestrogen receptor status. Flatter diurnal cortisol slopes were associated with taking megestrol ($p=0.000$), more nocturnal awakenings ($p=0.003$), marital disruption ($p=0.040$), fewer circulating NK cells ($p=0.007$) and suppressed NK cell activity ($p=0.05$). Steeper slopes were associated with metastases to the chest wall or adjacent lymph nodes ($p=0.023$).
Mormont et al, 1998 (159)	18 (14 M) metastatic colorectal cancer patients, age 35-72	Combination: 6 hourly blood for cortisol and melatonin (9-11 time points) on day 1 and 4 & 3-day actigraphy	Study 1: 7 of 18 (39%) patients had significant cortisol circadian rhythms ($p<0.05$). Group circadian rhythms for cortisol were validated ($p<0.00001$). Wide interindividual variation was noted between cancer patients.
Touitou et al, 1996 (56)	13 metastatic breast cancer patients, mean age 52 (gender not defined) 20 stage 2a-4 ovarian cancer patients, mean age 57	24-hour serum cortisol (4 hourly intervals)	Serum 0800 cortisol was low in 9 patients. 8 breast cancer patients had flattened cortisol patterns, a shift in the peak or trough time, or a plateau with high morning values. 15 ovarian cancer patients had high cortisol levels throughout a 24-hour period and/or erratic peak and trough locations and/or flattened profiles.
Touitou et al, 1995 (135)	13 (F) stage 1-4 metastatic breast cancer, median age 52	48-hour serum cortisol (4 hourly intervals)	The cortisol acrophase was near 0930 ± 110. A significant circadian rhythm was seen in patients with WHO PS1 or no liver metastases. Circadian cortisol rhythm was lost for patients with liver metastases.
Touitou et al, 1990 (130)	13 (F) metastatic breast cancer patients, mean age 52	36-48-hour serum cortisol (4 hourly intervals)	6 patients had normal rhythmicity with a peak at 0800 and trough 0000. 7 patients had altered peak and/or high concentration between 0400-1200 and/or flattened rhythms.

Table 1c. Actigraphy-related circadian rhythms and their associations in patients with advanced cancer

STUDIES WITH A CONTROL GROUP			
Article	Participants	Circadian measures	Outcomes relevant to review
Levi et al, 2020 (35)	Combined data IDEAs study: 25 (21 M) locally advanced or metastatic gastrointestinal cancer patients, median age 66 PicaPill study: 33 (15 M), control subjects, median age 35	7-day actigraphy and chest accelerometry & 2-day salivary cortisol (3-hourly) and 1-day melatonin samples (hourly from 1900)	13 patients had a dichotomy index (I<O, ratio of activity in and out of bed) of $\leq 97.5\%$ on chest accelerometry. Patients had worse I<O ($p=0.008$), levels of activity ($p<0.0001$) and rest probability P1-1 (probability of remaining in a rest state) than controls ($p=0.005$). The activity amplitude, r24 (autocorrelation coefficient, a measure of physical activity consistency between days), RI (rhythm index, measure of quality, regularity, and consistency of rest state), average center-of-rest time, and rest duration were not significantly different. Hospital Anxiety and Depression Scale (HADS) scores, performance status and Pittsburgh Sleep Quality Index (PSQI) scores did not differ significantly between I<O groups. Large inter-subject variability was noted. 91% of patients with a I<O $>97.5\%$ were physical active 30min/+ a day compared to 15% of patients with a I<O of $\leq 97.5\%$ ($p=0.001$). Controls aged 40/+ had a reduced I<O ($p=0.01$), P1-1 ($p=0.0009$) and phase-advanced activity acrophase (earlier peak activity time) and center-of-rest time ($p=0.01$). Patients aged 40/+ had similar I<O values to older controls. For patients, the I<O was associated with day-to-day variability in sleep duration ($r=-0.53$, $p=0.009$), self-reported exercise ($r=0.48$, $p=0.02$), rest-activity amplitude ($r=0.73$, $p<0.0001$), median activity out-of-bed ($r=0.68$, $p=0.0003$), level of activity ($r=0.56$, $p=0.005$), day-to-day variability in self-reported retiring time ($r=0.49$, $p=0.02$), physiologic chest temp ($p=0.03$), and chronotype (a measure of sleep timing preference) score ($r=-0.43$, $p=0.04$). The circadian amplitude in rest-activity and sleep duration variability were the best predictors of a patient's I<O.
Zeitzer et al, 2016 (149)	97(F) recurrent or metastatic breast cancer patients, age 57.6	2-week actigraphy (Actiwatch 2) and sleep diary &	No reported associated with actigraphy derived data.

	24 health age-matched controls, age 57.1 (gender not defined)	28-hour plasma cortisol (20-60-minute intervals) and polysomnography	
Natale et al, 2015 (45)	226 (149 M) metastatic colorectal cancer patients, mean age 58.4 182 (103 F) control subjects, mean age 38.7	At least 4-day actigraphy (Basic Mini-Motionlogger)	Patients had a lower median I<O than controls (97.8% VS. 99.6%) The lowest patient I<O was 75.7% compared to 97.2% in controls. Patients spent a longer time in bed (67 min longer on average) than controls but slept a similar amount of time. Patients had longer sleep onset latency, mean sleep motor activity, wake after sleep onset, number of awakenings more than 5 and lower sleep efficiency compared than controls. I<O was significantly correlated with sleep motor activity (movements during sleep within a given time frame), wake after sleep onset, number of awakenings more than 5 and sleep efficiency (all $p=0.0001$). Younger patients went to bed, and woke up, later than older patients and had a delay in the midpoint of sleep. The actigraphic parameter to best discriminate cancer patients was I<O.
Grutsch et al, 2011 (48)	84 (65 M), stage 2b-4 non-small cell lung cancer patients, mean age 62 35 control subjects from the Ambulatory Monitoring Inc. database (not further defined)	2-7-day actigraphy (Mini Motionlogger Basic Model 4)	Actigraphy parameters were abnormal for all cancer patients compared to controls. Same figures for actigraphy parameters as Du-Quiton et al 2010). Higher daytime activity was associated with lower PSQI daytime dysfunction ($r=-0.61$, $p=0.006$), higher PSQI sleep quality ($r=-0.48$, $p=0.014$) and less use of self-reported sleep medication ($r=-0.58$, $p<0.003$). Higher daytime inactivity was associated with more daytime dysfunction ($r=0.54$, $p=0.017$), lower PSQI global sleep quality ($r=0.41$, $p=0.014$) and higher self-reported use of sleep medication ($r=0.39$, $p=0.05$). A higher 24-hour rhythm quotient was associated with less daytime dysfunction ($r=-0.58$, $2p<0.01$). Patients who slept well during the night and less in the day slept for longer regardless ($p<0.03$) Higher levels of night-day sleep balance were associated with less nighttime sleep disturbance ($r=-0.44$, $p=0.067$), less daytime dysfunction ($r=-0.43$, $p=0.065$) and better global PSQI sleep ($r=-0.36$, $p=0.071$)

Grutsch et al, 2011 (38)	84 (65 M) stage 2b-4 non-small cell lung cancer patients 42 inpatients, mean age 57 42 outpatients, mean age 66 35 control subjects from reference database, age 20-50 (gender not defined)	2–7-day actigraphy (Ambulatory Monitoring Inc.)	All actigraphy parameters were abnormal in patients. A flatter activity circadian rhythm was observed for patients. A higher r24 was associated with less insomnia ($r=-0.48$, $p=0.003$) Loss of appetite was associated with decreased peak activity ($r=-0.41$, $p=0.005$) and the circadian quotient (the amplitude / MESOR) ($r=0.4$, $p=0.015$) A higher r24 was associated with higher quality-of-life index Health/Functioning domain scores ($r=0.34$, $p=0.05$). Higher satisfaction with health was associated with more stable circadian structures. Fatigue was associated with a diminished circadian quotient ($r=-0.40$, $p=0.04$), rhythm quotient ($r=-0.41$, $p=0.03$) and night-day sleep balance ($r=-0.52$, $p<0.01$). A more robust rhythm was associated with less fatigue. A higher rhythm quotient was associated with less pain ($r=-0.39$, $p=0.04$). Loss of appetite was negatively associated with night-day sleep balance ($r=-0.47$, $p<0.01$). Peak activity significantly correlated with all the Power and Ferrans QoL index domains (all $p\leq 0.02$). Robustness of circadian measures reflects all quality-of-life measured aspects. Higher r24 was associated with higher health/functioning domain scores ($r=0.45$, $p=0.02$) and global health scores ($r=0.53$, $p<0.01$). Night-day sleep balance was correlated with the health/functioning domain ($r=0.39$, $p=0.04$), social/economic domain ($r=0.40$, $p=0.04$) and psychological/spiritual domain ($r=0.45$, $p=0.02$). A larger difference in nocturnal and daytime activity correlated with the score in each QLI measure. Night-day balance was correlated with the EORTC QLQ C30 domains of role ($r=0.56$, $p<0.01$) and cognitive function ($r=0.45$, $p=0.02$). A more robust circadian rhythm was associated with greater patient satisfaction with health/functioning, and better overall quality of life.

Du-Quiton et al, 2010 (41)	84 (65 M) stage 2b-4 non-small cell lung cancer patients 42 inpatients, mean age 57 42 outpatients, mean age 66 Control subjects from the Ambulatory Monitoring Inc. database	3–7-day actigraphy (Ambulatory Monitoring Inc. action W-2)	All actigraphy parameters were abnormal for cancer patients compared to controls ($p<0.05$). Patients were 20-50% less active than controls. Patients had at least 3 times longer daytime inactivity, 4 times longer sleep/inactivity periods in the day (20.9% vs. 4.7%) than controls. Patients had more fragmented sleep, longer waking episodes and less nighttime sleep than controls. The longest patient night sleep episode was less than half of the controls. Patients had lower sleep efficiency (79.8% vs. 95.9%), shorter longest nighttime sleep duration (91.7 min vs. 255.6 min), less activity (126.9 accelerations/min vs. 182.6), shorter daytime wake time (797.5 min vs. 947.1 min), shorter sleep time at night (284.0 min vs. 417.8 min) and shorter % of time asleep at night (72.5% vs. 93.0%) than controls (all $p<0.05$). Patients took longer to fall asleep at night (20.8 min vs. 12.1 min), were awake more in the night (95.0 min vs. 31.1 min), slept for longer in the day (208.8 min vs. 47.1 min) and had longer longest daytime sleep periods (43.0 min vs. 23.6 min) than controls ($p<0.05$). Overall daytime and nighttime sleep were not associated with anxiety or depression. There were no statistically significant associations between sleep-activity circadian rhythm and anxiety or depression amongst inpatients.
Fouladiun et al, 2007 (180)	39 (28 M) mixed cancer patients (32 metastatic), mean age 71 31 control subjects, two cohorts mean ages 49 and 74 (genders not defined)	≥ 3 -day actigraphy (Actigraph)	Patients were less active in the day on weekdays and weekends than controls ($p<0.01$). Physical-rest activity was not different to age-matched and recently hospitalised non-cancer patients. Subjectively scored physical function and pain were predicted by objectively measured physical activity ($p<0.0001$).
Le Guen et al, 2007 (175)	29 (25 M) stage 1-4 limited and extensive small cell lung cancer patients, mean age 59 14 (12 M) obstructive sleep apnoea patients treated with nasal continuous positive airway pressure, mean age 55	5-day actigraphy (Actiwatch) and sleep log	Actigraphy parameters differed between the two groups. During the night, cancer patients had longer sleep times (7.4h vs. 6.5h, $p=0.03$), lower sleep efficiency (78% vs. 88.1%, $p=0.002$), higher mean activity scores (31.5 vs. 9.6, $p<0.001$), a higher fragmentation index (not described) (51.7 vs. 28.4, $p=0.002$) and lower immobile time (75.2% vs. 87.4%, $p=0.004$). Sleep latency was not significantly different between groups.

			Patients had lower daytime mean activity scores than controls (186.5 vs. 274.8, $p=0.001$) The PSQI and ESS scores were not significantly correlated with any actigraphic parameters.
Pati et al, 2007 (336)	31 (19 M) stage 2-4 mixed cancer patients, median age 43 35 (22 M) control subjects, median age 35	4-day actigraphy (Actiwatch) and sleep diary	Activity levels were higher, activity patterns more regular and day-night activity more distinct in controls compared to patients. Cancer patients demonstrated more frequent episodes of activity. Activity rhythms occurred in a 24-hour pattern for most participants except 4 patients and 1 control who had activity rhythms lasting 6 or 12 hours. MESOR, amplitude and I/O were lower in patients than controls (all $p<0.001$). The activity acrophase occurred early (~1 hour) in patients than controls ($p<0.001$). The mean r_{24} of the patient group was lower, but not significantly different, than the control group. Patients spent more time in bed ($p<0.02$), had more wake episodes ($p<0.001$), a higher nap frequency ($p<0.001$), more total naps ($p<0.001$) and longer naps ($p<0.001$) than controls.
Fernandes et al, 2006 (50)	25 (F) mixed cancer diagnoses patients (72% metastatic) median age 67 25 (F) control subjects, median age 63	3-day actigraphy (Actimeters) and sleep diary	All actigraphy parameters were significantly different between the two groups. Patients had lower median r_{24} values (0.28 vs. C 0.46, $p<0.001$), longer wake after sleep onset (68.34 min vs. 25.67 min, $p=0.004$), and lower sleep efficiency (85.75% vs. 94.63%, $p=0.001$). Sleep latency was not significantly different between groups. Actigraphy parameters were not significantly correlated with EORTC QLQ-C30 fatigue score in patients or controls.
Levin et al, 2005	33 stage 3-4 non-small cell lung cancer patients, 2 cohorts MRMC site: 21 (12 F), mean age 56.71 VAMC site: 12 (M) mean age 71.75 35 control subjects	4-7-day actigraphy (Ambulatory Monitoring Inc.)	Actigraphy parameters were significantly different between patients and controls. The I/O for the patient cohorts was 90.0 +/- 2.2 and 78.9 +/- 2.4. During wakeful periods patients had less daily activity (mean 92.8 minutes vs 127 minutes), more sleep time (mean 195 min vs. 46.5 min and % asleep 21.8 vs. 4.7) and more sleep episodes (17.8 vs. 5.4) than controls. During night-time periods, cancer patients spent more time awake (134.1 minutes vs. 31.1 minutes), had more sleep

