

**Acceptability, feasibility, and preliminary clinical  
usefulness of Bispectral index (BIS) monitoring in UK  
palliative care patients**

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*A thesis presented for the degree of Doctor of Philosophy (PhD)*

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## Declaration

I, Anna-Maria Krooupa, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the text.

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Date

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Anna-Maria Krooupa

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## **Abstract**

### **Background**

Bispectral index (BIS) is a technology using electroencephalographic (EEG) readings to assess levels of consciousness in patients undergoing general anaesthesia in the operating room where it has been shown to improve patient care and outcomes. Few previous studies have investigated BIS use in palliative care patients receiving sedative medication and none of these have been conducted in the United Kingdom (UK).

### **Aim**

To explore the acceptability, feasibility, and preliminary clinical usefulness of BIS monitoring in adult UK palliative care patients.

### **Methods**

Three empirical studies were undertaken to meet the research aim: (1) a qualitative study exploring the perceptions of patients, current patient relatives, and bereaved relatives regarding the possible use of BIS in palliative care, (2) an exploratory study of BIS monitoring in adult hospice inpatients, and (3) a further qualitative study investigating patients', relatives', and hospice clinicians' direct experiences of BIS monitoring. Qualitative data were analysed using the framework method. Quantitative data were analysed using descriptive statistics, correlation coefficients, and the Wilcoxon signed-rank test.

### **Results**

Ten palliative care patients, four current patient relatives, and eleven bereaved relatives participated in study (1). Forty hospice inpatients were monitored with BIS for study (2). Ten patients, two relatives, and ten clinicians participated in study (3). Findings suggest that conducting research with BIS in UK hospice inpatients is feasible and acceptable to key stakeholders. There was insufficient evidence to support the clinical usefulness of BIS monitoring in this population, probably due to a relatively small sample consisting of patients who were predominantly alert and responsive.

## **Conclusion**

This research is the first to explore the use of BIS in the UK palliative care context. Findings from this work support the feasibility and acceptability of BIS as a research tool. Further research is needed to determine the clinical usefulness of BIS in palliative care.

## Impact statement

Optimisation of symptom control has been repeatedly identified as a key priority for palliative care clinical practice and research. For palliative care patients' symptoms to be adequately managed, medication with sedative effects is sometimes used. In current clinical practice, the assessment of patients' level of consciousness, in response to sedative medication, is predominantly based on observational methods. However, these methods have several limitations. For a more reliable assessment of level of consciousness to be achieved, the use of monitoring devices based on electroencephalographic (EEG) data, such as the Bispectral index (BIS), has been suggested. However, only limited evidence about BIS monitoring in patients receiving sedative medication in palliative care currently exists. The data presented in this thesis, therefore, not only constitute an important contribution to the literature, but also demonstrate how using BIS as an adjunct to clinical observation can potentially aid the provision of individualised care to patients at the ends of their lives.

This research contributes to the limited international evidence base on BIS monitoring in palliative care and offers the first empirical data in this setting from the UK. Findings are, therefore, relevant to palliative care academics and researchers, and may be used to inform the uptake and design of future studies in this area. Outputs from this research have already been disseminated through peer-reviewed journals, presentations at scientific conferences, and meetings with international collaborators. Specifically, since I began my doctoral studies I have had one peer-reviewed paper published (Krooupa, Vivat, McKeever, Marcus, et al., 2020), given two poster (Krooupa, Stone, McKeever, & Vivat, 2020b; Krooupa, Vivat, McKeever, & Stone, 2020) and one oral (Krooupa, Stone, McKeever, & Vivat, 2019) presentations, and had an additional abstract accepted for print only (Krooupa, Vivat, McKeever, & Stone, 2018) at the European Association for Palliative Care (EAPC) international conference. I have also given two oral (Krooupa, Stone, McKeever, & Vivat, 2018, 2020a) and two poster presentations (Krooupa et al., 2017; Krooupa, Vivat, McKeever, & Stone, 2019) at national conferences (UK Palliative Medicine Association Congress, Annual Marie Curie Palliative Care Conference). Abstracts from all presentations have been published in international journals. Moreover, I have presented parts of this research to palliative care researchers at Leiden University, Netherlands (January 2019). Further articles reporting on research findings are planned following thesis submission.

The clinical implications discussed in this thesis may be of interest to palliative care patients, their family members/carers, and healthcare professionals. If future evidence supports the clinical usefulness of BIS in palliative care, information obtained through BIS monitoring has the potential to increase the accuracy of level of consciousness assessments and, thus, aid the effective titration of medication with sedative effects according to patients' individualised needs. These clinical benefits could eventually contribute towards improving patient care and comfort in patients approaching the ends of their lives. However, it is important to emphasise that the current state of knowledge is insufficient to recommend the use of BIS in palliative care clinical practice. Further research is required before any recommendations can be made.

## Table of Contents

<b>Declaration</b> .....	<b>2</b>
<b>Acknowledgements</b> .....	<b>3</b>
<b>Abstract</b> .....	<b>4</b>
<b>Impact statement</b> .....	<b>6</b>
<b>Table of Contents</b> .....	<b>8</b>
<b>List of Tables</b> .....	<b>13</b>
<b>List of Figures</b> .....	<b>14</b>
<b>List of Abbreviations</b> .....	<b>16</b>
<b>Outline of Research</b> .....	<b>18</b>
<b>CHAPTER 1 BACKGROUND</b> .....	<b>20</b>
<b>1.1 Chapter outline</b> .....	<b>20</b>
<b>1.2 The concept of palliative care</b> .....	<b>20</b>
Origins and evolution.....	20
Challenges in defining “palliative care” .....	21
Definition of palliative care adopted in this thesis .....	22
<b>1.3 Recommendations and priorities for palliative care clinical practice and research</b>	<b>23</b>
<b>1.4 Use of sedative medication in palliative care</b> .....	<b>24</b>
Lack of uniformity in terminology and clinical practice of sedative use.....	24
Ethical acceptability of sedative use at the end of life .....	25
Literature review of clinical practice guidelines on sedative use in palliative care.....	26
<b>1.5 Assessment and monitoring of level of consciousness in palliative care patients receiving sedative medication</b> .....	<b>48</b>
Observational methods.....	48
EEG-based level of consciousness monitors .....	50
<b>1.6 Bispectral index monitoring</b> .....	<b>54</b>
Description of Bispectral index monitor .....	54
Calculation of the BIS parameter .....	56
Smoothing rates, response time, and signal quality indicators.....	58
BIS monitoring value range.....	59
Clinical impact of BIS monitoring.....	60
Literature review of BIS monitoring in palliative care patients receiving sedative medication .....	61
<b>1.7 Chapter summary</b> .....	<b>70</b>



<b>1.8</b>	<b>Research aim and objectives .....</b>	<b>72</b>
<b>CHAPTER 2</b>	<b>SYSTEMATIC REVIEW OF OBSERVATIONAL MEASURES FOR THE ASSESSMENT AND/OR MONITORING OF LEVEL OF CONSCIOUSNESS IN ADULT PALLIATIVE CARE PATIENTS .....</b>	<b>73</b>
<b>2.1</b>	<b>Chapter outline .....</b>	<b>73</b>
<b>2.2</b>	<b>Review objectives .....</b>	<b>73</b>
<b>2.3</b>	<b>Methodology .....</b>	<b>73</b>
	Design.....	73
	Search strategy .....	74
	Inclusion and exclusion criteria.....	74
	Selection procedure.....	76
	Data extraction .....	77
	Assessment of psychometric performance .....	77
<b>2.4</b>	<b>Results.....</b>	<b>81</b>
	Search results.....	81
	Description of included studies .....	81
	Description of identified measures.....	97
	Psychometric performance of appraised measures .....	99
<b>2.5</b>	<b>Discussion.....</b>	<b>107</b>
	Key findings.....	107
	Limitations .....	110
	Implications for this doctoral project .....	111
<b>2.6</b>	<b>Chapter summary.....</b>	<b>111</b>
<b>CHAPTER 3</b>	<b>PATIENTS' AND RELATIVES' PERCEPTIONS REGARDING THE POTENTIAL USE OF BISPECTRAL INDEX TECHNOLOGY IN PALLIATIVE CARE: METHODOLOGY .....</b>	<b>113</b>
<b>3.1</b>	<b>Chapter outline .....</b>	<b>113</b>
<b>3.2</b>	<b>Study design, aim, and objectives .....</b>	<b>113</b>
<b>3.3</b>	<b>Study approvals .....</b>	<b>113</b>
<b>3.4</b>	<b>Setting and participants .....</b>	<b>114</b>
	Eligibility criteria .....	114
	Sample size.....	114
	Sampling strategy.....	115
<b>3.5</b>	<b>Ethical considerations .....</b>	<b>116</b>
<b>3.6</b>	<b>Participant recruitment and consent processes .....</b>	<b>116</b>
<b>3.7</b>	<b>Data collection .....</b>	<b>117</b>
<b>3.8</b>	<b>Data handling and management.....</b>	<b>119</b>
<b>3.9</b>	<b>Data analysis.....</b>	<b>120</b>

3.10	Chapter summary.....	123
<b>CHAPTER 4 PATIENTS' AND RELATIVES' PERCEPTIONS REGARDING THE POTENTIAL USE OF BISPECTRAL INDEX TECHNOLOGY IN PALLIATIVE CARE: RESULTS.....124</b>		
4.1	Chapter outline .....	124
4.2	Recruitment of study participants.....	124
4.3	Participant characteristics .....	125
4.4	Framework analysis of focus group and interview transcripts.....	127
	Prior knowledge and experience of sedation .....	128
	Any helpful intervention is acceptable .....	129
	Acceptability in principle of BIS monitoring in palliative care .....	130
4.5	Chapter summary.....	138
<b>CHAPTER 5 EXPLORATORY STUDY OF BISPECTRAL INDEX MONITORING WITH HOSPICE INPATIENTS: METHODOLOGY.....139</b>		
5.1	Chapter outline .....	139
5.2	Study aim and objectives.....	139
5.3	Study approvals .....	139
5.4	Setting and participants .....	140
	Eligibility criteria .....	140
5.5	Research design and procedures.....	141
	Study phases and consent process .....	141
	Capacity assessment .....	143
	Ethical considerations.....	144
	Sample size.....	145
5.6	Participant recruitment .....	145
5.7	Data collection.....	146
	Recruitment data .....	147
	Assessment data .....	147
	Monitoring completion data.....	153
5.8	Data handling and management.....	154
5.9	Data checking, input, and analysis .....	155
	Missing data .....	155
	Description of sample .....	156
	Description of outcome data .....	157
	Assessment of study outcomes .....	158
5.10	Chapter summary.....	166

<b>CHAPTER 6</b>	<b>EXPLORATORY STUDY OF BISPECTRAL INDEX MONITORING WITH HOSPICE INPATIENTS: RESULTS .....</b>	<b>167</b>
<b>6.1</b>	<b>Chapter outline .....</b>	<b>167</b>
<b>6.2</b>	<b>Recruitment and flow of participants through the study .....</b>	<b>167</b>
	Participant recruitment.....	167
	Phase 1 .....	169
	Phase 2 .....	170
<b>6.3</b>	<b>Participant characteristics .....</b>	<b>172</b>
<b>6.4</b>	<b>Medication use .....</b>	<b>174</b>
<b>6.5</b>	<b>Description of patient-, clinician-, researcher-reported pain and alertness outcome data, and BIS data .....</b>	<b>177</b>
	Patient-reported pain and alertness outcome data .....	177
	Clinician-reported pain and alertness outcome data .....	177
	Researcher-reported pain and alertness outcome data.....	178
	BIS data .....	179
	Participant experience questionnaires .....	182
<b>6.6</b>	<b>Assessment of study outcomes.....</b>	<b>184</b>
	Primary outcomes.....	184
	Secondary outcomes.....	195
<b>6.7</b>	<b>Chapter summary.....</b>	<b>200</b>
<b>CHAPTER 7</b>	<b>PATIENTS', RELATIVES', AND HOSPICE CLINICIANS' DIRECT EXPERIENCES AND PERCEPTIONS OF BISPECTRAL INDEX MONITORING: METHODOLOGY.....</b>	<b>201</b>
<b>7.1</b>	<b>Chapter outline .....</b>	<b>201</b>
<b>7.2</b>	<b>Study design, aim, and objectives .....</b>	<b>201</b>
<b>7.3</b>	<b>Setting and participants .....</b>	<b>201</b>
	Eligibility criteria .....	202
	Sample size.....	202
	Sampling strategy.....	202
<b>7.4</b>	<b>Participant recruitment and consent processes .....</b>	<b>204</b>
<b>7.5</b>	<b>Data collection .....</b>	<b>204</b>
<b>7.6</b>	<b>Data analysis.....</b>	<b>205</b>
<b>7.7</b>	<b>Chapter summary.....</b>	<b>206</b>
<b>CHAPTER 8</b>	<b>PATIENTS', RELATIVES', AND HOSPICE CLINICIANS' DIRECT EXPERIENCES AND PERCEPTIONS OF BISPECTRAL INDEX MONITORING: RESULTS .....</b>	<b>207</b>
<b>8.1</b>	<b>Chapter outline .....</b>	<b>207</b>
<b>8.2</b>	<b>Recruitment of study participants.....</b>	<b>207</b>

<b>8.3</b>	<b>Characteristics of interview participants .....</b>	<b>208</b>
<b>8.4</b>	<b>Framework analysis of interview transcripts .....</b>	<b>211</b>
	Perceptions and experiences of BIS monitoring .....	213
	Perceptions regarding participation in the exploratory study.....	222
	Clinician interviewees' views and experiences of observational pain and alertness measures.....	224
<b>8.5</b>	<b>Chapter summary.....</b>	<b>228</b>
<b>CHAPTER 9</b>	<b>DISCUSSION, IMPLICATIONS, AND CONCLUSIONS .....</b>	<b>230</b>
<b>9.1</b>	<b>Chapter outline .....</b>	<b>230</b>
<b>9.2</b>	<b>Summary, discussion, and interpretation of main findings.....</b>	<b>230</b>
	Acceptability of BIS monitoring in palliative care .....	230
	Feasibility of conducting research with BIS in hospice inpatients.....	237
	Preliminary evaluation of clinical usefulness of BIS monitoring.....	242
	Relationship between BIS and clinician-rated alertness measures .....	244
	Psychometric properties of clinician-rated RASS-PAL, pain and alertness NRSs .....	245
	Use of BIS in the assessment of pain in hospice patients.....	248
	Relationship between researcher-rated and other outcome measures .....	248
<b>9.3</b>	<b>Strengths and limitations .....</b>	<b>249</b>
	Qualitative studies .....	249
	Exploratory study.....	251
<b>9.4</b>	<b>Originality of research and contribution to the evidence base .....</b>	<b>255</b>
<b>9.5</b>	<b>Directions and recommendations for future research.....</b>	<b>256</b>
<b>9.6</b>	<b>Implications for clinical practice.....</b>	<b>258</b>
<b>9.7</b>	<b>Conclusions.....</b>	<b>260</b>
	<b>References.....</b>	<b>261</b>
	<b>Appendices .....</b>	<b>287</b>
	Appendix 1 Published systematic review paper .....	287
	Appendix 2 Research materials for qualitative study exploring key stakeholders' perceptions about the potential use of BIS (Chapters 3–4) .....	318
	Appendix 3 Research materials for exploratory study (Chapters 5–6).....	324
	Appendix 4 Plotted BIS and alertness NRS data, and BIS and pain NRS data for selected individual participant cases.....	337
	Appendix 5 Research materials for qualitative study exploring key stakeholders' direct experiences of BIS monitoring (Chapters 7–8).....	340

## List of Tables

<b>Table 1.1:</b> Overview of guideline content and recommendations .....	30
<b>Table 1.2:</b> Overview of study characteristics and main findings .....	66
<b>Table 2.1:</b> Quality criteria for measure appraisal .....	80
<b>Table 2.2:</b> Description of identified studies and measures .....	84
<b>Table 2.3:</b> Appraisal of psychometric performance of observational level of consciousness measures .....	103
<b>Table 3.1:</b> Eligibility criteria for study participants .....	114
<b>Table 3.2:</b> Activities undertaken for the analysis of interview/focus group data .....	122
<b>Table 4.1:</b> Characteristics of interview/focus group participants .....	126
<b>Table 4.2:</b> Acceptability in principle of BIS monitoring: subthemes and categories .....	130
<b>Table 5.1:</b> Inclusion and exclusion criteria for study participation.....	140
<b>Table 5.2:</b> Four-point capacity test (Royal College of General Practitioners, 2011) .....	143
<b>Table 5.3:</b> Common diagnoses in palliative care .....	148
<b>Table 5.4:</b> Indications for the administration of medication with sedative effects .....	148
<b>Table 5.5:</b> Medication with sedative effects/side-effects relevant to the study .....	149
<b>Table 5.6:</b> Reasons for early monitoring termination .....	154
<b>Table 5.7:</b> Equivalent opioid doses .....	157
<b>Table 5.8:</b> Overview of data analysis plan .....	159
<b>Table 6.1:</b> Participant characteristics (n=40) .....	173
<b>Table 6.2:</b> Frequency of prescribed medication with sedative effects by category and class .....	175
<b>Table 6.3:</b> Frequency and median doses of prescribed regular and PRN medication with sedative effects .....	176
<b>Table 6.4:</b> Summary of patient-, clinician-, researcher-reported pain and alertness data, and BIS data.....	180
<b>Table 6.5:</b> Responses to Phase 1 (n=36) and Phase 2 (n=4) participant experience questionnaires.....	183
<b>Table 6.6:</b> Correlation coefficients for BIS, patient- and clinician-rated alertness NRSs by study phase .....	187
<b>Table 6.7:</b> Correlation coefficients for BIS and clinician-rated measures by study phase ..	195
<b>Table 6.8:</b> Correlation coefficients for BIS, patient- and clinician-rated pain NRSs by study phase .....	198
<b>Table 6.9:</b> Correlation coefficients between researcher-rated and other measures by study phase .....	199
<b>Table 7.1:</b> Eligibility criteria for study participants.....	202
<b>Table 8.1:</b> Interview participant characteristics .....	209
<b>Table 8.2:</b> Responses to participant experience questionnaire of interviewed patients (n=10) compared to the whole group of Phase 1 questionnaire respondents (n=36) ..	210
<b>Table 8.3:</b> Overview of core themes, subthemes, and categories .....	212

## List of Figures

<b>Figure 1.1:</b> Key brain areas (in colour) associated with the state of consciousness (reproduced with permission from Musizza & Ribaric, 2010).....	52
<b>Figure 1.2:</b> EEG patterns during different stages of anaesthesia-induced unconsciousness (adapted from Brown et al., 2010; Copyright Massachusetts Medical Society) .	53
<b>Figure 1.3:</b> Features of BIS™ monitoring system .....	55
<b>Figure 1.4:</b> Placement of BIS™ Quatro Brain Monitoring sensor .....	56
<b>Figure 1.5:</b> Processes involved in the calculation of BIS parameter (adapted from Nunes et al., 2012) .....	57
<b>Figure 1.6:</b> BIS monitoring value range and associated clinical states (adapted from Mathur et al., 2021).....	59
<b>Figure 1.7:</b> Flow diagram of publication selection process .....	62
<b>Figure 2.1:</b> Search strategy used in MEDLINE and modified for other databases.....	75
<b>Figure 2.2:</b> Forward and backward citation searching process .....	76
<b>Figure 2.3:</b> PRISMA flow diagram of study selection (Moher et al., 2009).....	83
<b>Figure 2.4:</b> Number of identified studies and measures by instrument category.....	97
<b>Figure 4.1:</b> Main themes and subthemes .....	127
<b>Figure 5.1:</b> Study phases and consent process .....	142
<b>Figure 5.2:</b> Data collection process for each monitoring phase .....	147
<b>Figure 5.3:</b> Richmond Agitation-Sedation Scale – Palliative version (RASS-PAL; adapted from Bush at al., 2014) .....	152
<b>Figure 6.1:</b> Recruitment flow chart.....	168
<b>Figure 6.2:</b> Phase 1 participation flow chart.....	169
<b>Figure 6.3:</b> Phase 2 participation flow chart.....	171
<b>Figure 6.4:</b> BIS and alertness NRS data collected for participant 003 in Phase 1.....	181
<b>Figure 6.5:</b> BIS and pain NRS data collected for participant 003 in Phase 1.....	181
<b>Figure 6.6:</b> Outcome data before and after breakthrough administration for Participant 004 in Phase 1.....	189
<b>Figure 6.7:</b> Outcome data before and after breakthrough administration for Participant 007 in Phase 1.....	189
<b>Figure 6.8:</b> Outcome data before and after breakthrough administration for Participant 011 in Phase 1.....	190
<b>Figure 6.9:</b> Outcome data before and after breakthrough administration for Participant 012 in Phase 1.....	190
<b>Figure 6.10:</b> Outcome data before and after breakthrough administration for Participant 018 in Phase 1 .....	191
<b>Figure 6.11:</b> Outcome data before and after breakthrough administration for Participant 019 in Phase 1 .....	191
<b>Figure 6.12:</b> Outcome data before and after breakthrough administration for Participant 031 in Phase 1 .....	192
<b>Figure 6.13:</b> Outcome data before and after breakthrough administration for Participant 036 in Phase 1 .....	192
<b>Figure 6.14:</b> Outcome data before and after breakthrough administration for Participant 008 in Phase 2 .....	193

<b>Figure 6.15:</b> Outcome data before and after breakthrough administration for Participant 019 in Phase 2 .....	193
<b>Figure 6.16:</b> Outcome data before and after breakthrough administration for Participant 036 in Phase 2 (Event: 1/2) .....	194
<b>Figure 6.17:</b> Outcome data before and after breakthrough administration for Participant 036 in Phase 2 (Event: 2/2) .....	194
<b>Figure 6.18:</b> Scatter plot of BIS and clinician alertness NRS scores in Phase 1.....	196
<b>Figure 6.19:</b> Scatter plot of BIS and clinician alertness NRS scores in Phase 2.....	196
<b>Figure 9.1:</b> Key elements of intervention development and evaluation process (reproduced with permission from Craig et al., 2008). .....	257

## List of Abbreviations

AHS	Alberta Health Services
ANH	Artificial Nutrition and Hydration
AUC	Area Under the ROC Curve
AVPU	Alert/Verbal/Painful/Unresponsive scale
BIS	Bispectral index
CCS	Communication Capacity Scale
CDSUP	Continuous Deep Sedation Until Death
CENTRAL	Cochrane Central Register of Controlled Trials
CF	Cognitive Function
CHPCP	Champlain Hospice Palliative Care Program
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPS	Continuous Palliative Sedation
CPS	Clinician Prediction of Survival
CS	Consciousness Scale
CSD	Continuous Sedation until Death
CSPC	Consciousness Scale for Palliative Care
dB	Decibels
DNAR	Do Not Attempt Resuscitation
DNR	Do Not Resuscitate
DOS	Delirium Observation Screening
EAPC	European Association for Palliative Care
EEG	Electroencephalogram
EMG	Electromyography
ESMO	European Society for Medical Oncology
FDA	United States Food and Drug Administration
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation
IAPC	Irish Association for Palliative Care
ICC	Intraclass Correlation Coefficient
ILD	Interstitial Lung Disease
IM	Intramuscular
IQR	Inter Quartile Range
IV	Intravenous
JCS	Japan Coma Scale
KNMG	Royal Dutch Medical Association
LACDP	Leadership Alliance for the Care of Dying People
LCP	Liverpool Care Pathway for the Dying Patient
MCHH	Marie Curie Hampstead Hospice
MRC	Medical Research Council
MSAT	Minnesota Sedation Assessment Tool
MWSS	Modified Wilson Sedation Scale
NCCN	National Comprehensive Cancer Network



NE	Not Evaluated
NHPCO	National Hospice and Palliative Care Organization
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Norwegian Medical Association
NR	Not Reported
NRS	Numerical Rating Scale
Nu-DESC	Nursing Delirium Screening Scale
OAA/S	Observer's Assessment of Alertness/Sedation
PAR	Parenteral
PCT	Patient Controlled Therapy
PCS	Patient Comfort Score
PFCS	Patient/Family Controlled Sedation
PPS	Palliative Performance Scale
PR	Per Rectum
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRN	<i>Pro Re Nata</i> ; "as needed"
PROSPERO	International Prospective Register of Systematic Reviews
PS	Palliative Sedation
RASS	Richmond Agitation-Sedation Scale
RASS-PAL	Richmond Agitation-Sedation Scale – Palliative version
RDOS	Respiratory Depression Observation Scale
RLS85	Reaction Level Scale 85
ROC	Receiver Operator Characteristic
RSS	Ramsay Sedation Scale
SC	Subcutaneous
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
SQI	Signal Quality Index
UCL	University College London
UCLH	University College London Hospitals NHS Foundation Trust
UK	United Kingdom
VAS	Visual Analogue Scale
VICS	Vancouver Interaction and Calmness Scale
WHO	World Health Organisation
WoS	Web of Science

## Outline of Research

The work presented in this thesis was conducted as part of the I-CAN-CARE research programme. I-CAN-CARE is a five-year project funded by Marie Curie centring on prognosis, symptom control, and communication in palliative care. The programme grant comprises two work packages: sedative use (WP1) and prognostication (WP2). The research that I have undertaken for this doctoral project pertains to WP1.

My personal motivation to undertake this doctoral project stemmed from my previous experience supporting people with learning disabilities who were approaching the ends of their lives. Through this role, I became interested in how sedative medication and innovative interventions that are not based on verbal communication could be used to improve the care and comfort of people who were entering the dying trajectory. This experience coupled with my background in health services research, prompted me to apply for the funded doctoral position which had become available on WP1 of the I-CAN-CARE programme, and which had been broadly outlined as aiming to explore the use of the Bispectral index (BIS) technology in palliative care. The objectives of the doctoral project were determined by myself in collaboration with my academic supervisors after I commenced my studies.

The I-CAN-CARE programme had an Advisory Group which met twice a year since the beginning of the project. Members of the Advisory Group included service user representatives, palliative care clinicians and researchers. Group members had oversight of the whole project and contributed to the design of individual studies, including those presented in this thesis, the development of research materials (i.e. research protocols, information sheets and consent forms, questionnaires and interview/focus group topic guides), and were involved in reflecting upon data analysis and dissemination methods.

The overarching aim of this doctoral project is to explore the acceptability, feasibility, and preliminary clinical usefulness of BIS monitoring in adult palliative care patients in the United Kingdom (UK). To achieve this aim, a number of studies, including literature reviews, qualitative studies, and a prospective exploratory study, were conducted with findings from preceding studies guiding the uptake and design of subsequent ones.

Individual studies conducted as part of this doctoral project adopt different methodologies (qualitative or quantitative). Decisions regarding which methodology to follow on each occasion were informed by what can provide the most comprehensive and valid answers to

specific research questions. Thus, assuming an approach which is consistent with pragmatism as a research paradigm (Morgan, 2007). Pragmatism advocates for a problem-solving, action-oriented process of inquiry where emphasis is placed on choosing the methodological approach that can best bridge the gap between research questions and research methods (Kaushik & Walsh, 2019). This pragmatic methodological stance is often associated with applied health research (Murphy, Dingwall, Greatbatch, Parker, & Watson, 1998), such as the research presented in this thesis.

The structure of the thesis is as follows. The first part of the thesis (Chapters 1 and 2) sets out the context of the doctoral project and introduces existing knowledge on the use of sedative medication and the concept and practices of level of consciousness monitoring in palliative care. This section comprises three reviews: (1) a literature review of clinical practice guidelines on sedative use (Chapter 1), (2) a literature review of BIS monitoring in palliative care patients receiving sedative medication (Chapter 1), and (3) a systematic review of observational measures used in primary research studies for the assessment and/or monitoring of palliative care patients' consciousness levels (Chapter 2).

The main body of the thesis (Chapters 3 to 8) presents the methodology and findings of three empirical studies: (1) a qualitative study exploring the perceptions of palliative care patients, relatives of current patients, and bereaved relatives regarding the possible use of BIS in palliative care, including its acceptability in principle (Chapters 3 and 4), (2) a prospective exploratory study of BIS monitoring in adult hospice inpatients (Chapters 5 and 6), and (3) a further qualitative study investigating patients', relatives', and hospice clinicians' direct experiences and perceptions of BIS monitoring (Chapters 7 and 8).

The thesis concludes (Chapter 9) with a discussion of main research findings in the context of existing evidence, a description of the strengths and weaknesses of the empirical studies comprising this doctoral project, and an exploration of key implications for clinical practice. Finally, recommendations for future research are made.

# **Chapter 1 Background**

## **1.1 Chapter outline**

This chapter sets the context of the doctoral project. It provides an overview of the concept of palliative care and its evolution. It goes on to outline key research and clinical priorities in palliative care and discusses how these relate to the practice of sedative use. A literature review exploring existing guidelines and recommendations for the appropriate use of sedative medication in the palliative care is then presented and discussed, and the role of level of consciousness monitoring in this context is considered. Following on from this, the limitations of existing methods for the monitoring of level of consciousness and the potential contribution of BIS, are described. A literature review of existing studies exploring the use of BIS monitoring in the palliative care setting is then presented, and limitations of current studies and reported evidence are identified. The chapter concludes by describing the research aim and objectives for this doctoral project.

## **1.2 The concept of palliative care**

### **Origins and evolution**

The concept of palliative care as a set of practices and values aiming to improve the quality of life of patients with life-limiting conditions and their families has its origins in the modern hospice movement developed in the UK by Dame Cicely Saunders in the 1960s (Fallon & Smyth, 2008; Field & Addington-Hall, 1999). Even though from early in the development of the hospice movement it was recognised that its principles were relevant to all patients with incurable conditions, palliative care has been historically associated, and often perceived as synonymous, with terminal cancer care (Ahmedzai & Taylor, 1996; Field & Addington-Hall, 1999). This traditional view of palliative care was reflected in the first World Health Organization (WHO) definition of palliative care (World Health Organization, 1990) which restricted its scope to cancer patients not responsive to curative treatment (Sepúlveda, Marlin, Yoshida, & Ullrich, 2002).

A combination of various demographic changes and technological and health-related developments have challenged that original notion of palliative care (Meghani, 2004). Specifically, the observed upward global trends in ageing and associated increased life

expectancies have caused new patterns of disease to emerge (World Health Organization, 2004). A higher proportion of the population is now approaching the end of life while more people are dying as a result of progressive chronic illnesses (Guo, Jacelon, & Marquard, 2012; Murray, Kendall, Boyd, & Sheikh, 2005; World Health Organization, 2004). Moreover, there is increasing recognition that symptoms at the end of life originate from an earlier point in the illness trajectory and, if not adequately managed at onset, may become difficult to control at the end of life (World Health Organization, 2004). These factors, together with evidence that symptoms at the end of life tend to be similar for different chronic conditions, have collectively contributed towards an increased realisation of the need for palliative care regardless of diagnosis (World Health Organization, 2004). As a result of these developments, palliative care has evolved and expanded its scope to address the needs of a wide range of patient populations throughout the course of any chronic, ultimately fatal, illness (Meghani, 2004; World Health Organization, 2004).

### **Challenges in defining “palliative care”**

The dynamic nature of the palliative care concept has led to several disparate meanings, interpretations, and definitions of the term “palliative care” appearing in the scientific literature and in clinical practice over the past few decades (Hui, De La Cruz, et al., 2013; Pastrana, Jünger, Ostgathe, Elsner, & Radbruch, 2008). This lack of definitional clarity poses barriers to the effective delivery of palliative care services and research, and hinders the development of international standards and norms (Hui, De La Cruz, et al., 2013; Radbruch & Payne, 2009). In order to overcome the difficulties associated with the lack of a universally accepted definition of palliative care and aid the progress of the palliative care field as a whole, the EAPC has argued that a common terminology needs to be developed and adopted (Radbruch & Payne, 2009). However, reaching a consensus on a definition and quality standards for palliative care may not be a realistic endeavour given the differences in linguistic and cultural contexts, and healthcare systems across different countries (Radbruch & Payne, 2009). Instead, identifying and agreeing on the key elements of palliative care may be a more feasible approach towards achieving a unified understanding of the palliative care concept.

In a discourse analysis of definitions of palliative care found in specialist literature, Pastrana and colleagues (2008) identified six main categories which they considered fundamental elements of the concept of palliative care. These were: (1) theoretical principles (i.e. a patient-centred approach to care and a position towards life and death where death is

considered inseparable, or even part of, life), (2) goals (i.e. to preserve or enhance quality of life in the remaining time of patients' lives), (3) target groups (i.e. patients with a terminal illness and/or limited prognosis), (4) structure (i.e. multidisciplinary/multiprofessional approach to patient care, 24/7 access to services, provision of palliative care across different settings), (5) tasks (i.e. control of symptoms and comprehensive/holistic care), and (6) expertise (i.e. specialist knowledge and skills with emphasis on competencies such as communication, ethics, and counselling).

### **Definition of palliative care adopted in this thesis**

Given the plethora of palliative care definitions available in the literature, the intent for this thesis was to identify a definition that encompasses the key elements of the palliative care concept as described by Pastrana et al. (2008) and endorses a broad approach to palliative care. That is, acknowledging palliative care as being applicable to all life-limiting conditions and across the disease trajectory, from the onset of symptoms to the very end of life. The revised WHO definition of palliative care broadly fulfils these criteria and was, therefore, adopted in this thesis.

According to the WHO (Sepúlveda et al., 2002, pp. 94-95):

“Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care:

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten or postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated
- Will enhance quality of life, and may also positively influence the course of illness

- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.”

### **1.3 Recommendations and priorities for palliative care clinical practice and research**

In agreement with the relief of pain and other distressing symptoms being identified as one of the main tasks and objectives of palliative care (Pastrana et al., 2008; Sepúlveda et al., 2002), a number of recent high-impact reports in England have highlighted symptom control as a key priority for palliative care clinical practice and research (Leadership Alliance for the Care of Dying People, 2014; Neuberger et al., 2013; Parliamentary and Health Service Ombudsman, 2015). Following an investigation into complaints about the care patients had received in the last 12 months of their lives, the Parliamentary and Health Service Ombudsman issued the “Dying without Dignity” report in 2015. The report identified six key areas where care of patients approaching the end-of-life needed improvement. These were: “not recognising that people are dying and not responding to their needs”, “poor symptom control”, “poor communication”, “inadequate out-of-hours service”, “poor care planning”, and “delays in diagnosis and referrals for treatment” (Parliamentary and Health Service Ombudsman, 2015). These findings are in line with the Priorities for Care outlined by the Leadership Alliance for the Care of Dying People (LACDP) in their 2014 report “One Chance to Get it Right” (Leadership Alliance for the Care of Dying People, 2014) .

LACDP was established following an independent review of the Liverpool Care Pathway for the Dying Patient (LCP) commissioned by the UK government. The review concluded that generic protocols, such as the LCP, that intend to be applicable for all patients in any setting are not the right approach for dying patients. Instead, a more individualised approach to care considering the needs and wishes of patients and the setting in which they are cared for would need to be developed and implemented (Neuberger et al., 2013). The Priorities for Care were developed with the intention of replacing the LCP and providing guidance for the individualised care of patients in the last days and hours of life in England. Symptom control was outlined as an integral part of individualised care plans (Leadership Alliance for the Care of Dying People, 2014).

Another outcome of the Neuberger review of the LCP was the acknowledgement of a lack of research in key areas in palliative care together with the recommendation for greater investment in research to improve the care of patients at the end of life. One of the areas for which further research was recommended was the use of medication, with a particular emphasis on sedative and analgesic drugs for the management of patient symptoms and the extent to which these contribute to reduced consciousness (Neuberger et al., 2013). This recommendation formed the basis of WP1 of the I-CAN-CARE programme, part of which is the present doctoral project.

## **1.4 Use of sedative medication in palliative care**

### **Lack of uniformity in terminology and clinical practice of sedative use**

In the past 20 years, a number of pharmacological and psychosocial therapies have been found to effectively target symptoms that patients with life-limiting illnesses most frequently experience (Breitbart, 2002; Morrison & Meier, 2004). Despite these developments, symptom control is often inadequate, especially for patients who are approaching the end of life, when symptom burden tends to increase. As a result, some patients experience intolerable suffering from one or more treatment-resistant symptoms that may be termed “refractory” (Cherny, 2014; Maltoni, Scarpi, et al., 2012). For these symptoms, sedative medications are sometimes used to provide relief from intractable distress (Cherny, 2014). However, empirical evidence shows that the prevalence and practice of sedative use varies considerably according to country, setting, and types and doses of medication used (Claessens, Menten, Schotsmans, & Broeckeaert, 2008; Maltoni, Scarpi, & Nanni, 2013; Maltoni, Scarpi, et al., 2012)

Claessens and colleagues (2008) conducted a systematic review of primary studies about the use of sedative medication for refractory symptoms and found that the prevalence ranged from approximately 3% to 50% for studies carried out in palliative care units or hospices, and from nearly 1% to 25% for those conducted in hospitals. The same review also demonstrated large differences in the prevalence of sedative use among countries, with some countries reporting a prevalence of 2.5% and others a much higher prevalence of 10% (Claessens et al., 2008). Similarly, Maltoni et al. (2013; 2012) reported substantial variance in the type and doses of drugs used to induce sedation across different settings and countries, with the most commonly used drug being midazolam (dose range <30mg/24h to <120mg/24h), followed by



haloperidol, chlorpromazine, and morphine. The latter three were used either in combination with midazolam or alone.

The wide variability in the prevalence and practice of sedative prescribing is also reflected in the terminology used to label and define the practice of sedative use at the end of life (Beel, McClement, & Harlos, 2002; Cowan & Walsh, 2001). De Graeff and Dean (2007) identified at least 10 different terms reported in the literature to refer to and describe the use of sedatives for otherwise unmanageable symptoms. This ambiguity in terminology has considerable implications in terms of interpretation of research findings which, subsequently, inform clinical practice and policy making (Morita, Tsuneto, & Shima, 2001; Raus & Sterckx, 2016). Moreover, Raus and Sterckx (2016) argued that many of these terms are value-laden and can influence the ethical reasoning and clinical practice of palliative care professionals, while Twycross (2017) observed that some of the terms used to describe the practice of sedative use can be potentially misleading. In an attempt to overcome these problems, the use of broader and more descriptive definitions has been suggested (Raus & Sterckx, 2016; Twycross, 2017). In line with these recommendations, the term “sedative use in palliative care” has been adopted to refer to the relevant practice in this thesis.