			interruptions (14.6 vs. 6.9) and spent less time sleeping (71.2% vs. 93.0%). The r24 varied depending on the ECOG PS (PS0 0.31, PS1 0.17, PS2 0.21) The duration of long sleep episodes was longer in PS0 patients than PS2 (129 min vs. 96.5 min, $p<0.05$). No significant differences in I<O, peak activity and the circadian quotient were seen between groups. The ultradian (4 hourly rhythms) were significantly different ($p=0.046$). Circadian quotient was lower with a higher PS (PS0 0.55 ± 0.08, PS1 0.53 ± 0.04, and PS2 0.47 ± 0.06). Rhythm quotient was lower with a higher PS (PS0 1.05 ± 0.16, PS1 1.02 ± 0.09, and PS2 0.94 ± 0.16).
Chevalier et al, 2003 (170)	10 (5 M) metastatic colorectal cancer patients, median age 61 15 (M) control subjects (age not defined)	3-day actigraphy (Actigraph)	The median r24 for controls was 0.57 and 1 control had an r24 <0.40. Mean activity counts ranged from 118-163 with a median of 145. The peak activity time (acrophase) ranged between 1420-2010 with a median acrophase of 1700. The median r24 for patients was 0.57 and 2 patients had an r24 <0.40. Mean activity counts ranged from 76-275 counts with a median 148. The acrophase ranged from 1318-1754 with a median acrophase of 1524.
STUDIES WITHOUT A CONTROL GROUP			
Patel et al, 2023 (221)	44 (17 F) mixed locally advanced or metastatic cancer diagnoses, median age 66	72-hour actigraphy (Actiwatch)	Mean I<O 88.9% (70.9-98.1%) I<O correlated with r24, mean activity, sleep efficiency, WASO I<O not associated with survival (based on median or quartile groups) I<O negatively correlated with ECOG-PS ($p<0.0005$) Autocorrelation coefficient 0.16 (0.04-0.37), unrelated to survival No actigraphy-derived sleep parameters associated with survival Sleep efficiency and later get up time associated with survival
Block et al, 2022 (337)	30 (22 F), stage 2-4 mixed cancer diagnosis, median age 55	7-day actigraphy (Ambulatory Monitoring Inc) Day 6 overnight and morning urine 6-sulfatoxymelatonin	Baseline actigraphy from 22 patients r24 median 0.48, mean 0.47 (0.08-0.63) Intradaily stability median 0.73, mean 0.73 (0.43-0.86) Intradaily variability median 0.48, mean 0.53 (0.37-0.88) Relative amplitude median 0.87, mean 0.86 (0.76-0.95)

Padron et al, 2022 (177)	Cognitive behavioural therapy for insomnia and pain (CBTi.p): 18 (F) stage 1-3 mixed gynaecological cancer patients, mean age 58.9 Psychoeducation (PE): 17 (F) stage 1-4 mixed gynaecological cancer patients, mean age 59.9	14-day actigraphy (Actiwatch-L) and sleep diary a post-surgical polysomnography	Actigraphy and sleep diary data were not correlated. Baseline mean values (polysomnography vs. actigraphy) CBTi.p.: sleep efficiency was 75.5% vs. 80.8%, sleep onset latency (time between being in bed and falling asleep) was 24.7 min vs. 29.3 min, and wake after sleep onset was 91.1 min vs. 50.5 min PE: sleep efficiency was 71.0% vs 79.4%, sleep onset latency was 36.2 min vs. 33.6 min, wake after sleep onset was 94.8 min vs. 53.4 min Baseline objective data (CBT.i.p and PE): 29% and 24% of patients had a sleep efficiency >85% 76% and 50% of patients had sleep onset latency <30 min 6% and 13% of patients had wake after sleep onset <30 min
Cheung et al, 2021 (28)	30 (16 M) stage 3b-4 non-small cell lung cancer patients Group 1 – Aerobic exercise, mean age 61.00 Group 2 – Tai-Chi, mean age 61.11 Group 3 – Self-management group, mean age 58.36	3-day actigraphy (Ambulatory Monitoring Inc.) & salivary cortisol rhythms (0.5, 4, 8 and 12 hours after waking)	Patients had a total sleep time of (1) 283.03 min, (2) 240.46 min and (3) 295.48 min. Sleep efficiency (total sleep time to time in bed ratio) was (1) 91.13%, (2) 89.69%, and (3) 90.70%
Bernatchez et al, 2020 (179)	57 (30 M) mixed cancers patients (45 stage 3-4, 53 metastatic), mean age 65.8	7-day actigraphy (Actiwatch-64) and sleep diary	No objective measures were significantly correlated with time to death or quality of life (QoL). Higher sleep efficiency was associated with less pain and depressive symptoms (all $r=-0.23$, $p\leq 0.05$). Longer napping time was associated with increased pain ($r=0.38$, $p\leq 0.01$), fatigue ($r=0.37$, $p\leq 0.01$), daytime sleepiness ($r=0.38$, $p\leq 0.01$) and depressive symptoms ($r=0.23$, $p\leq 0.05$). Gastrointestinal symptoms were associated with increased sleep onset latency ($r=0.33$, $p\leq 0.01$), nighttime awakenings ($r=0.30$, $p\leq 0.05$) and time in bed ($r=0.34$, $p\leq 0.01$). Maladaptive sleep behaviours were associated with longer sleep onset latency ($r=0.27$, $p\leq 0.05$), increase nighttime awakening ($r=0.24$, $p\leq 0.05$), early morning awakening ($r=0.24$, $p\leq 0.05$), and poorer sleep efficiency ($r=-0.35$, $p\leq 0.01$). None of the objective measures were significantly correlated to erroneous sleep beliefs or 24-hour light exposure.

Jakobsen et al, 2020 (47)	40 (24 M), metastatic mixed cancer patients, median age 70	Overnight actigraphy (Actiwatch 2) and polysomnography	Actigraphy: mean total sleep time was 418 min (SD±138), mean sleep onset latency was 35 min (SD±61), mean number of awakenings was 24 (SD±15), mean total time awake was 40 min (SD±21), and mean percent of time in bed asleep was 78% (SD±23). Actigraphy measured total sleep time ($r_s=0.61$, $p<0.005$) and sleep efficiency ($r_s=0.48$, $p<0.005$) were associated with patient reported outcomes measures (PROMs). Sleep onset latency, number of awakenings and wake after sleep onset were not associated with PROMs. Longer wake after sleep onset (actigraphy) was “significantly” associated with worsening of total subjective sleep quality ($r_s = 0.45$, significance level not reported).
Fujisawa et al, 2019 (49)	51 (20 M), stage 4 non-small cell lung cancer patients, mean age 66.8	3-day actigraphy (Actiwatch 2) and activity log	The hazard ratio was 1.48 for each 10% increment of time awake spent immobile ($p<0.05$). The odds ratio for death within 6 months was 2.99 for each 10% increment of time awake spent immobile ($p<0.05$). Eastern Cooperative Oncology Group (ECOG) performance status (PS) was non-discriminatory for survival in patients with a PS 0-1. For those who died at 6 months, discriminating factors for survival were 10% increment of time awake spent immobile (OR 2.99, $p<0.05$), ECOG PS >1 (OR 9.23, $P<0.05$), and the percentage of time awake spent immobile (OR 5.09, $p<0.05$). Time awake spent immobile correlated with Functional Assessment of Cancer Therapy – Trial Outcome Index (FACT-TOI) ($p<0.01$) and ECOG PS ($p<0.01$).
Komarzynski et al, 2019 (46)	31 (17 M), mixed cancer patients (24 metastatic), median age 61	30-day actigraphy (Micro Motionlogger)	Median sleep efficiency was 92.0% (20.2-100%), the sleep midpoint was 0329 (0038-1019), wake time was 0800 (0349-1539), bedtime was 2307 (1929-0500), sleep onset latency was 5 min, wake after sleep onset was 42 min, number of wake episodes was 11, and total sleep time was 7hr50 (6h50-8h44). Subjective sleep disturbance was associated with objective parameters ($p\leq0.05$). Worse MD Anderson Symptom Inventory (MDASI) sleep scores were found in those with lower sleep efficiency ($r=-0.13$, $p=0.002$), larger number of wake episodes ($r=0.12$, $p=0.005$),

			longer wake after sleep onset ($r=0.14$, $p<0.001$), and worse sleep fragmentation index (r not defined) ($p=0.01$). The number of wake episodes was associated with fatigue ($p=0.02$), drowsiness ($p=0.03$) and interference with activity ($p=0.03$). Sleep efficiency was associated with daytime drowsiness ($p = 0.01$). MDASI sleep correlated with sleep efficiency, wake minutes, wake episodes, sleep episodes, and longest sleep episodes (all $p<0.01$) MDASI sleep correlated with wake after sleep onset ($p<0.001$) MDASI fatigue correlated with total sleep time, total time in bed and sleep episodes ≥ 5 min (all <0.01) MDASI drowsiness correlated with wake after sleep onset and total time in bed (all $p<0.01$) MDASI interference with activity correlated with sleep episodes ≥ 5 min and longest sleep episode (all $p<0.01$).
Bernatchez et al, 2018 (26)	55 (29 M) mixed cancer patients (44 stage 3-4, 52 distant metastases), mean age 65.9 Actigraphy data available for 55 patients, outliers removed and 51 analysed	7-day actigraphy (Actiwatch-64) and sleep diary	The R-squared (rhythmicity coefficient of the sleep-wake cycle) was 0.27 (0.09-0.51), acrophase was 1335 (1034-2010), MESOR (average activity level) was 45.4 (3.6-167.8), amplitude was 47.0 (5.4-178.8), up-MESOR (mean time from low to high activity) was 8.18 (2.00-14.00) and down-MESOR (mean time from high to low activity) was 19.23 (16.20-22.00). Less rhythmic sleep-wake cycle, as characterised by lower amplitude ($r=0.32$), MESOR ($r=0.27$), and R-squared ($r=0.31$) was associated with shorter survival (all $p\leq 0.05$). No circadian activity rhythm parameter was correlated with pain, fatigue, depression, or maladaptive sleep behaviours. A lower amplitude ($r=0.24$, $p\leq 0.01$), lower MESOR ($r=0.27$, $p\leq 0.05$) and later acrophase ($r=-0.23$, $p\leq 0.01$) was associated with poorer global QoL. A higher down-MESOR was associated with poor global ($r=-0.31$, $p\leq 0.05$) and functioning QoL ($r=-0.30$ $p\leq 0.05$). A more robust rest-activity rhythm (higher amplitude ($r=0.33$, $p\leq 0.05$), MESOR ($r=0.42$, $p\leq 0.01$), and r-squared ($r=0.24$, $p\leq 0.05$)) was associated with greater 24-hour exposure to light intensity >1000 lux.

			There were no significant differences between any rest-activity rhythm variable between ECOG 2 vs. 3.
Bernatchez et al, 2018 (43)	57 (26 M) mixed cancer patients (40 stage 3-4, 48 distant mets) 51 analysed, mean age 66.4	7-day actigraphy (Actiwatch-64) and sleep diary	The wake after sleep onset ranged between 48.2-70.9 min. The longest daytime napping was 100.3 min. Patients with no perceived sleeping difficulty had a mean sleep onset latency of 10.2 min, wake after sleep onset of 48.2 min, total wake time of 68.5 min, total sleep time of 479.9 min, time in bed of 548.4 min and sleep efficiency of 87.3%. Subjective assessments differed from objective assessment, significance not reported. No significant differences for sleep-wake parameters were noted between males and females.
Cash et al, 2018 (178)	55 (33 M) stage 0-4 head and neck cancer patients, mean age at diagnosis 58.5	6-day actigraphy (Mini-Motion logger) and sleep diary	The mean rest-activity rhythm (RAR) correlation coefficient (r ₂₄) was 0.132 and mean nighttime restfulness was 92.82%. The activity acrophase occurred at 1446. 2-year survival was impacted by RAR disruption (HR 0.073, p = 0.012), lower nighttime restfulness (HR 0.910, p=0.009) and the acrophase (HR 1.196, p=0.288). Depression was associated with RAR disruption (r=-0.338, p=0.041). Overall and somatic depressive symptoms were associated with activity phase shifts (morning to evening) (r=0.370, p=0.024).
Innominato et al, 2018 (126)	11 (5 M) advanced or metastatic colorectal or pancreatic cancer patients, median age 60	30-day actigraphy (Micro-Motionlogger)	Activity was prominent at daytime and restful at nighttime. Mean I<O values ranged from 96.3-98.5%. The average sleep efficiency was 81.9-90.8% and <70% in approximately 1/10 of the nights. The average total sleep time was 8.6-9.7 hours with an average midpoint of sleep of 0102-0530. I<O was independent predictive factor for all selected MDASI PROMs.
Innominato et al, 2018 (125)	Cohort 1: 237 metastatic colorectal cancer patients, not receiving anticancer Cohort 2: 31 advanced or metastatic gastrointestinal cancer patients	Cohort 1: 3-day actigraphy (Mini-Motionlogger) Cohort 2: 30-day actigraphy (Micro-Motionlogger)	The I<O was ≤97.5% in 54.9% of cohort 1 and 44.4% in cohort 2. A reduced I<O was significantly associated with increasing fatigue (p<0.0001), anorexia (p<0.0001), pain (p<0.0001), and sleep trouble (p<0.003). An increased I<O was significantly associated with greater values of global quality of life (p<0.0001), physical (p<0.0001),

			and social ($p<0.0001$) functioning but not role ($p=0.02$) functioning. Patients with a reduced I<O values had more interference with enjoyment of life, activity, relations with others and work (all $p<0.0001$).
Chang and Lin, 2017 (169)	82 (59 M) stage 1-4 lung cancer patients, mean age 66.54	3-day actigraphy (Ambulatory Monitoring Inc.) and sleep diary	The I<O was 88.50 and higher I<O was associated with improved QoL ($p<0.001$).
Palesh et al, 2017 (40)	237 (148 M) metastatic colorectal cancer patients, median age 60.4	3-day actigraphy (Mini-Motionlogger)	Median values were a total sleep time of 7hr22, sleep efficiency of 90.56%, sleep latency of 8m40s, wake after sleep onset of 46m15s, I<O of 96.9%, bathyphase (lowest activity time) of 0233, and average activity of 99 accelerations/minute. Patients with subjective sleep complaints had more circadian disruption (lower I<O) compared to those without sleep complaints ($p=0.005$). 40.1% of patients had subjective and circadian disruption (I<O <97.5%), 25.3% had subjective disruption alone, 14.8% had circadian disruption alone and 19.8% had neither. Lowest health-related quality of life scores (including global, physical, social and role functioning), and highest symptom scores (including fatigue and appetite loss), were seen in those with subjective and circadian disruption. Subjective difficulty sleeping was not associated with actigraphy sleep parameters.
Chen et al, 2016 (42)	Intervention group: 56 (24 M) stage 1-4 lung cancer patients, mean age 64.64 Standard care group: 55 (25 M) stage 1-4 lung cancer patients, mean age 62.51	3-day actigraphy (Micro-Mini actigraph) and sleep diary	Baseline (mean values): The r24 values were 0.42 (I) and 0.36 (C). A poor r24 was seen in 11/56 in the intervention group and 18/55 in the standard care group (26% overall). The I<O values were 94.68 (I) and 92.65 (C). A poor I<O was seen in 11/56 in the intervention group and 23/55 in the standard care group (30% overall). The total sleep time was 380.32 (I) and 395.06 (C). The sleep efficiency was 88.94 (I) and 88.36 (C). The sleep onset latency was 27.14 (I) and 31.85 (C). The wake after sleep onset was 45.86 (I) and 50.56 (C).
Ortiz-Tudela et al, 2016 (39)	24 (11 M), gastrointestinal cancer patients (21 metastatic), median age 63	4 and 8 days of wrist temperature activity and body position (accelerometry)	The L5 timing (centre of least 5 active hours) was 01.13 +/- 42 min. I<O before chemotherapy was 83.88%.

			Females had stronger and less fragmented rhythms than males. Significant gender differences were seen for interdaily stability (IS, a measure of rhythm stability) ($p = 0.002$), intradaily variability (IV, a measure of rhythm fragmentation) ($p = 0.001$), relative amplitude (RA, the difference between the mean of ten consecutive hours with the highest values and the mean of five consecutive hours with highest values divided by the combined value of both) ($p = 0.001$), circadian function index (CFI, combined IV/IS/RA) ($p < 0.001$) and I < O ($p = 0.008$).
Rebholz et al, 2018 (158)	57 (F) stage 0-5 breast cancer patients, mean age 52.32	3-day actigraphy (Ambulatory Monitoring Inc.) & 3-day salivary cortisol (waking, +30 min, 1600, bedtime)	The r24 was 0.28 and wake after sleep onset was 0.15. African American females had more wake after sleep onset ($p=0.017$) and lower r24 ($p=0.037$) which persisted after adjusting for age and cancer stage. Wake after sleep onset and r24 were not significantly correlated with QoL.
Cash et al, 2015 (31)	43 (F) stage 0-4 breast cancer patients, mean age 52.49	3-day actigraphy (Micro Mini-motionlogger) and sleep diary & salivary cortisol (3 days – on waking, +30 min, 1600, pre-bed)	The mean r24 was 0.27, nighttime restfulness (proportion of activity in bed that falls below the median out of bed activity) was 97.21%, daytime sedentariness (proportion of activity out of bed that is below the median in bed activity) was 6.59%, mean sleep time was 386.94 minutes, sleep efficiency was 89%, and wake after sleep onset was 13 minutes. Uncoordinated rest-activity rhythm, such as poor inter-daily stability, was associated with elevated markers VEGF, TGF-beta, MMP-9 (associated with angiogenesis, immunosuppression, epithelial-mesenchymal transition, tumour invasion and metastasis).
Dean et al, 2015 (173)	29 (18 M) stage 2a-4 non-small cell lung cancer patients, mean age 66.6	7-day actigraphy (Motionlogger) and sleep diary	Baseline actigraphy demonstrated poor sleep with 45% of patients sleeping <6 hours. The mean sleep efficiency was 77%, sleep latency was 51 minutes and sleep duration was 5.9 hours. Baseline sleep efficiency and wake after sleep onset were not associated with FACT-TOI, FACT-L, FACT-G or the subscales. There were however associated after receiving chemotherapy.
Zeitzer et al, 2015 (34)	97 (F) recurrent or metastatic breast cancer patients, age 57.4	2-week actigraphy (Actiwatch 2) and sleep diary logs &	No relevant findings from actigraphy

		Serum cortisol (20–60-minute intervals from 3 hours prior to bedtime to 1 hour after wake time) Salivary cortisol 0900, awakening and 30 minutes	
Chang and Lin, 2014 (123)	68 (34 M) stage 2-4 mixed cancer patients, median age 54.0	3-day actigraphy (Ambulatory Monitoring Inc.) and sleep diary	The median I<O was 89.5%. 34 patients were classified having a “disrupted” circadian rhythm ($I<O \leq 89.4$) and 34 patients were classified as having a “regular” circadian rhythm ($I<O \geq 89.5$) Survival was longer for patients with a “regular” circadian rhythm than a “disrupted” rhythm (3.9 months vs. 1.8 months, $p<0.001$, HR 2.19, $p=0.006$) Controlling for age, gender, cancer diagnosis, cancer stage, PSQI, Brief Pain Inventory-Chinese version (BPI-C), and Karnofsky Status (KPS) scale, a “dampened” circadian rhythm impacted survival (HR 4.59 $p=0.001$). Significant difference in cumulative patient survival rates were reported between “disrupted” and “regular” rhythm ($p=0.005$).
Levi et al, 2014 (114)	436 (273 M) colorectal cancer patients (427 metastatic), median age 59	2-7-day actigraphy (Mini-Motion logger)	The median I<O was 97.5% and a lower I<O was associated with poor WHO performance status (PS0 98.2%, PS1 96.5% PS1 and PS2/+ 91.5%, $p<0.001$). Females had a higher I<O than males (98.0% vs. 97.1%, $p=0.04$). Overall survival was longer in patients with an I<O $>97.5\%$ than those with an I<O $\leq 97.5\%$ (21.6 months vs. 11.9 months, $p<0.001$). A 1% increase of I<O had a HR 0.954 ($p=0.003$). Progression free survival was also longer in patients with an I<O $>97.5\%$ than those with an I<O $\leq 97.5\%$ (9.3 months vs. 5.8 months, $p<0.001$). Median I<O varied between patients without metastases (99.4%), with one metastatic site (97.4%), and with two or more metastatic sites (97.1%) ($p=0.03$).
Ma et al, 2014 (128)	68 (34 M) mixed advanced cancer patients, mean age 52.40	3-day actigraphy (Actigraph) and sleep diary	The median and mean r_{24} were 0.19 (-0.03-0.64). The median was I<O 89% and the mean I<O 85.29% (51-100%). Patients spent a mean total time in bed of 461.19 min, mean total sleep time was 314.92 min, mean sleep efficiency was 75.95%, mean wake after sleep onset was 99.48 min, mean

			sleep onset latency was 40.65 min and mean waking episodes was 12.66. Higher r24 was associated with longer total sleep time ($r=0.26$), improved sleep efficiency ($r=0.29$), shorter sleep onset latency ($r=-0.24$) and less wake after sleep onset ($r=-0.28$) (all $p<0.05$). Higher I<O was associated with longer total sleep time ($r=0.38$, $p<0.001$) and shorter sleep onset latency ($r=-0.49$, $p<0.01$), improved sleep efficiency ($r=0.30$, $p<0.05$) and less wake after sleep onset ($r=-0.25$, $p<0.05$). r24 and I<O were negatively correlated with worst pain, pain intensity and global PSQI score (all $p<0.01$). r24 predicted sleep quality and pain intensity ($p<0.001$).
Ortiz-Tudela et al, 2014 (127)	49 (25 M) mixed cancer patients (47 metastatic), median age 61.6	3-10-day actigraphy (Mini-Motionlogger)	A mean rhythmic 24-hour pattern was observed for the whole group of patients. Circadian disruption during or after chemotherapy was significantly associated with developing clinically relevant fatigue (OR 5.1, $p=0.028$), or body weight loss (OR 6.1, $p=0.05$).
Palesh et al, 2014 (153)	97 (F) metastatic or locally advanced breast cancer patients, mean age 54.6	3-day actigraphy (Micro Mini-Motionlogger) and sleep diary & 2-day salivary cortisol (waking, +30 minutes, 1200, 1700 and 2100)	Patients had mean total sleep time of 390 minutes, wake after sleep onset of 71.2 minutes, 14.5 wake episodes and 4.8 minutes duration of wake episodes. The mean sleep efficiency was 84.6%, total time in bed of 478.3 min and a sleep latency of 11.5 min. A higher sleep efficiency was associated with lower mortality (HR 0.96, $p<0.001$). A 10% increase in sleep efficiency reduced subsequent mortality by 32%. The mean survival with a sleep efficiency of $\geq 85\%$ was 68.9 ± 4.0 months compared with 33.2 ± 4.3 for a lower sleep efficiency ($p<0.001$). The sleep efficiency effect on survival remained after adjusting for age, oestrogen receptor status, treatments received, metastases, depression, and cortisol (HR 0.94 $p<0.001$). There was no association between sleep duration and survival.
Dean et al, 2013 (172)	35 (34 M) stage 1-4 lung cancer patients, mean age 63.5	7-day actigraphy (Motionlogger) and sleep diary	77% patients had a sleep latency of more than 30 minutes and 61% slept less than 5 hours per night. 88% of patients had a sleep efficiency of $<85\%$ and 91% were awake more than 30 minutes after sleep onset.

			Considering “good” and “poor” sleepers, actigraphy measures of sleep and measures of mood were not significantly different. Subjective and objective measures of sleep efficiency, sleep latency, sleep hours and wake after sleep onset were significantly different (all <0.05). There were no significant associations between the sleep diary and actigraphy variables of interest.
Dedert et al, 2012 (171)	57 (F) stage 1-4 breast cancer patients, mean age 52	3-day actigraphy and sleep diary & 3-day salivary cortisol (waking, 30 minutes after, 1600 and bedtime)	The mean r24 was 0.27. Nighttime inactivity was 97.3% and daytime inactivity was 6.1%. Intrusive thoughts were associated with a lower r24 and with daytime sedentariness. There was no association between intrusive thoughts and nighttime inactivity. More avoidant coping was associated with a lower r24 (p<0.05) and daytime inactivity (p<0.001). A higher autocorrelation co-efficient was significantly correlated with a steeper diurnal cortisol slope (p = 0.003).
Dhruva et al, 2012 (174)	73 (F) breast cancer patients (43.8% locally advanced), mean age 55.1	2-day actigraphy (Ambulatory Monitoring Inc.) and sleep diary	87% of patients had an “excessive” number of awakenings, 46% had abnormal wake after sleep onset and 58% had total sleep times below healthy adult values. 25.6% had abnormal sleep onset latency and the mean value was 14.7. 46.2% had abnormal wake after sleep onset and the mean value was 11%. 87.2% had an abnormal number of awakenings with the mean number being 15.1. 57.7% had abnormal total sleep time with the mean of 419.8 minutes. 26.9% had abnormal sleep efficiency and the mean was 85.5%.
Innominato et al, 2012 (124)	77 (65 M) metastatic colorectal cancer patients, median age 62.3	At least 3-day actigraphy (Mini-Motionlogger)	The median and mean I<O were 97.5% and 95.1%. 39 patients (50.6%) had altered I<O of <97.5%. There was no significant association between I<O and progression free survival. Overall survival was associated with a more robust circadian rhythm (22.3 months vs. 14.7 months, p=0.013). This was independent of gender, treatment schedule, number of metastatic sites, rank of chemotherapy course of interest and performance status on day 1 (p = 0.004).

			Patients with an altered rhythm during chemotherapy had a higher risk of earlier death (HR 2.12, $p=0.004$). There were no significant differences between I<O and response rate or overall grade 3-4 toxicity rate. No clinical or biological parameters predicted the occurrence of a rhythm disturbance on treatment. Baseline disruption did not predict subsequent disruption and there was no significant correlation between baseline and on-treatment I<O). There was no significant difference in toxicity in relation to circadian parameters.
Gibbins et al, 2009 (44)	60 (27 M) mixed advanced and incurable cancer patients, median age 67	7-day actigraphy (Actiwatch W-4) and sleep diary	Sleep efficiency was >90% for most patients with 12% of patients having a sleep efficiency <86%. Patients had 14-17 naps per day, lasting around 9 minutes each and 42-48% of the day was spent immobile. Cancer diagnosis was not significantly related subjective or objective data. Subjective sleep quality was not correlated with objective sleep efficiency, sleep fragmentation or daytime activity.
Innominato et al, 2009 (112)	130 (74 M) metastatic colorectal cancer patients, median age 60	At least 3-day actigraphy (Mini-Motionlogger)	The mean r24 was 0.38 and the median r24 was 0.37. The mean I<O was 94.3 and the median I<O was 97.0. The I<O and r24 were associated ($r = 0.74$, $p<0.001$) I<O and r24 were also associated with meanAct (mean activity levels) ($p<0.001$). There were no significant associations between progression free survival and any CircAct parameter (I<O, r24, meanAct). Patients in the lowest I<O quartile (<92.4%) had the poorest survival (12.0 months), and patients in the highest I<O quartile ($\geq 99.2\%$) had better survival (23.5 months). I<O and r24 were related to survival (HR 0.95, $p<0.0001$ and HR 0.20, $p=0.004$). Higher I<O, r24 and meanAct were associated with improved QoL and role functioning and less fatigue and appetite loss (all $p\leq 0.01$). Higher I<O and r24 were associated with improved social functioning, and less pain and dyspnoea ($p\leq 0.01$). Higher I<O and meanAct were associated with improved physical functioning ($p\leq 0.01$).