### **Ethical acceptability of sedative use at the end of life**

The moral acceptability of using sedative medication as a medical intervention at the end of life has been often debated in the literature (Claessens et al., 2008). The focus of the debate has mostly centred on whether the practice of sedative use has a negative impact on patient survival and the extent to which it differs from interventions explicitly aiming to end a patient’s life, such as euthanasia or physician-assisted suicide (Maeda et al., 2016; Olsen, Swetz, & Mueller, 2010).

The possibility, in principle, for sedative use at the end of life to hasten death as a result of the withdrawal or withholding of artificial nutrition and hydration, and the potential adverse effects of high doses of sedatives on respiration and/or circulation, have led some authors to view and label the practice of sedative use as “euthanasia in disguise” or “slow euthanasia” (Maltoni et al., 2009; Rietjens et al., 2006). Others, however, have argued that there is a clear distinction between sedative use and euthanasia or physician-assisted suicide (Olsen et al., 2010; ten Have & Welie, 2014). According to these authors, the practice of sedative use is distinguished from euthanasia and physician-assisted suicide by intent and outcome (Olsen et al., 2010; ten Have & Welie, 2014). The intent and desired outcome of sedative use is the

alleviation of patient suffering through the use of sedative medication to control resistant to treatment symptoms, with the possible risk of shortening patient survival. In contrast, the intent and desired outcome of euthanasia and physician-assisted suicide is the termination of life (Olsen et al., 2010). Furthermore, a number of recent studies found no statistically significant differences in mean survival time between groups of patients who had received sedative medication and those who had not, therefore suggesting that the use of sedative medication does not have an adverse impact on survival duration in terminally ill patients (Bakthavatsalu & Chandra, 2013; Maltoni et al., 2009; Muller-Busch, Andres, & Jehser, 2003). These data have been cited in support of the argument that sedative use at the end of life does not cause or hasten death (Maltoni et al., 2009).

In view of the ethical, definitional and clinical practice controversies associated with the practice of sedative use, various professional bodies and organisations have developed guidelines aiming to standardise clinical practice and provide guidance regarding the appropriate use of sedative medication in palliative care (Schildmann & Schildmann, 2014). To obtain a better understanding of what constitutes good clinical practice in relation to the use of sedative medication in the context of palliative care, relevant published guidelines were identified and recommendations for clinical practice were narratively synthesised for the purposes of this doctoral project. The processes of guideline identification and selection, and findings of the narrative synthesis are discussed in the following section.

## **Literature review of clinical practice guidelines on sedative use in palliative care**

### **Guideline identification, selection, and data extraction**

Two electronic databases (MEDLINE, PsycINFO) were searched from first record published until November 2019 to identify any existing systematic reviews of clinical practice guidelines on the use of sedative medication in palliative care. Search terms included a combination of subject headings and free-text terms for: palliative/terminal care, recommendations/guidelines, and literature/systematic reviews.

Three recently published systematic reviews were identified (Abarshi et al., 2017; Gurschick, Mayer, & Hanson, 2015; Schildmann & Schildmann, 2014; Schildmann, Schildmann, & Kiesewetter, 2015). Findings from one of these reviews were published in two separate papers (Schildmann & Schildmann, 2014; Schildmann et al., 2015). Each of these reviews included different sets of guidelines. Data from individual guidelines from each review were extracted and, subsequently, all data were narratively synthesised focusing particularly on

recommendations regarding drugs and dosages, and patient monitoring during and after the administration of sedative medication.

Previously published reviews identified 28 clinical practice guideline documents. Of these, 5 were included in 2 of the 3 reviews, resulting in 23 unique records. Of these, four were published in languages other than English, and hence were not included in the narrative synthesis as data could not be directly extracted from original publications. A further two documents constituted older versions of included guidelines, and, therefore, were also excluded. A supplementary database search was performed to identify any guidelines published after the search conducted by the authors of the most recently published review (Abarshi et al., 2017). The same electronic databases as above (MEDLINE, PsycINFO) were searched between March 2016 and March 2020 using Boolean operators (AND, OR) to combine the following search terms: “palliative”, “terminal”, “continuous”, “deep”, “sedation”, “guideline”, “framework”, “recommendation”. No eligible publications were identified through this search. However, updated versions of publications included in previous reviews were identified for three guidelines, and therefore older versions were replaced. As a result, a total of 17 guideline documents were included in the narrative synthesis.

All selected documents adhered to the definition of clinical practice guidelines of the Institute of Medicine (1990, p.8) according to which “practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances”. Data extraction was based on the following predefined categories: terms and definitions of the practice of sedative use, type and target level of sedation, target population, indications for sedative use, recommendations on life-sustaining treatments, recommended medication and doses, and suggestions for patient monitoring during and after the administrations of sedative medication. Information on guideline characteristics were also extracted.

### **Guideline characteristics**

Of the 17 guidelines included in the narrative synthesis, 3 were developed internationally (Cherny, 2014; Cherny & Radbruch, 2009; De Graeff & Dean, 2007), 8 were country-level or national organisation-level guidelines (M. Dean, Cellarius, Henry, Oneschuk, & Taskforce, 2012; Irish Association for Palliative Care, 2011; Kirk & Mahon, 2010; Legemaate, Verkerk, van Wijlick, & de Graeff, 2007; Morita, Bito, Kurihara, & Uchitomi, 2005; National Comprehensive Cancer Network, 2019; Norwegian Medical Association, 2014; Royal Dutch

Medical Association, 2009), 5 were developed at a regional level (Alberta Health Services, 2018; Braun, Hagen, & Clark, 2003; Champlain Hospice Palliative Care Program, 2018; Fraser Health Authority, 2011; Hospice & Palliative Care Federation of Massachusetts, 2004) and 1 was a local institution guideline (Schuman, Lynch, & Abraham, 2005).

Most guidelines were developed following a formal consensus-based method, such as the Delphi method, or informal consensus approaches involving a panel of experts in the field of palliative care. In addition to consensus-based methods, the incorporation of findings from relevant reviews of available evidence was reported in eight guidelines (Braun et al., 2003; Cherny, 2014; Cherny & Radbruch, 2009; De Graeff & Dean, 2007; M. Dean et al., 2012; Legemaate et al., 2007; Morita et al., 2005; Royal Dutch Medical Association, 2009). For two guidelines no information was available on the development methods followed (Norwegian Medical Association, 2014; Schuman et al., 2005).

## **Description of guideline content and recommendations**

### **Terms and definitions**

The majority of guidelines (n=12) used the term “palliative sedation” to describe the practice of sedative use for the management of treatment-resistant symptoms in palliative care patients. In four guidelines authors opted for the term “palliative sedation therapy” to place emphasis on the therapeutic aspect of the practice (Champlain Hospice Palliative Care Program, 2018; De Graeff & Dean, 2007; Fraser Health Authority, 2011; Morita et al., 2005). Similarly, authors of the Canadian guideline chose the term “continuous palliative sedation therapy” to highlight the ongoing component of the intervention which, according to their definition, is continued until the patient’s death (M. Dean et al., 2012).

The practice of sedative use was defined in similar ways by the majority of guidelines (n=12). That is, as an intervention aiming to relieve otherwise intolerable suffering/symptoms through the intentional reduction of patients’ consciousness levels. One guideline did not provide a definition (National Comprehensive Cancer Network, 2019). Two guidelines included in their definition an additional statement on the ethical acceptability of the intervention to patients, families, and health professionals (Champlain Hospice Palliative Care Program, 2018; Cherny & Radbruch, 2009). This was done to emphasise the patient-centred nature of the intervention and the importance of initiating sedation only in appropriate situations and after holding pre-emptive discussions about the potential role of the intervention in patients’ care. Lastly, the use of sedative medication was described as a measure of “last resort” in seven of the included guidelines (Champlain Hospice Palliative

Care Program, 2018; Cherny, 2014; Cherny & Radbruch, 2009; De Graeff & Dean, 2007; M. Dean et al., 2012; Irish Association for Palliative Care, 2011; National Comprehensive Cancer Network, 2019). A summary of the content and recommendations of included guidelines is provided in **Table 1.1**.

**Table 1.1:** Overview of guideline content and recommendations

Guideline	Terms and definitions	Type(s) and target level of sedation	Target population	Indications	Life-sustaining treatments	Medication selection and doses	Patient monitoring
<b>International guidelines</b>							
<b>EAPC framework</b> Cherny & Radbruch (2009)	<b>Palliative (or therapeutic) sedation</b> “Monitored use of medications intended to induce a state of decreased or absent awareness (unconsciousness) in order to relieve the burden of otherwise intractable suffering in a manner that is ethically acceptable to the patient, family and health-care providers.”	<b>Type(s):</b> Distinction between different types from “short term, intermittent, light, mild” to “continuous deep sedation”.  “Emergency” and “transient or respite” sedation listed separately.  <b>Target level:</b> Lowest necessary to provide adequate relief of suffering. Intermittent or mild sedation to be generally be attempted first.	Palliative care patients with intolerable distress.  For continuous deep sedation: Patients with an expected prognosis of hours or days.  For transient or respite sedation: Patients earlier in the illness trajectory whilst waiting for treatment benefit from other therapeutic approaches.	Intolerable distress due to refractory physical symptoms.  Common refractory symptoms listed: agitated delirium, dyspnoea, pain, convulsions.  Sedation may be considered for severe non-physical symptoms such as refractory depression, anxiety, demoralization or existential distress (special guidelines to be followed).	Decision about ANH independent of the decision about sedation and should be individually decided through comprehensive evaluation of the patient’s wishes and the estimated benefits/harms in light of the treatment aim (palliation of suffering).	<b>Benzodiazepines</b> 1. Midazolam Starting dose: 0.5-1mg/h, 1-5mg PRN. Usual effective dose: 1-20mg/h. 2. Lorazepam Dose: 0.05mg/kg q2-4h. 3. Flunitrazepam Dose: A bolus dose of 1-2mg, continuous infusion 0.2-0.5mg/h.  <b>Neuroleptics/antipsychotics</b> 1. Levomepromazine Starting dose: 12.5-25mg and 50-75mg continual infusion. Usual effective dose: 12.5 or 25mg q8h and q1h PRN for breakthrough agitation or up to 300mg/24h continuous infusion. 2. Chlorpromazine Starting dose: 12.5mg q4-12h IV/IM, or 3-5mg/h IV or 25-100mg q4-12h PR. Usual effective dose: 37.5-150mg/24h PAR; 75-300mg/24h PR.  <b>Barbiturates</b> Pentobarbital Loading dose: 2-3mg/kg IV, infusion at 1-2mg/kg/h; titrate to desired level of sedation.  <b>General anaesthetics</b> Propofol Starting dose: 0.5mg/kg/h. Usual dose: 1-4mg/kg/h.	<b>Parameters</b> 1. Severity of suffering 2. Level of consciousness 3. Adverse effects related to sedation (delirium, agitation, aspiration)  Consciousness assessed by the patient’s response to stimuli, agitation or motor activity, and facial expression.  <b>Monitoring tool/scales</b> 1. Critical-Care Pain Observation Tool for severity of suffering 2. RASS  <b>Frequency</b> Parameters to be monitored regularly.

Continued overleaf

Guideline	Terms and definitions	Type(s) and target level of sedation	Target population	Indications	Life-sustaining treatments	Medication selection and doses	Patient monitoring
<b>ESMO guideline</b> Cherny (2014)	<b>Palliative sedation</b> “A measure of last resort used at the end of life to relieve severe and refractory symptoms. It is carried out by the administration of sedative medications in supervised settings and is aimed at inducing a state of decreased awareness or absent awareness (unconsciousness).”	<b>Type(s):</b> Distinction between different types from “intermittent, mild, conscious” to “continuous, deep” sedation.  “Emergency” and “respite” sedation listed separately.  <b>Target level:</b> The least necessary to provide adequate relief of suffering.	Terminally ill patients (adults or children) suffering from severe distress.	Severe symptoms that are refractory to other forms of treatment.  Common refractory symptoms listed: pain, dyspnoea, agitated delirium, convulsions.  Sedation for refractory existential or psychological distress to be considered only in advanced stages of a terminal illness and after certain conditions are met.	Decisions regarding ANH independent of the decision about whether to administer palliative sedation.  Decisions to reflect a morally acceptable plan based on the patient’s best interests.	<b>Drug of choice:</b> Midazolam Starting dose: 0.5-1 mg/h, 1-5mg PRN. Usual effective dose: 1-20 mg/h.  <b>Neuroleptics/antipsychotics</b> 1. Levomepromazine Starting dose: 12.5-25mg and 50-75 mg continual infusion. Usual effective dose: 12.5 or 25 mg q8h and q1h PRN for breakthrough agitation or up to 300 mg/24h continual infusion. 2. Chlorpromazine Starting dose: 12.5mg q4-12h IV/IM or 3-5 mg/h IV or 25-100mg q4-12h PR. Usual effective dose: 37.5-150 mg/24h PAR, 75-300 mg/24h PR.  <b>Barbiturates and anaesthetics</b> 1. Phenobarbital Dose: 1-3mg/kg SC/IV bolus dose, followed by starting infusion of 0.5 mg/kg/h. Usual maintenance dose: 50-100mg/h. 2. Propofol Dose: loading dose of 20mg, followed by an infusion of 50-70mg/h.	<b>Parameters</b> For imminently dying patients: 1. Patient comfort 2. Respiratory rate  For non-imminently dying patients: 1. Level of sedation 2. Routine physiological parameters (heart rate, blood pressure, oxygen saturation)
<b>International guideline</b> De Graeff & Dean (2007)	<b>Palliative sedation therapy (PST)</b> “The use of specific sedative medications to relieve intolerable suffering from refractory symptoms by a reduction in patient consciousness.”	<b>Type(s):</b> 1. Mild (somnolence) 2. Intermediate (stupor) 3. Deep (coma)  Sedatives can be used: 1. Intermittently 2. Continuously	Patients with progressive and terminal disease with a life expectancy of days to maximally a few weeks (primarily cancer patients).	Refractory physical symptoms.  Common refractory symptoms listed: delirium and/or terminal restlessness, dyspnoea, pain, nausea/vomiting.	Decision on withholding/ withdrawal of ANH separate to initiation of PST.  ANH to be offered only if it is considered likely that the benefit	<b>Benzodiazepines</b> First-line choice in the absence of delirium. 1. Midazolam 2. Lorazepam	<b>Parameters</b> 1. Distress levels 2. Sedation levels 3. Adverse effects of sedation  <b>Monitoring tools/scales</b> 1. Edmonton Symptom Assessment Scale 2. Communication Capacity Scale

Continued overleaf

Guideline	Terms and definitions	Type(s) and target level of sedation	Target population	Indications	Life-sustaining treatments	Medication selection and doses	Patient monitoring
		<p>“Emergency” sedation for catastrophic events listed separately.</p> <p><b>Target level:</b> Sufficient, but not more than is needed, to alleviate distress by reducing the level of consciousness (proportionate sedation).</p>	For continuous deep sedation: Death should be expected within hours to days.	PST for psychological or existential distress should be initiated only under exceptional circumstances and only after consultations with experts in this area.	(including psychological and cultural benefits) will outweigh the harm.	<p><b>Neuroleptics/antipsychotics</b> For refractory delirium in combination with midazolam. Levomepromazine</p> <p><b>Barbiturates and anaesthetics</b> For severe agitation unresponsive to other sedatives. 1. Phenobarbital 2. Propofol</p>	<p>3. Ramsay Sedation Scale 3. Glasgow Coma Scale 4. RASS 5. Riker Sedation-Agitation Scale 6. Agitation Distress Scale 7. Motor Activity Assessment Scale</p> <p>For measuring consciousness, clinical assessment (somnolence vs stupor vs coma) may be sufficient.</p> <p><b>Frequency</b> Daily</p>
<b>National guidelines</b>							
<p><b>Canadian framework</b> M. Dean et al. (2012)</p>	<p><b>Continuous Palliative Sedation Therapy (CPST)</b> “The use of pharmacological agent(s) to reduce consciousness which is continued until the patient’s death.”</p>	<p><b>Type(s):</b> Restriction to continuous palliative sedation.</p> <p><b>Target level:</b> Titration to adequately relieve suffering with “no intention to bring about complete loss of consciousness, although this may sometimes be necessary.”</p>	Patient with an advanced progressive illness in the last two weeks of life.	<p>Refractory and intolerable symptoms.</p> <p>Sedation for existential symptoms to be considered only in rare cases and after expert consultation.</p>	Decision-making regarding life supportive therapies (including ANH) needs to be made both in light of CPST and independently, after considering the psychological, ethical, cultural, religious, and/or legal implications of each decision.	<p><b>Benzodiazepines</b> Midazolam: Most frequently used for CPST.</p> <p><b>Neuroleptics/antipsychotics</b> Helpful for patients with terminal delirium. 1. Chlorpromazine 2. Methotrimeprazine</p> <p><b>Barbiturates</b> 1. Phenobarbital (may be used as an adjunct to midazolam or an antipsychotic, or alone) 2. Propofol</p>	<p><b>Parameters</b> 1. Relief of suffering Assessed by verbal comments of patient/caregiver(s), facial expressions, body movements/posture. 2. Level of consciousness Assessed by responses to verbal/nonpainful physical stimuli. 3. Adverse effects related to sedation</p> <p><b>Frequency</b> Frequently until adequate sedation achieved and then at least once per day.</p>

Continued overleaf



Guideline	Terms and definitions	Type(s) and target level of sedation	Target population	Indications	Life-sustaining treatments	Medication selection and doses	Patient monitoring
<b>Dutch guideline</b> Legemaate et al. (2007)	<b>Palliative sedation</b> "The intentional lowering of consciousness of a patient in the last phase of his or her life."	<b>Type(s):</b> 1. Continuous sedation until death 2. Short-term or intermittent sedation  "Acute" sedation listed separately.  <b>Target level:</b> Proportionate to symptom severity.	Patients in the last phase of life, imminently dying.  For deep and continuous sedation: Death expected within one to two weeks.	Presence of one or more refractory symptoms which lead to unbearable suffering for the patient.  Common refractory symptoms listed: Pain, dyspnoea, delirium.	Decision separate to sedation.  For continuous deep sedation withdrawal of artificial hydration recommended.	1. Midazolam First-choice drug.  2. Morphine To be given or continued only (alongside midazolam or another sedative) to relieve pain and/or dyspnoea.	<b>Parameters</b> Effect of palliative sedation.  <b>Frequency</b> To be assessed by treating physician at least once per day.
<b>IAPC guideline</b> Irish Association for Palliative Care (2011)	<b>Palliative sedation</b> "An important and necessary therapy in the care of selected palliative care patients with otherwise refractory distress."	<b>Type(s):</b> Distinction between "palliative sedation" where medications used to induce a state of decreased or absent awareness and "temporary or respite sedation" where sedation is used as part of symptom management without the intention of inducing deep sleep or unconsciousness.  Sedation for emergency situations listed separately.  <b>Target level:</b> To be adjusted until refractory symptom(s) are controlled.	Adult palliative care patients.  For sedation used for existential distress: Prognosis of hours or days.	Refractory distress.  Common refractory symptoms listed: Agitated delirium, dyspnoea, pain, convulsions.  Occasionally palliative sedation to be considered for severe non-physical refractory symptoms of existential, spiritual, emotional or psychological distress, when the prognosis is estimated in terms of hours or days.	Decision about ANH independent of the decision about sedation.  Each decision should be made following consideration of benefits and burdens of each treatment for each individual patient.	No information available	<b>Parameters</b> Assessment of effect of sedation after sedative medication prescribed.

Continued overleaf

Guideline	Terms and definitions	Type(s) and target level of sedation	Target population	Indications	Life-sustaining treatments	Medication selection and doses	Patient monitoring
<b>Japanese guideline</b> Morita et al. (2005)	<b>Palliative sedation therapy</b> “The use of sedative medications to relieve suffering by the reduction in patient consciousness level or the intentional maintenance of reduction in patient consciousness level resulting from symptomatic treatments.”	<b>Type(s):</b> Distinction between different types from “intermittent-mild” to “deep-continuous” based on duration and degree of sedation.  <b>Target level:</b> Proportional considering the following parameters: 1. Patient conditions (intensity of suffering, lack of other methods for palliation, and expected survival). 2. Expected benefits (palliation of suffering). 3. Expected harms (effects on the consciousness and survival).	Terminally ill palliative care patients with an estimated prognosis of less than 2-3 weeks (primarily cancer patients).	Intolerable and refractory distress/suffering.  Target symptoms listed: delirium, dyspnoea, excessive bronchial secretion, pain, nausea/vomiting, fatigue, convulsion/myoclonus, anxiety, depression, and psycho-existential suffering.  The appropriateness of sedation for psycho-existential suffering should be very carefully addressed.	Decision independent to sedation. To be discussed with patients/families whether medical interventions inconsistent with the treatment aim (palliation of suffering) should be continued.	Midazolam: first-choice drug.  If midazolam ineffective, flunitrazepam, chlorpromazine, levomepromazine, or barbiturates recommended.	<b>Parameters</b> 1. Severity of suffering Assessed by verbal complaints, facial expressions, and body movements. 2. Level of consciousness Assessed by responses to verbal and physical stimulations in ordinal nursing care. 3. Undesirable effects such as psychiatric symptoms (e.g., delirium), respiratory suppression (e.g., sudden changes in the respiratory rate and/or respiratory pattern), lowering of the root of tongue, aspiration, and circulatory suppression. 4. Potential treatment options for symptom palliation other than sedation, underlying aetiologies, and family wishes.  <b>Frequency</b> At least once every 20 minutes before adequate sedation achieved. Three times per day after adequate sedation achieved.

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Guideline	Terms and definitions	Type(s) and target level of sedation	Target population	Indications	Life-sustaining treatments	Medication selection and doses	Patient monitoring
<b>KNMG guideline</b> Royal Dutch Medical Association (2009)	<b>Palliative sedation</b> “The deliberate lowering of a patient’s level of consciousness in the last stages of life.”	<b>Type(s):</b> Distinction between “continuous sedation until the moment of death” and “temporary or intermittent sedation”.  <b>Target level:</b> Proportional to the degree of symptom control that needs to be achieved.	Patients in last stages of life, in which death is expected to ensue in the near future.  For sedation for existential suffering or continuous deep sedation: Death expected within 1-2 weeks.	One or more intractable or refractory symptoms causing the patient unbearable suffering.  Common refractory symptoms listed: Pain, dyspnoea, delirium, nausea/vomiting.  Existential suffering can be regarded as refractory symptom, but assessment of refractoriness should be based on joint expertise with professionals in psychosocial/spiritual disciplines.	Separate decision preceding the decision to initiate sedation.  Decisions regarding continuing or withholding treatments prolonging life (such as resuscitation, artificial respiration, hydration, nutrition, and kidney dialysis) to be based on patient’s wishes.	<b>Phase 1</b> <b>Midazolam</b> (first-choice drug) Bolus: Start with 10 mg SC. If necessary, 5mg SC q2h. Continuous administration: Initial dose 1.5-2.5mg/h SC/IV. If desired effect not achieved, increase by 50% after a minimum of 4h in combination with a bolus of 5mg SC.  <b>Phase 2</b> <b>Levomepromazine</b> Bolus: 25 mg SC/IV, possibly 50mg after 2h. Continuous administration: 0.5-8mg/h SC/IV in combination with midazolam.  <b>Phase 3</b> <b>Propofol</b> Bolus: 20-50mg IV. Continuous administration: 20mg/h IV increased by 10 mg/h q15min.  Morphine to be only given or continued (alongside sedatives) to relieve pain and/or dyspnoea.	<b>Parameters</b> 1. Patient comfort Assessment of symptom severity. 2. Depth of sedation  <b>Monitoring tools/scales</b> KNMG sedation scoring scale.  <b>Frequency</b> At least once a day.
<b>NCCN guideline</b> National Comprehensive Cancer Network (2019)	<b>Palliative sedation</b> Definition not provided.	<b>Type(s):</b> Restriction to continuous sedation to unconsciousness.  <b>Target level:</b> Sedation to be established and maintained at a level that relieves the patient’s symptoms.	Imminently dying patients with a prognosis of hours to days.	Presence of refractory symptoms.	Discontinuation of life-prolonging therapies (e.g. ANH/or withholding cardiopulmonary resuscitation) accompanies palliative sedation.	Typical sedatives for palliative sedation parenteral infusions: 1. Midazolam 2. Propofol	<b>Parameters</b> 1. Symptom severity 2. Drug interactions  <b>Frequency</b> Parameters to be monitored regularly.

Continued overleaf

Guideline	Terms and definitions	Type(s) and target level of sedation	Target population	Indications	Life-sustaining treatments	Medication selection and doses	Patient monitoring
<b>NHPCO guideline</b> Kirk & Mahon (2010)	<b>Palliative sedation</b> “The lowering of patient consciousness using medications for the express purpose of limiting patient awareness of suffering that is intractable and intolerable.”	<b>Type(s):</b> Distinction between different types from “light” to “moderate” and “deep” sedation.  “Respite” sedation listed separately.  <b>Target level:</b> Minimum level of consciousness reduction necessary to render symptoms tolerable.	Imminently dying patients with a prognosis of less than 14 days.	Symptoms that are otherwise intolerable and intractable.  Common refractory symptoms listed: pain, dyspnoea, delirium, restlessness.  Unable to reach agreement on a recommendation for the use of sedation for existential suffering.	DNR/DNAR order to be in effect prior to palliative sedation initiation.  Decision about ANH should be made separately from decisions for palliative sedation, after reviewing benefits and burdens.	No information available	No information available
<b>NMA guideline</b> Norwegian Medical Association (2014)	<b>Palliative sedation</b> “The pharmacological depression of the level of consciousness in order to alleviate suffering that cannot be relieved in any other way.”	<b>Type(s):</b> Distinction between different types according to duration and depth of sedation.  “Acute” sedation listed separately.  <b>Target level:</b> Sufficient depth to satisfactorily alleviate suffering.	Generally, for patients with a life expectancy of a few days. If life expectancy somewhat longer, palliative sedation may be periodically attempted under continuous assessment.	Intolerable suffering that stems from, and is dominated by, treatment-refractory physical symptoms.  Mental symptoms alone are only in rare cases an indication for palliative sedation.	For patients who stopped drinking: no need for infusion of fluids. For patients drinking significant amounts: fluids should be administered. If administration of fluids started before sedation, it should be continued, but assessed periodically.	No information available	<b>Parameters</b> 1. Level of consciousness 2. Maintenance of unrestricted respiratory passage 3. Symptom severity 4. Adverse effects

Continued overleaf

Guideline	Terms and definitions	Type(s) and target level of sedation	Target population	Indications	Life-sustaining treatments	Medication selection and doses	Patient monitoring
<b>Regional guidelines</b>							
<b>AHS framework</b> Alberta Health Services (2018)	<b>Palliative sedation</b> "The process of inducing and maintaining deep sleep, in the final hours to days of life, for the relief of severe suffering caused by one or more intractable symptoms when all appropriate alternative interventions have failed to bring adequate symptom relief."	<b>Type(s):</b> Restriction to deep continuous sedation.  <b>Target level:</b> Deep sedation	Patients with progressive, irreversible, life-limiting illness, wherein death is expected within hours to days and with a maximum life expectancy of two weeks.	Refractory symptoms which are contributing to intolerable suffering.	Decisions about life-sustaining treatments and interventions made following patient's wishes prior to initiation of palliative sedation.	Midazolam Loading dose: 1-5mg. Continuous dose: 1-10mg/h. Titration dose: 0.5-1mg/h.	<b>Parameters</b> 1. Relief of suffering 2. Level of sedation 3. Adverse effects of sedation  <b>Monitoring tools/scales</b> RASS for level of sedation.  <b>Frequency</b> Every 20-30 minutes until deep sedation achieved. Every 2-8 hours and PRN, at a minimum of three times per day, after deep sedation achieved.
<b>Calgary health region guideline</b> Braun, Hagen, & Clark (2003)	<b>Palliative sedation</b> "The intention of deliberately inducing and maintaining deep sleep in very specific circumstances: (1) for the relief of one or more intractable symptoms when all other possible interventions have failed (2) for the relief of profound anguish that is not amenable to spiritual, psychological, or other interventions, and the patient is perceived to be close to death."	<b>Type(s):</b> Restriction to deep continuous sedation.  <b>Target level:</b> State of unconsciousness	Patients with a terminal disease and a prognosis of days.	One or more refractory symptoms.  Guidelines mostly applicable for physical symptoms.	DNR order to be in effect prior to initiation of sedation.	No information available	Appropriate monitoring of the patient to ensure effective sedation by a professional with experience in symptom management.

Continued overleaf

Guideline	Terms and definitions	Type(s) and target level of sedation	Target population	Indications	Life-sustaining treatments	Medication selection and doses	Patient monitoring
<p><b>Champlain region guideline</b> Champlain Hospice Palliative Care Program (2018)</p>	<p><b>Palliative Sedation Therapy (PST)</b> “Monitored use of medications intended to induce a state of decreased awareness or absent awareness (unconsciousness) in order to relieve the burden of otherwise intolerable suffering for terminally ill patients in a manner that is ethically acceptable to the patient, family and health-care providers.”</p>	<p><b>Type(s):</b> Distinction between different types from “intermittent-mild” to “deep-continuous” based on duration and degree of sedation.</p> <p><b>Target level:</b> Proportionate to achieve the required goal, namely comfort and alleviation of the refractory symptom(s). The aim is to use the lowest dose of medication that achieves this goal.</p>	<p>A progressive, incurable illness is present with a limited life expectancy. Especially for deep sedation death to be imminent within days.</p>	<p>Presence of a refractory/intractable symptom(s).</p> <p>Common refractory symptoms listed: dyspnoea, delirium, seizures, pain, nausea.</p> <p>Additional consideration required for existential/spiritual/psychological suffering.</p>	<p>DNR order in effect prior to initiation of sedation.</p> <p>ANH not to be routinely offered to patients actively dying.</p>	<p><b>Option 1:</b> Midazolam by continuous infusion (Preferred option) Initiation: 0.2-1mg/h SC/IV. Maintenance: 1-6mg/h.</p> <p><b>Option 2:</b> Methotrimeprazine Initiation: 5-25mg SC. Follow-up dose: 5-25mg SC q2-q8h.</p> <p><b>Option 3:</b> Phenobarbital Loading dose: 30-120mg SC. Maximum dose: 720mg/24h.</p> <p><b>Option 4:</b> Combination of medications</p> <p><b>Option 5:</b> Propofol To be used only in settings in which it is approved and where appropriate monitoring and support is available.</p>	<p><b>Parameters</b> 1. Level of sedation 2. Symptom severity</p> <p><b>Monitoring tools/scales</b> 1. RASS-Palliative version for sedation level. 2. Edmonton Symptom Assessment System or other structured symptom(s) monitoring tool for symptom severity.</p> <p><b>Frequency</b> Every 30min-1h until target level of sedation achieved and symptoms controlled. Then, every 4 to 8 hours.</p>
<p><b>Fraser health guideline</b> Fraser Health Authority (2011)</p>	<p><b>Palliative Sedation Therapy (PST)</b> “The intentional lowering of a patient’s level of consciousness in the last days of life. It involves the proportional and monitored use of sedative medications to relieve intolerable suffering from refractory symptoms by a reduction in patient consciousness.”</p>	<p><b>Type(s):</b> Restricted to continuous sedation.</p> <p>“Respite” sedation listed separately.</p> <p><b>Target level:</b> Proportionate to the severity of refractory symptoms.</p>	<p>Adult patients (age 19 years and older) living with advanced life-threatening illness in the last hours to days of life.</p>	<p>Refractory symptoms.</p> <p>Common refractory symptoms listed: pain, dyspnoea, delirium, nausea, vomiting.</p> <p>PST for existential suffering to be undertaken after consultation with a member of an interdisciplinary team with knowledge and understanding of the patient’s belief system.</p>	<p>DNR order in effect prior to initiation of sedation.</p> <p>Decision about ANH to be made separately, but as part of the plan for PST.</p>	<p><b>Benzodiazepines</b> Initial choice for PST. 1. Midazolam Initiation: 1-5mg SC/IV q5min until settled. Maintenance: 30-100mg/24hrs. 2. Lorazepam Initiation: 0.5-1mg SC/IV q5min. Maintenance: 4-40mg/24hrs.</p> <p><b>Neuroleptics/antipsychotics</b> Second-line choice for PST. Methotrimeprazine Initiation: 10-25mg SC/IV q15-30min until settled. Maintenance: 25-250 mg/24h.</p>	<p><b>Parameters</b> 1. Response to PST Assessed through signs of symptom relief, Richmond Agitation Sedation Scale. 2. Balance between symptom relief and level of sedation, along with appropriate drug and/or dosage changes. 3. Assessment of physical care needs and provision of care (skin care, mouth care, repositioning, bowel care, other care as needed). 4. Indicators for need to re-assess continuation of PST.</p> <p><b>Monitoring tools/scales</b> RASS for sedation depth.</p>

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Guideline	Terms and definitions	Type(s) and target level of sedation	Target population	Indications	Life-sustaining treatments	Medication selection and doses	Patient monitoring
						<p><b>Barbiturates</b> Phenobarbital Initiation: 1-10mg/kg induction bolus SC/IV or 100-200mg SC. Maintenance: 600-1600mg/24h.</p> <p><b>General Anaesthetics</b> Propofol Initiation: bolus dose 0.25-0.5mg/kg IV. Maintenance: 500-1100mg/24h.</p>	<p><b>Frequency</b> Assessments to be carried out by the team members who are caring for the patient regularly throughout the shift.</p>
<p><b>Federation of Massachusetts protocol</b> Hospice &amp; Palliative Care Federation of Massachusetts (2004)</p>	<p><b>Palliative sedation</b> “The monitored use of medications (sedatives, barbiturates, neuroleptics, hypnotics, benzodiazepines or anaesthetic medication) to relieve refractory and unendurable physical, spiritual, and/or psychosocial distress for patients with a terminal diagnosis, by inducing varied degrees of unconsciousness.”</p>	<p><b>Type(s):</b> Distinction between different levels from mild to deep (mild/intermediate sedation recommended).  “Respite” sedation listed separately.  <b>Target level:</b> “First stage anaesthesia” is the goal of sedation; defined as the onset of disorientation to loss of consciousness.</p>	<p>Patients with a terminal diagnosis and a prognosis of hours to days.</p>	<p>Refractory symptoms (mostly physical).  For spiritual/psychosocial symptoms, “respite” sedation could be attempted.</p>	<p>DNR order in effect prior to initiation of sedation.  Decisions about the provision of nutrition and hydration separate to decision about palliative sedation.</p>	<p><b>Benzodiazepines</b> 1. Midazolam (first choice for “respite” sedation) Initiation: Infusion IV/SQ at 0.5-1.5mg/h after a loading dose of 1-5mg. Maintenance: 30-100mg/24h. 2. Lorazepam Initiation: Infusion at 0.5-1 mg/h. Maintenance: 4-40mg/24h.</p> <p><b>Barbiturates</b> 1. Pentobarbital Initiation: 60-200mg q4h PR; 1-3mg/kg IV loading dose followed by 1 mg/h. Maintenance: 50-150mg. 2. Phenobarbital Initiation: 1-3 mg/kg SQ/IV bolus dose, followed by infusion of 0.5 mg/kg/hr. Maintenance: 50mg/h.</p> <p><b>Neuroleptics/antipsychotics</b> 1. Chlorpromazine Initiation: 12.5mg q4-12h IV or 3-5mg/h IV or 25-100mg q4-12h PR. Maintenance: 12.5-50mg q4-12h. 2. Haloperidol Initiation: 1-2mg PO or 0.5-1mg SQ/IV. Maintenance: 5-15mg/24h.</p>	<p><b>Parameters</b> 1. Symptom severity 2. Level of sedation Assessed through eyelash reflex to soft tactile stroke over a closed eyelid. 3. Adverse effects</p> <p><b>Frequency</b> Continuously during initiation of therapy and every one-hour until stable dose achieved by a registered nurse.</p>

Continued overleaf

Guideline	Terms and definitions	Type(s) and target level of sedation	Target population	Indications	Life-sustaining treatments	Medication selection and doses	Patient monitoring
<b>Local institution guidelines</b>							
<b>Institutional guideline</b> Schuman, Lynch, & Abrahm (2005)	<b>Palliative sedation</b> "The use of medication to induce sedation to relieve an imminently dying patient's severe distress that cannot be controlled despite other aggressive measures."	<b>Type(s):</b> Restriction to deep continuous sedation.  <b>Target level:</b> Loss of consciousness to relieve otherwise intractable symptoms.	Patient dying imminently from a severe, irreversible, life-threatening illness.	Refractory symptoms.  Common refractory symptoms listed: pain, dyspnoea, intractable cough, myoclonus, agitation.	Active order to withhold at least the following life-sustaining treatments: chest compressions, defibrillation, endotracheal intubation, mechanical ventilation, use of pressors prerequisite for palliative sedation.	<b>1. Midazolam</b> First-choice if potential reversal of sedation is desired. Dose: Loading dose of 0.01-0.05mg/kg IV and infusion of 0.02-0.1 mg/kg/h titrated to the desired level of sedation.  <b>2. Pentobarbital</b> If there is a contraindication to benzodiazepines, if immediate sedation is required or if reversal of sedation is not contemplated. Dose: Loading dose of 1-2mg/kg IV and infusion of 1-2mg/kg/h titrated to the desired level of sedation.	<b>Parameters</b> 1. Pain 2. Stridor 3. Tachypnoea 4. Effect on target symptom(s)  <b>Frequency</b> At least every 15 minutes for the first hour, then at least every 30 minutes for the second hour, then at least hourly for the duration of therapy.

EAPC: European Association for Palliative Care; ANH: Artificial Nutrition and Hydration; PRN: Pro Re Nata, "as needed"; IV: intravenous administration; IM: intramuscular administration; PR: per rectum administration; PAR: parenteral administration; RASS: Richmond Agitation-Sedation Scale; ESMO: European Society for Medical Oncology; SC: subcutaneous administration; IAPC: Irish Association for Palliative Care; DNR: Do Not Resuscitate; KNMG: Royal Dutch Medical Association; NCCN: National Comprehensive Cancer Network; NHPCO: National Hospice and Palliative Care Organization; DNAR: Do Not Attempt Resuscitation; NMA: Norwegian Medical Association; AHS: Alberta Health Services.