			Higher I<O was associated with less insomnia ($p \leq 0.01$). Actigraphy parameters were not correlated with emotional or cognitive functioning, nausea/vomiting, constipation, or diarrhoea. Patients with a good WHO PS had a more robust CircAct (I<O ($p=0.01$), r24 ($p=0.0014$), meanAct ($p=0.047$) that those with a poor PS. Lower I<O and r24 was associated with poorer WHO PS (PS0 I<O 98.2, r24 0.44, PS1 I<O 95.7, r24 0.36, PS2 I<O 95.3, r24 0.24). Use of analgesia was associated with a disturbed circadian rhythm ($p < 0.05$ for all parameters). CircAct parameters did not correlated with age, gender, body mass index, number of metastases, site of primary tumour, blood tests, previous chemotherapy, or percent of liver involvement, $p > 0.10$). CircAct parameters did not predict for tumour response or toxicity.
Palesh et al, 2008 (150)	99 (F) metastatic breast cancer patients, mean age 54.65	3-day actigraphy (Micro Mini-Motionlogger) & 2-day salivary cortisol (waking, +30 min, 1200, 1700, 2100)	Cancer patients had a time in bed of 478.5 min, sleep onset latency of 11.50 min, wake after sleep onset of 71.44 min, sleep efficiency of 84.5% and 15 wake episodes. Longer time in bed was associated with lower pain intensity ($r = -0.23$, $p = 0.03$), depression ($r = 0.21$, $p = 0.05$), younger age ($r = -0.24$, $p = 0.02$), and chemotherapy ($r = -0.29$, $p = 0.006$). Longer mean sleep latency was associated with lower perceived stress scale scores ($r = -0.22$, $p = 0.04$) and the use of radiation ($r = 0.21$, $p = 0.05$). Mean sleep efficiency was associated with the dominant metastatic site being the chest alone vs. bone or viscera ($r = 0.27$, $p = 0.01$). Longer wake after sleep onset was negatively related to metastases to the chest only ($r = -0.31$, $p = 0.003$) and positively correlated to hormone therapy ($r = 0.24$, $p = 0.03$). Higher mean number of wake episodes were associated with younger age ($r = -0.23$, $p = 0.03$), metastases to the chest only ($r = -0.23$, $p = 0.03$), sleep medication ($r = 0.26$, $p = 0.012$) and hormone therapy ($r = 0.23$, $p = 0.03$).
Rich et al, 2005 (154)	80 (52 M) metastatic colorectal cancer patients	3-day actigraphy (Actigraph) & 2-day serum cortisol (0800 and 1600)	"Good" circadian rhythm patients had a higher median r24 (0.58 vs. 0.22), I<O (98.45% vs. 91.36%), O>I (96.57% vs.

	Group 1 (40) – “Good” circadian rhythm ($r_{24} > 0.47$, < 0.77), median age 59.6 Group 2 (40) – “Dampened” rhythm ($r_{24} > 0.03$, < 0.35), median age 60		83.89%) and mean activity levels (107.5 vs. 84.0) than patients with “dampened” circadian rhythm (all $p \leq 0.0001$) “Good” circadian rhythm patients survived longer than “dampened” circadian rhythm patients (13.8 months vs. 11.1 months, $p = 0.0176$). r_{24} and $I<O$ were prognostic ($p = 0.001$ and $p < 0.0001$ in a univariate analysis). Patients with “Dampened” circadian rhythms had higher fatigue (60% vs. 40%, $p = 0.003$), nausea/vomiting (33% vs. 10%, $p = 0.007$) and appetite loss (50% vs. 28%, $p = 0.004$) than patients with “good” circadian rhythms. “Good” circadian rhythm patients had higher QoL emotional and social functioning scores ($p < 0.0001$). PS was worse in patients with “dampened” circadian rhythms ($p < 0.0008$).
Mormont et al, 2002 (136)	192 (128 M) metastatic colorectal cancer patients, mean age 58	3–5-day actigraphy (Actigraph)	r_{24} was associated with $I<O$ ($r = 0.67$, $p < 0.001$) and both r_{24} and $I<O$ were associated with mean activity ($r = 0.38$ and 0.21, $p < 0.01$). $I<O$ and r_{24} were highest in patients with a performance status 0 and lowest in those with a performance status 2. Higher $I<O$, r_{24} and mean activity was associated with less fatigue, appetite loss and nausea/vomiting (all $p \leq 0.05$) Higher $I<O$ was associated with less pain, constipation, and dyspnoea (all $p \leq 0.002$). Higher $I<O$ and r_{24} were associated with less depression (all $p \leq 0.01$). Higher $I<O$ and r_{24} were associated with improved global quality of life, physical functioning, social functioning, and emotional functioning (all $p \leq 0.04$).
Mormont et al, 2002 (129)	18 14(M) metastatic colorectal cancer patients, mean age 58	3-day actigraphy (Actigraph) & serum melatonin, 6- alphasulfatoxymelatonin and salivary cortisol Blood and saliva collected 3-6 hours apart over 10-13 time points on day 1 and day 4	Actigraphy demonstrated a mean r_{24} of 0.37, median r_{24} of 0.41, mean $I<O$ of 92.8 and median $I<O$ of 94.2. 13 patients had an $r_{24} > 0.28$, 10 patients had $I<O > 25\%$ quartile Interindividual variation was noted in circadian rhythms of activity, hormonal, and haematological markers of circadian system function.
Mormont et al, 2000 (113)	192 (128 M) metastatic colorectal cancer patients, mean age 58	3-day actigraphy (Actigraph) and sleep diary %	The r_{24} ranged from -0.06 to 0.77 with a median 0.42. The dichotomy index ($I<O$) ranged from 49-100% with a median of 97%.

		2 days of blood cortisol (0800 and 1600)	Patients with a higher r24 or I<O had longer survival ($p<0.0001$). Patients in the upper quartiles had a longer 2-year survival than those in the lower quartiles (38% vs. 8%). Higher I<O and r24 were associated with improved global quality of life and physical functioning, and lower depression scores ($p\leq 0.01$). Higher I<O, r24 and mean activity were associated with less fatigue and less appetite loss ($p<0.001$). Higher I<O was also associated with less pain ($p=0.002$). Higher mean cortisol was seen in patients with a low r24 ($r=-0.17$, $p=0.04$), or low I<O ($r=-0.24$, $p=0.007$). Cortisol rhythmicity was correlated with the r24 ($r=0.16$, $p=0.04$). Self-rated sleep disturbances were not correlated to the rest-activity rhythm or mean activity levels. A poor performance status was associated with lower r24 and I<O ($p<0.0001$), and lower mean activity ($p=0.04$). The probability of an objective response was significantly influenced by r24 ($p=0.02$) and I<O ($p<0.0001$).
Mormont et al, 1998 (159)	Study 1: 18 (14 M) metastatic colorectal cancer patients, age 35-72 Study 2: 109 (72 M) metastatic colorectal cancer patients, median age 59	Study 1: 3-day actigraphy & melatonin and cortisol (blood 9-11 time points, 6 hourly) Study 2: At least 3-day actigraphy activity	9/18 patients had a marked circadian activity rhythm. Wide interindividual variation was noted. High r24 ($p=0.0005$), dichotomy indices ($p=0.0005$) and activity levels ($p=0.0002$) were related to survival. Increases in r24 were correlated with less fatigue ($r=-0.33$, $p=0.03$), less appetite loss ($r=-0.34$, $p=0.01$), less depression ($r=-0.24$, $p=0.04$), improved global quality of life ($r=0.29$, $p=0.009$), improved social functioning ($r=0.28$, $p=0.01$) and performance status ($p=0.008$).

M = male; F = female; I<O = dichotomy index; r24 = 24-hour autocorrelation coefficient

Table 1d. Polysomnography-related circadian rhythms and their associations in patients with advanced cancer

STUDIES WITH A CONTROL GROUP			
Article	Participants	Circadian measures	Outcomes relevant to review
Zeitzer et al, 2016 (149)	97 (F) recurrent or metastatic breast cancer, age 57.6 24 age-matched control subjects, age 57.1 (gender not identified)	28-hour polysomnography and plasma cortisol (20-60-minute intervals) & 2-week actigraphy (Actiwatch 2) and sleep diary	Abnormal cortisol peaks were associated with polysomnography sleep disruption (p=0.004).
Silberfarb et al, 1993 (182)	Cancer patients: 17 (10 M) limited stage small-cell lung cancer or stage 2-4 non-small cell lung cancer, mean age 60.1 15 (F) stage 1-3 breast cancer, mean age 57.5 32 sex- and age-matched control subjects 32 patients with insomnia	3-day polysomnography and 2-week sleep diary	Cancer patients had longer total time in bed than any other group (vs. normal p<0.001, vs. patients with insomnia p<0.003). There was no difference in total time asleep between cancer groups (p=0.05) Sleep efficiency was lower in cancer patients (lung cancer vs. control subjects (p=0.007) and breast cancer vs. control subjects, (p=0.10)). Sleep latency was longer for lung cancer patients than control (p=0.03). Lung cancer patients had more difficulty remaining asleep than breast cancer patients (p=0.01) and control subjects (p=0.001).
STUDIES WITHOUT A CONTROL GROUP			
Padron et al, 2022 (177)	Cognitive behavioural therapy for insomnia and pain (CBT.i.p) group: 18 (F) stage 1-3 mixed gynaecological cancers, mean age 58.9 Psychoeducation (PE) group: 17 (F) stage 1-4 mixed gynaecological cancers, mean age 59.9	14-day polysomnography & actigraphy (Actiwatch-L) and sleep diary	Actigraphy and sleep diary data were not correlated. Baseline mean values (polysomnography vs. actigraphy) CBTi.p.: sleep efficiency was 75.5% vs. 80.8%, sleep onset latency was 24.7 min vs. 29.3 min, and wake after sleep onset was 91.1 min vs. 50.5 min PE: sleep efficiency was 71.0% vs 79.4%, sleep onset latency was 36.2 min vs. 33.6 min, wake after sleep onset was 94.8 min vs. 53.4 min Objective (CBT.i.p and PE): 29% and 24% of patients had a SE >85% at baseline 76% and 50% of patients had SOL <30 min 6% and 13% of patients had WASO <30 min
Jakobsen et al, 2020 (47)	40 (24 M) mixed metastatic cancer diagnoses, median age 70	Overnight polysomnography and actigraphy (Actiwatch 2)	Results detail actigraphy findings and associations. Polysomnography findings not reported.

Parker et al, 2008 (181)	114 (58 M) stage 3-4 mixed cancer diagnoses, mean age 55.2	24-hour polysomnography	Patients slept approximately 382 minutes/night (normal 340-466 minutes) and 17.5% had <5 hours sleep/night. Nocturnal sleep latency was <30 minutes (normal defined as <30 min) and sleep efficiency was 77.2% (normal defined as 86-100%). >60 brief arousals occurred per hour and approximately 6 of the awakenings lasted at least 60 seconds/h. Patients slept in the daytime for an average of 89.3min. Total daytime sleep was associated with less nocturnal total sleep time ($r_s=-0.21$, $p=0.025$) and less sleep efficiency ($r_s=-0.25$, $p=0.008$), and more wake episodes (nocturnal index of awakenings) lasting at least 60 seconds ($r_s=0.27$, $p=0.003$). Females had higher sleep efficiency than males (80.0% vs. 74.9%, $p=0.042$). White patients had more nocturnal total sleep time (409.8 min vs. 364.4 min, $p=0.017$) and higher sleep efficiency than non-white patients (80.2% vs. 75.3%, $p=0.021$). Patients living with another had greater nocturnal total sleep time (392.5 min vs. 336.9 min, $p=0.035$) and shorter sleep latency (23.5 min vs. 57.2 min, $p=0.018$) than patients living alone. A higher level of education was associated with a higher sleep efficiency (79.2% vs. 74.6%, $p=0.013$). Lung cancer patients had higher index of awakenings lasting at least 60 seconds than breast cancer patients (3.9 vs. 2.4, $p=0.002$). Total sleep time was increased in patients that use SSRIs (430.4 min vs. 372.7 min, $p=0.009$) and reduced in patients taking beta blockers (345.7 min vs. 388.5 min, $p<0.047$). Antineoplastics agents were associated with an increased sleep efficiency (83.4% vs. 76.1%, $p=0.000$). Beta blockers significantly decreased sleep efficiency (72.3% vs. 78.1%, $p=0.047$).

M = male; F = female

Appendix 2. Research Ethics Committee (REC) Approval Forms

2a. REC approval for the e-Delphi study.



**Tallaght
University
Hospital**

An Academic Partner of Trinity College Dublin

Ospidéal
Ollscoile
Thamhlachta



Research Office

Project ID: 1926

Dr Craig Gouldthorpe,

Our Lady's Hospice & Care Services

Approval Date: 16 August 2022

Submission Number: 1009

Submission Title: Circadian activity Rhythm

Disorders in Cancer (CaRDIC) study

Submission Date: 11.Jul.2022 11:24

Dear Dr Gouldthorpe,

On behalf of the Chair and members of the SJH/TUH Joint Research Ethics Committee I wish to inform you that your study has received **FULL APPROVAL**. Your study can now proceed.

The following comments were made:

Title	Comment
Participant Information Leaflet/Consent Form (Please note that templates are available for download within this portal).	The legal basis needs to be explained in the PIL - Please add response from letter to PIL. Please also note Consent isn't the most appropriate legal basis for processing data. Consent is a legal requirement but doesn't need to be the legal basis. The issue is when a patient withdraws. Their data, collected up to the point of withdrawal cannot continue to be processed as they have withdrawn their consent. The more appropriate legal basis is 6(1)(e) and 9(2)(j). If the patient withdraws you still have a legal basis to continue processing the data collected up to the point of withdrawal. If you change the legal basis a sentence that data will be continue to be processed following withdrawal needs to be added to the PIL.

The following documents were reviewed and approved.

Document Type	File Name	Date	Version
Principle Investigator C.V.	CVAndrewDavies 08.02.2022		
Proof of additional Insurance	2021-2022 TWIMC		
Indemnity Proof for Non-TUH researchers	2021-2022 TWIMC		
Data Collection Case Report Form	CRF	10.Mar.2022	1.0
Protocol	Circadian activity rhythm disorder assessment tool protocol	10.Mar.2022	1.0
Telephone Script	Telephone script	10.Mar.2022	1.0
Data Collection Case Report Form	Data	12.Jun.2022	1.0
Participant Consent Form	Patient consent form v1.1	13.Jun.2022	1.1
Participant Information Leaflet	Patient information leaflet v1.1	13.Jun.2022	1.1
Default	Ethics clarifications	13.Jun.2022	1.0

Please note that ethical approval for this study is only active under the following conditions:

1. Applicants must submit an annual report for ongoing projects.
2. Applicants must submit an end of study declaration/end of study report upon completion of the study.
3. All adverse events must be reported to the JREC.
4. All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Dr Sadhbh O'Neill

Research Ethics &

Clinical Trials

Manager, SJH/TUH

Joint Research

Ethics Committee

The SJH/TUH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

2b. REC approval for the observational and feasibility study (joint submission).