### Type and target level of sedation

A distinction between different types of sedative use according to the duration of the intervention (continuous, intermittent) and/or the depth of sedation (mild, moderate, deep) was made by most guidelines (n=11). Three guidelines restricted their recommendations to continuous sedation (M. Dean et al., 2012; Fraser Health Authority, 2011; National Comprehensive Cancer Network, 2019), and an equal number to deep, continuous sedation (Alberta Health Services, 2018; Braun et al., 2003; Schuman et al., 2005). Five guidelines listed the use of sedative medication for the management of acute or emergency situations, such as massive haemorrhage, asphyxiation, or severe terminal dyspnoea, as a separate category to the usual practice of sedative use (Cherny, 2014; Cherny & Radbruch, 2009; De Graeff & Dean, 2007; Legemaate et al., 2007; Norwegian Medical Association, 2014). “Respite” or “transient” sedation as a short-term intervention to provide temporary relief from distressing symptoms whilst waiting for treatment benefit from other therapeutic approaches was also described as a distinct intervention in some of the included guidelines (Cherny, 2014; Cherny & Radbruch, 2009; Fraser Health Authority, 2011; Hospice & Palliative Care Federation of Massachusetts, 2004; Kirk & Mahon, 2010).

All guidelines acknowledged that the goal of sedative use is the management of otherwise intractable symptoms. However, guidelines differed on their recommendations for the level/degree of sedation needed to achieve this goal. The majority of guidelines (n=13) recommended that the target level of sedation should be proportionate to the severity of experienced symptoms. One guideline included the expected benefits and harms of sedative use as additional parameters to guide the titration of sedative medication (Morita et al., 2005), while five guidelines additionally specified that, in general, the degree of sedation should be the “lowest” or “least” necessary to alleviate patient suffering (Champlain Hospice Palliative Care Program, 2018; Cherny, 2014; Cherny & Radbruch, 2009; Irish Association for Palliative Care, 2011; Kirk & Mahon, 2010). In contrast, inducing a state of unconsciousness was recommended by three guidelines (Alberta Health Services, 2018; Braun et al., 2003; Schuman et al., 2005). One guideline described “first stage anaesthesia”, defined as the onset of disorientation to loss of consciousness, as the target depth of sedation for controlling intolerable distress (Hospice & Palliative Care Federation of Massachusetts, 2004).

In addition to recommendations regarding the type and target level of sedation, ten guidelines included statements separating the practice of sedative use from interventions explicitly aiming to end a patient’s life. This distinction was primarily made by acknowledging proportionality (i.e. the use of drugs and dosages tailored to the degree of symptom control

that needs to be achieved with the primary intention to provide relief from intolerable suffering) as a fundamental characteristic of the practice of sedative use (Cherny, 2014; Cherny & Radbruch, 2009; De Graeff & Dean, 2007; M. Dean et al., 2012; Fraser Health Authority, 2011; Kirk & Mahon, 2010; Legemaate et al., 2007; Morita et al., 2005; Royal Dutch Medical Association, 2009; Schuman et al., 2005).

### **Target population**

Almost all guidelines (n=15) identified palliative care patients in the last stage of life as the target population for sedative use. Ten guidelines included a specific time frame of estimated prognosis as a prerequisite for the use of sedative medication. This time frame varied from “hours to days” to “days to weeks” with a maximum life expectancy of two to three weeks (Alberta Health Services, 2018; Braun et al., 2003; De Graeff & Dean, 2007; M. Dean et al., 2012; Fraser Health Authority, 2011; Hospice & Palliative Care Federation of Massachusetts, 2004; Kirk & Mahon, 2010; Morita et al., 2005; National Comprehensive Cancer Network, 2019; Norwegian Medical Association, 2014). In contrast, five guidelines identified a specific life expectancy estimate as a criterion for sedative use only in the context of deep continuous sedation or sedation for refractory existential distress (Champlain Hospice Palliative Care Program, 2018; Cherny & Radbruch, 2009; Irish Association for Palliative Care, 2011; Legemaate et al., 2007; Royal Dutch Medical Association, 2009).

### **Indications for the use of sedative medication**

All guidelines (n=17) described the presence of one or more refractory physical symptoms as the main indication for the use of sedative medication. Sixteen of the seventeen guidelines defined refractory symptoms as symptoms that cannot be adequately controlled despite aggressive efforts to identify a tolerable therapy within an acceptable time frame that does not compromise consciousness. Thus, broadly adhering to the definition of refractory symptoms provided by Cherny and Portenoy (1994). The Canadian guideline did not provide a definition for refractory symptoms (M. Dean et al., 2012).

Pain, dyspnoea, agitated delirium and/or terminal restlessness, convulsions, nausea and/or vomiting were the most commonly listed physical refractory symptoms. Apart from the presence of refractory symptoms, eight guidelines identified intolerable distress caused by refractory symptoms as an essential indication for sedative use (Alberta Health Services, 2018; Cherny & Radbruch, 2009; M. Dean et al., 2012; Kirk & Mahon, 2010; Legemaate et al., 2007; Morita et al., 2005; Norwegian Medical Association, 2014; Royal Dutch Medical Association, 2009).

Recommendations varied regarding the use of sedatives for the management of intractable non-physical symptoms, such as existential, spiritual, emotional, or psychological distress. Some guidelines suggested that sedative use for non-physical symptoms could be a treatment option in exceptional circumstances and only after certain conditions were met. These included an expected prognosis of hours or days (Irish Association for Palliative Care, 2011; Royal Dutch Medical Association, 2009), repeated assessments by health professionals with expertise in psychosocial and/or spiritual care (Cherny, 2014; Cherny & Radbruch, 2009), multidisciplinary case evaluations (Champlain Hospice Palliative Care Program, 2018; Cherny, 2014; Cherny & Radbruch, 2009; De Graeff & Dean, 2007; M. Dean et al., 2012; Fraser Health Authority, 2011; Royal Dutch Medical Association, 2009), and trials of respite sedation with downward titration of medication after pre-specified intervals (Cherny, 2014; Cherny & Radbruch, 2009; Hospice & Palliative Care Federation of Massachusetts, 2004). Six guidelines did not provide specific recommendations for the use of sedatives to address psycho-spiritual symptoms (Alberta Health Services, 2018; Braun et al., 2003; Kirk & Mahon, 2010; Legemaate et al., 2007; National Comprehensive Cancer Network, 2019; Schuman et al., 2005). One reported a lack of consensus among committee members on a recommendation regarding the use of sedatives for suffering that is primarily non-physical (Kirk & Mahon, 2010), while the authors of another guideline viewed psychological distress more as an effect of refractory physical symptoms, rather than an independent indication for the use of sedatives (Legemaate et al., 2007).

### **Life-sustaining treatments**

Most guidelines (n=12) recommended that decisions regarding withholding, discontinuing or continuing of life-sustaining treatments, and particularly those pertaining to artificial nutrition and/or hydration, should be independent of the decision about the administration of sedative medication. Guidelines generally highlighted that such decisions should be made on an individual basis through comprehensive evaluation of the patient's wishes, and the estimated benefits and harms of life-sustaining interventions in light of the treatment aim (i.e. the palliation of suffering). For cases of continuous deep sedation or in patients who have stopped drinking prior to the administration of sedative medication, four guidelines recommended the avoidance of artificial nutrition/hydration (Champlain Hospice Palliative Care Program, 2018; Legemaate et al., 2007; National Comprehensive Cancer Network, 2019; Norwegian Medical Association, 2014). Moreover, six guidelines stated that a do-not-resuscitate order should be in effect before the initiation of sedation (Braun et al., 2003; Champlain Hospice Palliative Care Program, 2018; Fraser Health Authority, 2011; Hospice &

Palliative Care Federation of Massachusetts, 2004; Kirk & Mahon, 2010; Schuman et al., 2005).

### **Medication selection and doses**

Thirteen guidelines provided recommendations for specific medications, with eight also including information on indicated initiation and maintenance doses (Alberta Health Services, 2018; Champlain Hospice Palliative Care Program, 2018; Cherny, 2014; Cherny & Radbruch, 2009; Fraser Health Authority, 2011; Hospice & Palliative Care Federation of Massachusetts, 2004; Royal Dutch Medical Association, 2009; Schuman et al., 2005). From the guidelines that did not provide information on medication, one cited the absence of high-quality and reliable evidence to guide decisions regarding the use of specific medication as a reason (Braun et al., 2003).

Midazolam was named the drug of choice or the most frequently used drug either in general or for particular situations, such as if potential reversal of sedation is desired, by 10 of the 13 guidelines that provided drug-specific recommendations (Alberta Health Services, 2018; Champlain Hospice Palliative Care Program, 2018; Cherny, 2014; M. Dean et al., 2012; Hospice & Palliative Care Federation of Massachusetts, 2004; Legemaate et al., 2007; Morita et al., 2005; National Comprehensive Cancer Network, 2019; Royal Dutch Medical Association, 2009; Schuman et al., 2005). A further two guidelines stated that benzodiazepines in general, including midazolam, were the preferred option for inducing sedation (De Graeff & Dean, 2007; Fraser Health Authority, 2011).

Sedating antipsychotic medication, such as levomepromazine, chlorpromazine or methotrimeprazine, were recommended by nine guidelines principally as an option for patients manifesting symptoms of delirium, either in combination with midazolam or alone (Champlain Hospice Palliative Care Program, 2018; Cherny, 2014; Cherny & Radbruch, 2009; De Graeff & Dean, 2007; M. Dean et al., 2012; Fraser Health Authority, 2011; Hospice & Palliative Care Federation of Massachusetts, 2004; Morita et al., 2005; Royal Dutch Medical Association, 2009). Barbiturates (pentobarbital, phenobarbital) were mostly suggested as a second-choice option, if benzodiazepines alone were ineffective to provide adequate symptom control, in nine guidelines (Champlain Hospice Palliative Care Program, 2018; Cherny, 2014; Cherny & Radbruch, 2009; De Graeff & Dean, 2007; M. Dean et al., 2012; Fraser Health Authority, 2011; Hospice & Palliative Care Federation of Massachusetts, 2004; Morita et al., 2005; Schuman et al., 2005). The use of propofol was described in eight guidelines mainly as an option of last resort for patients who have developed high levels of tolerance to

other sedating medication (Champlain Hospice Palliative Care Program, 2018; Cherny, 2014; Cherny & Radbruch, 2009; De Graeff & Dean, 2007; M. Dean et al., 2012; Fraser Health Authority, 2011; National Comprehensive Cancer Network, 2019; Royal Dutch Medical Association, 2009). One guideline specified that propofol should be used only in settings in which it is approved and where appropriate monitoring and support is available (Champlain Hospice Palliative Care Program, 2018). Information on indicated doses for recommended medication is provided in **Table 1.1**.

The majority of guidelines that provided drug-specific recommendations cautioned against using opioids as primary sedatives primarily due to the increased risk of respiratory depression associated with the doses required to achieve sedation (Alberta Health Services, 2018; Champlain Hospice Palliative Care Program, 2018; Cherny, 2014; Cherny & Radbruch, 2009; De Graeff & Dean, 2007; M. Dean et al., 2012; Fraser Health Authority, 2011; Hospice & Palliative Care Federation of Massachusetts, 2004; Legemaate et al., 2007; Morita et al., 2005; Royal Dutch Medical Association, 2009). The authors of the Dutch guideline in particular, characterised the use of opioids alone to achieve sedation “bad practice” (Legemaate et al., 2007). However, the continuation of pre-existing opioid regimens during sedation for the purposes of symptom palliation, and particularly for the management of pain and dyspnoea, was recommended by nine guidelines (Cherny, 2014; Cherny & Radbruch, 2009; M. Dean et al., 2012; Fraser Health Authority, 2011; Hospice & Palliative Care Federation of Massachusetts, 2004; Legemaate et al., 2007; Morita et al., 2005; Royal Dutch Medical Association, 2009; Schuman et al., 2005).

### **Patient monitoring**

All but one of the included guidelines (Kirk & Mahon, 2010) provided recommendations regarding the monitoring of patients during and/or after the initiation of sedation. However, the level of detail of these recommendations varied considerably between guidelines. Thirteen guidelines listed specific outcome parameters to be monitored following the administration of sedative medication. The most frequently reported among these were: severity of targeted symptoms/patient comfort (n=13), level of consciousness/depth of sedation (n=11), and adverse effects relating to the use of sedative medication (such as agitation, delirium, respiratory/circulatory depression, or aspiration; n=7). Other listed parameters included: respiratory rate/maintenance of unrestricted respiratory passage (n=3), drug interactions (n=1), and patients’ physical care needs (e.g. mouth care, skin care, repositioning; n=1). Three guidelines provided very limited information on monitoring parameters, stating that the “effect of sedation” should be monitored (Irish Association for

Palliative Care, 2011; Legemaate et al., 2007) or that “effective sedation” should be ensured through patient monitoring (Braun et al., 2003). In relation to routine monitoring of vital signs (blood pressure, oxygen saturation, heart rate), seven guidelines recommended that such observations should be discontinued as they do not contribute to the primary goal of care (i.e. patient comfort), unless sedation is intended to be short-term/intermittent and the patient is not imminently dying, or the patient or family wishes such monitoring to continue (Cherny, 2014; Cherny & Radbruch, 2009; De Graeff & Dean, 2007; M. Dean et al., 2012; Morita et al., 2005; National Comprehensive Cancer Network, 2019; Schuman et al., 2005).

Regarding the methods of assessment of the aforementioned parameters, three guidelines mentioned patients’ responses to verbal and non-painful physical stimulation as means of evaluating consciousness level/depth of sedation (Cherny & Radbruch, 2009; M. Dean et al., 2012; Morita et al., 2005). One guideline proposed level of consciousness to be assessed via eyelash reflex to soft tactile stroke over a closed eyelid (Hospice & Palliative Care Federation of Massachusetts, 2004). Another stated that clinical assessment to distinguish between pre-specified levels of consciousness (somnolence versus stupor versus coma) may be sufficient in most cases (De Graeff & Dean, 2007). For assessing symptom severity/patient comfort, verbal complaints, facial expressions, and body movements/posture were recommended as appropriate methods by two guidelines (M. Dean et al., 2012; Morita et al., 2005).

Six of the seventeen included guidelines provided recommendations regarding the use of structured tools for the assessment of outcome parameters (Alberta Health Services, 2018; Champlain Hospice Palliative Care Program, 2018; Cherny & Radbruch, 2009; De Graeff & Dean, 2007; Fraser Health Authority, 2011; Royal Dutch Medical Association, 2009). However, the authors of the Canadian guideline stated that no particular scale could be recommended given that the usefulness and appropriateness of these measures has not yet been proven in the palliative care setting (M. Dean et al., 2012). The original or palliative version of the Richmond Agitation-Sedation Scale (RASS, RASS-PAL) (Bush et al., 2014; Sessler et al., 2002) was the most commonly recommended tool for the monitoring of consciousness levels (n=5). Other recommended scales were: the Ramsay Sedation Scale (n=1) (Ramsay, Savege, Simpson, & Goodwin, 1974), Glasgow Coma Scale (n=1) (Teasdale & Jennett, 1974), Riker Sedation-Agitation Scale (n=1) (Riker, Fraser, & Cox, 1994), Motor Activity Assessment Scale (n=1) (Devlin et al., 1999), and the sedation score developed by the Royal Dutch Medical Association (n=1) (Royal Dutch Medical Association, 2009). For the monitoring of symptom severity during sedation, the following tools were suggested: the Edmonton Symptom Assessment Scale (n=2) (Bruera, Kuehn, Miller, Selmsler, & Macmillan, 1991) for patients able

to self-report symptoms, and the Communication Capacity Scale (n=1) (Morita, Tsunoda, Inoue, Chihara, & Oka, 2001), Agitation Distress Scale (n=1) (Morita, Tsunoda, et al., 2001), and Critical-Care Pain Observation Tool (n=1) (Gelinas, Fillion, Puntillo, Viens, & Fortier, 2006) for the observational monitoring of patient symptoms.

In terms of the recommended frequency of assessments, eight guidelines suggested specific time intervals for patient monitoring. These ranged from every 15 minutes to 1 hour during the initiation of sedation and until adequate sedation is achieved, and every hour to a minimum of once per day for the duration of the intervention (Alberta Health Services, 2018; Champlain Hospice Palliative Care Program, 2018; M. Dean et al., 2012; Hospice & Palliative Care Federation of Massachusetts, 2004; Legemaate et al., 2007; Morita et al., 2005; Royal Dutch Medical Association, 2009; Schuman et al., 2005). In addition to proposing specific time intervals for patient monitoring, M. Dean et al. (2012) stated that parameters such as the pharmacokinetics of the drugs used for sedation and the location of care should be taken into consideration when determining the frequency of monitoring.

### **Summary of review findings**

This literature review updated and synthesised the findings of three published systematic reviews of clinical practice guidelines on the practice of sedative use in palliative care. In total, 17 eligible guideline documents were identified and included in the narrative synthesis. Guidelines were broadly uniform in the terminology used to label and define the practice of sedative use, opting for the terms “palliative sedation” or “palliative sedation therapy” to describe the relevant practice. The use of sedative medication was mostly defined as an intervention aiming to relieve otherwise intolerable suffering/symptoms through the intentional reduction of patients’ consciousness levels.

All guidelines considered refractory physical symptoms as the main indication for the use of sedative medication. They took different approaches, however, regarding sedative use for non-physical symptoms. Most stated that such symptoms alone should be considered as adequate indication for sedative use only in rare cases and after certain conditions are met. Other guidelines restricted their recommendations solely to refractory physical symptoms. Likewise, although the majority of guidelines proposed that decisions relating to the continuation of life-sustaining treatments should be separate to the decision about sedative use itself, some considered the existence of an active do-not-resuscitate order as a prerequisite for initiating sedation.

Medications for inducing sedation were not consistently described in reviewed guidelines. From the guidelines that made drug-specific recommendations, almost all named benzodiazepines as the drug of choice with midazolam being the preferred agent in this category. The majority of guidelines highlighted the need for proportionality and/or adequacy of titration with the primary intent to relieve patient suffering, with most considering these as the main distinguishing factors between the practice of sedative use and other end-of-life interventions, such as euthanasia or physician-assisted suicide.

For a proportionate use of sedative medication to be achieved, guidelines generally recommended the close monitoring of patients during and after the initiation of sedation, with the majority listing specific parameters for patient monitoring. Symptom severity, depth of sedation/level of consciousness, and adverse effects of sedative drugs were the most frequently listed of these parameters. However, there was no consensus among guidelines on the best way to conduct patient monitoring. Some proposed either the use of informal clinical observation/judgement and/or structured observational scales, whilst other guidelines provided no specific recommendations on assessment methods.

The lack of consensus in reviewed guidelines on appropriate methods to monitor the effects of sedative medication, including those pertaining to the assessment of level of consciousness, hinders the application of uniform guidance in clinical practice and creates further uncertainty in this sensitive area of palliative care (Schildmann et al., 2015). Findings of this literature review, therefore, underline the importance of conducting research on how to best assess/monitor the effects of sedative medication in palliative care patients.

## **1.5 Assessment and monitoring of level of consciousness in palliative care patients receiving sedative medication**

### **Observational methods**

Findings from earlier work for the I-CAN-CARE programme grant demonstrated that in current practice clinicians in England generally assess sedative effects (i.e. patient comfort and level of consciousness) through clinical judgement and observation of possible signs of discomfort, such as facial expressions (Vivat, Bemand-Qureshi, Harrington, Davis, & Stone, 2019). Structured observer rating scales are also sometimes used for the assessment and/or monitoring of level of consciousness in palliative care clinical practice and research (Arevalo et al., 2012; Brinkkemper et al., 2013). However, there are several limitations to the use of



observational methods for the assessment of consciousness levels in palliative care patients receiving sedative medication (Deschepper, Bilsen, & Laureys, 2014; Six, Bilsen, et al., 2020).

An inherent limitation of observational assessment methods in general is that they are dependent on the subjective interpretation of observable signs and responses. Thus, different observers may perceive and interpret clinical signs differently, leading to disparate assessments of patients' conditions (Deschepper et al., 2014). Systematic differences in symptom severity estimates have been frequently reported between healthcare professionals and patients' family members, with healthcare professionals tending to underestimate patient distress compared to relatives (Kappesser & Williams, 2010). Even among healthcare professionals however, assessment discrepancies often occur (Deschepper et al., 2014). A European study of 2059 medical and paramedical professionals reported that factors relating to healthcare professionals' characteristics, such as professional background, religion and age, could affect their perceptions regarding the level of pain that patients diagnosed with disorders of consciousness are experiencing. Paramedical professionals, religious caregivers, and older caregivers were found to be more likely to report that vegetative patients may experience pain (Demertzi et al., 2009).

An additional difficulty in using level of consciousness assessment methods based on patients' responses, is that sedative medications have direct effects on motor responsiveness. Patients who are unable to display overt responses to external stimulation are sometimes considered to be unconscious and hence unable to experience pain or other symptoms (Deschepper et al., 2014). However, empirical evidence suggests that unresponsiveness does not automatically imply unawareness (Andrews, Murphy, Munday, & Littlewood, 1996; Sanders, Tononi, Laureys, & Sleight, 2012; Schnakers et al., 2009). Previous research has shown that between 9 and 43% of patients clinically diagnosed as being in a vegetative state demonstrated signs of conscious awareness when different diagnostic methods were used (Andrews et al., 1996; Cruse et al., 2011; Monti et al., 2010; Schnakers et al., 2009). As examples, Cruse et al. (2011) reported that 19% of patients considered to be entirely vegetative based on repeated specialist behavioural assessment could consistently generate appropriate electroencephalographic (EEG) responses to distinct commands. Similarly, a study using functional magnetic resonance imaging found that 5/54 patients presumed to be in a vegetative/minimally conscious state were able to modulate their brain activity by generating voluntary and repeatable blood oxygenation-level-dependent responses when prompted to perform imagery tasks (Monti et al., 2010). These findings suggest that standardised clinical assessment based on behavioural observation may not

reliably detect covert signs of cognitive function and awareness in patients with impaired motor function, resulting in the possible misdiagnosis and under-treatment of such patients (Andrews et al., 1996; Cruse et al., 2011).

A further limitation of observational methods is that they can only provide an intermittent assessment of patients' conditions. Thus, changes and fluctuations in patients' degree of distress and level of consciousness happening between assessments may remain undetected (Six, Bilsen, et al., 2020).

The limitations of existing procedures for assessing conscious level may impede the effectiveness of sedative use, and so result in suboptimal care (Pype, Teuwen, Mertens, Sercu, & De Sutter, 2018; Six, Bilsen, et al., 2020). Inappropriate use of sedative medication may have adverse consequences for the care and experience of patients and their family members (Morita et al., 2004; Pype et al., 2018). A survey among palliative care nurses found that sedative use was considered insufficiently effective by approximately 40% of respondents (Brinkkemper et al., 2011), while another study reported suboptimal use of palliative sedation by general practitioners in 11/27 of the studied cases (Pype et al., 2018). Inadequate symptom palliation can be traumatic for patients and a significant source of emotional distress for their families (Morita et al., 2004; Pype et al., 2018). Conversely, the use of disproportionately high doses of sedatives may be equally distressing or unacceptable for relatives due to the impaired ability of the patient to interact with family members and the possible risk of hastening death (Anquetin et al., 2013; Deschepper et al., 2014).

In order to overcome the problems associated with existing level of consciousness assessment methods and avoid the effects of over- or under-sedation, the use of monitoring devices based on EEG data has been suggested to supplement and validate observational assessments of level of consciousness in palliative care patients receiving sedative medication (Barbato, Barclay, Potter, & Yeo, 2015; Deschepper et al., 2014; Six, Bilsen, et al., 2020).

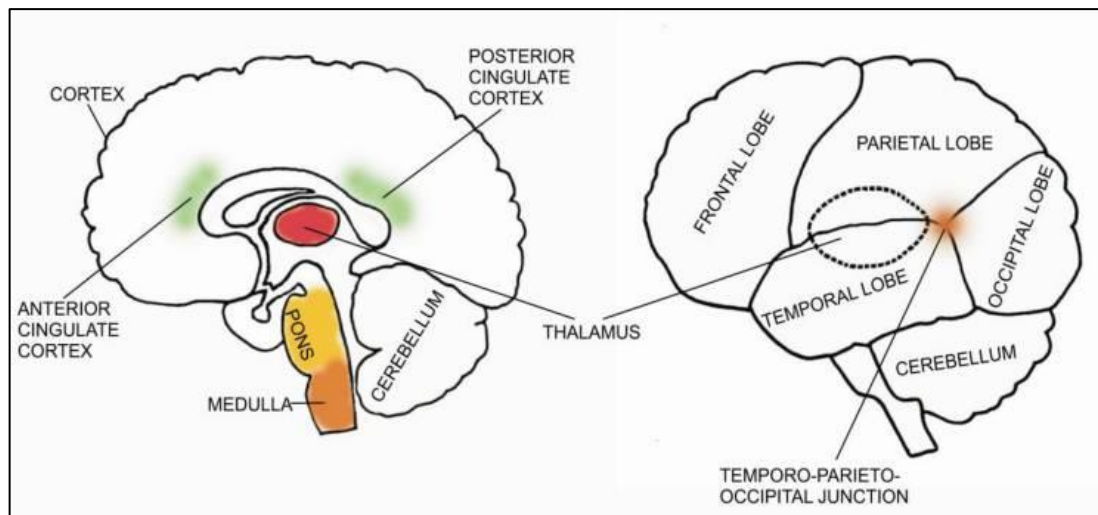
### **EEG-based level of consciousness monitors**

EEG-based monitors were originally developed as surrogate measures of anaesthesia depth, as an adjunct to guide anaesthetic delivery in the operating room (Musizza & Ribaric, 2010). The sensitivity of the EEG to the presence of anaesthetic agents was first noted by Gibbs, Gibbs and Lennox in 1937 (Gibbs, Gibbs, & Lennox, 1937). Since then, the actions of general

anaesthetics on brain receptors and their effect on the EEG have been extensively researched (Mashour, 2006; Musizza & Ribaric, 2010).

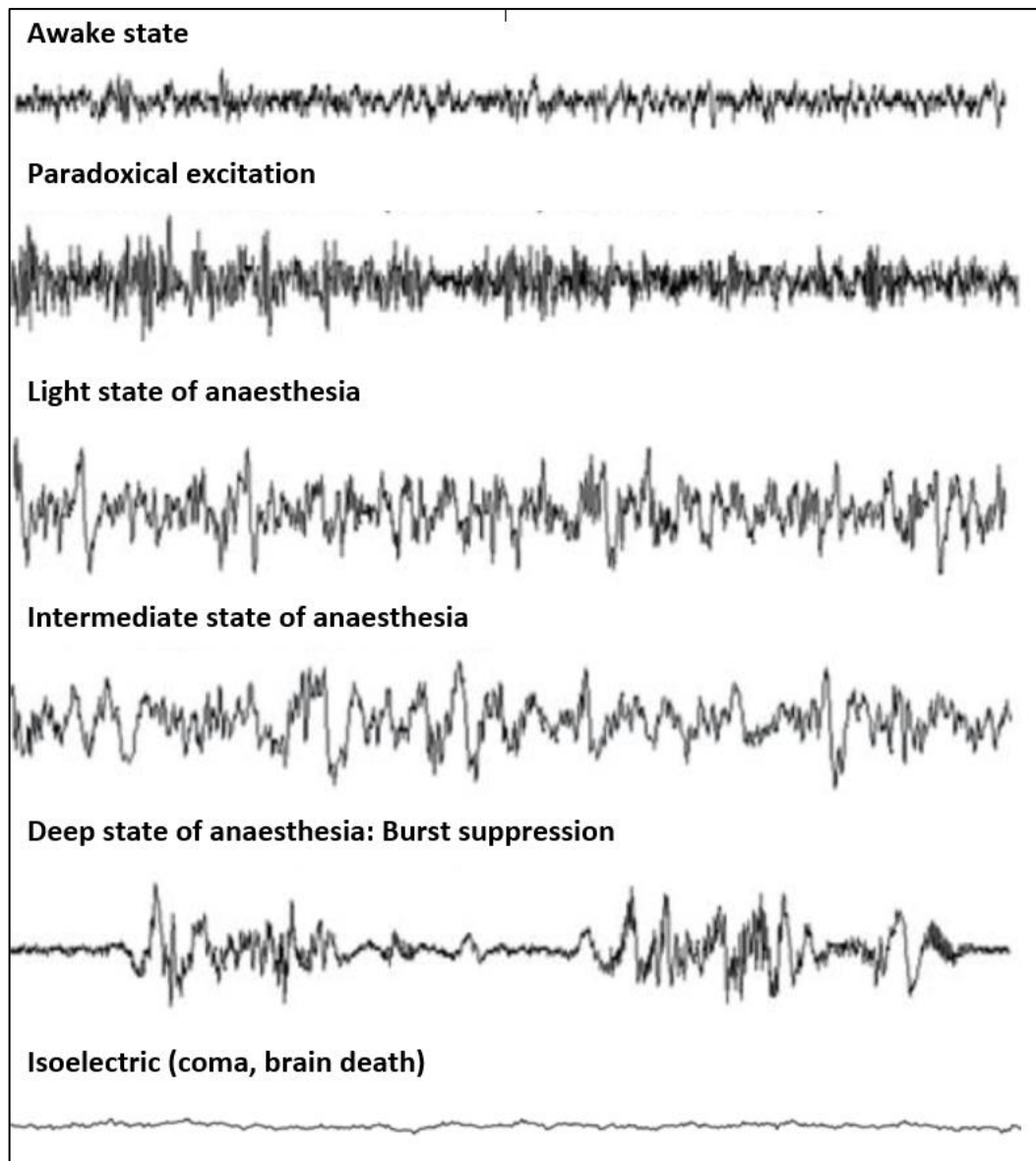
Anaesthetic agents generally act by causing a widespread neuro-depression in the central nervous system, either by increasing inhibitory neurotransmission or through reducing excitatory neurotransmission (Son, 2010). Specific mechanisms of action of general anaesthetics are not yet completely understood (Son, 2010). However, distinct functions of general anaesthetics have been recently associated with specific sites of the central nervous system. Immobility and analgesia effects have been correlated with the spinal cord, memory loss with actions of the limbic system, and loss of consciousness with the brain stem, pons, thalamus and brain cortex (see **Figure 1.1**) (Musizza & Ribaric, 2010; Son, 2010).

Despite some individual differences in targeted sites, most volatile and intravenous anaesthetic agents are thought to primarily target a specific cortical area: the posterior cortico-thalamic complex, comprising the lateral temporo-parieto-occipital junction and the mesial cortical core, to induce unconsciousness. Anaesthetics act in this area by disrupting two essential functions: cortical integration and cortical information capacity. This is achieved through deactivating or inducing a functional disconnection between the subregions of the targeted cortico-thalamic complex (Alkire, Hudetz, & Tononi, 2008; Musizza & Ribaric, 2010; Rani & Harsoor, 2012; Voss & Sleight, 2007). The use of anaesthetic agents has also been frequently associated with reductions in thalamic metabolism and blood flow (Alkire et al., 2008; Musizza & Ribaric, 2010). However, not all anaesthetic agents cause reductions in thalamic activity, while, conversely, significant reductions in thalamic activity have been observed in lower doses of anaesthetics that are insufficient to cause unconsciousness (Alkire et al., 2008; Musizza & Ribaric, 2010). Therefore, given the numerous interconnections between the thalamus and the cortex, it has been suggested that effects of general anaesthetics on the thalamus reflect global cortical activity, rather than thalamic activity alone (Musizza & Ribaric, 2010). In addition, general anaesthetics inhibit the excitatory arousal pathways of the brain stem and pons which are essential components of cortical arousal; thus, affecting wakefulness and sleep-wake transitions (Musizza & Ribaric, 2010; Rani & Harsoor, 2012).



**Figure 1.1:** Key brain areas (in colour) associated with the state of consciousness (reproduced with permission from Musizza & Ribaric, 2010)

At a molecular level, anaesthetics mediate neuronal activity by interacting with ion channels that regulate synaptic transmission and membrane potentials in key regions of the brain and spinal cord (Alkire et al., 2008). Being relatively apolar, anaesthetic agents cross the blood-brain barrier and interact with receptors leading to neuron hyperpolarisation due to increased inhibition or decreased excitation (Musizza & Ribaric, 2010). These actions alter the neuronal firing patterns from the sustained firing typical of the aroused brain to a bi-stable burst-pause pattern (Alkire et al., 2008; Musizza & Ribaric, 2010). Changes in neuronal firing patterns are reflected in the EEG with a general reduction of EEG activity during anaesthesia which is typically proportional to the dose of the anaesthetic drugs administered (Rani & Harsoor, 2012). The low voltage, high frequency pattern of wakefulness changes to lower frequency, higher amplitude activity as the level of anaesthesia deepens, and eventually to an EEG burst-suppression pattern (Alkire et al., 2008; Cascella, 2016). In some cases, after inducing anaesthesia and before reaching the maintenance period, patients may enter a state of “paradoxical excitation” characterised by disinhibition and loss of motor and affective control depicted on the EEG as an increase in beta activity (see **Figure 1.2**) (Brown, Lydic, & Schiff, 2010; Fulton & Mullen, 2000) .



**Figure 1.2:** EEG patterns during different stages of anaesthesia-induced unconsciousness (adapted from Brown et al., 2010; Copyright Massachusetts Medical Society)

Due to the ability of the EEG to reflect the effect of anaesthetic agents on brain activity and given the narrow therapeutic window of general anaesthetics, EEG-based methods were considered as an alternative means of monitoring anaesthetic depth that could guide anaesthetic titration (Mashour, 2006; Musialowicz & Lahtinen, 2014). However, the use of raw EEG data to assess anaesthetic depth in the operating room was deemed impractical mainly due to the time and skill required to interpret complex unprocessed EEG data (Hajat, Ahmad, & Andrzejowski, 2017). Therefore, efforts were made to compress and simplify these

data by using processed EEG algorithms, resulting in the development of processed EEG-based monitors (Hajat et al., 2017; Mashour, 2006).

Similar operating principles apply to most commercially available EEG-based monitors, although there are considerable differences in the EEG processing algorithms used (Hajat et al., 2017; Rani & Harsoor, 2012). EEG signals are obtained through gel-based electrodes applied on the forehead, and subsequently amplified, digitalised and cleared from artefact interfering with EEG signal. Common artefacts include signals caused by the movement of electrodes on the skin, orbital activity, and electrocardiogram waveforms. After amplification and conversion of EEG signals, various algorithms are typically applied to deconstruct EEG waveforms and perform analyses based on the frequency, amplitude, latency, and/or phase relationship of waveform components to provide a single number that reflects the patient's level of consciousness (Hajat et al., 2017; Kreuzer, 2017; Rampil, 1998; Rani & Harsoor, 2012).

A number of EEG-based monitors have been developed and marketed over the past 30 years, including: Bispectral index™ (Medtronic, Dublin, Ireland), Brain Anesthesia Response™ monitor (Cortical Dynamics Ltd., North Perth, Australia), Cerebral State Monitor™ (Danmeter, Odense, Denmark), Index of Consciousness™ (Morpheus Medical, Barcelona, Spain), M-Entropy™ (GE Healthcare, Helsinki, Finland), Narcotrend™ (MonitorTechnik, Bad Bramstedt, Germany), NeuroSENSE™ (NeuroWave Systems Inc., Cleveland Heights, OH), Patient State Analyser 4000™ (Physiometrix Inc., N. Billerica, MA), and State and Response entropy™ (GE Healthcare, Chicago, IL). The most extensively studied and validated of these monitors is the Bispectral index (Hajat et al., 2017; Mashour, 2006).

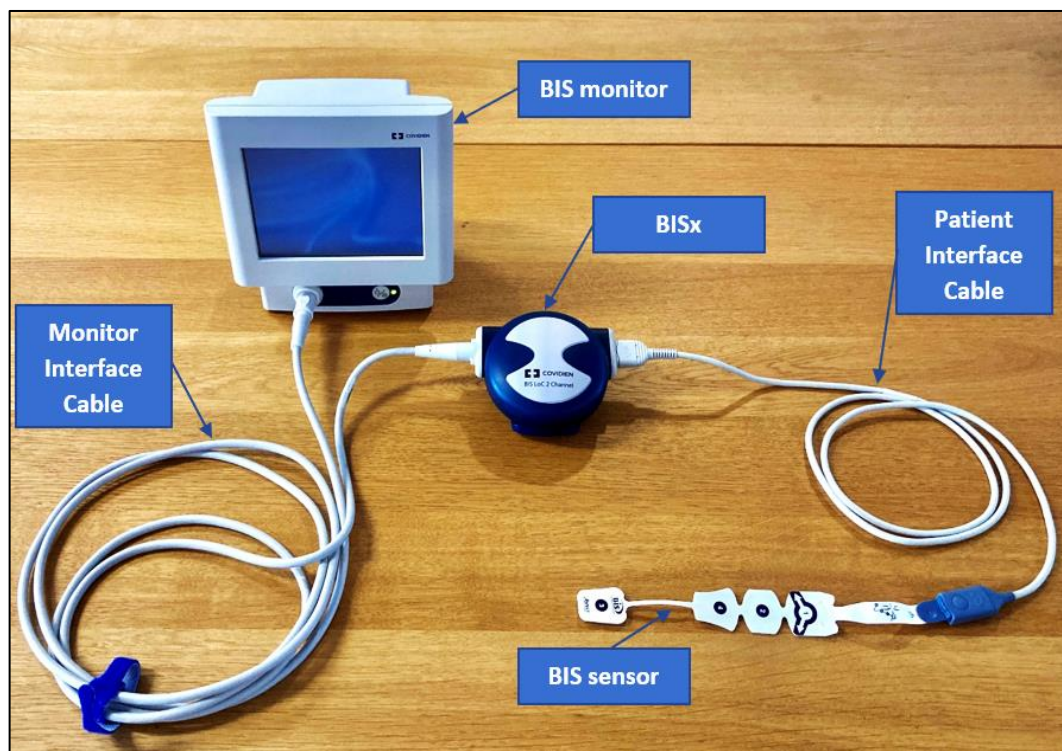
## **1.6 Bispectral index monitoring**

### **Description of Bispectral index monitor**

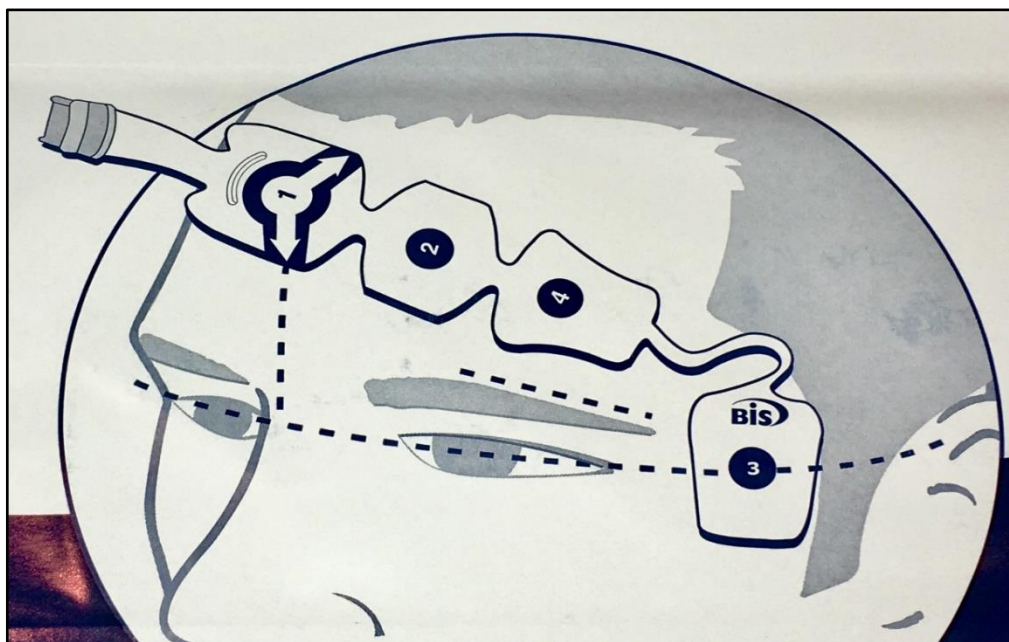
Bispectral index monitor (BIS) was introduced in 1992 by Aspect Medical Systems Inc. (now part of Medtronic, Dublin, Ireland), and was approved by the United States Food and Drug Administration (FDA) as a measure of the hypnotic effects of general anaesthetics and sedatives in 1996 (as cited in Dou, Gao, Lu, & Chang, 2014). BIS was the first commercially available EEG-based monitor to measure the pharmacodynamic effects of anaesthetic agents on the brain (Musialowicz & Lahtinen, 2014). From 1999 onward other depth of anaesthesia monitors were marketed. Due to its antecedence, BIS has been used as a standard against which other monitors are compared (Musialowicz & Lahtinen, 2014; Rani & Harsoor, 2012).

The National Institute for Health and Care Excellence (NICE) recommends the use of BIS during any type of general anaesthesia in patients considered at higher risk of adverse outcomes and in all patients receiving total intravenous anaesthesia (National Institute for Health and Care Excellence, 2012a).

The BIS™ monitoring system consists of a sensor, patient interface cable, processor unit (BISx), monitor interface cable, and monitor (see **Figure 1.3**). The most recent versions of the BIS monitoring system (v4.0 and onward) typically use a proprietary sensor comprising four self-prepping electrodes (BIS™ Quatro Brain Monitoring sensor) placed across the forehead (electrodes 1, 2, 4) and on either of the temporal areas (electrode 3) (see **Figure 1.4**). The frontal-temporal lead (electrode 3) serves as the ground electrode and captures electromyography activity of the frontalis muscle below the sensor. BISx receives raw EEG data through the sensor via the patient interface cable and subsequently analyses these data for artefact and processes them using digital signal processing techniques. Analysed data are sent to the monitor for display through the monitor interface cable (Aspect Medical Systems, 2006; Johansen, 2006; Luebbehusen, 2005).



**Figure 1.3:** Features of BIS™ monitoring system



**Figure 1.4:** Placement of BIS™ Quatro Brain Monitoring sensor

### **Calculation of the BIS parameter**

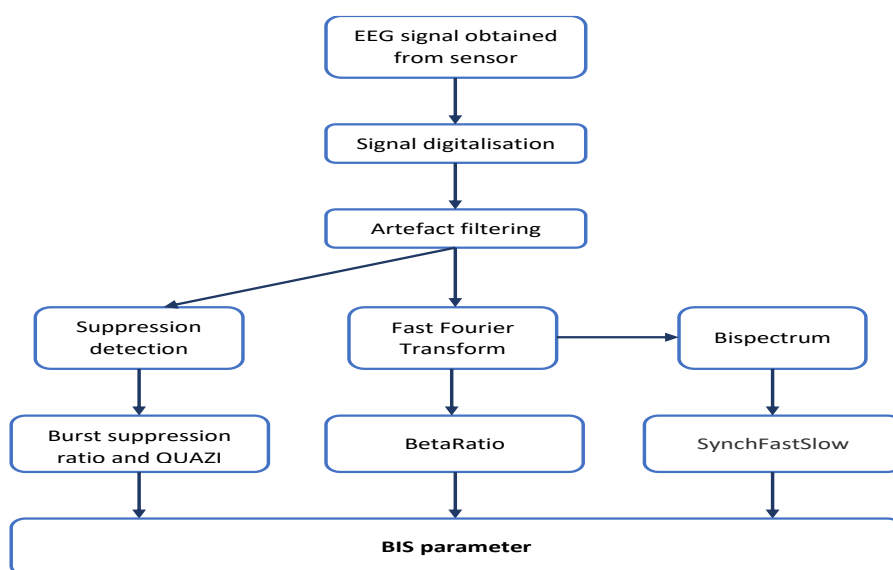
BIS output is a complex parameter combining information from four main EEG subparameters: Burst suppression ratio, “QUAZI” suppression index, BetaRatio, and SynchFastSlow (Nunes et al., 2012; Rampil, 1998). These subparameters are derived from distinct EEG signal processing analyses performed by the BIS algorithm (Nunes et al., 2012; Rampil, 1998). The BIS algorithm is proprietary and, therefore, it is not publicly available. However, some parts of the algorithm have been disclosed in published literature (Kreuzer, 2017; Musizza & Ribaric, 2010; Nunes et al., 2012; Rampil, 1998).

Burst suppression ratio represents the proportion of periods longer than 0.5 seconds during which the EEG is isoelectric (does not exceed  $\pm 0.5 \mu\text{V}$ ), while QUAZI suppression index detects burst suppression in the presence of erratic baseline EEG voltage (Nunes et al., 2012; Rampil, 1998; Schnakers, Majerus, & Laureys, 2005). Both of these subparameters are derived from analyses performed in the time domain, i.e. analyses based on EEG voltage changes over time (Nunes et al., 2012; Rampil, 1998). BetaRatio is the log ratio of voltage (or “band power”) in EEG waveform frequency bands 30-47 Hz over 11-20 Hz. This subparameter is obtained from the frequency domain using the Fast Fourier Transform, a method of



analysis based on decomposing EEG signals and expressing them as a spectrum of their component frequencies (Mashour, 2006; Rampil, 1998). Finally, SynchFastSlow subparameter is derived from bispectral analysis (i.e. an analysis method measuring the phase correlation of waves among different frequencies). SynchFastFlow is the log ratio of the sum of bispectrum activity in the band 0.5-47 Hz over the sum of bispectrum activity in the band 40-47 Hz (Kreuzer, 2017; Nunes et al., 2012; Rampil, 1998).

The combination of the subparameters comprising the BIS parameter was derived empirically by analysing a prospectively collected database of EEG recordings from approximately 2000 patients who received various commonly used general anaesthetic and sedative agents (Mashour, 2006; Rampil, 1998). Each component subparameter was selected on the basis of its ability to provide useful information in a specific range of anaesthetic effect (Rampil, 1998). Burst suppression ratio and QUAZI parameters correlate with deep anaesthesia. The SynchFastSlow identifies moderate sedation or light anaesthesia, and BetaRatio detects light sedation (Nunes et al., 2012; Rampil, 1998). The resulting BIS index is calculated from the weighted sum of these subparameters and it is expressed as a single dimensionless number ranging from 0 to 100 (Johansen & Sebel, 2000; Rampil, 1998). Values near 100 represent a fully awake clinical state, while 0 denotes complete cortical EEG suppression (isoelectric EEG) (Johansen & Sebel, 2000; Schnakers et al., 2005). **Figure 1.5** illustrates the processes involved in the calculation of the BIS parameter.



**Figure 1.5:** Processes involved in the calculation of BIS parameter (adapted from Nunes et al., 2012)

### **Smoothing rates, response time, and signal quality indicators**

BIS values appearing on the monitoring screen are derived from data gathered over the preceding 10 to 30 seconds of raw EEG recording (Medtronic, 2019). Using several seconds of EEG data for the calculation of each BIS value prevents excessive fluctuations in BIS values (i.e. “smoothing” of data), and enables the determination of values on occasions when the EEG signal may be briefly interrupted (Medical Advisory Secretariat, 2004; Medtronic, 2019). The BIS device allows the user to determine the smoothing rate used for calculating BIS values by selecting from pre-specified options (usually 10, 15 or 30 seconds) (Medtronic, 2019).

Like all EEG-based monitors, BIS requires some time for the processing of data and calculation of index values (Rani & Harsoor, 2012). Therefore, although BIS values are reasonably responsive, they cannot reflect changes to anaesthetic depth instantaneously. Hence, especially in cases where sudden changes to patients’ level of consciousness occur, BIS values may lag behind the observed clinical state (Medtronic, 2019). The average time delay in BIS response has been reported to range between 5 and 106 seconds (Medtronic, 2019; Rani & Harsoor, 2012).

Apart from the BIS value, the front panel of the monitor also displays a trend graph of BIS values over time, raw EEG waveforms in real time, a bar representing the quality of the obtained EEG signal (Signal Quality Index; SQI), and an electromyography (EMG) bar. SQI and EMG values are used as indicators of the reliability of BIS recordings (Mathur, Patel, Goldstein, & Ankit, 2021). The SQI is calculated based on impedance data and artefacts detected in EEG signal (Musialowicz et al., 2010). The EMG index indicates the presence of facial or forehead muscle activity caused by increased muscle tone or muscle movement. This activity can generate high-frequency signals that contaminate EEG signals which, in turn, can artificially elevate recorded BIS values (“EMG artefact”) (Luebbehusen, 2005; Mathur et al., 2021; Whyte & Booker, 2003). Like BIS output, SQI and EMG values can range from 0 to 100. Higher SQI numbers indicate better EEG signal quality while lower EMG values indicate decreased EMG artefact (Luebbehusen, 2005). SQI values >50 and EMG values <50 dB are generally considered to represent acceptable quality BIS readings (Bhargava, Setlur, & Sreevastava, 2004; J. M. LeBlanc, Dasta, & Kane-Gill, 2006; Luebbehusen, 2005; Musialowicz et al., 2010; Rampil, Kim, Lenhardt, Negishi, & Sessler, 1998).

## BIS monitoring value range

The BIS monitoring value range represents a scaled continuum of clinical state and expected EEG changes to the administration of anaesthetic and sedative agents (see **Figure 1.6**) (Medtronic, 2019; Nunes et al., 2012). The association between specific BIS values and ranges, and clinical endpoints during sedation and anaesthesia has been empirically demonstrated in adult volunteers and patient populations (Johansen & Sebel, 2000; Rampil, 1998). BIS values >90 are typically observed in awake, unsedated individuals. BIS values progressively decrease as drug-induced hypnotic effects deepen. Loss of consciousness tends to begin occurring at BIS values between 70 and 80. Patients with BIS values in this range have been found to respond to loud commands or gentle physical stimulation. BIS values <60 have been associated with drug-induced unconsciousness, with values between 40 and 60 indicating adequate levels for general anaesthesia. Values <40 generally represent a deep hypnotic state, while values <30 reflect increasing levels of EEG suppression (Medtronic, 2019; Nunes et al., 2012; Schnakers et al., 2005).

BIS monitoring value range	Clinical states
100	Awake
90	
80	Light/moderate sedation
70	
60	General anaesthesia
50	
40	Deep hypnotic state
30	
20	Burst suppression
10	
0	Isoelectric EEG

**Figure 1.6:** BIS monitoring value range and associated clinical states (adapted from Mathur et al., 2021)

## **Clinical impact of BIS monitoring**

The clinical impact of BIS monitoring as a measure of anaesthesia depth has been extensively researched. Several prospective clinical trials have investigated the effect of BIS-guided anaesthesia compared to standard practice alone (typically involving monitoring of somatic and autonomic signs) in the occurrence of intraoperative awareness, anaesthetic consumption, and postoperative patient outcomes. Findings from these studies demonstrated that the titration of primary anaesthetic agents to the recommended range of BIS values for general anaesthesia (between 40 and 60) resulted in significant reductions in risk of intraoperative awareness (Alkaissi, Tarayra, & Nazzal, 2017; Myles, Leslie, McNeil, Forbes, & Chan, 2004; Zhang et al., 2011), primary anaesthetic use (Aime et al., 2006; Alkaissi et al., 2017; Chan, Cheng, Lee, & Gin, 2013; Gan et al., 1997; Yli-Hankala, Vakkuri, Annila, & Korttila, 1999), emergence and recovery time (Gan et al., 1997; Luginbuhl, Wuthrich, Petersen-Felix, Zbinden, & Schnider, 2003; Yli-Hankala et al., 1999), and reduced the risk of postoperative nausea and vomiting (Fritz et al., 2013; Luginbuhl et al., 2003). These findings were confirmed by the results of two meta-analyses combining data from 36 and 11 randomised controlled trials of BIS monitoring versus standard practice for the titration of anaesthetic agents in surgical patients, respectively (Liu, 2004; Punjasawadwong, Phongchiewboon, & Bunchungmongkol, 2014). Moreover, a Cochrane review published in 2016 reported evidence of association between BIS-guided anaesthesia and reduced incidence of postoperative delirium in hospitalised non-intensive care unit patients (Siddiqi et al., 2016).

BIS monitoring has been most commonly used for patients undergoing general anaesthesia in the operating room. However, an emerging body of evidence examines its usefulness as a measure of sedation depth in a variety of other clinical settings. These include endoscopy (Bower et al., 2000; von Delius et al., 2009; Yamamoto, Igarashi, Tetsuka, & Endo, 2009), dentistry (Munoz Garcia, Vidal Marcos, Restoy Lozano, & Gasco Garcia, 2012), the intensive care unit (Kaplan & Bailey, 2000), and emergency departments (M. Gill, Green, & Krauss, 2003; Weaver, Hauter, Brizendine, & Cordell, 2007). In addition, a limited number of studies have explored the clinical application of BIS monitoring in patients receiving sedative medication in the palliative care setting. These studies are discussed in detail in the following section.

## **Literature review of BIS monitoring in palliative care patients receiving sedative medication**

In order to identify and summarise existing evidence on the use of BIS monitoring in the palliative care context, a literature review was undertaken. Relevant publications were located through searching four electronic databases (Cumulative Index to Nursing and Allied Health Literature [CINAHL], EMBASE, MEDLINE, Web of Science [WoS]) from 1992 (year of BIS introduction to the market) to February 2020. Search terms included medical subject headings and free text terms for: palliative care, sedation depth/level of consciousness, and Bispectral index monitoring.

Identified publications were selected if they constituted primary research studies reporting on using BIS for the monitoring of level of consciousness of palliative care patients, were written in English, and full-text articles were available. After eligible studies were located, the following information was extracted from each study: author(s), year of publication, country of origin, aim of study, study design, study population, summary statistics of main outcome measures, and data on the validity and clinical utility of BIS monitoring, where available. Where information on the feasibility and acceptability of BIS monitoring was available, it was also extracted. Extracted data were subsequently narratively synthesised.

### **Database search and publication selection results**

Database searching yielded a total of 232 records. Following removal of duplicates, and screening of titles and abstracts, 14 articles were taken forward for full-text review. Of these articles, five met criteria for inclusion. From the excluded articles, two reported using BIS for reasons other than the monitoring of level of consciousness of patients receiving sedative medication. In one of these studies, BIS monitoring was employed to measure the effect of mindful breathing on brain activity (Beng et al., 2019); in the other, it was used as a measure of sleep quality (Bertram, Stiel, Krumm, & Grözinger, 2013). **Figure 1.7** presents the article selection process as a flowchart.

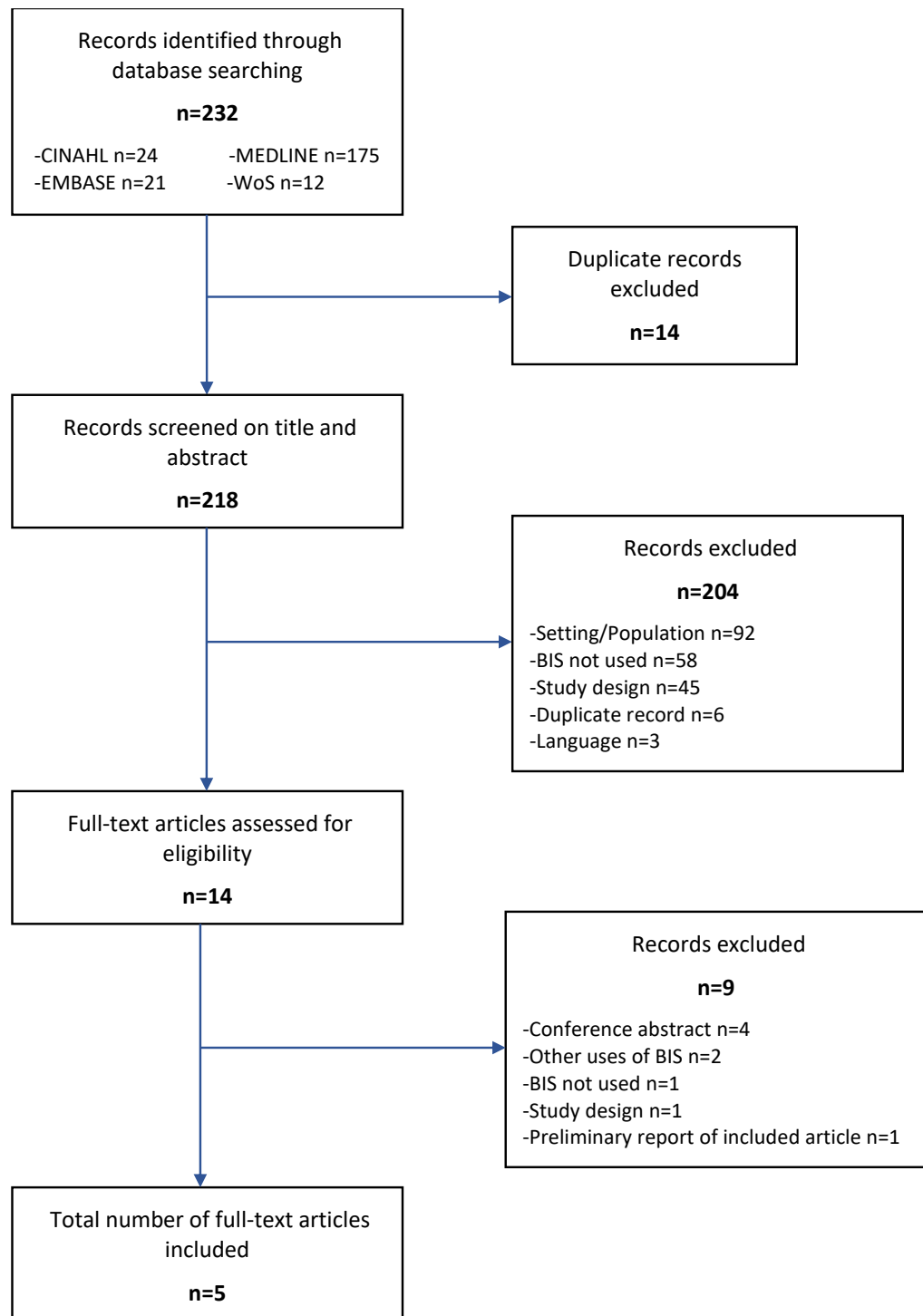


Figure 1.7: Flow diagram of publication selection process

### **Characteristics of included studies**

Of the five eligible articles identified through database searching, two were separate publications reporting findings from a single study (Barbato, Barclay, Potter, & Yeo, 2018; Barbato, Barclay, Potter, Yeo, & Chung, 2017). Four studies were therefore included in the narrative synthesis. Included studies were conducted in Australia (Barbato, 2001; Barbato et al., 2018; Barbato et al., 2017), Mexico (Monreal-Carrillo et al., 2017), and the Netherlands (Masman et al., 2016). All studies were published within the last 20 years (from 2001 onward), with three of the four studies published in or after 2016 (Barbato et al., 2018; Barbato et al., 2017; Masman et al., 2016; Monreal-Carrillo et al., 2017). All studies employed an observational research design with data collection conducted prospectively in a single setting on each occasion; either an inpatient palliative care unit (Barbato et al., 2018; Barbato et al., 2017; Masman et al., 2016; Monreal-Carrillo et al., 2017), or a hospice (Barbato, 2001).

The numbers of recruited patients varied between included studies, with sample sizes of 12 (Barbato, 2001), 20 (Monreal-Carrillo et al., 2017), 40 (Barbato et al., 2018; Barbato et al., 2017), and 58 (Masman et al., 2016). Participants in each of three of the studies had a variety of different diagnoses (Barbato, 2001; Barbato et al., 2018; Barbato et al., 2017; Masman et al., 2016), while in one study participants consisted solely of cancer patients (Monreal-Carrillo et al., 2017). Participants across all studies were at an advanced or terminal stage of disease.

In all studies participants received sedative medication for the management of refractory symptoms. Participants in three studies were continuously monitored with BIS either from the onset of unconsciousness following the administration of sedative medication (Barbato, 2001; Barbato et al., 2018; Barbato et al., 2017), or at onset of palliative sedation (Monreal-Carrillo et al., 2017). In one study (Masman et al., 2016), participants were monitored with BIS on separate occasions during their admission, with a median of two BIS registrations per patient (Interquartile range [IQR] 1 to 3) and a median duration of 520 minutes (IQR 249 to 844) per registration.

In addition to BIS monitoring, all studies used structured observational measures for the assessment of patients' level of consciousness/depth of sedation and/or other symptoms. The measures used were: the Ramsay Sedation Scale (RSS) (Masman et al., 2016; Monreal-Carrillo et al., 2017; Ramsay et al., 1974), Consciousness Scale (CS) (Barbato, 2001), and Richmond Agitation-Sedation Scale (RASS) (Barbato et al., 2018; Barbato et al., 2017; Sessler et al., 2002) for the assessment of level of consciousness/depth of sedation; the Patient

Comfort Score (PCS) (Barbato et al., 2018; Barbato et al., 2017; Bruera et al., 2003), and an 11-point (0-10) Numerical Rating Scale (NRS) for level of comfort (Masman et al., 2016); an 11-point NRS for pain severity (Masman et al., 2016); and the Delirium Observation Screening scale (DOS) for delirium severity (Masman et al., 2016; Schuurmans, Shortridge-Baggett, & Duursma, 2003). Observational assessments were performed every four hours during BIS monitoring in two studies (Barbato, 2001; Barbato et al., 2017), and at predetermined intervals throughout the first 24 hours of palliative sedation in another study (i.e. 0, 2, 4, 6, 12, and 24 hours) (Monreal-Carrillo et al., 2017). Masman et al. (2016) reported collecting observational data daily, with level of consciousness assessments performed more frequently where possible.

Primary outcomes in all included studies involved the examination of BIS values in relation to observational assessments of level of consciousness and/or patient symptoms. However, differing study aims were listed among studies. These were: the determination of the usefulness or the validity of BIS monitoring (Barbato, 2001; Masman et al., 2016), the evaluation of the validity of observational sedation and comfort measures (Barbato et al., 2017), the efficacy of breakthrough medication (Barbato et al., 2018), and the characterisation of level of consciousness in patients undergoing palliative sedation (Monreal-Carrillo et al., 2017). A summary of study characteristics and main findings is presented in **Table 1.2**.

### **Description of findings of included studies**

#### **Summaries of main outcome data**

All studies used summary statistics to describe the main outcome data collected. However, the way in which these statistics were derived and reported differed between studies, reflecting the variability of study aims and data collection methods employed.

Reported mean or median BIS values across all studies ranged from 42 to 71, indicating moderate to deep sedation. Monreal-Carrillo et al. (2017) reported a median BIS value of 42 (range 40 to 62) at 24 hours following the initiation of palliative sedation. Barbato (2001) provided information on mean BIS and CS (score range 24 [fully conscious state] to 6 [deep unconsciousness]) scores at baseline (onset of unconsciousness) and immediately before death. Mean baseline scores were 54 (SD 12, range 40 to 75) for BIS and 15.7 (SD 4.2, range 8 to 21) for CS. Immediately before death, these changed to 44 (SD 10.4, range 20 to 55) and 10.3 (SD 1.62, range 8 to 13), respectively.



Median scores for four-hourly observational assessments and time-matched BIS values were provided by Barbato et al. (2017). These were 54 (IQR 42 to 67) for BIS, -5 (IQR -5 to -4) for RASS (sedation score range 0 [calm and alert state] to -5 [patient not rousable]), and 0 (IQR 0 to 0) for PCS (score range 0 [complete comfort] to 10 [complete discomfort]). Median RASS and PCS scores suggested an absent patient response to vocal or physical stimulation and complete patient comfort.

Median BIS values were reported in relation to dichotomised pain, comfort and delirium assessment scores by Masman et al. (2016). An increase in median BIS values from 58 (IQR 48 to 75) to 68 (IQR 59 to 76) was reported in the presence of pain as measured by an 11-point NRS (pain NRS  $\geq 4$ ). Conversely, median BIS values decreased from 66 (IQR 60 to 80) to 54 (IQR 46 to 69) when patients were deemed comfortable (Comfort NRS  $\geq 6$ ). The median BIS score for patients in whom delirium symptoms were present (DOS scale score  $\geq 3$ ) was 71 (IQR 62 to 75). This remained unchanged (median BIS 71 [IQR 65 to 79]) when delirium was assessed as being absent (DOS  $< 3$ ).

#### **Correlations between BIS and observational measures**

Three of the four included studies explored the association between BIS and observational measures by using the Spearman rank correlation coefficient (Masman et al., 2016; Monreal-Carrillo et al., 2017; Spearman, 1904), or the method of Bland and Altman for calculating correlation coefficients with repeated within-participant observations (Barbato et al., 2017; Bland & Altman, 1995). Reported correlations between paired BIS and level of consciousness scale scores ranged from 0.42 to 0.68, indicating low to moderate correlations (Barbato et al., 2017; Masman et al., 2016; Monreal-Carrillo et al., 2017; Mukaka, 2012).

Two studies found a weak correlation ( $r=0.30$ ) between paired BIS and patient comfort scores, as assessed by an 11-point comfort NRS (Masman et al., 2016) or the PCS (Barbato et al., 2017). Masman et al. (2016) additionally explored the relationship between BIS and observational measures of pain (11-point pain NRS) and delirium (DOS). Spearman's rho varied from 0.03 for paired BIS-DOS scores to 0.11 for BIS-pain NRS scores, suggesting a negligible association (Mukaka, 2012). A full description of correlation coefficients and accompanying p values is provided in **Table 1.2**.

**Table 1.2:** Overview of study characteristics and main findings

Author(s), year, country	Study aim	Study design and setting	Study population	Summaries of main outcome data	Correlation coefficients	Effect of sedative medication on BIS	Changes in BIS/other outcomes over time
<b>Barbato (2001)</b> <b>Australia</b>	To assess the usefulness of BIS in monitoring level of awareness at the end of life	<b>Design</b> Prospective observational study  <b>Setting</b> Hospice	12 unresponsive palliative care inpatients	<ul style="list-style-type: none"> <li>• Baseline -Mean BIS: 54 (SD 12, range 40–75) -Mean CS: 15.7 (SD 4.2, range 8–21)</li> <li>• Before death -Mean BIS: 44 (SD 10.4, range 20–55) -Mean CS: 10.3 (SD 1.62, range 8–13)</li> </ul>	NE / NR	NE / NR	<ul style="list-style-type: none"> <li>• BIS baseline-before death: -t(9)=4.35 (p&lt;0.002)</li> <li>• CS baseline-before death: -t(9)=4.45 (p&lt;0.002)</li> </ul>
<b>Barbato et al. (2018; 2017)</b> <b>Australia</b>	To determine the validity of observational sedation and comfort measures, and the efficacy of breakthrough medication in unresponsive patients	<b>Design</b> Prospective observational study  <b>Setting</b> Hospital-based palliative care unit	40 unresponsive palliative care inpatients	<ul style="list-style-type: none"> <li>• Median BIS: 54 (IQR 42–67)</li> <li>• Median RASS: -5 (IQR -5 – -4)</li> <li>• Median PCS: 0 (IQR 0–0)</li> </ul>	<ul style="list-style-type: none"> <li>• BIS-RASS: 0.42 (p&lt;0.0004)</li> <li>• BIS-PCS: 0.30 (p=0.003)</li> </ul>	<ul style="list-style-type: none"> <li>• BIS before: 62</li> <li>• BIS after 30min: 55</li> <li>• BIS after 60min: 53</li> <li>➤ p&lt;0.0004 for both before-after analyses</li> </ul>	NE / NR
<b>Masman et al. (2016)</b> <b>Netherlands</b>	To determine the feasibility and validity of BIS monitoring	<b>Design</b> Prospective observational study	58 palliative care inpatients	<ul style="list-style-type: none"> <li>• For Pain NRS ≥4 Median BIS: 68 (IQR 59–76)</li> <li>• For Pain NRS ≤3 Median BIS: 58 (IQR 48–75)</li> <li>• For Comfort NRS ≥6 Median BIS: 54 (IQR 46–69)</li> <li>• For Comfort NRS ≤5 Median BIS: 66 (IQR 60–80)</li> </ul>	<ul style="list-style-type: none"> <li>• BIS-RSS: 0.47</li> <li>• BIS-Pain NRS: 0.11</li> <li>• BIS-Comfort NRS: 0.30</li> <li>• BIS-DOS: 0.03</li> </ul>	<ul style="list-style-type: none"> <li>• BIS before: 76 (IQR 65–82)</li> <li>• BIS after (30–60min): 60 (IQR 54–76)</li> <li>➤ p&lt;0.001</li> </ul>	NE / NR

		<b>Setting</b> Palliative care unit		<ul style="list-style-type: none"> <li>• For DOS <math>\geq 3/24</math>hrs Median BIS: 71 (IQR 62–75)</li> <li>• For DOS <math>&lt; 3/24</math>hrs Median BIS: 71 (IQR 65–79)</li> </ul>			
<b>Monreal-Carrillo et al. (2017)</b> <b>Mexico</b>	To characterise the level of consciousness in patients undergoing palliative sedation using Bispectral index monitoring	<b>Design</b> Prospective observational study  <b>Setting</b> Hospital-based palliative care unit	20 advanced cancer inpatients receiving palliative sedation	<ul style="list-style-type: none"> <li>• Median BIS at 24h after sedation initiation: 42 (range 40–62)</li> </ul>	BIS-RSS <ul style="list-style-type: none"> <li>• 0h: 0.58 (p=0.007)</li> <li>• 2h: 0.66 (p=0.002)</li> <li>• 4h: 0.48 (p=0.059)</li> <li>• 6h: 0.46 (p=0.087)</li> <li>• 12h: 0.68 (p=0.014)</li> <li>• 24h: 0.65 (p=0.053)</li> </ul>	NE / NR	<ul style="list-style-type: none"> <li>• % of patients for which BIS &gt;60</li> <li>• 0h: 95</li> <li>• 4h: 56.2</li> <li>• 6h: 53.3</li> <li>• 24h: 33.3</li> <li>• % of patients for which RSS <math>\leq 3</math></li> <li>• 0h: 70</li> <li>• 4h: 31.2</li> <li>• 6h: 26.7</li> <li>• 24h: 22.2</li> </ul>

BIS: Bispectral index; SD: Standard Deviation; IQR: Interquartile range; NE: Not Evaluated; NR: Not Reported; CS: Consciousness Scale; RASS: Richmond Agitation-Sedation Scale; PCS: Patient Comfort Score; RSS: Ramsay Sedation Scale; NRS: Numerical Rating Scale; DOS: Delirium Observation Screening scale; RSS: Ramsay Sedation Scale.

### **Effect of sedative medication on BIS scores**

Two studies (Barbato et al., 2018; Masman et al., 2016) explored the sensitivity of BIS to changes in patients' consciousness levels following the administration of medication with sedative effects. Barbato et al. (2018) investigated the effect of sedative medication on BIS by comparing BIS scores recorded just before, 30 and 60 minutes after the administration of breakthrough medication using paired sample t-tests. The most frequently administered breakthrough medications were opioids (either morphine or hydromorphone; 12.5%), opioid plus midazolam (45%), hyoscine hydrobromide (14%), and glycopyrrolate (10%). The reported mean subcutaneous morphine equivalent dose for breakthrough administrations was 22mg (SD 23.4, range 2.5 to 150), while the mean dose of midazolam was 5.1mg (SD 1.13, range 2.5 to 10). In addition, all studied patients were regularly receiving a subcutaneous infusion of an opioid plus midazolam at the time of data collection. The mean daily doses for regular prescriptions were 80.2mg (SD 70.3) and 25mg (SD 8.7), respectively. A reduction in mean BIS scores was described for the before-30min after interval (62 to 55), and the before-60min interval (62 to 53). Changes in BIS scores for both analyses were statistically significant ( $p < 0.0004$ ). However, there was no significant change found in the 30-60 min interval. Statistically significant reductions in scores in the same time intervals were also described for the PCS and RASS, but no further information on these analyses was provided.

Masman et al. (2016) reported using the Wilcoxon signed-rank test to compare BIS values before and after the administration of single midazolam doses. BIS-before values were calculated based on the 30 minutes before a midazolam administration, while BIS-after values were calculated from 30 to 60 minutes after administration to account for the maximal effect of midazolam (usually reached at 20 to 30 minutes after administration). The reported median BIS-before value was 76 (IQR 65 to 82). This was reduced to a median BIS-after value of 60 (IQR 54 to 76). The change in BIS scores was statistically significant ( $p < 0.001$ ). Information on mean doses for single midazolam or regular administrations received by patients included in the analysis was not provided by the study authors.

### **Changes in BIS and observational measure scores over time**

As noted earlier in this section, Barbato (2001) described a decrease in mean BIS and CS scores between baseline assessments and immediately before death. Mean BIS values decreased from 54 (SD 12, range 40 to 75) at the start of monitoring to 44 (SD 10.4, range 20 to 55) before death. Similarly, CS scores decreased from 15.7 (SD 4.2, range 8 to 21) to

10.3 (SD 1.62, range 8 to 13). These changes were statistically significant ( $t[9]=4.35$ ,  $p<0.002$  for BIS analysis;  $t[9]=4.45$ ,  $p<0.002$  for CS analysis).

Monreal-Carrillo et al. (2017) noted a decrease in the proportion of patients for whom BIS values were greater than 60 (i.e. patients who had not reached a level of deep sedation) in the first 24 hours following the initiation of palliative sedation. Specifically, BIS >60 was recorded for 95% ( $n=19$ ) of patients at baseline, 56.2% at 4 hours, 53.3% at 6 hours, and 33.3% at 24 hours. A similar decrease in proportions was found for assessments performed by the RSS. However, the statistical significance of these changes was not tested as this was outside the scope of the study.

### **Acceptability and feasibility of BIS monitoring**

Three of the four studies reported that BIS monitoring was feasible and acceptable to use in the palliative care context (Barbato, 2001; Masman et al., 2016; Monreal-Carrillo et al., 2017). However, the available information relating to these parameters was limited to short statements without providing a description of the criteria and assessment methods used for these evaluations.

The feasibility of BIS monitoring was mainly described in terms of user-friendliness and quality of obtained BIS recordings. The authors of two studies commented that BIS was easy to use in terms of handling the device and applying the sensor on patients' foreheads (Masman et al., 2016; Monreal-Carrillo et al., 2017). Masman et al. (2016) additionally noted that due to the user-friendliness of the technology, the training time of nursing staff in its use was no more than 10 minutes. Barbato (2001) described encountering minor issues with electrical interference that affected the quality of BIS data. These were mostly resolved through careful placement of the BIS sensor. Masman et al. (2016) also reported a low proportion of missing data due to poor quality.

In relation to the acceptability of BIS use, three studies reported that participant relatives/caregivers were not deterred or distracted by the appearance of the BIS sensor, and that they felt supported and reassured by the additional information on patients' conditions provided by BIS monitoring (Barbato, 2001; Masman et al., 2016; Monreal-Carrillo et al., 2017). Masman et al. (2016) mentioned that similar feelings of reassurance were also expressed by patients who took part in their study. Barbato (2001) commented that none of the patients or relatives who were approached for participation refused consent, nor asked for BIS monitoring to be stopped after it had begun.

## **Summary of review findings**

The aim of this literature review was to identify and narratively synthesise existing evidence on the use of BIS monitoring in palliative care patients receiving sedative medication. Of the 232 potentially eligible records retrieved through database searches, only four studies met the criteria for inclusion.

All four studies examined the utility of BIS monitoring by comparing BIS with structured observational assessments of level of consciousness and/or other patient symptoms. Reported evidence indicated low to moderate correlations between BIS and structured level of consciousness scales ( $r=0.42$  to  $0.68$ ), and mostly weak correlations between BIS and observational pain, comfort, and delirium measures ( $r=0.03$  to  $0.30$ ). Two studies reported statistically significant changes in BIS values before and after the administration of medication with sedative effects, suggesting that BIS was sensitive in capturing changes in patients' level of consciousness resulting from the administration of such medication. In addition, one study found a significant decrease in BIS values between baseline patient assessments and immediately before death. A second study also described a reduction in BIS values over time, but this finding was not tested for statistical significance. Finally, three studies reported that BIS monitoring was feasible and acceptable to use in the palliative care setting. However, none of these studies had systematically assessed the feasibility and acceptability of BIS use.

To conclude, although the studies included in this review provided some evidence to support the utility and applicability of BIS monitoring in the palliative care context, this was limited by the relatively small sample sizes used, and, on a few occasions, the lack of appropriate methods to verify reported findings. Therefore, further research is needed to determine whether BIS could be a valid, useful, and acceptable tool for monitoring the level of consciousness of palliative care patients in clinical practice.

## **1.7 Chapter summary**

Optimisation of symptom control is a key priority for palliative care clinical practice and research. For adequate symptom control to be achieved, especially towards the end of life when symptom burden tends to increase, sedative medication is sometimes used. However, the prevalence and practice of sedative use varies considerably across different countries and settings, and the ethical acceptability of using sedative medication as a medical intervention has been questioned.