**Tallaght
University
Hospital**

An Academic Partner of Trinity College Dublin

Ospidéal
Ollscoile
Thamhlachta



Research Office

Project ID: 1926

Dr Craig Gouldthorpe,

Our Lady's Hospice & Care Services

Approval Date: 14 April 2023

Submission Number: 2573

Submission Title: Circadian activity Rhythm Disorders in
Cancer (CaRDIC) study Submission Date: 23.Feb.2023
12:28

Dear Dr Gouldthorpe,

On behalf of the Chair and members of the SJH/TUH Joint Research Ethics Committee I wish to inform you that your study has received **FULL APPROVAL**. Your study can now proceed.

The following documents were reviewed and approved:

Document Type	File Name	Date	Version
Participant Information Leaflet	Screening Study - Patient Information Leaflet v1.1	21.Feb.2023	1.1
Participant Information Leaflet	Treatment Study - Patient Information Leaflet v1.0	21.Feb.2023	1.0
Participant Consent Form	Screening study - Patient consent form v1.1	21.Feb.2023	1.1
Participant Consent Form	Treatment study - Patient consent form v1.0	21.Feb.2023	1.0
Amended Documents	Circadian rest-activity rhythm disorder protocol v1.1	21.Feb.2023	1.1
Amended Documents	Amendments to protocol and documentation with rationale	21.Feb.2023	1.0

Please note that ethical approval for this study is only active under the following conditions:

1. *Applicants must submit an annual report for ongoing projects.*
2. *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
3. *All adverse events must be reported to the JREC.*
4. *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Dr Sadhbh O'Neill

Research Ethics &

Clinical Trials

Manager, SJH/TUH

Joint Research

Ethics Committee

The SJH/TUH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix 3. Participant information leaflets (PIL)

3a. PIL for the e-Delphi study

Circadian activity Rhythm Disorders Identification in Cancer – Participant Information Sheet



As a researcher investigating activity rhythms in cancer patients, we would like to invite you to take part in this study. It is important that you understand what this will involve and why it is happening. Please read the following information sheet to see if this study is something that you would like to take part in.

What is the purpose of this study?

A scoping review has highlighted several studies identifying disordered circadian activity rhythms in patients with cancer. Disordered activity rhythms appear to be associated with more symptom burden, poorer quality of life and a shorter survival. The review highlights that several actigraphy parameters have been reported. Activity parameters may consider the timing of activity levels, variation within the day, or variation between days. No diagnostic criteria for Circadian activity Rhythm Disorders exists.

Activity rhythms are currently identified using polysomnography or actigraphy, supported by a patient sleep diary. This often requires either an inpatient stay or a prolonged period of monitoring of between 3 and 7 days.

The aim of this Delphi study is to generate consensus expert opinion in several areas. Firstly, to establish expert opinion on the diagnostic criteria of a cancer-associated circadian activity rhythm disorder. Secondly, to establish expert opinion on which actigraphy parameters are important and which items should be included in a patient diary for future research. Thirdly, to establish expert opinion on important questions to be used in an assessment tool to identify circadian activity rhythm disorders in patients with cancer.

Why have I been invited?

As a researcher investigating activity patterns in patients with cancer, your opinion is relevant to generating consensus opinion.

Do I have to take part and can I change my mind?

Taking part in the study is voluntary. You can change your mind at any point. If you decide to leave the study, we would appreciate understanding why although this is not required.

What does being involved include?

The study will use the Delphi method through online questionnaires. The first round will provide the opportunity for sharing your opinions on the three areas. The group's responses will be combined with findings from the scoping review.

All participants will then be provided with anonymised responses from the previous round and asked to comment on their own agreement with various questions and statements. This process of providing feedback and reviewing responses will continue until a consensus is achieved. We aim for around 3-4 rounds of questionnaires and expect the process to be completed within 3 months. In the event of a consensus not being achieved, or participants have difficulty with the questionnaire, an online meeting may be held to discuss the topics further.

What are the possible benefits of the study?

The aim of the study is to identify diagnostic criteria for a cancer-associated circadian activity rhythm disorder, to highlight important actigraphy parameters and to generate an assessment tool to identify circadian activity rhythm disorders. This will hopefully standardise the approach to investigating activity rhythm disorders, allow for easier detection of patients suffering with circadian activity rhythm disorders and help in future studies which investigating the management of circadian activity rhythm disorders.

What are the possible risks of the study?

No risks have been identified to you taking part in the study.

Will be information be kept confidential?

Yes. At the beginning of the study, you will be assigned a unique code. This will be known by the research team and your responses will be anonymised. The other participants will be unable to identify you by your responses. Recorded information will be stored on a secure system which is only accessible by the research team.

What will happen to the results of the study?

This study is being carried out as a part of a PhD. A report will be made of the findings and provided to Trinity College Dublin. The study findings will also be submitted for publication in medical journals and presentation at medical conferences. The responses from the Delphi study aim to generate an open access assessment tool for circadian activity rhythm disorders which will be investigated during a second study.

Will I be paid to take part in the study?

No. Taking part in the study is voluntary and there will be no financial compensation in taking part. However, with your permission, we plan to acknowledge all collaborators in the study outputs.

Legal basis and data protection rights

The legal basis for data processing is provided by:

- General Data Protection Regulation (EU) 2016/679 Article 6 and Article 9
- The Data Protection Act 2018

Your explicit consent will be asked to process your personal and health related data for the purpose of this study. You have the following rights with respect to your personal data:

- Right to access the data held
- Right to restrict the use of the data held
- Right to correct inaccuracies
- Right to have information deleted
- Right to data portability

- Right to object to profiling

Is this research funded?

There is no commercial or pharmaceutical sponsorship of this research. The research is being conducted as part of a research qualification with Trinity College Dublin.

Has this study been reviewed by an ethics committee?

The St James' Hospital / Tallaght University Hospital Joint Research Ethics Committee has reviewed and approved the study.

CONTACT DETAILS

Dr Craig Gouldthorpe

Phone: +353 (0)1 498 6235

Email: cgouldthorpe@olh.ie / researchteam@olh.ie

Chief Investigator: Professor Andrew Davies

Data Controller: Trinity College Dublin, Ireland

Data Protection Officer: Patricia Pierce, Our Lady's Hospice & Care Services,
Harold's Cross

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Data Processors:

Dr Craig Gouldthorpe, Clinical Lecturer, Our Lady's Hospice & Care Services

Dr Jenny Power, Clinical Lecturer, Our Lady's Hospice & Care Services

Ms Elaine Hyland, Research Nurse, Our Lady's Hospice & Care Services

Ms Norah Fagan, Research Nurse, Our Lady's Hospice & Care Services

I wish to thank you for taking the time to consider participating in this study.

3b. PIL for the observational study



Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Adult Participant Information Leaflet

Identifying Circadian activity Rhythm Disorders in people with cancer

As a patient with cancer, we would like to invite you to take part in this study taking place at Trinity College Dublin, St James' Hospital, Tallaght University Hospital and Our Lady's Hospice & Care Services. It is important that you understand what this will involve and why it is happening. Please read the following information sheet to see if this is something that you would like to take part in.

What is the purpose of the study?

Normally, people are more physically active during the day and less physically active during the night. Research has shown that this is not always the case for people with cancer, and this can lead to more symptoms and poorer quality of life. One of the ways that this can be investigated is by completing a diary whilst wearing a monitor on your wrist and thigh to detect your activity levels over 4 days. This study aims to test if a short questionnaire can identify the people that have an altered activity pattern.

Why have I been invited?

You have been invited to join the study as a patient with cancer who is well enough to assess activity levels.

Do I have to take part and can I change my mind?

Taking part in the study is voluntary. You can change your mind at any point and withdraw your consent. If you decide you no longer want to take part in the study, you do not have to give a reason why and this decision will not affect your future medical care.

What will happen if I take part in the study?

If you are happy to take part in the study, you will be invited to meet with a member of the research team. This can happen at Our Lady's Hospice & Care Services, St James' Hospital or Tallaght University Hospital. This meeting provides the opportunity to discuss the study, answer any questions and complete a consent form. You will be asked to complete several questionnaires and to provide information about your health and medications, for example. A routine blood sample will also be taken at either visit to look at your blood count, liver function, kidney function and signs of inflammation. This first meeting is expected to take no longer than 1 hour.

At this first meeting you will be provided with two devices (a watch-like monitor and a thigh monitor), and a diary and shown how to use them. You will then wear the device and complete the diary over the next 4 days (including three nights).

At the end of the 4 days, you will be asked to return to meet with the research team. The device and diary will be collected, and you will be asked to complete the questionnaire about your physical activity for a second time, and a questionnaire about how you found taking part in the assessments. This meeting is expected to take around 30 minutes. After the initial 4 days, the research team will continue to monitor your progress through your hospital team, hospice team, or general practitioner.

We hope to include 100 people in this study.

There is currently a lack of evidence as to how to manage patients with altered activity patterns. If you are identified to have an altered activity pattern, you will be invited to take part in a second study. The second study aims to test a non-drug intervention to improve your activity patterns.

What are the possible benefits of the study?

This study hopes to find an easy and quick way to diagnose patients with changes to their physical activity pattern. If this is possible, then it will also help with future research looking at how we can improve patients' physical activity patterns. If you are

found to have an altered activity rhythm, you will be invited to take part in a follow-on study to address any potentially reversible causes and to try to improve your rhythm without using medication.

What are the possible risks of the study?

During the study, a blood test will be taken. As with any blood test, there is a chance of minor pain, bleeding, and bruising. There are no risks of completing the other assessments in this study. We may notice changes in your blood results or identify symptoms that may need to be looked into further. In that case, the research team will advise you further and, with your permission, contact your GP, hospital or hospice team.

What information about me will be used as part of this study? Will my medical records be accessed?

The study will involve answering several questionnaires and providing a blood sample. We would like to know your age, gender, cancer history, cancer treatments and current medications, for example. There will be questionnaires about your symptoms, quality of life, sleep, and general wellbeing. The devices will monitor your physical movements in minute periods over the 3-days. Your medical records may be accessed to find out about your recent blood tests and cancer history, for example.

What will happen to my personal data? Will my information be kept confidential?

When you decide to take part in the study you will be given a code number. Any information that identifies yourself, such as your name, date of birth, or address, will be removed to keep the information pseudonymous. The research team, including medical and non-medical staff, will only collect necessary information. The results of the questionnaires and blood test may be shared with your GP and/or hospital team if needed.

Your information will initially be collected on a paper form. This will then be uploaded to a secure electronic database at the Academic Department of Palliative Medicine in the Education and Research Centre at Our Lady's Hospice & Care Services in Harold's

Cross, Dublin. The information will be accessible only to the research team. Your information will then not leave the department. Your information will be stored for 5 years. After this time the information will be destroyed.

What will happen with the results of the study?

This study is being carried out as part of a university qualification. A report will be made from the results of the study and provided to Trinity College Dublin. A copy can be provided on request. This will then be submitted for publication in medical journals and/or presented at medical conferences.

The findings from this study may be relevant to future studies and your information may therefore be used in a future study.

The legal basis for data processing is provided by:

- General Data Protection Regulation (EU) 2016/679 Article 6 and Article 9
- The Data Protection Act 2018

Your explicit consent will be asked to process your personal and health related data for the purpose of this study. You have the following rights with respect to your personal data:

- Right to access the data held
- Right to restrict the use of the data held
- Right to correct inaccuracies
- Right to have information deleted
- Right to data portability
- Right to object to profiling

What are my rights?

- The right to access to your data held and a copy of your data, unless your request will make it impossible or very difficult to conduct the research
- The right to restrict or object to processing, unless your request would make it impossible or very difficult to conduct the research

- The right to have any inaccurate information about yourself corrected or deleted, unless your request would make it impossible or very difficult to conduct the research
- The right to have your personal data deleted, unless your request would make it impossible or very difficult to conduct the research
- The right to data portability, meaning you have a right to move your data from one controller to another in a readable format.
- The right to object to automated processing including profiling if you wish
- Right to withdraw consent
- Right to lodge a complaint with the Data Protection Commissioner

Will I be paid to take part in this study? Will it cost me anything if I agree to take part?

No. Taking part in the study is voluntary and there will be no financial compensation in taking part. You will be required to attend your usual hospital (St James' Hospital or Tallaght University Hospital) or to attend the hospice (Our Lady's Hospice & Care Services, Harold's Cross, Dublin).

Who is funding the study? Will the results of the study be used for commercial purposes?

The study is being funded by Professor Andrew Davies and is being conducted as part of a research qualification with Trinity College Dublin. There are no commercial investments in the study.

Has this study been reviewed by an ethics committee?

Yes. The St James' Hospital / Tallaght University Hospital Joint Research Ethics Committee has reviewed and approved the study.

Will my information be used in future studies?

Information collected in this study may be relevant to a future health-related study of activity levels and/or of people with cancer. You can provide consent for your

information to be used only in this study, or for it also to be used in future related studies.

CONTACT DETAILS

If you need any further information now, or at any time in the future, please contact:

Dr Craig Gouldthorpe

Phone: 014986235

Email: cgouldthorpe@olh.ie / researchteam@olh.ie

Chief Investigator: Professor Andrew Davies

Data Controller: Our Lady's Hospice & Care Services, Harold's Cross, Ireland

Data Protection Officer: Patricia Pierce, Our Lady's Hospice & Care Services,
Harold's Cross

01-4068725

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Data Processors:

Dr Craig Gouldthorpe, Clinical Lecturer, Our Lady's Hospice & Care Services

Dr Jenny Power, Clinical Lecturer, Our Lady's Hospice & Care Services

Dr Amy Taylor, Clinical Research Fellow, Our Lady's Hospice & Care Services

Ms Norah Fagan, Research Nurse, Our Lady's Hospice & Care Services

I wish to thank you for taking the time to consider participating in this study.

3c. PIL for the feasibility study



Adult Participant Information Leaflet

A multi-modal feasibility trial to improve Circadian activity Rhythm Disorders in people with cancer

As a person with cancer, who has been identified to have an activity rhythm disorder, we would like to invite you to take part in this study taking place at Trinity College Dublin, St James' Hospital, Tallaght University Hospital and Our Lady's Hospice & Care Services. It is important that you understand what this will involve and why it is happening. Please read the following information sheet to see if this is something that you would like to take part in.

What is the purpose of the study?

Normally, people are more physically active during the day and less physically active during the night. Research has shown that this isn't always the case for people with cancer, and this can lead to worse symptoms, worse quality of life, and potentially worse outcomes. This study aims to test whether a non-drug intervention can be given to people with cancer and altered activity rhythms. The study also aims to see if the intervention improves people's rest and activity patterns, symptoms and quality of life.