To standardise clinical practice and shed light on the ethical debates surrounding the practice of sedative use, several professional bodies and organisations have produced guidelines with recommendations on the appropriate use of sedative medication in the context of palliative care. The majority of these guidelines identify the proportional use of sedative medication (i.e. the use of drugs and dosages tailored to the degree of symptom control that needs to be achieved for each individual patient, with the primary intention of providing relief from intolerable suffering) as a fundamental characteristic of the practice of sedative use, and as the main factor that distinguishes this practice from interventions explicitly aiming to end a patient's life. In order to fulfil the requirements of proportionality, guidelines generally recommend close monitoring of patients during and after the administration of sedative medication, with patients' level of consciousness recognised as an important clinical parameter in guiding the titration of sedative medication.

In current clinical practice, the assessment and monitoring of level of consciousness is primarily based on the use of observational methods (either informal clinical observation or use of structured observer-rated scales). However, it has been demonstrated that these methods have several limitations and, therefore, may not be able to provide a reliable assessment of patients' level of consciousness, especially in cases where patients' motor responsiveness is impaired. For these people, the use of monitoring devices based on EEG data has been suggested as an adjunct to current clinical practice to supplement and validate observational assessments of level of consciousness.

Numerous EEG-based level of consciousness monitors have been developed and marketed over the last 30 years. The most thoroughly researched and validated of these is the BIS monitor. Despite being originally developed as a measure of anaesthetic depth for patients undergoing general anaesthesia in the operating room, the use of BIS has been extended to a number of clinical settings and populations to guide the titration of sedative medication. Nevertheless, only a small number of studies have explored the use of BIS in patients receiving sedative medication in the palliative care setting so far, and none of these have been conducted in the UK or used systematic methods for the assessing the feasibility and acceptability of BIS use. The research presented in this thesis, therefore, aimed to address this gap in the scientific literature.

## **1.8 Research aim and objectives**

### **Research aim**

The overall aim of this doctoral project was to explore the acceptability, feasibility, and preliminary clinical usefulness of BIS monitoring in adult UK palliative care patients.

For this aim to be achieved, the following primary and secondary objectives were set:

### **Primary objectives**

1. To investigate the acceptability in practice of BIS monitoring in a UK hospice using qualitative and quantitative methods.
2. To assess the feasibility of conducting research with BIS technology in a UK hospice by examination of the rates of recruitment and participation in an observational study, and evaluation of the quality of obtained BIS data.
3. To perform a preliminary evaluation of the clinical usefulness of BIS monitoring as an adjunct to clinical practice by investigating the validity and sensitivity of the technology in detecting changes in hospice inpatients' consciousness levels.

### **Secondary objectives**

1. To investigate the acceptability in principle of BIS monitoring in palliative care using qualitative methods.
2. To identify and appraise the psychometric quality of existing observational level of consciousness measures by conducting a systematic review and psychometric appraisal.



## **Chapter 2 Systematic review of observational measures for the assessment and/or monitoring of level of consciousness in adult palliative care patients**

### **2.1 Chapter outline**

As discussed in Chapter 1, observational level of consciousness measures are sometimes used in palliative care (Arevalo et al., 2012; Brinkkemper et al., 2013). There is limited knowledge, however, regarding which of these measures are the most appropriate, valid, and reliable to use in this setting (Arevalo et al., 2012). In order to address this gap in the literature and identify suitable outcome measures for a prospective, exploratory study of BIS monitoring (described in Chapters 5 and 6), a systematic review to evaluate the psychometric performance of existing tools for the assessment of consciousness levels of adult palliative care patients was undertaken.

This chapter provides a detailed description of the methodology and results of the systematic review of observational level of consciousness measures used in palliative care. An abbreviated version of this chapter was published in *Palliative Medicine* in January 2020 (Krooupa, Vivat, McKeever, Marcus, et al., 2020) (see **Appendix 1** for the full article).

### **2.2 Review objectives**

The objectives of this systematic review were to: i) identify all observational measures used in primary research studies for the assessment and/or monitoring of adult palliative care patients' consciousness levels, ii) provide a description of the content of identified measures, and iii) evaluate their psychometric performance.

### **2.3 Methodology**

#### **Design**

This was a systematic literature review which included the synthesis and appraisal of evidence on the psychometric performance of observational level of consciousness measures reported in primary research studies. The review was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) guideline (Moher, Liberati, Tetzlaff, & Altman, 2009). The study protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: [CRD42017073080](https://www.crd.york.ac.uk/PROSPERO/registration/CRD42017073080)) (Booth et al., 2011).

### **Search strategy**

The search strategy comprised four steps. Two databases, PsycINFO and MEDLINE, were initially searched to identify primary research studies reporting the use of observational measures to assess level of consciousness. Relevant text words contained in the title, abstract and authors' keywords of identified papers, and database index terms, were compiled to produce a list of search terms. Six databases were then searched; Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, Embase, MEDLINE, PsycINFO, WoS, using a combination of subject headings and free-text terms for palliative care, measurement instruments and sedative use, adjusted for each database (see **Figure 2.1** for the search strategy used for MEDLINE). Databases were searched from first record published until November 2018. No language restrictions were applied. Subsequently, the reference lists of all included papers were hand-searched for relevant publications. If eligible articles were identified, the process of backward reference searching was repeated until no more relevant publications could be located. A similar method, using Google Scholar, was applied for finding newer studies citing the included papers (i.e. forward citation searching) (see **Figure 2.2**). Lastly, authors of conference abstracts meeting inclusion criteria were contacted for full-text publications. Where relevant data were missing from included papers, authors were also contacted.

### **Inclusion and exclusion criteria**

Articles were included if they met all the following *a priori* specified criteria:

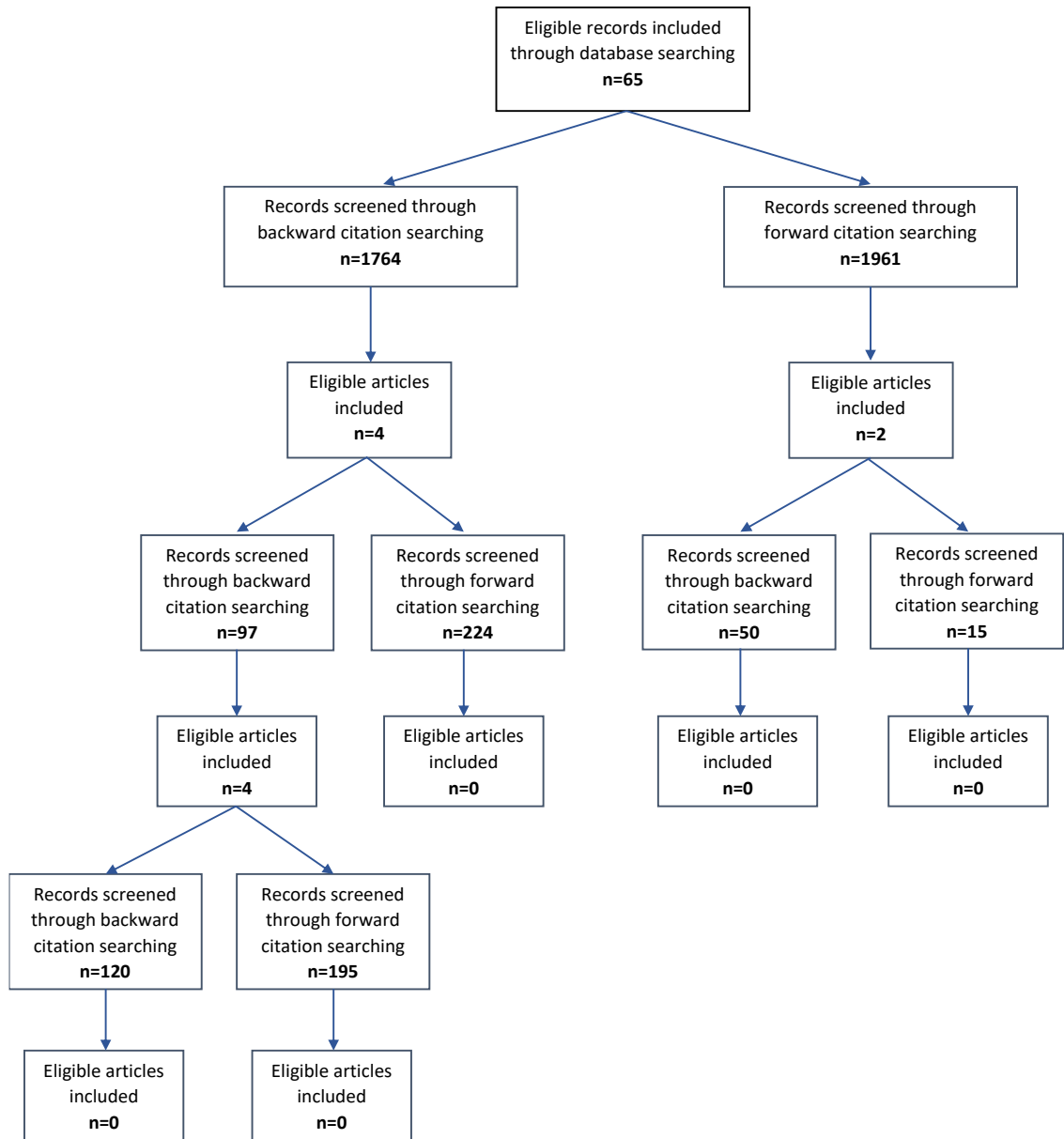
- Peer-reviewed, full-text publications
- Primary research articles reporting on empirical studies (prospective or retrospective; patient-based or clinician-based)
- Described the use of observational measures (validated or *ad hoc*) for the assessment and/or monitoring of level of consciousness/sedation in adult (18 years or older) palliative care patients.

Papers were excluded if they:

- Reported on case report studies or non-primary studies, including systematic reviews, opinion articles, editorials or book chapters
- Provided no information about sample size
- Reported information on self-reported or binary-response measures (e.g. sedated/not sedated)
- Were not written in English

1. Self Report/
2. Checklist/
3. (tool\* or assess\* or survey\* or question\* or measur\* or method\* or scale\* or checklist\* or rating\* or test\* or instru\* or inventor\* or technique\* or monitor\* or observ\* or rate\* or function\* or scoring system\* or outcome\*).mp.
4. 1 or 2 or 3
5. Palliative Care/
6. exp Terminal Care/
7. Hospices/
8. (palliat\* or terminal\* or endstage or hospice\*).mp.
9. (end adj3 life).mp.
10. (care adj3 dying).mp.
11. ((advanced or late or last or end or final) adj3 (stage\* or phase\*)).mp.
12. 5 or 6 or 7 or 8 or 9 or 10 or 11
13. ((continuous or deep or intermittent or intermediate or respite or mild) adj3 (sedat\* or an?esthe\*)).mp.
14. Deep Sedation/
15. Conscious Sedation/
16. sedat\*.mp.
17. 13 or 14 or 15 or 16
18. 4 and 12 and 17

**Figure 2.1:** Search strategy used in MEDLINE and modified for other databases



**Figure 2.2:** Forward and backward citation searching process

### **Selection procedure**

The study selection process involved two phases. First, all records were reviewed for eligibility by title and abstract. Then, a full-text review of studies that met the inclusion criteria according to the initial screening process was performed.

The database search yielded, after removing duplicates, 11,938 records. Screening of titles and abstracts against eligibility criteria was performed by myself (Anna-Maria Kroupa

[AMK]) for all records retrieved. A second reviewer (Elena Marcus [EM]) independently screened a random 10% sample of these records. The inter-rater agreement for the title and abstract screening was calculated using Cohen's kappa coefficient and found to be substantial ( $\kappa=0.707$ ). Full-text publications were independently assessed for eligibility by two reviewers. Discrepancies at either stage of study selection were resolved through discussion.

### **Data extraction**

Two reviewers (AMK, EM) independently extracted data on each study and on the characteristics of each measure using a standardised form developed for the purposes of this review. For each study, the following information was extracted and entered into the form: author(s), date of publication, country of origin, study aim(s), setting, sample size, and participant characteristics. For each measure identified, data extracted were: tool name, measurement aim/purpose, number of subscales and items, and response options. Data on psychometric performance of measures, where available, were also extracted using the same form. The results of data extraction were compared and any disagreements between reviewers were resolved by consensus.

### **Assessment of psychometric performance**

For the evaluation of the psychometric performance of included measures, a checklist that drew on that developed by Zwakhalen, Hamers, Abu-Saad, and Berger (2006) was used (see **Table 2.1**). The checklist was modified based on established quality criteria for developing and evaluating health outcome measures (Fitzpatrick, Davey, Buxton, & Jones, 1998; Streiner & Norman, 2003; Terwee et al., 2007) to extend some of the appraisal parameters and enhance the robustness of the quality evaluation. The measurement properties evaluated in this review were: validity, reliability, responsiveness, feasibility of measures, and origin (source) of tool items.

Validity of an instrument has been defined as an assessment of the extent to which it measures what it purports to measure (Fitzpatrick et al., 1998). There are four main types of validity: (1) content validity: the degree to which scale items comprehensively reflect the construct of interest, assessed through the extent of involvement of the target population in item selection and the provision of a clear description of the concept that the instrument is intended to measure (Terwee et al., 2007); (2) criterion validity: the extent to which a

proposed new measure correlates with another instrument generally accepted to accurately measure the construct of interest (“gold standard”) (Fitzpatrick et al., 1998). Correlations of 0.6 or above were considered as acceptable in this review (Zwakhaleh et al., 2006); (3) structural validity: the degree to which the scores of an instrument adequately represent the dimensionality of the construct of interest, evaluated through the degree of variance explained by factor analysis (Terwee et al., 2007); (4) construct validity: the extent to which scores of a particular measure relate to other measures in a manner that is consistent with theoretically derived hypotheses about the underlying constructs that are being measured (Terwee et al., 2007). This aspect of validity is often assessed by examining the relationship between the evaluated measure and other instruments that are known to measure related constructs (i.e. convergent validity) or with other instruments that are known to measure unrelated constructs (i.e. discriminant validity) using Pearson’s or Spearman’s correlation coefficient (Fitzpatrick et al., 1998; Zwakhaleh et al., 2006). Since there is no “gold standard” tool for measuring level of consciousness in palliative care patients (Arevalo et al., 2012), criterion validity was not assessed in this review.

Reliability refers to the internal consistency and reproducibility of a measuring instrument (Fitzpatrick et al., 1998). Four types of reliability estimates were considered in this review: (1) homogeneity (internal consistency): the degree to which the measure items are homogeneous, indicating that aspects of the same construct are being measured (Streiner & Norman, 2003), assessed through Cronbach’s alpha coefficient; (2) inter-rater reliability: the extent of agreement between two or more raters (Fitzpatrick et al., 1998); (3) intra-rater reliability: the extent of agreement between repeated measurements performed by the same rater on different occasions (Streiner & Norman, 2003); (4) test-retest reliability: the degree to which an instrument yields similar results on repeated measurements performed over time in individuals who are stable on the construct measured (Fitzpatrick et al., 1998). Common statistical methods for evaluating the latter three reliability properties are intraclass correlation coefficient (ICC) for continuous measures and Cohen’s kappa for nominal/ordinal measures (Terwee et al., 2007). Values of less than 0.6, between 0.6 and 0.8, and greater than 0.8 were considered as indicative of low, adequate and high reliability, respectively (Zwakhaleh et al., 2006).

Responsiveness concerns the ability of an instrument to detect clinically meaningful changes over time in the construct measured (Terwee et al., 2007). A number of methods have been proposed for assessing responsiveness. The most prevalent among these are: (1) the correlations of change scores for an instrument over time with changes in other available

variables, assessing the ability of the tested instrument to capture changes in the construct measured that are consistent with other available data (Fitzpatrick et al., 1998; Terwee et al., 2007); and (2) the area under the receiver operator characteristic (ROC) curve (AUC), measuring the ability of an instrument to correctly distinguish between patients who have and have not changed in the construct measured (Terwee et al., 2007). Although not a method for directly assessing responsiveness, the presence of floor and ceiling effects was also considered for the evaluation of this property. The lack of extreme items in the lower (floor) or higher (ceiling) ends of a measure may limit the ability of an instrument to detect changes in the construct measured beyond a certain level (Fitzpatrick et al., 1998; Terwee et al., 2007). A threshold of 15% of respondents achieving the highest or lowest score was adopted in this review as indicative of the presence of a ceiling or a floor effect, respectively (Terwee et al., 2007).

Feasibility has been described as the user-friendliness of a measure in terms of administration and processing (Fitzpatrick et al., 1998). The burden placed on staff from collecting and processing measure information is an important parameter to consider when selecting a tool for use in clinical practice or for research purposes (Fitzpatrick et al., 1998). In this review, feasibility was evaluated through considering the length, usability, and clarity of appraised measures.

Origin of items refers to whether the measure items were specifically developed for use with the target population, modified, or taken from a scale developed for another population without an assessment of the item's appropriateness for use in a palliative care context (Zwakhalen et al., 2006).

Evidence of psychometric performance of the appraised measures was categorised according to the measurement properties described above. For each property, measures were scored using a three-point rating scale: 2 if the property was evaluated and fully met criteria, 1 if criteria were partially met, and 0 when criteria were not met. If a property was not evaluated/not reported or the information provided was unclear, a rating was not given.

The assessment of psychometric properties for all measures was performed by two independent reviewers (AMK, EM), achieving a high initial agreement ( $\kappa=0.91$ ). Reviewers conferred over discrepancies until full consensus on ratings was reached.

**Table 2.1:** Quality criteria for measure appraisal

Domain	Property	Score	Description
	<b>Number of participants</b>	<b>2</b>	N ≥ 100 and the number of palliative care patients included was relative to the number of items/variables or 50 < N < 100 and corrected for multiple testing
		<b>1</b>	50 < N < 100 and the number of palliative care patients included was relative to the number of items/variables or N < 50 and corrected for multiple testing
		<b>0</b>	N < 50 or number of palliative care patients included not relative to the number of items/variables or N < 50 and not corrected for multiple testing
<b>Validity</b>	<b>Content validity</b>	<b>2</b>	A description of the construct that is being measured is provided and target population is involved in item selection
		<b>1</b>	A description of the construct that is being measured is provided or target population is involved in item selection
		<b>0</b>	The construct that is being measured is not described and limited / no involvement of target population is involved in item selection
	<b>Criterion validity</b>	<b>2</b>	Correlates acceptable to high ( $r > .60$ ) according to the 'gold standard' or according to a 'silver standard'
		<b>1</b>	Correlates moderate-acceptable ( $.40 < r < .60$ ) according to the 'gold standard' or according to a 'silver standard'
		<b>0</b>	Correlates low ( $r < .40$ )
	<b>Structural validity</b>	<b>2</b>	Appropriate method of factor analysis performed and factors account for ≥ 50% of the total variance
		<b>1</b>	Factor analysis performed but another method would have been more appropriate
		<b>0</b>	Factors account for < 50% of the total variance
	<b>Construct validity</b>	<b>2</b>	Correlates with other level of consciousness measures acceptable to high ( $r > .60$ )
		<b>1</b>	Correlates with other level of consciousness measures are moderate ( $r > .40 < .60$ )
		<b>0</b>	Correlates with other level of consciousness measures are low ( $r < .40$ )
<b>Reliability</b>	<b>Homogeneity (internal consistency)</b>	<b>2</b>	$.70 < \alpha < .90$
		<b>1</b>	$\alpha > .90$ or $.60 < \alpha < .70$
		<b>0</b>	$\alpha < .60$
	<b>Inter-rater reliability</b>	<b>2</b>	Reliability coefficient > .80
		<b>1</b>	$.60 < \text{reliability coefficient} < .80$
		<b>0</b>	Reliability coefficient < .60
	<b>Intra-rater and/or Test-retest reliability</b>	<b>2</b>	Reliability coefficient > .80
		<b>1</b>	$.60 < \text{reliability coefficient} < .80$
		<b>0</b>	Reliability coefficient < .60
<b>Responsiveness</b>	<b>2</b>	Appropriate method of detecting clinically meaningful change over time described and clinically meaningful change over time detected and 15% or less of respondents achieved the lowest or highest possible score, respectively	
	<b>1</b>	Appropriate method of detecting clinically meaningful change over time described and clinically meaningful change over time detected or 15% or less of respondents achieved the lowest or highest possible score, respectively	
	<b>0</b>	Appropriate method of detecting clinically meaningful change over time not followed or clinically meaningful change over time not detected or more than 15% of respondents achieved the lowest or highest possible score, respectively	
<b>Origin of items</b>	<b>2</b>	Items specifically developed for use with palliative care patients	
	<b>1</b>	Items were modified for use with palliative care patients	
	<b>0</b>	Items originated from a scale developed for another population	
<b>Feasibility</b>	<b>2</b>	Scale is short, manageable with instructions, scoring interpretation	
	<b>1</b>	Scale is manageable (one format)	
	<b>0</b>	Scale is more complex	



## 2.4 Results

### Search results

A total of 13,827 records were retrieved from database searches. After duplicates were removed, 11,938 studies were screened on the basis of titles, and 1,211 studies were screened on the basis of abstracts. Following screening of titles and abstracts, 491 potentially eligible articles remained, which were examined in full. Of these studies, 55 met criteria for inclusion. Forward and backward citation searching of the 55 eligible studies identified an additional 10 studies fitting the inclusion criteria, resulting in 65 included studies (see **Figure 2.3** for PRISMA flow diagram of study selection process).

Only 7 of the 65 included studies provided information on the psychometric performance of level of consciousness tools in the palliative population. The remaining 58 studies reported either using established scales (n=37) the majority of which had been validated in non-palliative care settings, or presented information on the use of *ad hoc* measures (i.e. measures developed specifically for the purposes of individual studies; n=21) without providing data on the psychometric properties of these measures. A summary of study and measure characteristics is presented in **Table 2.2**.

### Description of included studies

Morita and colleagues (2003a, 2003b) published two articles in which separate analyses of data collected from a single study were performed. Likewise, Van Deijck et al. (2015; 2010), Campbell et al. (2009, 2010), and Claessens et al. (2011, 2012, 2014) reported distinct findings from one study in multiple papers. Since each of these publications described distinct study aims and outcomes, they were treated as separate studies in this review.

The majority of included studies were patient-based (n=58), with recruitment and data collection conducted prospectively (n=49). In eight studies relevant data were obtained retrospectively through patients' medical records. In one study patients were recruited both prospectively (on admission) and retrospectively (after death) (Hendriks, Smalbrugge, Hertogh, & van der Steen, 2014). Another study reported mixed methods for data collection; a prospective quantitative survey and semi-structured interviews with general practitioners involved in the practice of palliative sedation (Pype et al., 2018). Six studies used questionnaires as a means of data collection. In these, clinicians, physicians (n=4) or nurses

(n=2), were asked to provide information about patients under their care who had received sedative medication.

Studies were mainly based in a single setting (n=36); principally hospices, palliative care units, or hospitals. Nine studies included home care patients, and a further nine studies included nursing home participants. In one study patients were recruited from a cancer centre (McMillan & Tittle, 1995).

Studies spanned different countries, with most studies conducted in the Netherlands (n=11), United States (n=8), Japan (n=8), Belgium (n=6), and Italy (n=6). Two studies included data collected in two or more countries (Fainsinger et al., 2000; Hui et al., 2014). It is noteworthy that only two studies involving level of consciousness measures were conducted in the United Kingdom (Boyd & Kelly, 1997; A. Dean, Miller, & Woodwork, 2014). Moreover, a large number of studies were published relatively recently, with 26 of the 65 (40%) included studies published within the last seven years (since 2013).

Sample size varied greatly, ranging from 8 to 1,944 participants (median 132 participants, IQR 44 to 266). The participant population mostly consisted of cancer patients (n=29). Other reported diagnoses included dementia (n=3) (Hendriks et al., 2014; Pasman et al., 2005; Van Der Steen, Pasman, Ribbe, Van Der Wal, & Onwuteaka-Philipsen, 2009) and interstitial lung disease (n=1) (Matsunuma et al., 2016). The remaining 32 studies reported mixed diagnoses or did not provide this information. Participants in almost all studies were at an advanced or an end stage of disease.

Reflecting the wide diversity of study aims, level of consciousness measures in each study were employed to serve a number of distinct purposes. The most frequently reported of these were: to assess/monitor sedation depth after the initiation of palliative sedation (n=29), to evaluate signs/symptoms of impending death (n=8), to assess the effects or side-effects of opioid use (n=7), and to examine the association between level of consciousness and discomfort or other symptoms (n=6). Notably, only four studies sought to validate level of consciousness instruments in the palliative care setting (Arevalo et al., 2012; Benitez-Rosario et al., 2013; Bush et al., 2014; Goncalves, Bento, Alvarenga, Costa, & Costa, 2008). Of these four studies, only one aimed to develop a new tool (Goncalves et al., 2008).

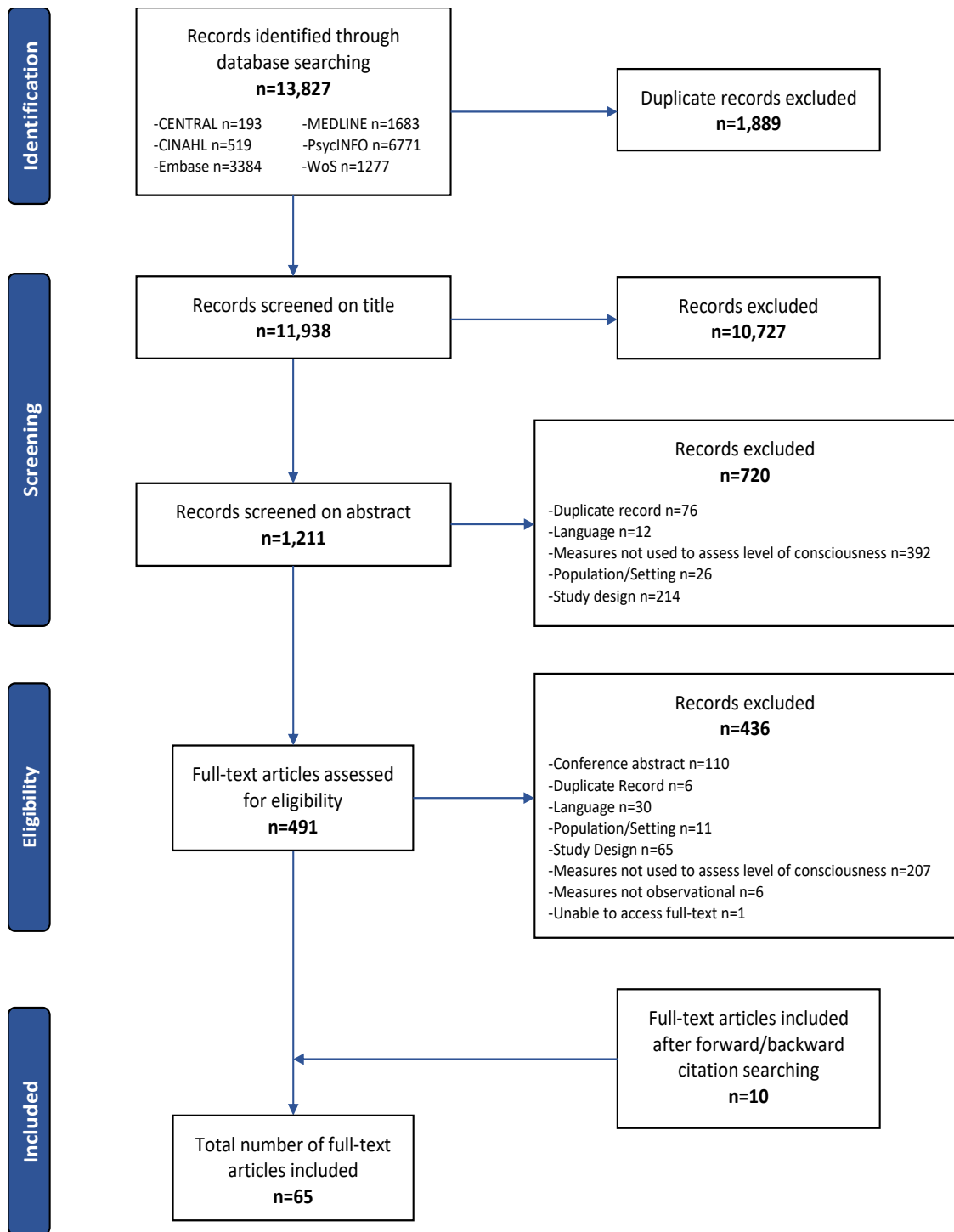


Figure 2.3: PRISMA flow diagram of study selection (Moher et al., 2009)

**Table 2.2:** Description of identified studies and measures

Author, year and country	Study aim	Study setting	Study population	Measure name and acronym	Purpose of measure	Subscales / Number of items	Response options
<b>Studies reporting <i>ad hoc</i> measures</b>							
Abernethy et al. (2003) Australia	To determine the efficacy of oral morphine for the management of refractory dyspnoea	Palliative, general, respiratory, cardiac medicine clinics	48 outpatients with refractory dyspnoea	–	To measure sedation depth as a side-effect of morphine use	S: - I: 1	4-level scale ('No', 'Mild', 'Moderate', 'Severe' sedation)
Aretha et al. (2009) Greece	Evaluation of patient/family-controlled sedation (PFCS) with midazolam for intractable symptom control	Tertiary care university hospital	8 terminal cancer inpatients	–	Monitoring of patients after terminal sedation initiation	S: - I: 1	4-point scale (1= 'Awake', 2= 'Arousable with voice', 3= 'Arousable with light pain', 4= 'Unarousable')
Arevalo et al. (2013) Netherlands	To describe nurses' experiences with the decision-making and performance of continuous palliative sedation (CPS)	Home care organisations, palliative care units (based in nursing homes or inpatient hospices), hospitals	199 nurses reporting on their last patient receiving CPS	– (Scale included in the study questionnaire)	Monitoring of CPS	S: - I: 1	6-level scale ('Drowsiness', 'Eyes closed, reaction to verbal stimuli', 'Eyes closed, reaction to physical stimuli', 'Eyes closed, no reaction to physical stimuli', 'Other', 'I don't know')
Barbato (2001) Australia	Exploration of the clinical application of Bispectral index (BIS) monitoring in palliative care	Hospice	12 unconscious palliative care inpatients	Consciousness Scale (modified Glasgow Coma Scale; Teasdale & Jennett, 1974)	Monitoring of consciousness level from the onset of unconsciousness and until death	S: 6 (breathing, movement, pulse volume, eyelash reflex, peripheries, response to name call) I: 1/subscale	4-point scale (1-4) for each subscale. Scores can be calculated per subscale and as a total score.
Baumann, Batenhorst, & Graves (1986) USA	Evaluation of the safety and efficacy of patient-controlled analgesia in patients with unsuccessfully treated chronic pain secondary to cancer	Not specified	8 terminally ill cancer patients	–	To evaluate sedation for the assessment of individual analgesic response	S: - I: 1	5-point scale (1= 'Wide awake', 2= 'Drowsy', 3= 'Dozing intermittently', 4= 'Mostly sleeping', 5= 'Only awakens when aroused')

Continued overleaf

Author, year and country	Study aim	Study setting	Study population	Measure name and acronym	Purpose of measure	Subscales / Number of items	Response options
A. Dean, Miller, & Woodwork (2014)  UK	Description of palliative sedation decision-making practices in a UK hospice over the course of five years	Hospice	234 patient charts	Sedation scale (modified Richmond Agitation-Sedation Scale; Sessler et al., 2002)	Assessing level of sedation to guide palliative sedation clinical decision-making and documentation	S: - I: 1	6-point scale (+2= 'Agitated/Distressed', +1= 'Anxious/Restless', 0= 'Alert, orientated, calm', -1= 'Drowsy: Opening eyes and establishing eye contact for periods of 10 seconds or more, responds to commands', -2= 'Moderate sedation: Rousable to voice or physical stimulation. Unable to communicate', -3= 'Deep sedation: Unrousable')
Fainsinger et al. (2000)  South Africa, Israel, Spain	To provide a better understanding of the use of sedation for the management of uncontrolled symptoms in terminally ill patients	Hospices and hospital-based palliative care unit	387 palliative care patients	–	To assess level of consciousness after initiation of sedation for uncontrolled symptoms	S: - I: 1	3-level scale ('Alert', 'Drowsy', 'Unresponsive')
Hendricks et al. (2014)  Netherlands	To investigate symptoms, treatment and quality of life in patients with end-stage dementia	Nursing homes	330 end-stage dementia patients (213 recruited on admission, 117 retrospectively)	–	To assess the level of consciousness that most frequently occurred during the last week of life	S: - I: 1	6-level scale ('Awake and alert', 'Awake', 'Awake but drowsy looking', 'Falling asleep', 'Light sleep', 'Deep looking sleep')
Jaspers et al. (2012)  Germany	Description of the practice of palliative sedation in Germany	Palliative care units, inpatient hospices	1944 electronic patient records	– (Depth of palliative sedation item included in the standardised documentation system for palliative care patients)	To assess depth of palliative sedation	S: - I: 1	3-level scale ('Somnolence', 'Stupor', 'Coma')
Morita et al. (1998)  Japan	To investigate the change of physical signs and medical interventions in the dying process	Palliative care unit	100 terminally ill cancer patients	Categorical scale (modified Riker Sedation-Agitation Scale; Riker et al., 1994)	To examine changes in the level of consciousness in the last four weeks of life	S: - I: 1	4-level scale ('Awake: arousable, follows commands', 'Drowsy: difficult to arouse or unable to attend to conversation or commands', 'Very drowsy: awakens to noxious stimuli only', 'Coma: does not awaken to any stimuli')

Continued overleaf

Author, year and country	Study aim	Study setting	Study population	Measure name and acronym	Purpose of measure	Subscales / Number of items	Response options
Morita et al. (2000) Japan	Identification of risk factors for the development and persistency of death rattle	Palliative care unit	245 terminally ill cancer patients (of whom 107 developed death rattle)	Categorical scale (modified Riker Sedation-Agitation Scale)	To assess conscious level as a risk factor for the development/persistency of death rattle	Same as above	Same as above
Morita et al. (2003a) Japan	To investigate the effects of partial opioid substitution and hydration on the occurrence of agitated delirium in the final stage of cancer	Palliative care unit	284 terminally ill cancer inpatient charts	Consciousness scale (Ad hoc scale described in Faisinger et al., 2000)	Evaluation of consciousness level as part of the assessment of the degree of cognitive impairment	S: - I: 1	3-level scale ('Alert', 'Drowsy', 'Unresponsive')
Morita et al. (2003b) Japan	To establish the communication capacity level and identify factors contributing to communication capacity impairment and agitated delirium in cancer patients in their final week of life	Palliative care unit	284 terminally ill cancer inpatient charts	Consciousness scale (Ad hoc scale described in Faisinger et al., 2000)	Evaluation of consciousness level in the last week of life	Same as above	Same as above
Papavasiliou et al. (2014) Belgium	To compare physician-reported practices on continuous deep sedation until death (CDSUD) between general practitioner and medical specialists	Not specified	561 cases of CDSUD reported by physicians	– (Level of unconsciousness item included in questionnaire on end-of-life practices)	Level of unconsciousness (comatose) used to assess the degree of patients' awareness during the practice of CDSUD	S: - I: 1	11-point scale (0= 'Symptom not present' to 10= 'Worst possible symptom')
Pasman et al. (2005) Netherlands	To study the level and course of discomfort, and factors that are associated with discomfort in patients with dementia for whom artificial nutrition and hydration is forgone	Nursing homes	178 patients with severe dementia	–	To assess the level of consciousness as a determinant of discomfort	S: - I: 1	6-point scale (response options not described)
Portenoy et al. (2006) USA	Exploration of the relationship between opioid use and survival at the end-of-life	Hospices	725 palliative care inpatients	–	Level of consciousness at the time of last opioid dose change assessed for its association with length of survival	S: - I: 1	4-level scale ('Full level of consciousness', 'Drowsy', 'Confused', 'Unable to respond')

Continued overleaf

Author, year and country	Study aim	Study setting	Study population	Measure name and acronym	Purpose of measure	Subscales / Number of items	Response options
Rys et al. (2014) Belgium	Investigation of the practice of continuous sedation until death (CSD) in nursing homes	Nursing homes	249 nurse reports of their most recent patient treated with CSD	– (Depth of sedation scale included in the study questionnaire)	To assess depth of sedation reached after the administration of CSD	S: - I: 1	5-level scale ('Drowsy', 'Eyes closed, response to voice', 'Eyes closed, response to painful stimuli', 'Eyes closed, no reaction to any stimulus', 'Other')
Swart et al. (2012) Netherlands	Description of the practice of continuous palliative sedation until death (CPS) after the introduction of a national palliative guideline	Not specified	370 physicians providing information about their last patient who received CPS until death	– (Depth of continuous sedation item included in the study questionnaire)	To assess depth of continuous sedation reached after the administration of CPS until death	S: - I: 1	5-point scale ('Drowsy', 'Eyes closed, responding promptly to verbal command', 'Eyes closed, arousable only by physical stimuli', 'Eyes closed, not arousable by physical stimuli', 'Other')
Van Deijck et al. (2010) Netherlands	Investigation of the practice of continuous palliative sedation (CPS) in elderly patients	Nursing homes	316 nursing home physicians reporting on their last case of CPS	– (Level of consciousness item included in the study questionnaire)	Evaluation of level of consciousness at adequate symptom relief after the administration of CPS	S: - I: 1	6-level scale ('Alert and orientated', 'Drowsy', 'Eyes closed, following directives', 'Eyes closed, responding to physical stimuli', 'Eyes closed, not responding to physical stimuli', 'Disturbed brainstem function')
Van Deijck et al. (2015) Netherlands	To explore the characteristics of patients with existential suffering treated with continuous palliative sedation (CPS) and the degree to which preconditions for administering CPS are fulfilled	Nursing homes	314 cases of patients who received CPS described by nursing home physicians	– (Level of consciousness item included in the study questionnaire)	Evaluation of level of consciousness at adequate symptom relief after the administration of CPS	Same as above	Same as above
Van Der Steen et al. (2009) Netherlands	To compare discomfort in dementia patients dying from pneumonia with patients dying after intake problems, and to assess associations with treatment	Nursing homes	725 end-stage dementia patients	–	To explore the association between level of consciousness and discomfort	S: - I: 1	6-level scale ('Awake and alert', 'Awake', 'Awake but drowsy looking', 'Falling asleep', 'Light sleep', 'Deep looking sleep')