Why have I been invited?

You have been invited to join the study as a person with cancer who has been identified to have an altered rest and activity rhythm pattern.

Do I have to take part and can I change my mind?

Taking part in the study is voluntary. You can change your mind at any point and withdraw your consent. If you decide you no longer want to take part in the study, you do not have to give a reason why and this decision will not affect your future medical care.

What will happen if I take part in the study?

If you are happy to take part in the study, you will be invited to meet with a member of the research team. This can happen at Our Lady's Hospice & Care Services, St James' Hospital or Tallaght University Hospital. This meeting gives you the opportunity to discuss the study, ask any questions and complete a consent form.

The study will take place over 8-weeks and involve receiving two clinical reviews, completing an online cognitive behavioural therapy course, daily light therapy and engaging with an activity plan. There will also be two face-to-face meetings to complete questionnaires about your symptoms and quality of life, and to complete a period of activity monitoring.

The two clinical reviews aim to identify any reversible causes of your rest and activity rhythm disturbance. This will include looking at uncontrolled symptoms, blood abnormalities and any medication that you are taking. It will also help to set activity goals, address barriers, and introduce you to the other treatments.

Cognitive behavioural therapy-I (CBT-I) has been shown to be effective at improving the time it takes for people to fall asleep and reducing the amount of time you wake up in the night. The online course will allow you to understand how to maximise your sleep, change how you think about sleep and improve the things that you do before and during sleep. In order to access the online course, you will need to accept a user agreement.

Light therapy mimics our natural exposure to sunlight. Light exposure may help to improve our sleep during the night, our mood, and our activity or attention levels during the day. Light therapy will be delivered using a light box. The study will involve sitting near a light box for at least 15 minutes every morning. This can take place whilst doing your normal morning activities, such as eating breakfast or reading a book.

We will also review your physical activity levels, including your most active and inactive periods. We will then discuss your interests, any barriers to activity, and work together to set goals for the study. This will be reviewed on an ongoing basis and aims to improve your activity levels throughout the day and to reduce the amount of time you

spend sitting or lying down. You will be provided with a device which will feedback on how active you have been.

Whilst taking part in the study you will also be asked to complete a diary to document your use of the interventions, how acceptable the interventions are, and any problems that have occurred.

During the 8-week study, there will be four face-to-face meetings. This will include two meetings with a clinician to address potentially reversible reason for your rest and activity rhythm patterns. These will take place at the start of the study and at 2 weeks. There will also be two meetings with the research team to carry out assessments (questionnaires and a period of activity monitoring). This will take place at week 4 and week 8.

Each week that you are not seeing a clinician or member of the research team, we will contact you to address any barriers or complications you have found with the interventions. A text message or email will also be sent to provide encouragement and remind you of your goals.

We hope to include around 30 people in this study. After the initial 3 month study, the research team will continue to monitor your progress through your hospital team, hospice team, or GP.

What are the possible benefits of the study?

This study hopes to find out if a combination of non-drug interventions is acceptable and can be tested on a group of people with your condition. It will also see if the interventions improve your rest and activity patterns, symptoms, and quality of life. If successful, the study will then be carried out on a larger scale with more people.

What are the possible risks of the study?

This study is not testing medications or invasive interventions. Following a clinical review, alternative treatments may be needed, such as a new medication to manage

pain or correct a blood abnormality. Any suggested changes are part of routine practice and are only being suggested within this study as we have identified a problem.

Cognitive behavioural therapy for insomnia (CBT-I) is as effective as medication to improve sleep and has less side effects. People may notice side effects of fatigue, sleepiness, and headache, for example. CBT-I also encourages you to try to avoid spending time in bed not sleeping. If you are feeling tired or unsteady in the evening and try to get out of bed, there is a risk that you may fall. You will be advised how to minimise this risk and by being aware of the risk, it makes it less likely. Sleep restriction can also cause problems if you have epilepsy, bipolar disorder or excessive sleepiness, for example, and may be removed from your treatment plan.

Light therapy may worsen symptoms of mania and so any person with a history of mania or bipolar disorder requires supervision whilst receiving light therapy. There is also a small risk of increased suicidal thoughts in susceptible people. These factors will be considered before you take part in the trial, and you will only be allowed to take part if there is no significant risk. Mild short-term side effects can include headache, nausea, and eye strain.

Without supervision, increasing physical activity levels can lead to more symptoms and falls for example. Before taking part in the study, you will be reviewed by the clinician to assess whether it is appropriate for you to take part. This will include assessing for symptoms such as angina, collapses, and uncontrolled high blood pressure.

As part of the study your information will be reviewed to see if you are suitable to take part. We may find that the intervention is not suitable and therefore you may not be able to take part. Any complications that happen during the study will be reviewed by the research team. If there is a complication, we will consider whether it is safe for you and other participants to continue with the study.

What information about me will be used as part of this study? Will my medical records be accessed?

The study will involve answering several questionnaires, completing activity diaries, and wearing an activity monitor. We would like to know your age, gender, cancer

history, cancer treatments and current medications, for example. There will be questionnaires about your symptoms and quality of life. The devices will monitor your physical movements in minute periods over the 3-days. Your medical records may be accessed to find out about your recent blood tests and cancer history, for example.

What will happen with my personal data? Will my information be kept confidential?

When you decide to take part in the study you will be given a code number. Any information that identifies yourself, such as your name, date of birth, or address, will be removed to keep the information pseudonymous. The research team, including medical and non-medical staff, will only collect necessary information. The results of the questionnaires and blood test may be shared with your GP and/or hospital team if needed.

Your information will initially be collected on a paper form. This will then be uploaded to a secure electronic database at the Academic Department of Palliative Medicine in the Education and Research Centre at Our Lady's Hospice & Care Services in Harold's Cross, Dublin. The information will be accessible only to the research team. Your information will then not leave the department. Your information will be stored for 5 years. After this time, the information will be destroyed.

What will happen with the results of the study?

This study is being carried out as part of a university qualification. A report will be made from the results of the study and provided to Trinity College Dublin. A copy can be provided on request. This will then be submitted for publication in medical journals and/or presented at medical conferences.

The findings from this study may be relevant to future studies and your information may therefore be used in a future study.

The legal basis for data processing is provided by:

- General Data Protection Regulation (EU) 2016/679 Article 6 and Article 9
- The Data Protection Act 2018

Your explicit consent will be asked to process your personal and health related data for the purpose of this study. You have the following rights with respect to your personal data:

- Right to access the data held
- Right to restrict the use of the data held
- Right to correct inaccuracies
- Right to have information deleted
- Right to data portability
- Right to object to profiling

What are my rights?

- The right to access to your data held and a copy of your data, unless your request will make it impossible or very difficult to conduct the research
- The right to restrict or object to processing, unless your request would make it impossible or very difficult to conduct the research
- The right to have any inaccurate information about yourself corrected or deleted, unless your request would make it impossible or very difficult to conduct the research
- The right to have your personal data deleted, unless your request would make it impossible or very difficult to conduct the research
- The right to data portability, meaning you have a right to move your data from one controller to another in a readable format.
- The right to object to automated processing including profiling if you wish
- Right to withdraw consent
- Right to lodge a complaint with the Data Protection Commissioner

Will I be paid to take part in this study? Will it cost me anything if I agree to take part?

No. Taking part in the study is voluntary and there will be no financial compensation in taking part. You will be required to attend your usual hospital (St James' Hospital or Tallaght University Hospital) or to attend the hospice (Our Lady's Hospice & Care Services, Harold's Cross, Dublin).

Who is funding the study? Will the results of the study be used for commercial purposes?

The study is being funded by Professor Andrew Davies and is being conducted as part of a research qualification with Trinity College Dublin. There are no commercial investments in the study.

Has this study been reviewed by an ethics committee?

Yes. The St James' Hospital / Tallaght University Hospital Joint Research Ethics Committee has reviewed and approved the study.

Will my information be used in future studies?

Information collected in this study may be relevant to a future health-related study of activity levels and/or of people with cancer. You can provide consent for your information to be used only in this study, or for it also to be used in future related studies.

CONTACT DETAILS

If you need any further information now, or at any time in the future, please contact:

Dr Craig Gouldthorpe

Phone: 014986235

Email: cgouldthorpe@olh.ie / researchteam@olh.ie

Chief Investigator: Professor Andrew Davies

Data Controller: Our Lady's Hospice & Care Services, Harold's Cross, Ireland

Data Protection Officer: Patricia Pierce, Our Lady's Hospice & Care Services, Harold's Cross

01-4068725

ppierce@olh.ie

Data Processors:

Dr Craig Gouldthorpe, Clinical Lecturer, Our Lady's Hospice & Care Services

Dr Jenny Power, Clinical Lecturer, Our Lady's Hospice & Care Services

Dr Amy Taylor, Clinical Research Fellow, Our Lady's Hospice & Care Services

Ms Norah Fagan, Research Nurse, Our Lady's Hospice & Care Services

I wish to thank you for taking the time to consider participating in this study

Appendix 4. Consent forms

4a. Consent form for the e-Delphi study

Circadian activity Rhythm Disorders Identification in Cancer – Delphi study (Online) Consent Form

**PLEASE INITIAL YOUR RESPONSE IN THE
APPROPRIATE BOX**



I confirm have read and understood the Participant Information Leaflet for the above study.

The study has been fully explained to me and I have been able to ask questions. Any questions have been satisfactorily answered.

I understand that this study is entirely voluntary, that I am free to withdraw from the study at any time.

I give my consent to have my data processed as part of this research study. I understand all data and information will be anonymised for analysis and kept private and confidential.

I understand that findings from the study will be shared anonymously with other researchers and that the findings may be published in journals or presented at educational events, for example.

I understand that I will not be paid for taking part in this study.

I know how to contact the research team if I need to.

I agree to take part in this research study.

Please initial your response in the appropriate box	Yes		No	

Participant's Signature: _____

Date: _____

Participant's Name in print: _____

4b. Consent form for the observational study

Circadian activity Rhythm Disorder identification in Cancer trial (CaRDiC) trial



Screening study patient consent form



General		
I confirm that I had read and understood the information leaflet for the above study and the information within the leaflet has been fully explained to me	YES ☐	NO ☐
I have had the opportunity to discuss the study, ask questions about the study and I have received satisfactory answers to all my questions	YES ☐	NO ☐
I understand that the study is entirely voluntary, and I can stop taking part in this study at any time without giving a reason and this will not affect my future medical care.	YES ☐	NO ☐
I understand that medical notes and records may be looked at by the research team where it is relevant. I understand that all information will be kept private and confidential, and I agree that the research team can access my medical records.	YES ☐	NO ☐
I understand research staff accessing records may not be staff at the hospital site that I visit	YES ☐	NO ☐
I agree to allow non-medical researchers to access my medical records and understand that my data will be kept confidential and that my name will not be disclosed.	YES ☐	NO ☐
I give my consent to a blood sample being taken and analysed for the purpose of the study.	YES ☐	NO ☐
I agree to my GP, hospital or hospice team being contacted in relation to medical records and symptoms or blood results if needed	YES ☐	NO ☐
I understand that I will not be paid for taking part in the study	YES ☐	NO ☐
I know how to contact the research team if I need to	YES ☐	NO ☐
I agree to be contacted by researchers by email, mail, or phone as part of this study	YES ☐	NO ☐
I consent to take part in this research study having been fully informed of the risks, benefits and purpose of the study as set out in the information leaflet which I have been provided with.	YES ☐	NO ☐
I understand that there are no direct benefits to me from participating in this study. I understand that results from analysis of my personal information will not be given to me.	YES ☐	NO ☐

Data Protection		
I understand that information collected in this study will be shared anonymously with other researchers and that findings will be published in journals or presented at research/educational events.	YES ☐	NO ☐
I consent to data collected in this study being used for future studies.	YES ☐	NO ☐
I give my explicit consent to have my data processed as part of this research study	YES ☐	NO ☐
Future use of information in health-related research (activity research and/or cancer research)		
OPTION 1: I give permission for the information collected in this study be stored for possible future research related to the current study <u>only if consent is obtained</u> at the time of the future research and the research is approved by a Research Ethics Committee.	YES ☐	NO ☐
OPTION 2: I give permission for the information collected in this study to be stored for possible future research related to the current study <u>without further consent</u> being required but only if the research is approved by a Research Ethics Committee.	YES ☐	NO ☐
OPTION 3: I understand <u>I will not be paid for any</u> future use of my samples/personal information or products derived from it.	YES ☐	NO ☐

Participant's Signature: _____ Date: _____

Participant's Name in print: _____

I have fully explained the purpose and nature (including benefits and risks) of this study to the participant in a way that he/she could understand.				
I have invited him/her to ask questions on any aspect of the study.				
I confirm that I have given a copy of the information leaflet and consent form to the participant.				
Please initial your response in the appropriate box	Yes	☐	No	☐

Investigator's Signature: _____ Date: _____

Investigator's Name in print: _____

4c. Consent form for the feasibility study

A multi-modal feasibility trial to improve Circadian activity Rhythm Disorders in people with cancer



Patient study consent form



General		
I confirm that I had read and understood the information leaflet for the above study and the information within the leaflet has been fully explained to me	YES ☐	NO ☐
I have had the opportunity to discuss the study, ask questions about the study and I have received satisfactory answers to all my questions	YES ☐	NO ☐
I understand that the study is entirely voluntary, and I can stop taking part in this study at any time without giving a reason and this will not affect my future medical care.	YES ☐	NO ☐
I understand that medical notes and records may be looked at by the research team where it is relevant. I understand that all information will be kept private and confidential, and I agree that the research team can access my medical records.	YES ☐	NO ☐
I understand research staff accessing records may not be staff at the hospital site that I visit	YES ☐	NO ☐
I agree to allow non-medical researchers to access my medical records and understand that my data will be kept confidential and that my name will not be disclosed.	YES ☐	NO ☐
I agree to my GP, hospital or hospice team being contacted in relation to medical records and symptoms or blood results if needed	YES ☐	NO ☐
I understand that I will not be paid for taking part in the study	YES ☐	NO ☐
I know how to contact the research team if I need to	YES ☐	NO ☐
I agree to be contacted by researchers by email, mail or phone as part of this study	YES ☐	NO ☐
I consent to take part in this research study having been fully informed of the risks, benefits and purpose of the study as set out in the information leaflet which I have been provided with.	YES ☐	NO ☐
I understand that there are no direct benefits to me from participating in this study. I understand that results from analysis of my personal information will not be given to me.	YES ☐	NO ☐

Data Protection		
I understand that information collected in this study will be shared anonymously with other researchers and that findings will be published in journals or presented at research/educational events.	YES ☐	NO ☐
I consent to data collected in this study being used for future studies.	YES ☐	NO ☐
I give my explicit consent to have my data processed as part of this research study	YES ☐	NO ☐
Future use of information in health-related research (activity research and/or cancer research)		
OPTION 1: I give permission for the information collected in this study be stored for possible future research related to the current study <u>only if consent is obtained</u> at the time of the future research and the research is approved by a Research Ethics Committee.	YES ☐	NO ☐
OPTION 2: I give permission for the information collected in this study to be stored for possible future research related to the current study <u>without further consent</u> being required but only if the research is approved by a Research Ethics Committee.	YES ☐	NO ☐
OPTION 3: I understand <u>I will not be paid for any</u> future use of my samples/personal information or products derived from it.	YES ☐	NO ☐

Participant's Signature: _____ Date: _____

Participant's Name in print: _____

I have fully explained the purpose and nature (including benefits and risks) of this study to the participant in a way that he/she could understand.				
I have invited him/her to ask questions on any aspect of the study.				
I confirm that I have given a copy of the information leaflet and consent form to the participant.				
Please initial your response in the appropriate box	Yes	☐	No	☐

Investigator's Signature: _____ Date: _____

Investigator's Name in print: _____

Appendix 5. Sleep and activity diaries

5a. Sleep and activity diary version 1.1

Participant no:

SLEEP AND ACTIVITY DIARY v1.1 (Please complete in the EVENING)	Day 1		Day 2		Day 3		Day 4	
	DD/MM		DD/MM		DD/MM		DD/MM	
How sleepy or tired have you felt today? (Please circle)	Extremely sleepy or tired		Extremely sleepy or tired		Extremely sleepy or tired		Extremely sleepy or tired	
	Quite sleepy or tired		Quite sleepy or tired		Quite sleepy or tired		Quite sleepy or tired	
	A little sleepy or tired		A little sleepy or tired		A little sleepy or tired		A little sleepy or tired	
	Not sleepy or tired at all		Not sleepy or tired at all		Not sleepy or tired at all		Not sleepy or tired at all	
If you had a nap during the day, how many times did you nap?								
If you had a nap today, how many minutes did you nap for?	min		min		min		min	
If you had a nap today, what time(s) did you nap? (Please circle all that apply)	Morning		Morning		Morning		Morning	
	Afternoon		Afternoon		Afternoon		Afternoon	
	Evening		Evening		Evening		Evening	
Did you take any extra medications or drugs today? (Please circle)	Yes	No	Yes	No	Yes	No	Yes	No
If you did, what did you take?								
How many cigarettes did you smoke today?								
What time did you smoke your last cigarette of the day?	HHMM		HHMM		HHMM		HHMM	

Participant no:

SLEEP AND ACTIVITY DIARY v1.1 (Please complete in the EVENING)	Day 1		Day 2		Day 3		Day 4	
	DDMM		DDMM		DD/MM		DD/MM	
How many caffeinated drinks did you have today? (e.g. coffee, tea, caffeinated fizzy drinks)								
If you had a caffeinated drink, what time did you have your last caffeinated drink today?	HHMM		HHMM		HHMM		HHMM	
How many alcoholic drinks did you have today?								
If you had an alcoholic drink, what time did you have your last alcoholic drink?	HHMM		HHMM		HHMM		HHMM	
How much time did you spend doing vigorous physical activity during the day? (e.g. running, jogging, fast cycling, carrying heavy objects)	hours		hours		hours		hours	
	minutes		minutes		minutes		minutes	
How much time did you spend doing moderate physical activity during the day? (e.g. brisk walking, steady cycling, hoovering, washing windows)	hours		hours		hours		hours	
	minutes		minutes		minutes		minutes	
How much time did you spend doing low level physical activity during the day? (e.g. slow walking, cooking, washing dishes)	hours		hours		hours		hours	
	minutes		minutes		minutes		minutes	
How much time did you spend lying, sitting, or relaxing during the day?	hours		hours		hours		hours	
	minutes		minutes		minutes		minutes	
Whilst being active, did you experience any symptoms? (e.g., pain, tiredness, breathlessness)	Yes	No	Yes	No	Yes	No	Yes	No
If so, what symptoms?								

Participant no:

SLEEP AND ACTIVITY DIARY (Please complete in the <u>EVENING</u>)		Day 1	Day 2	Day 3	Day 4
		DDMM	DDMM	DDMM	DDMM
Please highlight the most that you have exerted yourself today on a scale of 0-10					
0	Rest				
1	Really easy				
2	Easy				
3	Moderate				
4	Sort of hard				
5	Hard				
6					
7	Really hard				
8					
9	Really, really, hard				
10	Maximal: just like my hardest race				

What time would you like to be asleep for? (e.g. 10pm – 6am)	
What time in the day are you most alert? (e.g. noon – 2pm)	
What time in the day are you most sleepy? (e.g. 4pm – 6pm)	

Participant no:

SLEEP AND ACTIVITY DIARY v1.1 (Please complete in the MORNING)	Day 1	Day 2	Day 3	Day 4
	DDMM	DDMM	DDMM	DDMM
What time did you get into bed last night?	HHMM	HHMM	HHMM	HHMM
What time did you turn off the lights last night?	HHMM	HHMM	HHMM	HHMM
How many minutes did it take for you to fall asleep last night?	min	min	min	min
How many times did you wake up last night?				
How many minutes were you awake last night?	min	min	min	min
What time did you wake up this morning?	HHMM	HHMM	HHMM	HHMM
What time did you get out of bed this morning? (HH:MM)	HHMM	HHMM	HHMM	HHMM
How would you rate your sleep last night? (Please circle)	Terrible	Terrible	Terrible	Terrible
	Poor	Poor	Poor	Poor
	Good	Good	Good	Good
	Excellent	Excellent	Excellent	Excellent

Participant no:

5b. Sleep and activity diary version 1.2. Red font reflect changes in the second version.

SLEEP AND ACTIVITY DIARY v1.2 (Please complete in the EVENING)	Day 1		Day 2		Day 3		Day 4	
	DD/MM		DD/MM		DD/MM		DD/MM	
How sleepy or tired have you felt today? (Please circle)	Extremely sleepy or tired		Extremely sleepy or tired		Extremely sleepy or tired		Extremely sleepy or tired	
	Quite sleepy or tired		Quite sleepy or tired		Quite sleepy or tired		Quite sleepy or tired	
	A little sleepy or tired		A little sleepy or tired		A little sleepy or tired		A little sleepy or tired	
	Not sleepy or tired at all		Not sleepy or tired at all		Not sleepy or tired at all		Not sleepy or tired at all	
Did you find yourself resting or napping today?	Yes	No	Yes	No	Yes	No	Yes	No
If so, how many times?								
If so, for how long in minutes?	min		min		min		min	
If so, at what time(s) of the day?	Morning		Morning		Morning		Morning	
	Afternoon		Afternoon		Afternoon		Afternoon	
	Evening		Evening		Evening		Evening	
Did you take any extra medications or drugs yesterday? (Please circle)	Yes	No	Yes	No	Yes	No	Yes	No
If you did, what did you take?								
How many cigarettes did you smoke today?								
What time did you smoke your last cigarette of the day?	HHMM		HHMM		HHMM		HHMM	

Participant no:

SLEEP AND ACTIVITY DIARY v1.2 (Please complete in the <u>EVENING</u>)	Day 1		Day 2		Day 3		Day 4	
	DDMM		DDMM		DD/MM		DD/MM	
How many caffeinated drinks did you have today? (e.g. coffee, tea, caffeinated fizzy drinks)								
If you had a caffeinated drink, what time did you have your last caffeinated drink today?	HHMM		HHMM		HHMM		HHMM	
How many alcoholic drinks did you have today?								
If you had an alcoholic drink, what time did you have your last alcoholic drink?	HHMM		HHMM		HHMM		HHMM	
Have you spent time doing vigorous physical activity today? (e.g. running, jogging, fast cycling, carrying heavy objects)	Yes	No	Yes	No	Yes	No	Yes	No
Have you spent time doing moderate physical activity today? (e.g. brisk walking, steady cycling, Hoovering, washing windows)	Yes	No	Yes	No	Yes	No	Yes	No
Have you spent time doing low level physical activity today? (e.g. slow walking, cooking, washing dishes)	Yes	No	Yes	No	Yes	No	Yes	No
How many hours have you spent lying, sitting, or relaxing today?								
Whilst being active, did you experience any symptoms? (e.g., pain, tiredness, breathlessness)	Yes	No	Yes	No	Yes	No	Yes	No
If so, what symptoms?								

Participant no:

SLEEP AND ACTIVITY DIARY v1.2 (Please complete in the <u>EVENING</u>)		Day 1	Day 2	Day 3	Day 4
		DDMM	DDMM	DDMM	DDMM
Please highlight the most that you have exerted yourself today on a scale of 0-10					
0	Rest				
1	Really easy				
2	Easy				
3	Moderate				
4	Sort of hard				
5	Hard				
6					
7	Really hard				
8					
9	Really, really, hard				
10	Maximal: just like my hardest race				

What time would you like to be asleep for? (e.g. 10pm – 6am)	
What time in the day are you most alert? (e.g. noon – 2pm)	
What time in the day are you most sleepy? (e.g. 4pm – 6pm)	

Participant no:

SLEEP AND ACTIVITY DIARY (Please complete in the MORNING)	Day 1	Day 2	Day 3	Day 4
	DDMM	DDMM	DDMM	DDMM
What time did you get into bed last night?	HHMM	HHMM	HHMM	HHMM
What time did you turn off the lights last night?	HHMM	HHMM	HHMM	HHMM
What time did you try to go to sleep?	HHMM	HHMM	HHMM	HHMM
How many minutes did it take for you to fall asleep last night?	min	min	min	min
How many times did you wake up last night?				
How many minutes were you awake last night?	min	min	min	min
What time did you wake up this morning?	HHMM	HHMM	HHMM	HHMM
What time did you get out of bed this morning? (HH:MM)	HHMM	HHMM	HHMM	HHMM
How would you rate your sleep last night? (Please circle)	Terrible	Terrible	Terrible	Terrible
	Poor	Poor	Poor	Poor
	Good	Good	Good	Good
	Excellent	Excellent	Excellent	Excellent

Appendix 6. The impact of drug and lifestyle factors on adult sleep, nightmares, vivid dreams, restless legs, periodic limb movements, sedation and insomnia. Adapted from Foral (264)

Drug / drug class	Sleep latency	Sleep continuity	Sleep quantity	Sleep quality	Dreams and/or nightmares	Restless legs and/or periodic limb movements	Sedation	Insomnia
Acetylcholinesterase inhibitors								
Donepezil	-	-	-	Reduced	X	-	-	X
Rivastigmine	-	-	-	-	X	-	-	-
Tacrine	-	-	-	-	-	-	-	X
Analgesics								
Codeine	-	Reduced	Reduced	-	-	-	-	-
Diclofenac	-	-	-	-	-	-	X	X
Duloxetine	-	-	-	-	X	X	-	-
Gabapentin	-	-	-	-	-	-	-	-
Ibuprofen	-	-	-	-	-	-	X	-
Ketorolac	-	-	-	-	-	-	X	-
Mefenamic acid	-	-	-	-	-	-	X	X
Methadone	-	-	-	-	-	-	-	-
Morphine	-	Reduced	Reduced	-	-	-	-	-
Nabumetone	-	-	-	-	-	-	-	X
Naproxen	-	-	-	-	X	-	X	-
Pregabalin	-	-	-	-	-	-	-	-
Tramadol	-	-	-	-	-	X	-	-

Opioids	As a drug class can be sedating							
Antibiotics								
Ciprofloxacin	-	-	-	-	-	-	X	X
Clindamycin	-	-	-	-	-	X	-	-
Levofloxacin	-	-	-	-	-	-	-	X
Norfloxacin	-	-	-	-	-	-	X	-
Anticholinergics								
Benztropine	-	Reduced	-	-	-	-	X	
Oxybutynin	-	-	-	-	-	-	X	
Scopolamine	Reduced	Reduced	-	-	-	-	X	
Other	Dicyclomine, flavoxate, and trihexyphenidyl can be sedating							
Antidepressants								
SSRIs	Increased	Reduced	Reduced	Reduced				
Citalopram	-	-	-	-	-	X	X	X
Escitalopram	-	-	-	-	X	X	-	-
Fluoxetine	-	-	-	-	X	X	X	X
Fluvoxamine	-	-	-	-	-	-	-	X
Paroxetine	-	-	-	-	X	X	-	-
Sertraline	-	-	-	-	-	X	-	-
SNRIs								
Duloxetine	-	-	-	-	X	X	-	-
Venlafaxine	-	Reduced	Increased	-	X	X	-	X
TCAs	Reduced	-	increased					
Amitriptyline	-	-	-	-	X	-	X	X
Clomipramine	-	-	-	-	X	-	X	-

Desipramine	-	-	-	-	X	-	X	X
Doxepin	-	-	-	-	X	-	X	-
Imipramine	-	-	-	-	X	-	X	-
Nortriptyline	-	-	-	-	X	-	X	-
Antidepressant (other)								
Maprotiline	-	Increased	-	-	-	-	X	-
Mirtazapine	Reduced	Increased	Increased	Increased	X	X	X	-
Nefazodone	-	-	-	-	X		X	-
Trazadone	Reduced	Increased	Increased	-	-	-	X	-
MAOIs	Phenelzine/rasagiline/selegiline and tranylcypromine can be sedating, phenelzine/selegiline/tranylcypromine can cause insomnia							
Antiemetics								
Dolasetron	-	-	-	-	-	-	X	
Droperidol	-	-	-	-	-	-	X	
Granisetron	-	-	-	-	-	-	X	
Haloperidol	Reduced	Increased	Increased	-	-	-	X	
Metoclopramide	-	-	-	-	-	-	X	
Ondansetron	-	-	-	-	-	-	X	
Prochlorperazine	-	-	-	-	-	-	X	X
Anticancer therapy								
Flutamide	-	-	-	-	-	-	X	X
Interferon-α	-	-	-	-	-	X	-	-
Methotrexate	-	-	-	-	-	-	X	-
Procabazine	-	-	-	-	-	-	X	X
Thalidomide	-	-	-	-	-	-	X	-
Antiepileptics								