Continued overleaf

Author, year and country	Study aim	Study setting	Study population	Measure name and acronym	Purpose of measure	Subscales / Number of items	Response options
<b>Studies reporting established measures</b>							
Agar et al. (2017) Australia	To determine the efficacy of risperidone or haloperidol relative to placebo for delirium symptoms among palliative care patients	Hospice and hospital palliative care inpatient services	247 palliative care inpatients with various diagnoses; predominantly cancer	Richmond Agitation-Sedation Scale (RASS)	To measure sedation as an adverse effect of risperidone/haloperidol use	S: - I: 1	10-point scale (+4= 'Combative', +3= 'Very agitation', +2= 'Agitated', +1= 'Restless', 0= 'Alert and Calm', -1= 'Drowsy', -2= 'Light sedation', -3= 'Moderate sedation', -4= 'Deep sedation', -5= 'Unarousable')
Alonso-Babarro et al. (2010) Spain	Assessment of the incidence and efficacy of palliative sedation (PS) for patients who died at home	Home	245 terminally ill cancer patient records	Ramsay Sedation Scale (RSS; Ramsay et al., 1974)	To monitor level of sedation after administration of PS	S: - I: 1	6-point scale (1= 'Anxious and agitated or restless or both', 2= 'Co-operative, orientated, and tranquil, 3= 'Responds to commands only', 4= 'Brisk response to a light glabellar tap or loud auditory stimulus, 5= 'Sluggish response', 6= 'No response')
Barbato et al. (2017) Australia	To determine the validity of the Bispectral index monitor and two observational scales	Palliative care unit	40 unresponsive palliative care inpatients	Richmond Agitation-Sedation Scale (RASS)	To assess level of sedation for the exploration of the association with BIS values	Same as above	Same as above
Barbato et al. (2018) Australia	To examine the effectiveness of breakthrough medication in unresponsive patients and the perception of patient comfort made by nurses and family	Palliative care unit	40 unresponsive palliative care inpatients	Richmond Agitation-Sedation Scale (RASS)	To measure level of sedation for the assessment of the effect of breakthrough opioid/benzodiazepine use	Same as above	Same as above
Benitez-Rosario et al. (2012) Spain	To assess the feasibility of a quality care project in palliative sedation	Hospital-based palliative care service	204 patient charts	Richmond Agitation-Sedation Scale (RASS)	To assess the level of deep continuous sedation with the aim to reach a predetermined level (-5 RASS for patients with continuous dyspnoea at rest; -4 RASS for delirium or other reasons)	Same as above	Same as above
Boyd & Kelly (1997) UK	Evaluation of the effectiveness of oral morphine for the symptomatic treatment of dyspnoea in patients with advanced cancer	Home, hospice	15 advanced cancer patients with dyspnoea	Visual Analogue Scale (VAS)	To measure sedation as a side-effect of oral morphine	S: - I: 1	100mm line anchored by two verbal descriptors; 0: 'Fully awake' to 100: 'Asleep'

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Author, year and country	Study aim	Study setting	Study population	Measure name and acronym	Purpose of measure	Subscales / Number of items	Response options
Campbell et al. (2009) USA	To investigate the self-reporting of dyspnoea at the very end of life	Palliative care unit	89 palliative care inpatients at the risk of experiencing dyspnoea	Reaction Level Scale 85 (RLS85; Starmark, Stålhammar, & Holmgren, 1988)	To assess consciousness as patient characteristic for the exploration of the association with the ability to self-report dyspnoea symptoms	S: - I: 1	8-point scale (1= 'Alert; No delay in response', 2= 'Drowsy or confused; Responsive to light stimulation', 3= 'Very drowsy or confused; Responsive to strong stimulation' 4= 'Unconscious; Localizes but does not ward off pain', 5= 'Unconscious; Withdrawing movement on pain stimulation', '6= Unconscious; Stereotype flexion movements on pain stimulation', 7= 'Unconscious; Stereotype extension movements on pain stimulation', 8= 'Unconscious; No response to pain stimulation'
Campbell et al. (2010) USA	To establish the reliability and construct validity of a revised Respiratory Distress Observation Scale (RDOS)	Palliative care unit	89 palliative care inpatients at the risk of experiencing dyspnoea	Reaction Level Scale 85 (RLS85)	To assess consciousness for ascertaining the construct validity of RDOS	Same as above	Same as above
Campbell et al. (2013) USA	To determine the effect of oxygen administration at the very end of life	Hospice, hospital-based palliative care service	32 hospice and hospital inpatients at the very end of life	Reaction Level Scale 85 (RLS85)	To measure consciousness for the correlation with respiratory distress and nearness to death	Same as above	Same as above
Campbell et al. (2018) USA	Determination of the trajectory of dyspnoea and respiratory distress	Hospice	91 home-based palliative care patients	Reaction Level Scale 85 (RLS85)	To measure consciousness for the correlation with respiratory distress and nearness to death	Same as above	Same as above
Caraceni et al. (2018) Italy	Comparison of palliative sedation practices in home care and hospice settings	Home-based palliative care services, hospices	531 terminal cancer patients receiving palliative sedation	Modified Wilson Sedation Scale (MWSS; Némethy et al., 2002)	Level of consciousness assessed as part of the palliative sedation monitoring process	S: - I: 1	5-point scale (1= 'Fully awake and oriented', 2= 'Drowsy but rousable', 3= 'Eyes closed but rousable to command', 4= 'Eyes closed but rousable to mild physical stimulation (earlobe tug)', 5= 'Eyes closed but unrousable to mild physical stimulation'

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Author, year and country	Study aim	Study setting	Study population	Measure name and acronym	Purpose of measure	Subscales / Number of items	Response options
de la Cruz et al. (2015) USA	To describe the prevalence and severity of symptoms, including delirium, in the final week of life and evaluate the usefulness of the Nursing Delirium Screening Scale (Nu-DESC)	Hospice	78 terminally ill cancer patients	Richmond Agitation-Sedation Scale (RASS)	To measure sedation or agitation as the predominant features of delirium	Same as above	Same as above
Franken et al. (2018) Netherlands	To evaluate the variability in response to midazolam and to find clinically significant covariates that predict pharmacodynamic response	Palliative care centre	43 terminally ill inpatients receiving midazolam	Ramsay Sedation Scale (RSS)	To measure the effect of midazolam on patients' sedation level	Same as above	Same as above
Goncalves et al. (2012) Portugal	Description of the sedation practice of Portuguese palliative care teams	Palliative care inpatient, home care, hospital support care services	181 palliative care patients (of whom 27 received sedation)	Consciousness Scale for Palliative Care (CSPC; Goncalves et al., 2008)	To assess the deepest consciousness level reached after the administration of sedation	S: - I: 1	6-point scale (1= 'Awake', 2= 'Awakens when called by name and stays awake during discussion', 3= 'Awakens but falls asleep during discussion', 4= 'Reacts with movement/brief eye opening, but without eye contact, when called by name', 5= 'Reacts to trapezius muscle pinching', 6 = 'Does not react')
Goncalves et al. (2013) Portugal	To examine the activity of Portuguese palliative care teams	Inpatient, home care and hospital palliative care support care services	164 palliative care patients	Consciousness Scale for Palliative Care (CSPC)	Evaluation of consciousness level as a patient characteristic	Same as above	Same as above
Goncalves et al. (2016) Portugal	Comparison of haloperidol alone and in combination with midazolam for the treatment of acute agitation in palliative care	Palliative care unit	79 palliative care inpatients	Consciousness Scale for Palliative Care (CSPC)	To assess level of consciousness when control of agitation is reached	Same as above	Same as above
Hsu et al. (2013) Taiwan	To investigate the characteristics and outcomes of noncancer palliative care patients in an acute general care setting	Acute general medicine ward	258 inpatients (of whom 193 did not meet criteria for cancer palliative care)	Glasgow Coma Scale (GCS)	To measure Glasgow Coma Scale score as a clinical characteristic for the comparison between cancer and noncancer patients	S: 3 (motor response, verbal response, eye opening) I: 1/subscale	Eye opening: 4-point scale (1-4), Motor response: 6-point scale (1-6), Verbal response: 5-point scale (1-5)

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Author, year and country	Study aim	Study setting	Study population	Measure name and acronym	Purpose of measure	Subscales / Number of items	Response options
Hui et al. (2014) USA, Brazil	To examine the frequency and onset of bedside physical signs and their diagnostic performance for impending death	Acute palliative care units	357 advanced cancer inpatients	Richmond Agitation-Sedation Scale (RASS)	Decreased level of consciousness (RASS ≤ -2) assessed as a clinical sign of impending death	Same as above	Same as above
Hui et al. (2017) USA	To compare the effect of lorazepam vs placebo as adjuvant to haloperidol for persistent agitation	Acute palliative care unit	93 advanced cancer inpatients with agitated delirium	Richmond Agitation-Sedation Scale (RASS)	To measure sedation and agitation for the evaluation of the effect of pharmacological interventions for the treatment of agitation	Same as above	Same as above
Hwang et al. (2013) South Korea	To determine the events that herald the onset of dying process and evaluate their predictive value for death within 48 hours	Palliative care unit	181 terminal cancer inpatients	Alert/Verbal/Painful/Unresponsive Scale (AVPU; Kelly, Upex, & Bateman, 2004)	To measure conscious level as clinical sign of impending death	S: - I: 1	4-level scale (A= 'Eyes opened spontaneously, orientated speech, obeys commands, V= 'Any verbal, motor, or eye response to verbal stimulus', P= 'Any verbal, motor, or eye response to painful stimulus', U= 'Unresponsive to any stimulus')
Imai et al. (2018) Japan	To investigate the effect of two types of palliative sedation therapy: proportional and deep sedation	Palliative care unit	50 cancer inpatients	Modified Richmond Agitation-Sedation Scale (RASS; Benitez-Rosario et al., 2013)	To define deep sedation (RASS ≥ -4) and the absence of agitation (RASS ≤ 0)	S: - I: 1	10-point scale (+4= 'Combative' to -5= 'Unarousable')  Modifications to RASS: -Removal of reference to assisted ventilation from definition of agitation level -Score '+1' can be present in patients who are not fully alert
Klepstad et al. (2002) Norway	Investigation of the relationship between patient self-reports of cognitive function (CF) and sedation with objective assessments of CF and sedation	Hospital-based palliative care unit	29 cancer inpatients	Observer's Assessment of Alertness/Sedation (OAA/S)	To objectively assess sedation and compare scores with patient self-reports	S: 4 (responsiveness, speech, facial expression, eyes) I: 1/subscale	Responsiveness: 5-point scale (1-5), Speech: 4-point scale (2-5), Facial expression: 3-point scale (3-5), Eyes: 3-point scale (3-5)
Kohara et al. (2005) Japan	Investigation of the influence of sedative drugs on consciousness	Hospital-based palliative care unit	124 terminally ill cancer inpatients (of whom 63 received sedation)	Communication Capacity Scale- Item 1 (Conscious level; Morita, Tsunoda, et al., 2001)	To compare level of consciousness between sedated and unsedated patients	S: - I: 1 (for item 1)	6-point scale (0= 'Awake with no drowsiness' to 5= 'Cannot remain awake and cannot be awakened by physical stimuli')

Continued overleaf

Author, year and country	Study aim	Study setting	Study population	Measure name and acronym	Purpose of measure	Subscales / Number of items	Response options
Maltoni, Miccinesi, et al. (2012) Italy	Evaluation of the practice of palliative sedation (PS) in two Italian hospices	Hospice	327 inpatients (of whom 72 received PS)	Richmond Agitation-Sedation Scale (RASS)	RASS scores used for monitoring PS (negativisation of scores proxy indicator of the efficacy of PS)	Same as above	Same as above
Masman et al. (2016) Netherlands	To determine the feasibility and validity of Bispectral index (BIS) monitoring in terminally ill patients	Palliative care centre	58 terminally ill inpatients	Ramsay Sedation Scale (RSS)	To assess level of sedation and evaluate the correlation between Ramsay scores and BIS values	Same as above	Same as above
Matsunuma et al. (2016) Japan	Evaluation of the signs, symptoms, and treatments of patients with interstitial lung disease (ILD) before death	Community hospital	82 end-stage ILD and lung cancer inpatient records	Japan Coma Scale (JCS; Ohta et al., 1974)	To determine the frequency of loss of consciousness (defined as more than 1 point on JCS) before death and examine its causes	S: - I: 1	10-point scale (One level (0) for 'fully conscious', 3 levels (1-3) for the patient who is 'awake without any stimuli', 3 levels (10-30) for the patient who 'can be aroused after stimulation', 3 levels (100-300) for the patient who 'cannot be aroused with any forceful mechanical stimuli'
McMillan & Tittle (1995) USA	To describe cancer and palliative care patients' pain, pain-related side effects and the nurses' assessment and responses to these	Cancer centre, hospice home care service	44 patients treated for pain	Sedation Item of the Pain Flow Sheet (McMillan et al., 1988)	To evaluate level of sedation as an opioid-induced side-effect	S: - I: 1 (for sedation item)	5-point scale (0= 'Fully alert', 1= 'Relaxed, awake', 2= 'Drowsy, dozing', 3= 'Arousable sleep', 4= 'Comatose')
Mercadante et al. (2009) Italy	Assessment of the need and the effectiveness of sedation for intractable symptoms, and the thoughts of relatives regarding sedation	Acute pain relief and palliative care unit	77 terminally ill cancer patients (of whom 42 received sedation)	Communication Capacity Scale- Item 1 (Conscious level)	To assess the level of sedation of patient after the initiation of palliative sedation	Same as above	Same as above
Mercadante et al. (2017) Italy	To assess the attitudes of palliative care clinicians regarding palliative sedation at home	Home	150 physicians involved in end of life care decisions	-Richmond Agitation-Sedation Scale (RASS)  -Ramsay Sedation Scale (RSS)	Monitoring of palliative sedation	-RASS: Same as above  -RSS: Same as above	-RASS: Same as above  -RSS: Same as above

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Author, year and country	Study aim	Study setting	Study population	Measure name and acronym	Purpose of measure	Subscales / Number of items	Response options
				-Rudkin Sedation Scale (Rudkin et al., 1992)		-Rudkin Sedation Scale: S: - I: 1	-Rudkin Sedation Scale: 5-point scale (1= 'Fully awake', 2= 'Drowsy', 3= 'Eyes closed but rousable to command', 4= 'Eyes closed but rousable to mild physical stimulation', 5= 'Eyes closed and unrousable to mild physical stimulation')
Mercadante et al. (2018)  Italy	To assess the efficacy of Hyoscine Butylbromide for the management of death rattle	Hospices	132 cancer inpatients with reduced level of consciousness	Richmond Agitation-Sedation Scale - Palliative version (RASS-PAL; Bush et al., 2014)	Identification of patients with reduced level of consciousness (RASS-PAL ≤ -3)	S: - I: 1	10-point scale (+4= 'Combative' to -5= 'Unrousable')  Modifications to RASS <sup>19</sup> : -Descriptors related to 'pulling tubes'/'fighting the ventilator' modified -'Any movement' refers to eye and body -'Physical stimulation' changed to 'gentle physical stimulation' -Clarification on how to score a patient with a mixed type delirium
Monreal-Carrillo et al. (2017) Mexico	Characterisation of the level of consciousness of patients undergoing palliative sedation using Bispectral index monitoring	Palliative care unit	20 advanced cancer in patients receiving palliative sedation	Ramsay Sedation Scale (RSS)	Assessment of sedation level after initiation of palliative sedation	Same as above	Same as above
Morita, Tsunoda, et al. (2001)  Japan	Development and validation of the Communication Capacity Scale and the Agitation Distress scale	Palliative care unit based in a cancer institute	30 terminally ill cancer inpatients with delirium	-Communication Capacity Scale- Item 1 (Conscious level)  -Sedation Scale (modified Riker Sedation-Agitation Scale)	To test the association between Communication Capacity scores and Sedation Scale scores	-Communication Capacity Scale- Item 1 (Conscious level): Same as above  -Sedation Scale: S: - I: 1	-Communication Capacity Scale- Item 1 (Conscious level): Same as above  -Sedation Scale: 4-point scale (0= 'Calm and cooperative', 1= 'Over-sedated', 2= 'Very sedated', 3= 'Unrousable')

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Author, year and country	Study aim	Study setting	Study population	Measure name and acronym	Purpose of measure	Subscales / Number of items	Response options
Palacio et al. (2018) Colombia	Description of the practice of palliative sedation	Specialised palliative care unit based in a cancer institute	66 advanced cancer inpatients undergoing palliative sedation	Ramsay Sedation Scale (RSS)	Assessment of sedation level after initiation of palliative sedation	Same as above	Same as above
Porzio et al. (2010) Italy	Evaluation of the feasibility and efficacy of palliative sedation at home	Home care service	16 terminally ill cancer home patient charts	Ramsay Sedation Scale (RSS)	To monitor the level of sedation after the administration of PS with the aim to reach deep, continuous sedation (RSS $\geq$ 5)	Same as above	Same as above
Pype et al. (2018) Belgium	To explore the practice of suboptimal palliative sedation in primary care	Home	7 PC home teams and 7 general practitioners reporting on 27 cases of palliative sedation	Richmond Agitation-Sedation Scale (RASS)	To measure depth of sedation throughout the procedure of palliative sedation	Same as above	Same as above
Schmitz et al. (2016) Germany	To investigate the effectiveness of intravenous opioid patient-controlled therapy (PCT) in reducing breathlessness in patients with advanced malignant disease	Palliative care centre	18 patients with moderate or severe breathlessness	Richmond Agitation-Sedation Scale (RASS)	To monitor changes in sedation and agitation levels after PCT onset	Same as above	Same as above
Van Deijck et al. (2016) Netherlands	To explore which patient-related factors at admission are associated with receiving continuous palliative sedation (CPS) in the terminal phase of life	Hospices, nursing home-based palliative care units	467 palliative care inpatients (of whom 130 received CPS)	Glasgow Coma Scale (GCS)	To evaluate the level of consciousness on admission as a patient-related characteristic and examine its association with CPS	Same as above	Same as above

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Author, year and country	Study aim	Study setting	Study population	Measure name and acronym	Purpose of measure	Subscales / Number of items	Response options
<b>Studies reporting measure psychometric properties</b>							
Arevalo et al. (2012) Netherlands	To study the reliability and validity of observer-based sedation scales in palliative sedation (PS)	Hospices, nursing home	54 inpatients receiving PS	-Minnesota Sedation Assessment Tool (MSAT; Dutch version; Weinert & McFarland, 2004)  -Richmond Agitation-Sedation Scale (RASS; Dutch version)  -Vancouver Interaction and Calmness Scale (VICS; Dutch version; de Lemos, Tweeddale, & Chittock, 2000)  -Sedation score proposed in the Guideline for Palliative Sedation of the Royal Dutch Medical Association (KNMG; Royal Dutch Medical Association, 2009)	To assess level of consciousness before and during the course of palliative sedation	-MSAT: S: 3 (motor activity, arousal, quality of sedation therapy) I: 1/subscale  -RASS: Same as above  -VICS: S: 2 (interaction, calmness) I: 5/subscale  -KNMG: S: - I: 1	-MSAT: Motor activity: 4 levels (1-4), Arousal: 6 levels (1-6), Quality of sedation therapy: 3 levels ('Adequate', 'Oversedated', 'Undersedated')  -RASS: Same as above  -VICS: Interaction: 6-point Likert-type scale per item (1= 'Strongly disagree' to 6= 'Strongly agree'; reverse scoring for last item) Calmness: 6-point Likert-type scale per item (1= 'Strongly disagree' to 6= 'Strongly agree'; reverse scoring for first item)  -KNMG: 6-point scale (Level 1: a) 'Awake and oriented', b) 'Drowsy', c) 'Eyes closed, responds promptly to verbal commands', d) 'Eyes closed, arousable only by physical stimuli', Level 2: 'Eyes closed, not arousable by physical stimuli', Level 3: 'Basic brain functions affected')

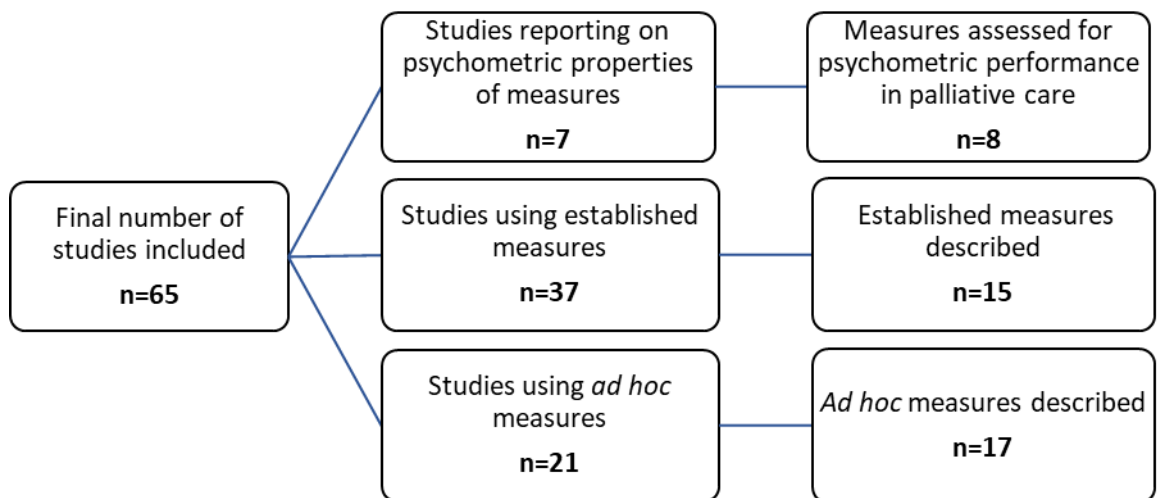
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Author, year and country	Study aim	Study setting	Study population	Measure name and acronym	Purpose of measure	Subscales / Number of items	Response options
Benitez-Rosario et al. (2013) Spain	To test the appropriateness and reliability of the Richmond Agitation-Sedation Scale (RASS) in Spanish patients with advanced cancer	Palliative care unit	156 advanced cancer inpatients	Modified Richmond Agitation-Sedation Scale (RASS)	To monitor sedation and agitation	Same as above	Same as above
Bush et al. (2014) Canada	Exploration of the validity and feasibility of a version of the Richmond Agitation-Sedation Scale (RASS) modified for palliative care populations	Acute palliative care unit	10 inpatients with agitated delirium or receiving palliative sedation	Richmond Agitation-Sedation Scale - Palliative version (RASS-PAL)	To assess the level of sedation and agitation	Same as above	Same as above
Claessens et al. (2011) Belgium	Description of the characteristics of palliative care patients receiving sedation for the management of refractory symptoms	Palliative care units	266 terminally ill cancer inpatients (of whom 20 received PS)	Glasgow Coma Scale (GCS; Dutch version)	Evaluation of level of consciousness at the start and during palliative sedation	S: 3 (motor response, verbal response, eye opening) I: 1/subscale	Eye opening: 4-point scale (1-4), Motor response: 6-point scale (1-6), Verbal response: 5-point scale (1-5)
Claessens et al. (2012) Belgium	To examine the impact of palliative sedation (PS) on the level of consciousness of terminally ill patients	Palliative care units	266 terminally ill cancer inpatients (of whom 20 received PS)	Glasgow Coma Scale (GCS; Dutch version)	Evaluation of level of consciousness with the aim to assess the effect of PS	Same as above	Same as above
Claessens et al. (2014) Belgium	Description of the effect of palliative sedation on oral and/or artificial food and fluid intake in terminally ill patients	Palliative care units	266 terminally ill cancer inpatients (of whom 20 received PS)	Glasgow Coma Scale (GCS; Dutch version)	To evaluate patients' level of consciousness at admission	Same as above	Same as above
Goncalves et al. (2008) Portugal	Validation of a consciousness scale for palliative care	Palliative care unit	38 advanced cancer inpatients	Consciousness Scale for Palliative Care (CSPC)	To assess level of consciousness	S: - I: 1	6-point scale (1= 'Awake', 2= 'Awakens when called by name and stays awake during discussion', 3= 'Awakens but falls asleep during discussion', 4= 'Reacts with movement/brief eye opening, but without eye contact, when called by name', 5= 'Reacts to trapezius muscle pinching', 6 = 'Does not react')



## Description of identified measures

In total, 35 different measures assessing level of consciousness were described in the 65 articles included in this review. Of these measures, 17 were tools constructed for the purposes of individual studies and no evidence about their psychometric properties was provided (i.e. *ad hoc* measures). Fifteen were established instruments or single items extracted from compound scales validated as a whole, and eight were measures developed and/or tested for aspects of psychometric performance in palliative care populations. Information on psychometric performance in palliative care was provided for five of the fifteen established measures; therefore, there is an overlap between the latter two described categories (see **Figure 2.4** below).



**Figure 2.4:** Number of identified studies and measures by instrument category

Twenty-seven of the thirty-five identified measures (77.1%), comprised one item with a categorical grading representing decreasing levels of consciousness, mostly assessed by patients' responses to stimulation of increasing intensity. The majority of these tools (n=23) evaluated a single construct, consciousness in terms of arousal. Four measures incorporated assessment of agitation into single scales for consciousness/sedation. The remaining eight measures (22.9%) consisted of multiple scales and/or items. The most frequently used tool for the evaluation of level of consciousness was the original Richmond Agitation-Sedation Scale (RASS; Sessler et al., 2002) or modified versions of it (n=17).

From the 17 *ad hoc* measures identified in this review, three were modified versions of existing tools; namely, the Glasgow Coma Scale (GCS) (Barbato, 2001; Teasdale & Jennett, 1974), RASS (A. Dean et al., 2014; Sessler et al., 2002), and Riker Sedation-Agitation Scale (Morita, Ichiki, Tsunoda, Inoue, & Chihara, 1998; Riker et al., 1994). All other *ad hoc* measures (n=14) comprised unique tools. A formal validation process had not been undertaken before use for any of these measures.

Of the established measures, the most commonly employed were the RASS (n=11) and the Ramsay Sedation Scale (RSS; n=7) (Ramsay et al., 1974). The majority of measures in this category had been developed and validated for use in settings other than palliative care; mainly the intensive care unit. No information on the psychometric performance of these measures was provided in the studies with palliative care patients in which they were used.

Of the existing measures, two consisted of items extracted from multi-item tools developed to assess constructs other than level of consciousness (i.e. the conscious level item of the Communication Capacity Scale [CCS]) (Kohara, Ueoka, Takeyama, Murakami, & Morita, 2005; Mercadante et al., 2009; Morita, Tsunoda, et al., 2001) and the sedation item of the Pain Flow Sheet (McMillan & Tittle, 1995; McMillan, Williams, Chatfield, & Camp, 1988). Although these tools had been subjected to psychometric evaluation in the palliative setting, validity and reliability have only been established for each measure as a whole, not for the individual items measuring levels of consciousness.

Evidence of psychometric performance was available for the following eight measures: (1) the Minnesota Sedation Assessment Tool (MSAT) (Arevalo et al., 2012; Weinert & McFarland, 2004); (2) RASS (Arevalo et al., 2012; Sessler et al., 2002); (3) Vancouver Interaction and Calmness Scale (VICS) (Arevalo et al., 2012; de Lemos, Tweeddale, & Chittock, 2000); (4) Sedation score proposed in the Guideline for Palliative Sedation of the Royal Dutch Medical Association (KNMG) (Arevalo et al., 2012; Royal Dutch Medical

Association, 2009); (5) Modified RASS (Benitez-Rosario et al., 2013); (6) Richmond Agitation–Sedation Scale–Palliative version (RASS-PAL) (Bush et al., 2014); (7) GCS (Claessens et al., 2011, 2012, 2014; Teasdale & Jennett, 1974); (8) Consciousness Scale for Palliative Care (CSPC) (Goncalves et al., 2008).

All but one of the identified measures (RASS-PAL) (Bush et al., 2014) were developed and/or validated in languages other than English. Dutch versions of original English language scales were created by researchers for the MSAT, the RASS, the VICS and the GCS (Arevalo et al., 2012; Claessens et al., 2011, 2012, 2014). The RASS modified by Benitez-Rosario and colleagues (2013) was translated and further adjusted for use with Spanish palliative care patients. Modifications to the original RASS (Sessler et al., 2002) included the removal of descriptors relating to mechanical ventilation of patients and a clarification to the scoring instructions addressing the possibility that restless behaviour may be present in patients who are not fully alert. Similarly, Bush and colleagues (2014) reported performing minor changes to the RASS when testing its psychometric performance with palliative care patients. The KNMG (Royal Dutch Medical Association, 2009) sedation score was first developed in Dutch and then translated into English. Likewise, the CSPC (Goncalves et al., 2008) was developed and validated in its native language (Portuguese) and, subsequently, translated into English.

### **Psychometric performance of appraised measures**

As noted earlier in this chapter, criterion validity was not assessed in this review due to the lack of an acceptable “gold standard” for measuring level of consciousness in palliative care. Similarly, evidence regarding structural validity, test-retest and intra-rater reliability was not provided by study authors for any of the evaluated measures. Therefore, findings relating to these properties are not presented.

The highest overall ratings for psychometric performance were achieved by the CSPC (Goncalves et al., 2008) and the RASS modified by Benitez-Rosario et al. (2013). However, quality assessments were based on evidence obtained from just one study for each measure, rather than using evidence from multiple validation studies. **Table 2.3** provides a summary of the quality appraisal process for each instrument.

### **Content validity**

All studies provided a clear description of the construct measured by the reported instruments. However, the involvement of the target population in selecting or modifying scale items was described only for three of the eight evaluated measures: the CSPC (Goncalves et al., 2008), RASS-PAL (Bush et al., 2014) and Modified RASS (Benitez-Rosario et al., 2013). Goncalves and colleagues (2008) reported receiving feedback on the content of the CSPC from seven palliative care doctors and nurses at the development stage of the measure. Likewise, the input of palliative care professionals guided the modification of scale items for the RASS-PAL (Bush et al., 2014) and Modified RASS (Benitez-Rosario et al., 2013).

### **Construct validity**

Information on construct validity was available for six of the eight appraised measures: the MSAT, VICS, RASS, KNMG, CSPC, and Modified RASS (Arevalo et al., 2012; Benitez-Rosario et al., 2013; Goncalves et al., 2008). For these measures, construct validity was evaluated through correlation of the tested instrument with others that were assumed to measure the same construct (i.e. convergent validity). Discriminant validity was not assessed for any of the appraised measures.

Correlations were reported per subscale for the MSAT and VICS (Arevalo et al., 2012). The MSAT arousal subscale performed better than the motor activity subscale with Spearman's correlation coefficient ranging from 0.48 to 0.83, depending on the measure with which it was correlated (RASS, KNMG, VICS). Moderate correlations were reported for the motor activity subscale of the MSAT ( $r=0.42$  to  $0.61$ ). Mostly moderate correlations were found between both subscales of the VICS and other tools measuring level of consciousness (interaction subscale:  $r=0.31$  to  $0.72$ , calmness subscale:  $r=0.31$  to  $0.57$ ).

Construct validity of the RASS and KNMG was supported by moderate-high associations when compared with corresponding instruments (RASS:  $r=0.57$  to  $0.84$ , KNMG:  $r=0.44$  to  $0.84$ ) (Arevalo et al., 2012). High correlations with other tools measuring level of consciousness were reported for the Modified RASS and CSPC (Benitez-Rosario et al., 2013; Goncalves et al., 2008). Depending on the group of professionals performing the scoring (palliative care physicians or medical residents) Spearman's correlation coefficient for the Modified RASS to the GCS ranged from  $0.81$  to  $0.85$ , and  $0.82$  to  $0.89$  for the Modified RASS to the RSS (Benitez-Rosario et al., 2013). Likewise, the CSPC correlated highly with a 100 mm visual analogue scale (VAS) anchored with the terms "awake" and "unarousable" ( $r=0.94$  to  $0.95$ ) and with the GCS ( $r=0.82$  to  $0.85$ ) (Goncalves et al., 2008).

### **Homogeneity (internal consistency)**

Since the aim of some of the studies was not to address unique measurement characteristics, homogeneity was evaluated for only one of the appraised measures, the CSPC. This instrument was specifically developed for the evaluation of level of consciousness in palliative care. The reported Cronbach's alpha coefficient for the CSPC was very high ( $\alpha=0.99$ ) (Goncalves et al., 2008).

### **Inter-rater reliability**

ICC or weighted Cohen's kappa was used for the assessment of inter-rater reliability in all included studies. From the tested measures, inter-rater reliability was found to be high or very high for the CSPC (ICC=0.99) (Goncalves et al., 2008), the Dutch version of the GCS (ICC=0.81) (Claessens et al., 2011, 2012, 2014), RASS-PAL (ICC=0.84 to 0.98) (Bush et al., 2014) and Modified RASS ( $\kappa=0.85$  to 0.95) (Benitez-Rosario et al., 2013).

Moderate correlations within paired observational assessments were reported for the RASS (ICC=0.71 to 0.73) and KNMG (ICC=0.66 to 0.71) (Arevalo et al., 2012). Of the MSAT and VICS subscales, the VICS interaction scale performed best with ICC ranging from 0.77 to 0.85, followed by the MSAT arousal scale (ICC=0.59 to 0.64) (Arevalo et al., 2012). Depending on the time interval between paired assessments, Cohen's kappa coefficient ranged from 0.44 to 0.54 for the MSAT overall quality of sedation subscale, suggesting low agreement between scale assessors. No correlations were found for the MSAT motor activity and VICS calmness subscales (Arevalo et al., 2012).

### **Responsiveness**

Change scores indicating clinically meaningful change over time in consciousness/sedation levels were not described for any of the appraised measures. Bush and colleagues (2014) provided some information on the floor and ceiling effects of the RASS-PAL, but it was not sufficient to assess responsiveness.

### **Origin of items**

Scale items of just two measures for which evidence of psychometric performance was available, the KNMG and CSPC, were specifically developed for monitoring palliative care patients' level of consciousness (Goncalves et al., 2008; Royal Dutch Medical Association, 2009). For the RASS-PAL and Modified RASS, items of the original RASS were modified for use with palliative care patients prior to testing the tools in this population (Benitez-Rosario et al., 2013; Bush et al., 2014).

Items for the remaining four appraised measures originated from scales developed for non-palliative care patients. Specifically, aspects of the psychometric performance of the Dutch versions of the MSAT, VICS, RASS and GCS were appraised by study authors adopting the original items of these scales without assessing their appropriateness for the palliative care setting (Arevalo et al., 2012; Claessens et al., 2011, 2012, 2014).

### **Feasibility**

In a comparison for user-friendliness between the Dutch versions of the RASS and VICS, Arevalo et al. (2012) reported that most palliative care professionals found RASS the least time-consuming, clearest and easiest to use. Acceptable ratings were achieved for the MSAT, while the VICS was evaluated as the least clear and least easy to use among the three tools. The RASS-PAL (Bush et al., 2014), CSPC (Goncalves et al., 2008) and Modified RASS (Benitez-Rosario et al., 2013) were also regarded as feasible and useful tools by healthcare professionals. No information on feasibility was provided for the GCS (Claessens et al., 2011, 2012, 2014).