Amobarbital	Reduced	Increased	Increased	-	-	-	-	-
Carbamazepine	Reduced	-	Increased	-	-	-	X	-
Ethosuximide	-	-	-	Reduced	-	-	X	X
Ethotoin	-	-	-	-	-	-	X	X
Felbamate	-	-	-	-	-	-	-	X
Gabapentin	-	-	-	-	-	-	-	-
Lamotrigine	-	-	-	-	-	-	-	X
Levetiracetam	-	-	-	-	-	-	X	-
Mephobarbital	-	-	-	-	X	-	-	X
Oxcarbazepine	-	-	-	-	-	-	X	-
Pentobarbital	Reduced	Increased	Increased	-	-	-	-	-
Phenytoin	Reduced	-	-	-	-	-	X	-
Phenobarbital	Reduced	Increased	Increased	-	-	-	X	-
Pregabalin	-	-	-	-	-	-	-	-
Primidone	-	-	-	-	-	-	X	-
Secobarbital	Reduced	Increased	Increased	-	-	-	-	-
Tagavine	-	-	-	-	-	-	-	-
Tigabine	-	-	-	-	-	-	-	-
Topiramate	-	-	-	-	-	X	-	-
Valproate	Reduced	Increased	Increased	-	-	-	X	-
Zonisamide	-	-	-	-	-	X	X	-
Antihistamines – sedation common but require high doses for ‘non-sedating’ antihistamines								
Brompheniramine	-	-	-	-	-	-	-	X
Cetirizine	Reduced	-	-	-	-	-	-	-
Chlorpheniramine	-	-	-	-	X	-	-	-

Cimetidine	-	-	-	-	-	-	-	-
Cyproheptadine	-	-	-	-	-	-	-	-
Diphenhydramine	Reduced	-	-	-	-	-	-	-
Loratadine	-	-	-	-	-	-	-	-
Promethazine	-	-	-	-	-	-	-	-
Antipsychotics								
Aripiprazole	-	-	-	-	-	-	-	X
Chlorpromazine	Reduced	Increased	Increased	-	-	-	X	-
Clozapine	-	-	-	-	X	-	X	-
Haloperidol							X	-
Fluphenazine	-	-	-	-	-	-	X	-
Loxapine	Reduced	Increased	Increased	-	-	-	X	-
Molindone	-	-	-	-	-	-	X	-
Olanzapine	-	-	-	-	-	X	X	-
Perphenazine	-	-	-	-	-	-	X	-
Quetiapine	-	-	-	-	-	X	X	X
Risperidone	-	-	-	-	X	X	X	-
Thioridazine	-	-	-	-	-	-	X	-
Thiothixene	Reduced	-			-	-	X	-
Trifluoperazine	Reduced	Increased	Increased	-	-	-	X	-
Antivirals								
Abacavir	-	-	-	-	-	-	-	X
Amantadine	-	-	-	-	X	-	X	X
Efavirenz	Increased	-	-	-	X	-	X	X
Raltegravir	-	-	-	-	-	-	-	X

Benzodiazepines – the drug class can cause sedation and rebound insomnia								
Alprazolam	Reduced	-	-	-	-	-	-	
Clonazepam	Reduced	-	-	-	-	-	-	
Diazepam	Reduced	Increased	Increased	-	-	-	-	
Estazolam	Reduced	Increased	Increased	-	-	-	-	
Flurazepam	Reduced	Increased	Increased	-	-	-	-	
Midazolam	Reduced	Increased	Increased	-	-	-	-	
Quazepam	Reduced	Increased	Increased	-	-	-	-	
Temazepam	Reduced	Increased	Increased	-	X	-	-	
Triazolam	Reduced	Increased	Increased	-	X	-	-	
Cardiovascular – ACEI/ARB e.g. enalapril, losartan and quinapril can all cause dreams or nightmares								
Cardiovascular – Beta blockers – as a drug class can reduce sleep continuity and sleep quality, and cause insomnia								
Acebutolol	-	-	-	-	X	-	-	-
Atenolol	-	-	-	-	X	-	-	-
Carteolol	-	-	-	-	-	-	X	-
Labetalol	-	-	-	-	X	-	X	-
Metoprolol	-	-	-	-	X	-	X	-
Nadolol	-	-	-	-	X	-	-	-
Pindolol	-	-	-	-	X	-	-	-
Propranolol	-	-	-	-	X	-	-	-
Sotalol	-	-	-	-	X	-	-	-
Timolol	-	-	-	-	X	-	-	-
Cardiovascular – Calcium channel blockers								
Felodipine	-	-	-	-	X	-	-	X
Nisoldipine	-	-	-	-	X	-	-	X

Verapamil	-	-	-	-	X	-	-	-
Cardiovascular – Clonidine, methyldopa, nitroprusside, papaverine, prazosin and reserpine are sedating, clonidine can cause insomnia								
Corticosteroids – as a drug class can cause insomnia, dexamethasone and hydrocortisone can cause dreams or nightmares								
HMG-CoA reductase inhibitors (statins)								
Atorvastatin	-	-	-	-	X	-	-	-
Cerivastatin	-	-	-	-	-	-	-	X
Fluvastatin	-	-	-	-	-	-	-	X
Lovastatin	-	-	-	-	-	-	-	X
Simvastatin	-	-	-	-	X	-	-	X
Miscellaneous								
Allopurinol	-	-	-	-	-	-	X	-
Amiodarone	-	-	-	-	X	-	-	-
Bupropion	-	-	-	-	X	-	-	-
Chloral hydrate	Reduced	-	Increased	-	-	-	-	-
Clindamycin	-	-	-	-	-	-	-	-
Clonidine	-	Increased	Increased	-	X	-	X	X
Digoxin	-	-	-	-	X	-	-	-
Efavirenz	-	-	-	-	X	-	-	-
Estrogen	Reduced	-	Increased	-	-	-	-	-
Flutamide	-	-	-	Reduced	-	-	-	-
Gaba-hydroxybutyrate	-	-	-	-	X	-	-	-
Ganciclovir	-	-	-	-	X	-	-	-
L-thyroxine	-	-	-	-	-	X	-	-
Lithium	-	-	Increased	-	-	X	X	-

Mifepristone	Reduced	-			-	-	-	-
Phenelzine	-	-	Reduced	-	X	-	X	X
Procarbazine	-	-	-	Reduced	-	-	-	-
Progesterone	-	-	-	-	-	-	X	-
Reserpine	-	-	Reduced	-	X	-	-	-
Rizatriptan	-	-	-	-	-	-	X	-
Salmeterol	-	-	-	Increased	-	-	-	X
Sibutramine	-	-	-	-	X			-
Spironolactone	-	-	-	-	-	-	X	-
Sumatriptan	-	-	-	-	-	-	X	-
Theophylline	Increased	Reduced	-	-	-	-		X
Varenicline	-	-	-	-	X			-
Antiarrhythmics	Lidocaine and propfenone can be sedating, amiodarone and propafenone can cause insomnia							
Antitussives	Benzonatate and dextromethorphan can be sedating							
Muscle relaxants	Baclofen, carisoprodol, cyclobenzaprine, dantrolene, orphenadrine, tizanidine can be sedating / carisoprodol and tizanidine can cause insomnia							
Respiratory drugs	Albuterol, ipratropium, metaproterenol, salmeterol and theophylline can cause insomnia							
Thyroid supplementation	Can cause insomnia							
Parkinson's Disease								
Amantadine	-	-	-	-	X	-	X	-
Apomorphine	-	-	-	-	-	-	X	-
Bromocriptine	-	-	-	-	-	-	X	-
Cabergoline	-	-	-	-	-	-	X	-
Entacapone	-	-	-	-	-	-	X	-

L-dopa / carbidopa	-	-	-	-	X	X	-	X
Lisuride	-	-	-	-	-	-	X	-
Methyldopa	-	-	Increased	-	X	-	-	-
Pergolide	Reduced	-	-	Increased	-	X	X	X
Pramipexole	Reduced	-	-	Increased	-	X	X	-
Ropinirole	Reduced	-	-	-	X	-	X	-
Selegiline	Reduced	Reduced	-	-	X	-	X	X
Trihexyphenidyl	-	Reduced	-	-	-	-	-	-
Tolcapone	-	-	-	-	-	-	X	-
Stimulants								
Amphetamine	Increased	-	Reduced	-	-	-	-	X
Methylphenidate	-	Reduced	Reduced	-	-	-	-	X
Pemoline	-	Reduced	Reduced	-	-	-	-	X
Z-drugs								
Zolpidem	Reduced	Increased	-	Increased	-	-	X	-
Lifestyle								
Alcohol (acute)	Reduced	Increased	Increased	Reduced	X	-	X	
Alcohol (withdrawal)	Increased	Reduced	Reduced	-	-	-	-	X
Caffeine	Increased	Reduced	Reduced	-	-	-	-	X
Cocaine	-	-	-	-	-	-	-	X
Nicotine	Increased	Reduced	Reduced	-	-	-	-	-
Nicotine patch	-	-	-	-	X	-	-	-

Appendix 7. Participant information sheets for the feasibility study

7a. Information sheet on bright light therapy



Harold's Cross
Blackrock
Wicklow
Respite Rehabilitation Reassurance



Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Light Therapy

Our bodies naturally try to align with our environment's light and dark periods. We will try to sleep during the dark night-time hours and be awake in the light daytime environment.

When we are awake, exposing ourselves to sunlight, or bright light, can help to synchronise our bodies with our environment. This may improve how well we sleep during the night, our mood, and how active or alert we are during the day.

It might not always be possible to go outside and be exposed to sunlight. Bright light therapy (BLT) uses a light box to recreate this natural light exposure and can be performed in the home. To be effective, light therapy needs to be used for at least 15 minutes every morning. Exposure for at least 30 minutes may have added benefits.

The light box needs to be a certain distance from your face and is often placed just to your side. You should avoid staring directly at the light. The box is portable, so you can carry on doing your usual morning activities, such as having your breakfast or reading a book.

Some people may find that the box is too bright. In which case, the box can be moved slightly further away to see if that helps.

7b. Information sheet on physical activity



Harold's Cross
Blackrock
Wicklow
Respite Rehabilitation Reassurance



Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Physical Activity

Benefits of physical activity

People with a cancer diagnosis engaging in exercise may notice several benefits, including:

- Less anxiety
- Less low mood
- Less fatigue
- Less side effects from cancer treatments
- Better sleep quality
- Better quality of life
- Better physical function
- Longer survival

General recommendations for people with a cancer diagnosis

These recommendations should be seen as a long-term goal and is not possible for every person straight away.

- 150 to 300 minutes of moderate exercise each week. This is the same as 20 to 40 minutes of moderate exercise each day.
 - During 'moderate' exercise you are still able to comfortably hold a conversation e.g. brisk walking, light swimming.
- OR
- 75 to 150 minutes of vigorous exercise each week. This is the same as 10 to 20 minutes of vigorous exercise each day.
 - During 'vigorous' exercise, you would find it difficult to comfortably hold a conversation e.g. jogging, running, fast swimming.
- Muscle strengthening and flexibility exercises 2-3 times a week
- Try to avoid periods of inactivity and be as physically active as possible

This study aims to help you be active throughout the waking day and focuses less on how intensely you exercise.

The recommendation doesn't consider your current fitness level, the things that stop you from being active, your goals, or the things that you enjoy doing.

Feedback from the study

Your most active time period was HHMM-HHMM

You spent (n) minutes doing moderate-to-vigorous activity

You spent (n) minutes doing low level activity or resting

Your most inactive time-period was HHMM-HHMM

You spent (n) minutes standing

You spent (n) sitting

You spent (n) lying down

Tips to improve your activity levels

- Choose physical activities that you enjoy
- Be physically active whilst doing other things that you enjoy, such as listening to music or audiobooks
- Consider being physically active with a friend or family member
- Try to spread physical activity across the day
- Try to avoid resting for long periods
- Set yourself realistic short- and long-term goals
- Consider whether things are working, and if not, why?
- Steady and slow progress is better than over-exerting yourself too quickly

The watch that we have provided you with can detect how active or inactive you are, and it can let you know if you have been inactive for a long time ('inactivity stamps'). The watch might help you to increase how active you are. Aim to avoid being inactive for more than an hour at a time during the waking day.

Personalised recommendations

Try to increase your activity levels gradually during the study. This should help to make your goals more achievable and to continue being active. In the first weeks, this might be simply trying to move more and taking short regular walks.

The top 3 activities that you enjoy doing are:

1) _____

2) _____

3) _____

The main things that might limit you from being active are:

1) _____

2) _____

3) _____

We can try to address them by:

1) _____

2) _____

3) _____

When thinking about setting a goal, using 'SMART' goals can help us to be more successful.

'SMART' goals are:

Specific

Measurable

Achievable

Realistic

Timely

Reflect on your current activity levels and how we might be able to improve them.

Try to choose goals that you will enjoy achieving.

Week 1 activity goal:

Week 2 activity goal:

Week 3 activity goal:

Week 4 activity goal:

You are in control of how you increase your physical activity levels. You may want to increase the number of steps you take, how much you exert yourself when being active, or just how active you are in general. We will meet throughout the study to see how you are getting on, address any challenges you are facing, and work together to set goals.

7c. Information sheet on sleep



Harold's Cross
Blackrock
Wicklow
Respite Rehabilitation Reassurance



Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Sleep

People with a cancer diagnosis often have problems with their sleep. They may find that they struggle to get to sleep, wake up throughout the night, or wake up in the early morning. As a result, they may feel tired the next day and might even need to spend time napping during the waking day.

There are several reasons why people might not sleep well. Sleep may be improved by using cognitive-behavioural therapy-I (CBT-I). CBT-I can help you to understand important things that you can do to sleep better. This might include changing how you think about sleep and the things that you do before and during sleep. 'Sleep hygiene' may also help to improve your sleep and is often included within CBT-I.

Sleep hygiene tips to improve your sleep

Try to...

- Be consistent – wake up at the same time every day whether you have slept well or not
- Make your bedroom dark, quiet and a comfortable temperature
- Be physically active during the day
- Relax in the evening
- Limit how much time you spend looking at electronic devices (e.g. your phone, TV, or computer screen) late in the evening and particularly in the bedroom
- Get up and do something relaxing if you are struggling to sleep

Try to avoid...

- Large meals, alcohol, caffeine, or nicotine late in the evening
- Exercising late in the evening
- Long daytime naps (>30 minutes)
- Naps after 3pm

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