**Table 2.3:** Appraisal of psychometric performance of observational level of consciousness measures

Measure and studies	Number of participants	Content validity	Criterion validity	Structural validity	Construct validity	Homogeneity (internal consistency)	Inter-rater reliability	Intra-rater and/or Test-retest reliability	Responsiveness	Origin of items	Feasibility
Minnesota Sedation Assessment Tool (MSAT; Dutch version)  Arevalo et al. (2012)	n=54 No correction for multiple testing	Description of construct provided. No involvement of target population in item selection	Gold standard not available	NE / NR	Assessed per subscale  MSATa: Spearman's correlation coefficient ranged from 0.48 to 0.83 (mostly above 0.60)  MSATm: Spearman's correlation coefficient ranged from 0.42 to 0.61	NE / NR	Assessed per subscale	MSATa: ICC ranged from 0.59 (95% CI: 0.45–0.70) to 0.64 (95% CI: 0.46–0.77) depending on time difference between paired assessments  MSATm: ICC ranged from 0.01 (95% CI: -0.25–0.25) to 0.11 (95% CI: -0.09–0.29) depending on time difference between paired assessments  MSATq: Cohen's kappa ranged from 0.44 to 0.55 depending on time difference between paired assessments	NE / NR	NE / NR	Items originated from a scale developed for another population  Evaluated as clear and easy to use (when compared with the Dutch versions of RASS and VICS)
<b>Rating</b>	<b>1</b>	<b>1</b>	<b>-</b>	<b>-</b>	MSATa: <b>2</b> MSATm: <b>1</b>	<b>-</b>	MSATa: <b>1</b> MSATm: <b>0</b> MSATq: <b>0</b>	<b>-</b>	<b>-</b>	<b>0</b>	<b>2</b>

Continued overleaf

Measure and studies	Number of participants	Content validity	Criterion validity	Structural validity	Construct validity	Homogeneity (internal consistency)	Inter-rater reliability	Intra-rater and/or Test-retest reliability	Responsiveness	Origin of items	Feasibility
Vancouver Interaction and Calmness Scale (VICS; Dutch version)  Arevalo et al. (2012)	n=54 No correction for multiple testing	Description of construct provided. No involvement of target population in item selection	Gold standard not available	NE / NR	Assessed per subscale  VICSi: Spearman's correlation coefficient ranged from 0.31 to 0.72 (mostly above 0.40)  VICSs: Spearman's correlation coefficient ranged from 0.31 to 0.57 (mostly above 0.40)	NE / NR	Assessed per subscale  VICSi: ICC ranged from 0.77 (95% CI: 0.64–0.86) to 0.85 (95% CI: 0.73–0.92) depending on time difference between paired assessments  VICSs: ICC ranged from 0.12 (95% CI: -0.18–0.40) to 0.34 (95% CI: 0.10–0.52) depending on time difference between paired assessments	NE / NR	NE / NR	Items originated from a scale developed for another population	Evaluated as the least clear and easy to use (when compared with the Dutch versions of RASS and MSAT)
<b>Rating</b>	<b>1</b>	<b>1</b>	<b>-</b>	<b>-</b>	VICSi: <b>1</b> VICSs: <b>1</b>	<b>-</b>	VICSi: <b>2</b> VICSs: <b>0</b>	<b>-</b>	<b>-</b>	<b>0</b>	<b>1</b>
Richmond Agitation-Sedation Scale (RASS; Dutch version)  Arevalo et al. (2012)	n=54 No correction for multiple testing	Description of construct provided. No involvement of target population in item selection	Gold standard not available	NE / NR	Spearman's correlation coefficient ranged from 0.57 to 0.84	NE / NR	ICC ranged from 0.71 (95% CI: 0.60–0.79) to 0.73 (95% CI: 0.58–0.83) depending on time difference between paired assessments	NE / NR	NE / NR	Items originated from a scale developed for another population	Evaluated as the least time-consuming, clearest, and easiest to use (when compared with Dutch MSAT and VICS)
<b>Rating</b>	<b>1</b>	<b>1</b>	<b>-</b>	<b>-</b>	<b>2</b>	<b>-</b>	<b>1</b>	<b>-</b>	<b>-</b>	<b>0</b>	<b>2</b>

Continued overleaf



Measure and studies	Number of participants	Content validity	Criterion validity	Structural validity	Construct validity	Homogeneity (internal consistency)	Inter-rater reliability	Intra-rater and/or Test-retest reliability	Responsiveness	Origin of items	Feasibility
Sedation score proposed in the Guideline for Palliative Sedation of the Royal Dutch Medical Association (KNMG)  Arevalo et al. (2012)	n=54 No correction for multiple testing	Description of construct provided. No involvement of target population in item selection	Gold standard not available	NE / NR	Spearman's correlation coefficient ranged from 0.44 to 0.84	NE / NR	ICC ranged from 0.66 (95% CI: 0.54–0.76) to 0.71 (95% CI: 0.55–0.82) depending on time difference between paired assessments	NE / NR	NE / NR	Measure specifically developed for use with palliative care patients	NE / NR
<b>Rating</b>	<b>1</b>	<b>1</b>	<b>-</b>	<b>-</b>	<b>2</b>	<b>-</b>	<b>1</b>	<b>-</b>	<b>-</b>	<b>2</b>	<b>-</b>
Modified Richmond Agitation-Sedation Scale (RASS)  Benitez-Rosario et al. (2013)	n=156	Description of construct provided. Target population involved in item modification	Gold standard not available	NE / NR	Spearman's correlation coefficient ranged from 0.81 to 0.89 (p<0.001)	NE / NR	Weighted Cohen's kappa ranged from 0.85 (95% CI: 0.85–0.92) to 0.95 (95% CI: 0.91–0.98)	NE / NR	Not adequate information provided	Items modified for use with palliative care patients	Reported as a useful, manageable tool that could facilitate fluid communication among the PC team
<b>Rating</b>	<b>2</b>	<b>2</b>	<b>-</b>	<b>-</b>	<b>2</b>	<b>-</b>	<b>2</b>	<b>-</b>	<b>-</b>	<b>1</b>	<b>2</b>

Continued overleaf

Measure and studies	Number of participants	Content validity	Criterion validity	Structural validity	Construct validity	Homogeneity (internal consistency)	Inter-rater reliability	Intra-rater and/or Test-retest reliability	Responsiveness	Origin of items	Feasibility
Richmond Agitation-Sedation Scale - Palliative version (RASS-PAL)  Bush et al. (2014)	n=10 No correction for multiple testing	Description of construct provided. Target population involved in item modification	Gold standard not available	NE / NR	NE / NR	NE / NR	ICC ranged from 0.84 (95% CI: 0.56–0.95) to 0.98 (95% CI: 0.95–1.00)	NE / NR	NE / NR	Items modified for use with palliative care patients	Evaluated as easy to use, simple and brief
<b>Rating</b>	<b>0</b>	<b>2</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>2</b>	<b>-</b>	<b>-</b>	<b>1</b>	<b>2</b>
Glasgow Coma Scale (GCS; Dutch version)  Claessens et al. (2011, 2012, 2014)	n=266	Description of construct provided. No involvement of target population in item selection	Gold standard not available	NE / NR	NE / NR	NE / NR	ICC=0.81 (95% CI: 0.67–0.89; p=0.000)	NE / NR	NE / NR	Items originated from a scale developed for another population	NE / NR
<b>Rating</b>	<b>2</b>	<b>1</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>-</b>	<b>2</b>	<b>-</b>	<b>-</b>	<b>0</b>	<b>-</b>
Consciousness Scale for Palliative Care (CSPC)  Goncalves et al. (2008)	n=38 No correction for multiple testing	Description of construct provided. Target population involved in item selection	Gold standard not available	NE / NR	Spearman's correlation coefficient ranged from 0.88 to 0.98 (p<0.001)	Cronbach's $\alpha$ =0.99	ICC=0.99 (p<0.001)	NE / NR	NE / NR	Scale specifically developed for use with palliative care patients	Evaluated as easy to use and useful in clinical practice
<b>Rating</b>	<b>0</b>	<b>2</b>	<b>-</b>	<b>-</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>-</b>	<b>-</b>	<b>2</b>	<b>2</b>

NE: Not evaluated; NR: Not reported; MSAT: Minnesota Sedation Assessment Tool; MSATa: Minnesota Sedation Assessment Tool arousal subscale; MSATm: Minnesota Sedation Assessment Tool motor activity subscale; ICC: Intraclass Correlation Coefficient; VICS: Vancouver Interaction and Calmness Scale; VICSi: Vancouver Interaction and Calmness Scale interaction subscale; VICSs: Vancouver Interaction and Calmness Scale calmness subscale; RASS: Richmond Agitation-Sedation Scale; KNMG: Sedation score proposed in the Guideline for Palliative Sedation of the Royal Dutch Medical Association; RASS-PAL: Richmond Agitation-Sedation Scale - Palliative version; GCS: Glasgow Coma Scale; CSPC: Consciousness Scale for Palliative Care.

## 2.5 Discussion

### Key findings

A total of 65 studies reporting the use of 35 different level of consciousness tools were reviewed. Evidence of psychometric performance, however, was available for only 8 of these instruments. Of the identified tools, two were specifically developed for palliative care populations (the CSPC and KNMG) (Goncalves et al., 2008; Royal Dutch Medical Association, 2009), two constituted versions of an existing tool (i.e. the RASS) modified for use in palliative care (Benitez-Rosario et al., 2013; Bush et al., 2014), and four were measures developed for different populations, tested for aspects of validity and/or reliability in the palliative setting (Arevalo et al., 2012; Claessens et al., 2011, 2012, 2014). No tools had been evaluated for all relevant psychometric properties; hence none of the appraised measures had been fully validated in the palliative care population.

The majority of identified measures were either *ad hoc* tools for which no formal validation had been undertaken (n=17) or tools developed and validated mainly in non-palliative care settings (n=15). This widespread use of untested measures raises questions regarding the methodological robustness of studies and the quality of reported evidence (Hewlett, Hehir, & Kirwan, 2007). Moreover, when testing the psychometric performance of a measure the context is critical; so, although measures may have established psychometric performance in specific contexts, this does not transfer to different settings (Shilling, Matthews, Jenkins, & Fallowfield, 2016). It is therefore essential, as with any measures to be used in palliative care, that tools assessing level of consciousness should be thoroughly validated with palliative care patients in order to be certain that they provide a valid and reliable assessment of consciousness level for this population.

Most identified tools sought to measure consciousness in terms of wakefulness and, therefore, mostly comprised one item with a range of mutually exclusive scoring options (n=23). These usually involved observation of spontaneous activities, such as eye opening, or responses to auditory and/or tactile stimuli performed in a logical progression. Apart from consciousness, a small number of tools included the assessment of agitation, as a domain related to sedative and analgesic use, in a single scale (n=4). These tools have received criticism for various reasons including the lack of clarity in the definition of different consciousness levels and the poor

standardisation of employed stimuli (Goncalves et al., 2008; Williams et al., 2016). Furthermore, the assessment of patients presenting decreased consciousness and restlessness at the same time may be compromised when both conditions are evaluated on the same scale (De Jonghe et al., 2000; Williams et al., 2016). Nevertheless, the most commonly employed measure was the RASS or modified versions of it (n=17). An explanation for this may be that the RASS requires minimal training and can be quickly and easily administered at the bedside (Sessler et al., 2002). These are particularly desirable features for a scale intending to measure level of consciousness, an often unstable characteristic, in clinical environments where patients are looked after by professionals of different backgrounds, as in palliative care (Goncalves et al., 2008).

Limited information was available on the measurement properties of tools, thus making it difficult to draw definitive conclusions about their psychometric performance. Assessments of psychometric quality were based on evidence obtained from a single study, rather than a group of studies, for each measure. Some studies did not aim to specifically develop and/or validate level of consciousness measures (Arevalo et al., 2012; Claessens et al., 2011, 2012, 2014). As a result, these studies assessed only certain psychometric properties on each occasion, and no tools were tested across all measurement properties.

Information on inter-rater reliability and internal consistency was provided in all studies, with most tools performing adequately on both properties. Due to the lack of a “gold standard” level of consciousness measure in palliative care, criterion validity could not be assessed. Instead, in three studies tools were compared with other instruments known to measure level of consciousness (Arevalo et al., 2012; Benitez-Rosario et al., 2013; Goncalves et al., 2008). However, although the reported correlations between the assessed scales and other comparable measures were acceptable to high, the reference measures were not themselves tested for their psychometric performance in palliative care.

It is noteworthy that even though all studies described collecting data at more than one time point, no publications provided any information regarding test-retest or intra-rater reliability. This might be explained by the lack of stability of the construct measured. Palliative care patients often have fluctuating levels of consciousness, hampering the assessment of these psychometric properties.

The measures with the highest ratings for psychometric quality were the CSPC, a tool developed by Goncalves and colleagues (2008) to specifically measure level of consciousness in palliative

care, and a version of the RASS modified for use with palliative care patients (Benitez-Rosario et al., 2013). However, given that the only information available about the psychometric performance of either of these measures was restricted to that of initial validation studies and insufficient for the assessment of all appraised measurement properties, palliative care clinicians and researchers should use these tools with caution.

The findings of this review agree with those of previously published reviews. De Jonghe and colleagues (2000) reported that responsiveness had not been tested for any of the scales identified in their review of level of sedation instruments. De Jonghe et al. (2000) commented that responsiveness is an important measurement property as it can inform the titration, initiation, and withdrawal of sedative drugs. Likewise, there was insufficient evidence to appraise responsiveness in the present review. Future studies should address the testing of this psychometric property as, apart from the clinical benefits described by De Jonghe et al. (2000), a measure that can reliably detect changes in patients' level of consciousness over time may provide a useful outcome measure for palliative care research.

Brinkkemper and colleagues (2013) identified seven scales measuring level of awareness reported in primary studies. Of these, similar to the findings of the present review, a significant proportion were *ad hoc* measures and the RASS was the most commonly used of the established scales. Brinkkemper et al. (2013) found only one tool, the CCS (Morita, Tsunoda, et al., 2001), for which information on psychometric performance was available. Although the authors presented this information, they did not formally evaluate the psychometric quality of the CCS because this was outside the scope of their review. The CCS was also identified in the present review, however its psychometric quality was not appraised because the scale used for the assessment of consciousness level constitutes an individual item extracted from a compound measure for assessing the ability of terminally ill patients to communicate that was developed and tested as a whole. Hence, the psychometric evidence provided pertains to the CCS measure as a whole, not to its individual items.

Brinkkemper et al.'s (2013) review identified considerably fewer measures than the present review, because it was focused specifically on the effects of palliative sedation. The inclusion criteria for the review presented here were broader, allowing for the inclusion of studies reporting the use of observational measures regardless of the purpose for which these were employed. Moreover, an increasing number of studies using level of consciousness measures

have been published since the publication of Brinkkemper and colleagues' review in 2013. Of the 65 studies included in the present review, 26 (40%) have been published since 2013. A possible explanation for this upwards trend may be the recent publication of high impact guidelines recommending the use of observational measures for the monitoring of the level of consciousness of palliative care patients receiving sedative medication (Cherny & Radbruch, 2009; M. Dean et al., 2012).

### **Limitations**

Despite taking a systematic approach to locate relevant articles in this review, using six databases and a combination of subject headings and free-text terms, there may have been publications which were missed. The identification of ten additional publications meeting eligibility criteria through citation searching may be suggestive of this. Moreover, the exclusion of grey literature and non-English language publications may mean that studies providing evidence on measurement properties of translated versions of tools or those published outside the traditional academic channels were also missed. There is at least one validation study which was excluded from this review due to language restrictions (Imai, Morita, Mori, Yokomichi, & Fukuta, 2016).

Two reviewers (AMK, EM) independently performed the appraisal of the psychometric performance of identified measures against well-defined quality criteria. Nonetheless, comparability of evidence was hindered by the heterogeneity of studies reporting data on psychometric properties in terms of setting, sample size, participant population, study design and objectives, and of the purposes for which tools were employed on each occasion. In addition, for some of the included studies it was unclear whether certain psychometric properties were not tested or were just not reported. Where information on measurement properties was missing or inadequate, a rating was not given. This, in turn, affected the overall quality scores of measures. For these reasons, quality evaluation outcomes should be interpreted with caution, and palliative care clinicians and researchers should consider the individual characteristics of studies and measures when choosing between different level of consciousness tools.

A final limitation of this review stems from the limitations of the literature itself. Of the 65 studies reporting the use of level of consciousness measures, only 7 provided information on the psychometric performance of just 8 tools, while available psychometric evidence was restricted

to that of initial validation studies for each tool. Therefore, this review is ultimately limited by a paucity of evidence from which definitive conclusions can be drawn.

### **Implications for this doctoral project**

As discussed earlier in this chapter, one of the reasons for undertaking this review was to identify a suitable outcome measure for the exploratory study of BIS monitoring with palliative care patients conducted as part of this doctoral project. The CPRS (Goncalves et al., 2008) and Modified RASS (Benitez-Rosario et al., 2013) achieved the highest ratings for psychometric performance among the measures appraised. However, these measures were developed or modified and validated in languages other than English. Although both tools were translated by study authors into English, it is unclear whether robust translation processes were followed to ensure that translated versions are conceptually and linguistically equivalent to source measures (Acquadro et al., 2018). Given that poorly translated tools can introduce measurement bias and taking into account the considerable resources required for the adequate adaptation and translation of health outcome measures (Manchaiah et al., 2020), it was decided to choose an outcome measure that was developed in English and validated for use in English-speaking palliative care settings. Of the measures identified in this review, the RASS-PAL (Bush et al., 2014) was the only tool meeting these criteria. Moreover, the RASS-PAL scored highly on feasibility with palliative care health professionals regarding it as easy to use, simple and brief (Bush et al., 2014). For these reasons and in order to minimise the burden on clinical staff collecting research data, it was considered appropriate to use the RASS-PAL for the exploratory study of BIS monitoring (see Chapter 5).

## **2.6 Chapter summary**

This chapter has described the methodology and findings of the systematic review of observational level of consciousness measures undertaken as part of this doctoral project. The systematic review was conducted to identify, describe, and appraise the psychometric performance of observational level of consciousness measures used in palliative care. Sixty-five studies reporting the use of thirty-five different level of consciousness measures were reviewed. Of these studies, seven provided information on the psychometric performance of eight tools. All other studies used either *ad hoc* measures for which no formal validation had been

undertaken or established tools mainly developed and validated in non-palliative care settings. The CSPC and a modified version of the RASS received the highest ratings for psychometric performance. However, since psychometric evidence was limited to that of initial validation studies for each appraised measure, no tool could be assessed for all psychometric properties. Therefore, further evidence on the measurement properties of these tools is needed before they can be recommended as valid and reliable measures for use in palliative care practice and research.



## **Chapter 3 Patients' and relatives' perceptions regarding the potential use of Bispectral index technology in palliative care: Methodology**

### **3.1 Chapter outline**

Given the paucity of research on BIS monitoring in palliative care in the UK, it was considered appropriate to determine the acceptability in principle of BIS monitoring in this context before exploring its use in clinical practice. For this to be achieved, a qualitative study exploring the views and opinions of UK palliative care patients and their relatives about the potential use of BIS monitoring in palliative care was undertaken. The present chapter describes the research design and methodology of this study.

### **3.2 Study design, aim, and objectives**

This was a qualitative study using focus groups and semi-structured interviews with the aim of exploring the perceptions of palliative care patients, relatives of current patients, and bereaved relatives about the potential use of BIS technology in palliative care. Key research objectives were to: i) determine the acceptability in principle of BIS monitoring in the palliative care setting and ii) identify suggestions to inform the development and design of a subsequent study trialling BIS monitoring in clinical practice.

### **3.3 Study approvals**

The study protocol and research materials (see **Appendix 2**) were initially drafted and then refined and further developed based on feedback from members of the I-CAN-CARE Advisory Group. Ethical approval was obtained by the Camberwell St Giles Research Ethics Committee on 3<sup>rd</sup> June 2016 (reference number: 16/LO/0686). Following this, the study was approved by the Health Research Authority on 27<sup>th</sup> June 2016 (IRAS project ID: 199211).

### 3.4 Setting and participants

Participants were palliative care patients, relatives of current patients, and bereaved relatives recruited through the day therapy unit of Marie Curie hospice in Hampstead, London (MCHH). The day therapy unit offers symptom management, specialist rehabilitation, counselling, spiritual care, and bereavement support services for people diagnosed with terminal illnesses and their families/carers.

#### Eligibility criteria

Patients and relatives were eligible to take part in the study if they met the criteria outlined in **Table 3.1** below.

**Table 3.1:** Eligibility criteria for study participants

Inclusion criteria
<ul style="list-style-type: none"><li>• Adults (i.e. <math>\geq 18</math> years of age)</li><li>• People receiving palliative care OR Relatives of people currently receiving palliative care OR Relatives of people who had died under the care of a palliative care team four to twenty-two months prior to approach for participation</li><li>• People who are able to provide fully informed consent</li></ul>
Exclusion criteria
<ul style="list-style-type: none"><li>• People who cannot communicate verbally in English</li><li>• People for whom the nature and/or procedures of the study might be too distressing (as deemed by the attending clinical team)</li></ul>

#### Sample size

The target was to recruit 10–12 participants in each of the three participant groups: palliative care patients, current relatives, and bereaved relatives. Based on other qualitative research exploring the use of health technologies in palliative care (Allsop, Taylor, Bennett, & Bewick, 2019; Egoavil et al., 2017; Funderskov et al., 2019), it was expected that this sample size would

be adequate to achieve a comprehensive exploration of key themes across all participants and would also enable comparisons between participant groups.

### **Sampling strategy**

Potential study participants were identified via convenience sampling and snowballing. Convenience sampling is a type of non-random sampling where members of the target population that meet the required eligibility criteria are selected on the basis of their accessibility and/or proximity to the research (Jager, Putnick, & Bornstein, 2017; Robinson, 2014). Snowball sampling is another non-random sampling technique which is widely used in qualitative medical and social science research (Kirchherr & Charles, 2018; Noy, 2008). This sampling method relies on referrals made from initially sampled participants to others who share or are believed to possess characteristics that are of research interest (Biernacki & Waldorf, 1981; Johnson, 2005). Both sampling methods are affordable, efficient, and relatively straightforward to implement; thus, they can be particularly useful for pragmatic research that has limited resources, time, and workforce, such as the present study (Etikan, Musa, & Alkassim, 2016; Jager et al., 2017; Johnson, 2005). However, according to the hierarchy of qualitative research evidence proposed by Daly and colleagues (2007), studies using samples that are not purposively selected based on a well-developed conceptual framework (i.e. descriptive studies), can only demonstrate that a phenomenon exists in a defined group. Therefore, evidence from such studies are of limited generalisability and cannot provide a firm basis for policy or clinical practice (Daly et al., 2007).

In this study, patients and relatives of current patients were initially identified from those who were present at the hospice day therapy unit during the recruitment period and were approached for participation on a “first-come, first-served” basis (i.e. convenience sampling). After taking part in the study, patients and relatives were asked to identify other family members who met the inclusion criteria and might be willing to participate in this research (i.e. snowball sampling). The selection of bereaved relatives for participation was also based on practical criteria, such as willingness to participate, geographical proximity, and availability at the time of data collection.

### **3.5 Ethical considerations**

The hospice clinical team identified and initially approached people who they felt would be suitable and interested to participate. However, it was recognised that some participants might find the topic area difficult, and that the discussions might touch on some issues which some might find upsetting. At the beginning of each interview/focus group, therefore, participants were reassured that if, at any time, they wanted to take a break or withdraw from the discussion, they could do so without providing a reason. They were also assured that everything discussed would remain strictly confidential. Moreover, participants were informed that if they required further information, support, or advice during or following the research activity, they would be able to access the clinical team directly at that time. Participants were familiar with the clinical team because the interviews/focus groups were conducted in the same hospice from which themselves or their family members were receiving/had received palliative care and support services.

### **3.6 Participant recruitment and consent processes**

#### **Patients receiving palliative care**

Patients who attended the hospice day therapy unit during the recruitment period were screened for eligibility by the clinical team. Those who were deemed eligible were approached for participation by a member of the clinical team who described the study and provided patients with an information sheet. The information sheet contained detailed information about the study procedures and what participation would involve (**Appendix 2.1**). Patients who expressed interest in taking part in individual interviews/focus groups, were subsequently contacted by the researcher. At this stage, patients were given more information about the purpose and content of interviews/focus group discussions and had the opportunity to ask questions.

#### **Relatives of current patients**

Eligible relatives of current patients were either directly approached by a member of the hospice clinical team or, if referred by a family member who had previously participated in the study, were contacted by telephone to discuss participation. A study information leaflet was given to relatives in person at that stage or posted to them by the hospice team. Relatives who expressed

interest in participation were then contacted by the researcher who answered any study-related questions and provided a comprehensive description of the study.

### **Bereaved relatives**

Suitable bereaved relatives to be approached were identified through the hospice bereavement service and were sent invitation letters signed by the bereavement coordinator, enclosing the study information sheet. Bereaved relatives who were willing to participate in the study, were able to contact the researcher directly by responding to the invitation letter. As with the other two participant groups, the researcher then provided more information about the study and answered study-related questions. Invitation letters were initially posted to people who were between four and eleven months post-bereavement. This mirrored practice adopted in the VOICES national survey of bereaved people (UK Office of National Statistics, 2016). However, due to a low response rate, the upper time limit was later increased to 22 months.

All potential participants had at least 24 hours to consider participation. Those who agreed to take part were asked to sign a consent form prior to the commencement of data collection activities and were given a copy of the signed consent form to keep (**Appendix 2.2**).

## **3.7 Data collection**

Patients and relatives were given the option either to participate in a focus group or to be individually interviewed. This flexible approach to data collection was based on considerations regarding the logistical difficulties of scheduling group discussions (Guest, Namey, Taylor, Eley, & McKenna, 2017), especially given the often fluctuating health status of palliative care patients, and the potentially sensitive nature of the research topic.

Focus groups and individual interviews constitute the most commonly employed methods of data collection in qualitative healthcare research (P. Gill, Stewart, Treasure, & Chadwick, 2008). The purpose of individual research interviews is to collect detailed accounts of participants' views, attitudes and knowledge relating to a specific research question or phenomenon of interest (Lambert & Loiselle, 2008). Individual interviews are typically conducted one-to-one between a participant and a researcher (Frances, Coughlan, & Cronin, 2009; Namey, Guest, McKenna, & Chen, 2016). This interview format allows the researcher to focus attention on a single participant, their individual characteristics, and particular circumstances, so that in-depth

insights of the participant's personal thoughts, feelings and experiences can be obtained (Gaskell, 2000).

A focus group is a group interview method that gathers information on a defined topic of research interest through a moderated interaction among participants (P. Gill et al., 2008; Kingry, Tiedje, & Friedman, 1990; O.Nyumba, Wilson, Derrick, & Mukherjee, 2018). The size of a focus group is dependent on a number of theoretical and practical considerations including: the nature of the study, the complexity of the research topic, the number of questions asked, the diversity of group members, the facilitation skills of the researcher, and the duration of the focus group session (Morgan, 1997; Tang & Davis, 1995). For qualitative health research studies, a group size of four to twelve participants has been proposed to provide adequate numbers in order for a range of detailed accounts to be elicited whilst allowing all participants to contribute to the discussion (Kingry et al., 1990; Tang & Davis, 1995).

The distinctive characteristic of focus groups, which also constitutes the main advantage of this method, is the interaction that occurs between participants as well as between participants and the researcher who facilitates the discussion (Tausch & Menold, 2016; Wilkinson, 1998). These interactions enable participants to respond, query, and comment on one another's contributions (Willig, 2013). Thus, through the interactive and interpersonal nature of focus groups, rich data pertaining to both individual views and experiences, and to the extent of consensus and diversity among group participants, can be generated (Guest et al., 2017; Lambert & Loiselle, 2008; Morgan, 1996; Tausch & Menold, 2016). However, as group interaction involves mutual self-disclosure, focus groups may not be an appropriate method of data collection for all research questions and/or for all participants. Instead, individual interviews may be more appropriate for some participants especially when the research topic is sensitive (P. Gill et al., 2008; Morgan, 1996; Willig, 2013).

Individual interviews and focus groups were conducted with the aid of a topic guide adapted for use with each participant group (see **Appendix 2.3**). Topic guides consisted of an introductory section presenting the BIS technology to participants, and a series of open-ended questions and prompts designed to explore:

- Participants' knowledge and experiences of using sedative medication
- Their knowledge and experiences of the methods available for the monitoring of consciousness levels
- Their views and opinions about the potential use of BIS in palliative care, including the perceived advantages and disadvantages of BIS monitoring in this setting
- Participants' perceptions regarding the acceptable duration of BIS monitoring

At the beginning of each focus group/interview, participants were asked to complete a form which collected information on their socio-demographic characteristics. The following information was collected from all participants: age, gender, ethnicity, and employment status. Information on patients' functional status was also collected using the WHO performance status classification (World Health Organization, 1979). Bereaved relatives were additionally asked to record the time since their family member died.

### **3.8 Data handling and management**

In line with the NHS Code of Confidentiality (Department of Health, 2003), all participants chose a pseudonym for the purposes of data collection and analysis. These pseudonyms were used for the recorded interviews, forms of socio-demographic characteristics, and in interview transcripts. The only personal data kept were participants' names and signatures on copies of signed consent forms, and relatives' addresses for sharing research findings.

Collected data were handled and managed in compliance with the General Data Protection Regulation (GDPR) (European Parliament and Council of European Union, 2016) and the UCL Research Data Policy (Ayriss, 2013). Interviews/focus group discussions were audio-recorded on password-protected portable recording devices. Audio files were encrypted. Once data collection concluded, all audio files were transferred onto a password-protected university computer, where they were saved using the pseudonym chosen. After transfer onto the university computer, the audio files were deleted from the portable recorder. Following the transcribing of audio files and checking of transcripts for accuracy, the audio files were securely deleted from the university computer. Complete transcripts and participants' socio-demographic information were categorised and stored using QSR NVivo 11 software package (QSR International Pty Ltd, 2015).

### 3.9 Data analysis

Interview and focus group transcripts were analysed following the framework method. Framework analysis is a systematic and flexible approach for managing and analysing qualitative data that was first developed for applied policy research and is increasingly used in the context of qualitative health and medical research (Gale, Heath, Cameron, Rashid, & Redwood, 2013; Srivastava & Thomson, 2008).

Framework was deemed the most appropriate analysis method for a number of reasons. First, the framework approach is particularly suitable for pragmatic research that has a specific set of questions that need to be answered, a limited time frame and a pre-defined sample (Srivastava & Thomson, 2008); characteristics that are directly applicable to the present study. Second, the framework method is mostly appropriate for the thematic analysis of textual data, which is the type of data analysed in this research. Third, due to its lack of affiliation to a particular epistemological position, the framework method enables both the inductive and deductive analysis of data and generation of themes (Gale et al., 2013). In this study, a combined approach to analysis was adopted. Themes were primarily identified deductively from topics included in interview guides, with additional themes emerging inductively through an open coding process “grounded” in participants’ accounts (Pope, Ziebland, & Mays, 2000). This analytical approach was chosen so that, on the one hand, specific issues stemming from research questions could be explored, while on the other hand, unprompted aspects of participants’ experiences relating to the phenomenon under investigation could emerge.

A further advantage of the framework method is that it permits comparisons and associations to be made within as well as between individual cases or groups of cases (Ritchie & Spencer, 1994; Ritchie, Spencer, & O'Connor, 2013). This is particularly pertinent to the present study as data were collected from three participant groups and the analysis aimed to identify both themes unique to individual participants or participant groups, and common themes spanning across all participant groups. Finally, one of the key features of the framework approach is that it provides an audit trail of the analytical processes and of the interpretations made, permitting other researchers to review the process and judge the robustness of analysis (Gale et al., 2013; Ritchie & Spencer, 1994; Srivastava & Thomson, 2008).



Richie and Spencer (1994) describe five key stages for analysing qualitative data involved in the framework approach: familiarisation with data; identification of a framework; indexing; charting; and mapping and interpretation. These stages were broadly followed in this research. **Table 3.2** provides an outline of the activities undertaken for each stage of the analysis. Even though the analytical process may be presented as being a linear progression through a series of mutually exclusive stages, in practice it is an iterative process that involves constant movement across the different stages of analysis until a clear conceptual structure that provides a coherent account of the constructs explored emerges (Ritchie & Spencer, 1994; Ritchie et al., 2013).

In keeping with recommendations for conducting rigorous qualitative research (Abdul Hadi & Closs, 2015; Krefting, 1991; Noble & Smith, 2015), additional strategies were employed in this study to ensure the credibility of the analysis and enhance the trustworthiness of findings. After the initial analysis of transcripts, the emerging framework was discussed with one supervisor, Bella Vivat, a researcher with extensive experience in qualitative research in palliative care. Preliminary categories and emerging themes were reviewed and refined following discussion. Preliminary findings were also presented to the project Advisory Group to ensure that emergent categories and themes corresponded with participants' accounts.

Finally, acknowledging that the researcher influences and informs the research process (Willig, 2013), I sought to focus my attention on my own position within the research process and reflect upon the ways in which my own beliefs and past training may have influenced research findings. Through the analytical process specifically, I aimed to remain aware and critically reflect on any preconceived assumptions by revisiting the interview transcripts and actively considering alternative interpretations while reviewing the coding structure and hierarchy. By assuming this self-reflective stance, I endeavoured to ensure that the analysis accurately represented participants' perspectives and findings were derived from the data in a rigorous way.

**Table 3.2:** Activities undertaken for the analysis of interview/focus group data

Analytical stages	Activities undertaken
<b>1. Familiarisation</b>	<ul style="list-style-type: none"> <li>➤ A holistic overview of collected data was gained through:               <ul style="list-style-type: none"> <li>• Listening to audio-recordings</li> <li>• Transcribing interviews/focus group discussions</li> <li>• Repeated reading of transcripts</li> </ul> </li> <li>➤ Initial ideas, recurrent themes and patterns were recorded in memos</li> </ul>
<b>2. Identification of framework</b>	<ul style="list-style-type: none"> <li>➤ Transcripts and memos were imported to NVivo 11</li> <li>➤ A working framework was developed by reviewing one transcript from each participant group and coding relevant data into initial index categories</li> <li>➤ Index categories were created deductively from the topic guide and inductively through pertinent issues emerging directly from data</li> <li>➤ The framework was refined by making decisions regarding the relevance and importance of indexes, and where similarities were identified, indexes were grouped into broader categories</li> </ul>
<b>3. Indexing</b>	<ul style="list-style-type: none"> <li>➤ All remaining data were “indexed” into conceptual categories according to the thematic framework</li> <li>➤ New codes and categories were developed until constructs of interest were adequately explored</li> <li>➤ The framework was further refined and some categories were removed or subsumed within others allowing the development of higher level categories and themes</li> </ul>
<b>4. Charting</b>	<ul style="list-style-type: none"> <li>➤ A matrix was generated using NVivo 11 and data were “charted” into the matrix:               <ul style="list-style-type: none"> <li>• Each case was represented by a row</li> <li>• Cases were ordered by participant group</li> <li>• Core themes/categories were represented by different columns</li> <li>• Data from each case were summarised by categories/themes</li> <li>• Illustrative quotations were included in the matrix</li> </ul> </li> </ul>
<b>5. Mapping and interpretation</b>	<ul style="list-style-type: none"> <li>➤ Connections and relationships between data were explored by:               <ul style="list-style-type: none"> <li>• Reviewing the matrix and researcher’s memos</li> <li>• Comparing and contrasting data within and between individual participants, participant groups, and categories/themes</li> </ul> </li> <li>➤ Hierarchical structure of themes and categories was redesigned to reflect emergent relationships</li> <li>➤ A concept map of relationships between core themes and higher-level categories was created to guide the interpretation process</li> </ul>

### **3.10 Chapter summary**

This chapter has described the methodology of the qualitative study exploring the perceptions of patients, relatives of current patients, and bereaved relatives regarding the potential use of BIS technology in palliative care. Participants were recruited from the day therapy unit of MCHH using convenience sampling and snowballing. Qualitative data were collected by means of individual semi-structured interviews and focus groups. Interview and focus group transcripts were analysed in line with the five key stages of the framework method, and several additional strategies were employed to ensure the robustness of analysis and trustworthiness of findings.

## **Chapter 4 Patients' and relatives' perceptions regarding the potential use of Bispectral index technology in palliative care: Results**

### **4.1 Chapter outline**

This chapter presents the results of the qualitative study exploring the potential use of BIS technology in palliative care. It discusses the recruitment processes, participant characteristics, and presents findings from the analysis of interviews and focus groups.

### **4.2 Recruitment of study participants**

#### **Patients receiving palliative care**

Overall, 21 patients attending the day therapy unit of MCHH were approached for participation, first by hospice clinicians and subsequently by the researcher. Of these, 18 expressed willingness to take part in a focus group or an individual interview. Of the three patients who refused, one gave lack of interest in the research topic as their reason for refusing. The other two did not volunteer a reason. Eight of the eighteen patients who agreed to participate did not take part because their conditions/symptoms deteriorated subsequent to being initially approached. Ten patients eventually participated, therefore.

#### **Relatives of current patients**

Eight relatives of current palliative care patients were contacted for participation. Of these, seven were identified and initially approached by hospice clinicians and one was referred by a patient who had previously participated in a focus group discussion. The low number of relatives approached by clinicians reflected the overall low number of relatives who attended the day therapy unit during the recruitment period. Three of the approached relatives, refused to take part in the study because of the required time investment associated with participation. These relatives felt that due to their full-time caring responsibilities, it was not feasible to allocate time for participation. Of the five relatives who agreed to participation, one became ineligible due to

their family member dying between the time of approach and participation, resulting in four relatives of current patients participating in the study.

#### **Bereaved relatives**

A total of 206 bereaved relatives were sent participant invitation letters about the study. Of these, 13 relatives responded by sending their contact information to the researcher (response rate: 6.3%). Eleven out of the thirteen who responded, took part in either a focus group or an interview. The other two relatives did not respond again following further contact.

### **4.3 Participant characteristics**

**Table 4.1** provides an overview of study participants' characteristics by participant group.

#### **Patients receiving palliative care**

Of the ten patients who participated in focus groups/interviews, six were men and four were women. Four patients were between the ages of 45 and 64, four were between the ages of 65 and 74, and two were 75 years old or older. Most patient participants were White British/Northern Irish (7/10), and had a performance status score of 2 ("symptomatic but up and about more than 50% of waking hours"; 3/10) or 3 ("symptomatic and in a chair or in bed for greater than 50% of the day"; 4/10). Two patients had a performance status score of 4 ("completely disabled") at the time of participation and used a wheelchair to attend the interview/focus group.

#### **Relatives of current patients**

Two male and two female relatives of current patients took part in the study. They were either the spouses/partners (2/4) or adult children (2/4) of patients receiving palliative care services at the participating hospice. Two relatives were between the ages of 55 and 64, one was between the ages of 35 and 44, and one relative was 75 years old or more. Three relatives were White (British or other), and one self-defined as British Pakistani.

#### **Bereaved relatives**

The majority of bereaved relatives who took part in focus groups/interviews were women (8/11), White British/Northern Irish (8/11), and were 65 years old or more (6/11). There were four

spouses/partners, four adult children, and three siblings of palliative care patients who had died six to twenty-two months prior to the time of study participation.

**Table 4.1:** Characteristics of interview/focus group participants

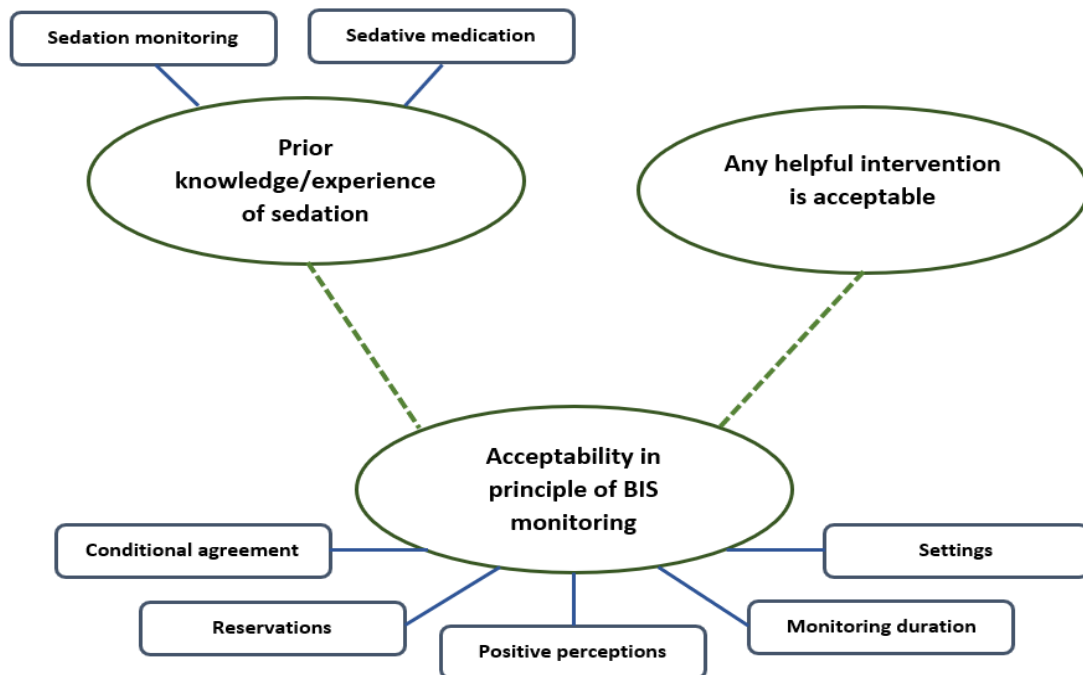
Characteristics	Patients (n=10)	Current patient relatives (n=4)	Bereaved relatives (n=11)
<b>Age group (years)</b>			
35–44	–	1	–
45–54	2	–	5
55–64	2	2	–
65–74	4	–	4
75+	2	1	2
<b>Gender</b>			
Female	4	2	8
Male	6	2	3
<b>Ethnic Group*</b>			
White English/ Welsh/ Scottish/ Northern Irish/ British	7	1	8
Any other White background	3	2	3
Asian/ Asian British Pakistani	–	1	–
<b>Performance status**</b>			
0: Fully active	–	–	–
1: Restricted in strenuous activity but ambulatory	1	–	–
2: Symptomatic, <50% in bed during the day	3	–	–
3: Symptomatic, >50% in bed, but not bedbound	4	–	–
4: Completely disabled	2	–	–
<b>Relationship to patient</b>			
Spouse/Partner	–	2	4
Adult child	–	2	4
Sibling	–	–	3
<b>Time since family member passed away</b>			
6–12 months	–	–	5
12–18 months	–	–	4
18–22 months	–	–	2

\*Ethnic group categories as recommended by the Office for National Statistics (2015), \*\*WHO performance status classification (World Health Organization, 1979).

#### 4.4 Framework analysis of focus group and interview transcripts

Semi-structured interviews and focus groups were conducted between February and December 2017. In total, 3 individual interviews (with 1 current and 2 bereaved relatives), and 7 focus groups with 22 participants: 10 patients (3 groups), 3 current relatives (1 group) and 9 bereaved relatives (3 groups), were held. All focus groups and all but one interviews took place in private rooms at MCHH. The other interview was held at UCL. The duration of focus groups was between 55 and 82 minutes. The three individual interviews lasted 42, 43 and 46 minutes.

The analysis of focus group and interview transcripts identified three main themes: (1) prior knowledge and experience of sedation, (2) any helpful intervention is acceptable, and (3) acceptability in principle of BIS monitoring. Themes 1 and 3 were developed deductively from the topic guide framework. Theme 2 was identified through inductive analysis of participant data. **Figure 4.1** below presents the main themes, subthemes, and their relationships. To aid comparison, patient, current relative, and bereaved relative views are discussed side by side throughout the following sections. Patient quotes are presented in blue, current relative quotes in purple, and bereaved relative quotes are presented in brown.



**Figure 4.1:** Main themes and subthemes

### **Prior knowledge and experience of sedation**

During each focus group/interview patient and relative participants were prompted to share their knowledge, views, and/or experiences of using medication with sedative effects and of the methods available to assess depth of sedation or level of consciousness.

### **Knowledge and/or experience of sedative medication**

Almost all participants had either personally received medication with sedating effects in or outside palliative care or observed friends or relatives who had. Their perceptions about sedative medication were mixed. Some had negative views, mainly expressing that sedative medication had been ineffective to adequately control their symptoms while having distressing side effects.

I didn't really find the sedatives sedating, they didn't make me sleep at all, kept me awake if anything... I don't know if those sorts of things help necessarily if you're agitated about dying, I'm not sure if taking such medication is helpful. (Maria, patient)

I got very confused and I basically didn't like what I was feeling. I just didn't feel in control and I couldn't sleep at night. It [*medication*] was making me feel very drowsy but I wasn't actually able to sleep. (Kathy, patient)

In contrast, other participants reported having benefitted from using sedatives and described experiencing reduced anxiety and fear after taking such medication.

I've had sedation and it was perfectly pleasant. I was extremely relaxed, and it took any kind of fear away. (Ellie, bereaved relative)

One bereaved relative specifically commented on the positive effects of sedative medication both for the patient and their carers:

The important thing about sedation, is that it reduces the anxiety in both the patient and the carer. (Matthew, bereaved relative)



### **Knowledge and/or experience of sedation monitoring methods**

Although most participants had knowledge and/or personal experience of the use of sedative medication, most had no knowledge or experience of how depth of sedation/level of consciousness is monitored. Only a few mentioned clinical observation and responding to verbal stimulation as monitoring methods.

Every time they [*clinical staff*] came in the room they wrote things down. They'd come in, have a look, and give her a bit more, if it was needed. (Pauline, bereaved relative)

In my wife's case, they came in and they would ask her "Can you hear me?" and that's how it went. They'd see if she responded and her general behaviour, and they kept her calm to the very time that she died. (Charles, bereaved relative)

### **Any helpful intervention is acceptable**

Participants' generally positive disposition towards medical/technological interventions in palliative care was an unprompted theme which emerged directly from participants' accounts. In particular, many participants stated that "anything" that could help patients to become more comfortable at the end of life would be acceptable.

I mean from a personal point of view, anything that a clinician can use to help me at end of life to be comfortable... Going from the state of health I'm in now to the state I'll be in at the end, it's this journey, if you like... If it's an unpleasant journey, anything that helps to make it a pleasant one is to be desired. (Archie, patient)

I think my mum would have said "Yes, do anything you need to do", she would say "Just hook me up to anything". I think she would have just welcomed anything that could have helped her. (Pauline, bereaved relative)

## Acceptability in principle of BIS monitoring in palliative care

The acceptability in principle of BIS monitoring in the palliative care setting was the principal topic of discussions held with palliative care patients, their relatives, and bereaved relatives and, therefore, generated the most subthemes and categories (see **Table 4.2**). Chief subthemes are discussed in the sections below. As shown in **Figure 4.1**, the two themes presented previously, participants' prior knowledge/experiences of sedation and their overall attitude towards medical/technological interventions in palliative care, appeared to influence patients' and relatives' perceptions of BIS, including its acceptability in principle in palliative care.

**Table 4.2:** Acceptability in principle of BIS monitoring: subthemes and categories

Acceptability in principle of BIS monitoring
<b>1. Positive perceptions</b>
<ul style="list-style-type: none"><li>• Potential advantages</li><li>• Non-invasive</li><li>• Acceptable appearance of sensor/monitor</li></ul>
<b>2. Conditional agreement</b>
<ul style="list-style-type: none"><li>• As long as patient and/or family involved in decision to use BIS</li><li>• As long as it is clinically useful</li><li>• As long as it is used as an addition to usual care</li></ul>
<b>3. Reservations</b>
<ul style="list-style-type: none"><li>• Medicalisation of care and/or death</li><li>• Appearance of sensor</li><li>• Skin irritation</li></ul>
<b>4. Monitoring duration</b>
<ul style="list-style-type: none"><li>• As long as necessary</li><li>• As long as not causing distress to patient</li><li>• Intermittent use – Until appropriate doses of medication established</li><li>• Continuous use – Until the end of life</li></ul>
<b>5. Settings</b>
<ul style="list-style-type: none"><li>• Acceptable across all settings</li><li>• Home use</li></ul>

## Positive perceptions

Most participants expressed that they would be willing to use BIS technology, if it was offered to them or a family member after receiving sedative medication in a palliative care setting. Their positive attitude towards BIS monitoring stemmed from its perceived potential benefits to patient care and from viewing BIS as a non-invasive intervention.

Patients and relatives in this study mostly saw BIS as a potentially useful means for clinical teams to provide personalised patient care. They felt that the information obtained from BIS monitoring could enable the systematic assessment and monitoring of patients' consciousness levels and, therefore, aid the adjustment of medication according to each patient's individual needs.

Primarily it's actually information for the [clinical] teams themselves. I mean, to me, it would be interesting because we are having to do so much by guesswork at the moment. I have a feeling that Mum thankfully has a lot less pain now than she might have had a few weeks ago. So, I've asked the question of "Can we try slightly less medication?". It seems to be something that the monitoring system would be able to provide perhaps a more accurate way of understanding what level of sedation she's at and whether that's appropriate for what her needs are at the time. (Liz, current patient relative)

Relating to the use of BIS information for the titration of sedative medication, participants additionally commented that BIS information might assist clinicians to ensure patient comfort, and possibly improve it. This was considered one of the main potential benefits of incorporating BIS into clinical practice, especially for people who were no longer able to communicate and might be experiencing pain at the end of their lives.

I hope they start using it in practice and you know, save a lot of people's suffering [at the] end of their life. Because [at the] end of our life [it] doesn't matter who I know, who comes to visit me or anything... [We are] all probably ourselves, we won't be able to say how much the pain [is]. Once we can't talk... this machine will communicate between we [sic] and the professional person. It seems to me there's a technology there helping professional people how to comfort us. (Sheba, patient)

I think also with palliative care, from my understanding, the feeling is really about keeping patients or getting patients to an acceptable level of comfort. So, to my mind, you know, there would be a lot of benefit in something that is a bit more factual perhaps, in getting to understand how one person who might not be able to say anything but actually might need some need some help, some more medication. So, I think on that sort of, understanding what palliative care is all about, it seems to have a good relevance. It seems to be something that would be helpful in achieving that goal. (Liz, current patient relative)

Another perceived benefit, specifically emphasised by relatives of current and previous patients, was that BIS could provide continuous monitoring of patients' level of consciousness, which would not be feasible through physical observation alone. In particular, these participants expressed that if BIS had been part of patient care they would have felt relieved and reassured that their family member's needs were being met and that they were comfortable.

In my experience I think the nurses, if you're in a hospital, they're so busy, you know... If people can't be physically monitored 24 hours a day, I think it might be reassuring to know "Oh well, they've got the monitor and they are being checked on and they are comfortable". (David, bereaved relative)

I'd feel relieved to know there was something that was just keeping an eye on what's going on, if it's a monitor and you can record the data over the day or however... someone comes in and checks it and says "Oh, hold on, this is what we need to be aware". That'd be really worthwhile, just another way of things being watched and monitored. (Liz, current patient relative)

Most participants felt that, unlike other medical interventions, BIS was non-invasive. This was an important factor in perceiving BIS as acceptable in palliative care. Some participants explicitly said that the intrusion caused by the monitor would be minimal, comparing it to wearable technological devices.

It's not invasive so I have no problems with it whatsoever. If it was invasive, like sticking a needle in your arm or a bit like a cannula, I might get a different answer but it's not invasive. It's just stuck to your skin, it's almost like wearing your, what they call now, smart watch. (Archie, patient)

I mean I don't want her end of life cluttered with wires and stuff, but such monitoring devices are very common. I have this fitness watch and if I wear it overnight, I can then open my phone and see how many hours I've slept, how many hours were deep sleep, how many times I got up. If I wear it, I get this information so it's an incentive. But if I don't wear it, maybe it's slightly more comfortable not to have a watch on, but then I don't have the information. I think this is the way of the future, we're just gonna get a lot more information on ourselves and our spouses. So, this is a very minor intrusion. (Bob, current patient relative)

Patients and relatives in this study mostly considered that the appearance of BIS monitor and sensor was acceptable. They described the monitor and sensor as being small or discreet, and, therefore, unlikely to be noticeable to patients or visitors.

The monitor seems quite discreet really and the strip is pretty small. Once it's been put in place, I don't imagine they [*patients*] would be aware of it, you would probably not notice it. (Ellie, bereaved relative)

I think it's a fairly subtle design... I mean I've got no issue with the appearance itself and if it [*sensor*] was something that someone was wearing, it wouldn't be notable at all. (Liz, current patient relative)

### **Conditional agreement to BIS use**

Some participants expressed that using BIS in palliative care would be acceptable as long as certain conditions were met. These mostly related to the clinical usefulness of the technology, its role in complementing usual care and practice, and patients' or families' consent to its use.

At the beginning of each interview/focus group, the researcher presented BIS to participants and explained that only a small number of studies had explored its use in palliative care. Building on this, participants said that if further evidence indicated that BIS monitoring was beneficial to patients, they would have no objections to its use.

I mean, as long as there's a medical advantage, I just can't see any reason to not use it. (David, bereaved relative)

I think the research needs to be done obviously first and [*find out*] if it does have an effect and whether it's a beneficial effect. If it proves to be beneficial, yeah, I'm all for it. (Bobbie, bereaved relative)

Patient and relative participants mostly viewed BIS as an adjunct to existing clinical practice, rather than a standalone intervention. They particularly emphasised that BIS should be used as an additional tool to supplement, rather than replace, clinical observation and decision-making.

If it's [*BIS*] a tool to aid the care but it's not the only thing, then I think that's fine... If it's used as a guide, as a tool, as an extra, then fine. But there's nothing that beats, you know, somebody walking into a room and going "Oh goodness, I think we need to do something here". (Liz, current patient relative)

I mean they should be able to use it as a guide alongside everything else. Their experience in end-of-life care, their experience of the process of dying, if you like, all the rest of it. But it's a guide, as long as they don't depend on it, that's fine. (Archie, patient)

Participants also felt that patients should be informed of the option to receive BIS monitoring, have its potential benefits explained by clinical teams, and consent to its use, ideally before entering the final stage of life. Alternatively, if patients were unable to consent, family members should be consulted on whether BIS should be included in their care.

I think with all of this, it's all good... but it's important to let the patient choose as much as possible, like before they get into a state of being unconscious, to make sure you've had this conversation and that they're aware of these things. And you can ask the patient "If it comes to the point where you are not conscious, would you like to be monitored?". It should really be up to the patient, and if the patient can't decide, then possibly the family. (Maria, patient)

I think it [*BIS monitoring*] would have to be done with consent. Perhaps before they got to a level where they weren't able to sort of express their feelings. (Bobbie, bereaved relative)

## Reservations

Despite the generally positive comments about the potentially beneficial role of BIS in supporting usual care and practice, patients and relatives in this study also expressed reservations about its use in palliative care. These reservations mainly pertained to the employment of medical/technological interventions at the end of life, the appearance of BIS sensor, and the possibility for skin irritation to be caused by the sensor.

A few participants expressed that the incorporation of BIS into the care of patients who enter the dying trajectory would be opposed to their understanding of hospice care which is associated with minimal intervention at the end of life. These participants felt that, similar to other medical interventions, BIS use could increase the medicalisation of the dying process and so take away from a more “peaceful” end-of-life experience.

Obviously, I'm not against technology. I just would like it to be as calm and peaceful as possible. And I think that, on the whole, that's what hospices are really good at, they're good at pain management, they're good at making you comfortable, they're good at letting you alone and so I wouldn't want anything more than the kind of basic minimum. (Julie, bereaved relative)

I think there's always this image in mind to try and make dying as comfortable as possible and somehow that's a bit separate... a slight step away from that, the vision of having a nice, peaceful end of life. (Rob, patient)

Some patient and relative participants, distinct from the views of others (see subtheme on positive perceptions), felt that the application of the BIS sensor on patients' foreheads made BIS more overt and noticeable than other monitoring methods. A few expressed that from an aesthetic point of view, the sensor could be more “sophisticated” or suggested that it could be covered with accessories such as caps or made to look “prettier” with decoration.

I've worked with these brain things, they never look very good, you'd hope that it gets something a little bit, you know, cool... so it looks cool... doesn't look as if you're putting an electrode on someone's head. There's always a bit of a horror about that kind of thing. So, maybe something slightly more sophisticated might look better. (Rob, patient)

I wonder if there's something you could sort of make that it's not so obvious? Maybe like a cap or something so that it doesn't look like this... Maybe you could make it look prettier, put some flowers on them [sensors], but it's very clever. (Pauline, bereaved relative)

The possibility of the BIS sensor causing skin irritation was another concern voiced by a few patient and relative participants. They specifically said that given the skin sensitivity commonly experienced by palliative care patients, the BIS sensor could cause skin irritation and increase the risk of tissue breakdown in the area of the forehead where it is applied.

The one concern I have is often with patients and particularly palliative care cancer, skin breakdown is seen. And that is something that my mum is suffering from badly at the moment. So, I mean, the actual sort of adhesiveness of it, I'm thinking that it might cause further deterioration or further problems. That would be my one concern. (Liz, current patient relative)

Although some participants expressed reservations about BIS monitoring, none were negatively disposed overall towards it, and none raised objections to its potential use in palliative care. Their concerns related to particular aspects of BIS and how it might be implemented in palliative care settings.

### **Monitoring duration**

Considering how long the BIS monitor could be used for, patients and relatives in this study felt that the duration of BIS monitoring should be informed by the stability and severity of patients' symptoms. Some participants expressed that BIS should be used for "as long as necessary", provided that patients were not distressed by having it attached.

It's difficult to come up with a sort of uniform answer for this [monitoring duration]. I think that it depends on each patient's symptoms, how bad they are, if they fluctuate at all and so on... But, generally, I would say that it needs to be used for as long as necessary for every patient which is sort of individual to how they are on that given time... and obviously if they get distressed by it or anything, it should be taken off. (Bob, current patient relative)



There were various opinions regarding monitoring endpoint and preferred approach to BIS use. Some participants preferred the idea of continuous monitoring until the very end of life, while others thought it would be better to use BIS intermittently. The latter group suggested attaching BIS when patients' condition changed and maintaining it until patients had been rendered comfortable.

As soon as the person is starting to receive sedation right up until possibly the day they die because you've got then a whole picture in front of you of what's actually happening... I would say, that would give you the most valuable feedback. (Bobbie, bereaved relative)

I can't see it being necessary to sort of have it on permanently. If you're on it for a day for instance, while they're [clinicians] determining what your dosage needs to be... Once they've made a decision as to what dosages you need to keep you comfortable, you wouldn't need that on anymore unless something changes and then you can be back on it for them to decide again the dosages. (Archie, patient)

## Settings

Regarding the settings where BIS could be used, the majority of participants felt that BIS monitoring would be acceptable in all settings where people receive palliative care. Some expressed that BIS would be particularly useful for home care patients mainly looked after by informal carers who do not have a clinical training. In this setting, BIS could guide the administration of medication, if clinical support was available and home carers were trained in using the technology and interpreting BIS readings.

I think it should be used everywhere. If it works and it helps people, then... I mean, it's not, it's not a big bit of kit, is it? Plug it in and strap it on. It's not a large device, so yeah, use it at home, use it here [hospice], use it in the hospitals, use it where you can. (David, bereaved relative)

At home, I think to help district nurses or to anybody that's caring for somebody that's able to administer medication, I think it would be invaluable, yes. To know, especially in those like last few weeks, am I giving too much, too little, you know, what's a good rate? But without any of the monitoring on... nobody's gonna know, so I'm all for it. (Bobbie, bereaved relative)

## **4.5 Chapter summary**

The findings presented in this chapter provide an insight into patients' and relatives' perspectives on the potential use of BIS technology in palliative care. Ten palliative care patients, four current patient relatives, and eleven bereaved relatives recruited from the day therapy unit of MCHH participated in individual interviews or focus group discussions held between February and December 2017.

Study participants generally considered that BIS technology would be acceptable, in principle, for monitoring patients' consciousness level in the palliative care setting. Overall, BIS was perceived as a potential non-intrusive means of assisting clinical assessment and decision-making at the end of life which could possibly improve patient care and comfort. Despite expressing some reservations, participants were willing to trial BIS monitoring, as long as patients and/or relatives would be involved in decisions about its use and BIS would be an addition to, rather than a replacement of, usual care practices.

Given the favourable views of patients and relatives in this study about the possible use of BIS in palliative care, it was considered appropriate to proceed to the next step of the doctoral project; the evaluation of the acceptability, feasibility, and preliminary clinical usefulness of BIS monitoring in palliative care clinical practice.

## **Chapter 5 Exploratory study of Bispectral index monitoring with hospice inpatients: Methodology**

### **5.1 Chapter outline**

This chapter describes the methodology employed in the exploratory study of BIS monitoring with hospice inpatients. The following sections provide an overview of the study design and the recruitment, consent, and data collection processes. The chapter concludes with a description of the data analysis plan and criteria used for the assessment of research outcomes.

### **5.2 Study aim and objectives**

A prospective exploratory study was conducted aiming to trial the use of BIS monitoring in a sample of adult hospice inpatients in London, England. Primary research objectives were to investigate the: i) acceptability in practice, ii) feasibility, and iii) preliminary clinical usefulness of BIS monitoring in hospice inpatients. Secondary objectives were to explore the: i) use of BIS as a measure of pain detection, ii) relationship between BIS readings and clinician-reported pain and alertness measures, iii) inter-rater reliability of RASS-PAL and convergent validity of clinician-rated RASS-PAL and alertness NRS, and iv) the relationship between researcher-reported and other outcome measures.

### **5.3 Study approvals**

The study protocol and research materials (**Appendix 3**) were reviewed and approved by the project Advisory Group, and by the UCLH/UCL Joint Research Office. Sponsorship was obtained on 17<sup>th</sup> July 2017 (Reference number: 17/0179). An application for ethical approval was submitted to the Camden and King's Cross Research Ethics Committee on 8<sup>th</sup> August 2017 and a favourable opinion was given on 6<sup>th</sup> October 2017 (Reference number: 17/LO/1430). One of the two service user representatives on the project Advisory Group was particularly involved in the application for ethical approval and, along with myself and principal supervisor (Paddy Stone), attended the meeting of the Research Ethics Committee that considered the

application. The study was also registered with UCL Data Protection Office (Reference number: Z6364106/2017/05/93).

## 5.4 Setting and participants

Participants were recruited from the inpatient unit of MCHH between November 2017 and November 2018. The MCHH is a specialist hospice offering inpatient, outpatient, and day care services to adults with life-limiting conditions. The inpatient unit of the hospice is comprised of two wards with a capacity of sixteen beds each, providing symptom control, respite, rehabilitation, and terminal care services.

### Eligibility criteria

Participant eligibility criteria were based on methodological, ethical and pragmatic considerations. In particular, eligibility criteria were identified to ensure the suitability of study participants to address research questions, while minimising the potential for exposure to avoidable risks, and taking into account the available resources for recruitment and data collection. All hospice inpatients were considered potential participants. The attending clinical team determined which patients were eligible for participation according to the criteria outlined in **Table 5.1** below.

**Table 5.1:** Inclusion and exclusion criteria for study participation

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>Adults (i.e. <math>\geq 18</math> years of age)</li> <li>Hospice inpatients</li> </ul>	<ul style="list-style-type: none"> <li>Patients unable to understand English</li> <li>Patients for whom study procedures might be too distressing (as deemed by the attending clinical team)</li> </ul>
<ul style="list-style-type: none"> <li>Patients able to communicate in English</li> </ul>	<ul style="list-style-type: none"> <li>Patients who are too unwell at the time of screening (as deemed by the attending clinical team)</li> </ul>
<ul style="list-style-type: none"> <li>Patients able to provide fully informed consent</li> </ul>	

## 5.5 Research design and procedures

### Study phases and consent process

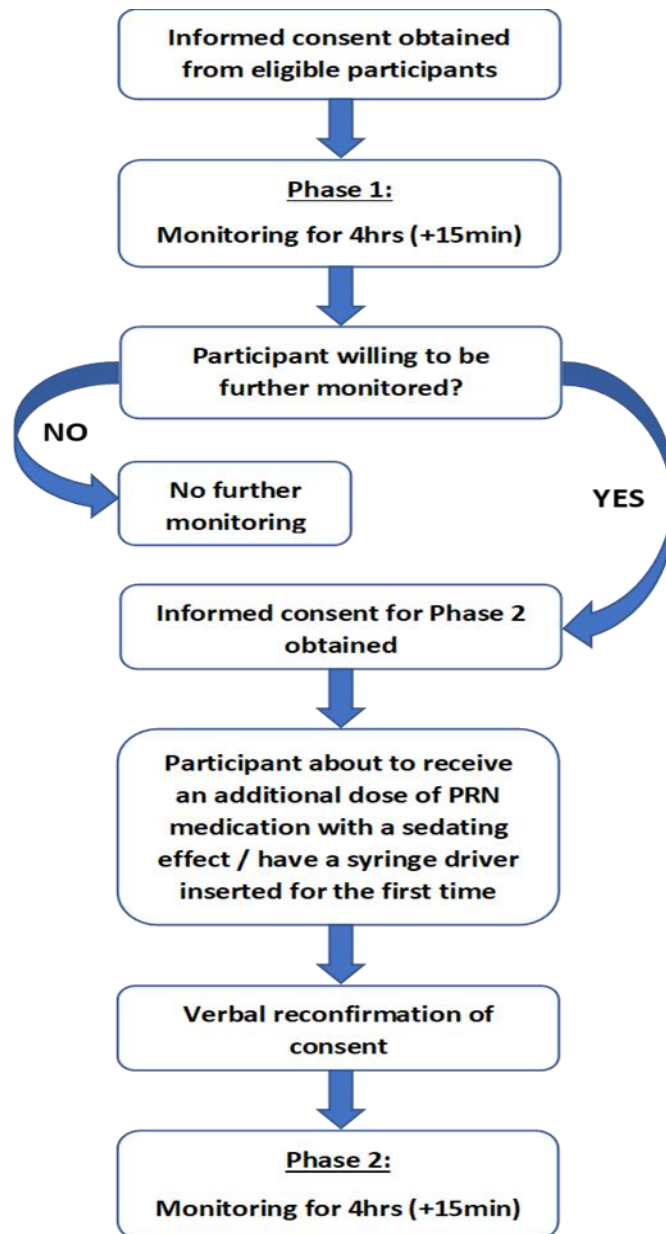
As discussed in the previous chapter, preliminary qualitative work found that patient and relative participants considered the need for informed consent to be an important aspect of the acceptability of using BIS in palliative care clinical practice. Furthermore, the MORECare guidance recommends that consent should be regarded as a continuous process in order to adequately capture potential changes in an individual's attitude and ability to participation (Gysels et al., 2013). Therefore, a staged approach to data collection and patient consent was employed in this study.

The study involved two phases and separate informed consent was sought for each phase (see **Figure 5.1**). Eligible patients who provided informed consent entered Phase 1 initially. During this phase, patients were monitored with BIS for four hours (plus an additional 15 minutes, if required). They also completed hourly self-report measures to record their level of pain and alertness using 11-point Numerical Rating Scales (NRSs). Matching observational measures were obtained by staff and by the researcher. All patients who took part in Phase 1 were considered eligible for Phase 2. After Phase 1 was completed, participants were approached for consent to be part of Phase 2.

Phase 1 allowed for the acceptability of BIS monitoring to be evaluated by patients and enabled comparisons between patient scores, BIS values, and researcher and clinician ratings. Patients who participated in Phase 1 were able to provide feedback on their experience of using the BIS monitor and to complete outcome measures. Having had an experience of using BIS, patients were given the option to decide whether they would be willing to be further monitored (as part of Phase 2).

The purpose of Phase 2 was to examine the ability of BIS to capture changes in patients' levels of consciousness following the administration of medication with sedative effects. Phase 2 began when and if, as part of their routine care, participants were given an additional dose of "as required" (*pro re nata*; PRN) medication with sedative effects/side-effects or received sedative medication via a syringe driver for the first time. Patients who consented to participate in Phase 2 but did not receive any additional doses of sedative medication, were not enrolled. Just before the relevant medication was administered to participants, they were asked to

verbally reconfirm their consent to be further monitored. Those who agreed, had the BIS monitor reattached for a second period of four hours (plus 15 minutes, if required) and the same data collection procedures as in Phase 1 were followed. Since patients who agreed to participate in Phase 2 could receive sedative medication at any time after providing consent, it was unpredictable how long the gap between Phase 1 and Phase 2 would be.



**Figure 5.1:** Study phases and consent process

## Capacity assessment

Only patients who were able to provide informed consent were approached for participation. If any potential participant's capacity was in doubt, an attending clinician would carry out a four-point capacity test (see **Table 5.2** below) and document the answers on the Royal College of General Practitioners' Mental Capacity Act toolkit for adults in England and Wales (Royal College of General Practitioners, 2011). The same procedure would be followed in all cases where capacity of consented patients was in doubt before entering the study monitoring phases.

**Table 5.2:** Four-point capacity test (Royal College of General Practitioners, 2011)

Communicate (C)	Can the person communicate their decision?
Understand (U)	Can they understand the information given to them?
Retain (R)	Can they retain the information given to them?
Balance (B)	Can they balance, weigh up or use the information?

### Patients with fluctuating capacity

If consented patients were found to be lacking capacity before entering Phase 1, they would be withdrawn from the study. Participation of patients who had consented to take part in Phase 2, but who subsequently lost capacity to verbally re-consent to data collection, was managed in accordance with section 32 of the Mental Capacity Act (Department of Health, 2005). The Act states that the input of a consultee must be sought for decisions regarding participation in a research project when patients lack capacity. In this study, every effort was made for a personal consultee (an individual not acting in a professional or paid capacity) to be identified and involved in the consent process. All Phase 2 patients were asked to nominate a person to act as a consultee in case they lost capacity prior to the commencement of data collection activities.

If a patient was unable to identify a personal consultee or the personal consultee was unable to provide advice on the participant's continuation in the study, a member of staff who was not involved in the patient's care and who was willing to undertake this role would be

nominated. Members of staff who acted as consultees would not be otherwise involved in the study.

If a participant should lose capacity after providing written consent, but prior to starting data collection, the personal/nominated consultee would be contacted to discuss the details of the study and their role as a consultee. If the consultee agreed to undertake the role, a detailed information leaflet would be provided. If the consultee was present at the hospice at the time when their advice regarding a patient's continuation in the study was sought, they would be asked to provide written evidence of their agreement (i.e. a signed "agreement" form). In cases where the consultee was not present at the hospice, they would be contacted by telephone to seek advice. Verbal agreement would initially be deemed sufficient to allow the patient to be further monitored. In these circumstances, an "assent" form would be posted to the consultee to be signed and returned within two weeks of the patient entering Phase 2. If no signed "assent" form was received within this time frame, then the patient would be withdrawn from the study.

### **Ethical considerations**

This research raised several ethical issues. Appropriate strategies were developed to identify, minimise, and manage potential risks.

It was recognised that patients or relatives might become distressed by the use of BIS. However, previously published studies where the same monitor was used with palliative care patients reported positive experiences for both patients and relatives (see Chapter 1) (Barbato et al., 2017; Masman et al., 2016; Monreal-Carrillo et al., 2017). Moreover, findings from the preceding qualitative study, indicated that patients at the same hospice and their relatives had mostly favourable views about the potential use of BIS (see Chapter 4). Nonetheless, in order to minimise any potential upset, the involvement of service user representatives at the design stage of the study was sought. Furthermore, before being approached about the study, patients were screened by the palliative care team and when clinical staff deemed that involvement in the study could cause emotional distress then such patients were not approached. If any patients were to become upset during their participation in the study, appropriate support from palliative care clinical services, including onward referral to counselling or psychological support services, was in place.



Study participants were required to have a 12 cm sensor strip attached on an area between the middle of the forehead and the temple. The BIS sensor was not expected to be painful to attach or detach, there was however potential for skin irritation to occur due to the self-adhesive of the contact pads (Pousman, Eilers, Johns, & Jung, 2002). Participants were informed of this risk in the information sheet and were verbally reminded of this when approached for participation. In addition, the period of BIS monitoring was kept to four hours (+15 minutes) to minimise the risk of skin irritation due to prolonged use (Pousman et al., 2002). If, however, participants' skin was to become irritated following the application of the BIS sensor, the sensor would be removed, and patients would receive appropriate care from clinical staff.

It is recognised that time is precious to patients with a terminal illness (Casarett & Karlawish, 2000), so patient-researcher contact was kept to a minimum, and the outcome measures employed were chosen on the basis of being brief and simple to complete. The total contact time for obtaining research data was approximately 30 minutes.

### **Sample size**

This was an exploratory study and no previous studies evaluating the use of BIS with conscious palliative care inpatients were available. Thus, it was not appropriate to conduct a sample size calculation (Jones, Carley, & Harrison, 2003). Instead, an estimated sample size of 100 patients was determined on pragmatic grounds by taking into account the following considerations: i) the admission rate to the hospice (estimated by hospice's senior clinicians to be 2–3 patients/day), ii) the previously documented challenges of participant recruitment and retention in this setting (Chaiviboontham, 2011; McMillan & Weitzner, 2003; Stone et al., 2013), and iii) the available time (12 months) and resources (one researcher) for recruitment and data collection.

## **5.6 Participant recruitment**

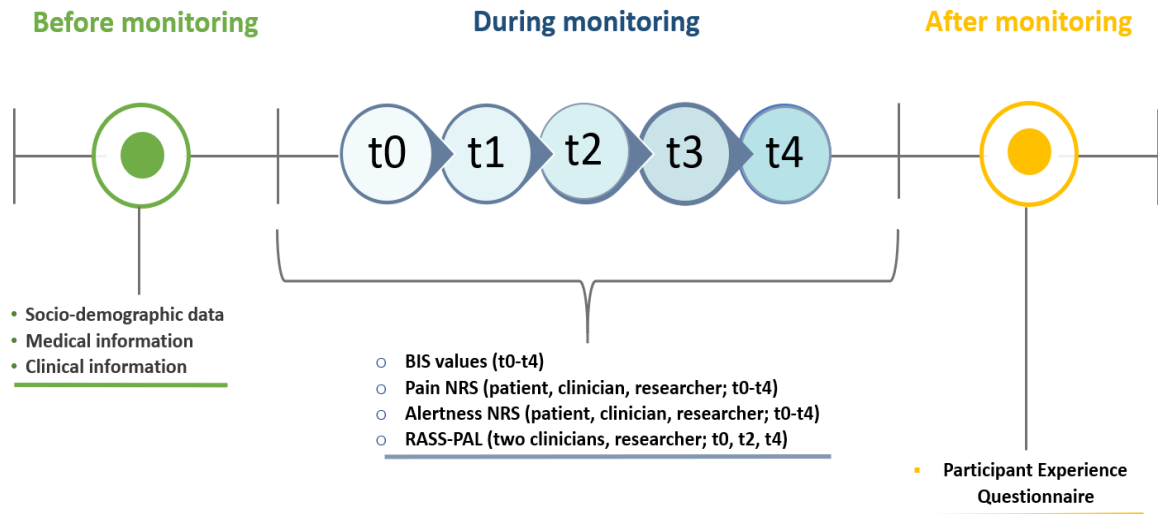
The recruitment strategy was designed to minimise the risk that patients would feel obligated to participate. Participants had at least 24 hours to consider their participation and to ask additional questions before providing written informed consent. Eligible patients were initially approached by a member of the hospice clinical team. Staff briefly explained the study and provided patients with a short information sheet (**Appendix 3.1**). If patients expressed interest

in participating in the study, a meeting with the researcher was arranged and family members/members of the patient's circle of support were encouraged to attend. At this meeting, the study was explained further and a more detailed information sheet was provided (**Appendix 3.2**). Potential participants were informed that, if they decided to participate, they could withdraw their consent at any time and that withdrawal of consent or refusal to participate would not affect their clinical care. The possibility of participating in Phase 2 and/or in a subsequent one-off, semi-structured interview focusing on participants' experiences of BIS monitoring (see Chapters 7–8) was also discussed at this meeting. It was explained that, at that stage, patients were only being asked to consider taking part in the first phase of monitoring and could decide if they would like to participate in either of the additional research activities after the end of Phase 1. If, after at least 24 hours, patients expressed willingness to participate, they were asked to provide written informed consent (**Appendix 3.3**).

Patients who had consented arranged with the researcher an appropriate time for the monitoring to take place. The monitoring could commence soon after patients had consented to take part in the study and no later than three days after consent had been obtained. At the end of Phase 1, those participants who had indicated that they would be willing to consider being monitored again were given a separate information sheet about Phase 2 (**Appendix 3.4**) and had at least a further 24 hours to consider their decision.

## **5.7 Data collection**

Three types of data were collected: i) recruitment data, ii) participant assessment data, and iii) monitoring completion information. **Figure 5.2** illustrates the data collection process for participant assessments. The same assessment schedule was employed for both monitoring phases.



**Figure 5.2:** Data collection process for each monitoring phase

### Recruitment data

Information about all admissions to the hospice was entered onto a screening log and patients' progress through the different stages of the recruitment process was tracked. For each potential participant the following information was recorded: 1) whether the patient was eligible for participation, 2) whether they had been approached by a member of the clinical team, 3) whether they had agreed to speak to the researcher, 4) whether they consented to participation. Reasons for ineligibility, non-approach and non-participation, where volunteered and relevant, were documented at each stage.

### Assessment data

#### Socio-demographic and medical information

Socio-demographic and medical data: age, gender, ethnicity, primary diagnosis and comorbidities, were extracted from participants' medical records. Ethnicity was classified according to the categories recommended by the Office for National Statistics (Office for National Statistics, 2015). Primary diagnoses were coded according to a list of conditions commonly requiring palliative care compiled for the purposes of this study (Connor & Sepulveda, 2014; Franks et al., 2000; Holloway et al., 2014; Traue & Ross, 2005) (see **Table 5.3**).

**Table 5.3:** Common diagnoses in palliative care

• Cancer	• Dementia	• Chronic liver disease
• Chronic respiratory disease	• Parkinson disease	• Multiple sclerosis
• Cardiovascular disease	• HIV/AIDS	• Rheumatoid arthritis
• Diabetes	• Motor neurone disease	• Other
• Kidney Failure	• Acute stroke	

### Medication use

A record of concomitant medication was kept, which included times, doses and routes of administration, and whether medication was administered regularly or PRN. If PRN medication with sedative effects was administered during the study monitoring periods, clinicians were asked to record the reasons for administration from a list of common indications (see **Table 5.4**). Common indications were identified through the literature review of palliative sedation guidelines (discussed in Chapter 1) and those reported by Vivat et al. (2019).

Medications that were considered to have a sedative effect are shown in **Table 5.5**. This list was compiled on the basis of the same literature review and the properties of commonly used palliative care medications (National Institute for Health and Care Excellence, 2017; Twycross, Wilcock, & Howard, 2017). Of note, this list included drugs such as opioids and anti-muscarinics, which are not primarily used for sedation, but which nonetheless have sedative effects.

**Table 5.4:** Indications for the administration of medication with sedative effects

• Agitation	• Discomfort	• Sleeping difficulties
• Restlessness	• Anxiety	• Nausea and/or vomiting
• Confusion	• Breathing difficulties	• Convulsions
• Pain	• Chest secretions	• Other

**Table 5.5:** Medication with sedative effects/side-effects relevant to the study

<b>Anaesthetics</b>	<ul style="list-style-type: none"><li>• Propofol</li></ul>
<b>Antimuscarinics</b>	<ul style="list-style-type: none"><li>• Glycopyrronium bromide</li><li>• Hyoscine hydrobromide</li></ul>
<b>Barbiturates</b>	<ul style="list-style-type: none"><li>• Pentobarbital</li><li>• Phenobarbital</li><li>• Thiopental</li></ul>
<b>Benzodiazepines</b>	<ul style="list-style-type: none"><li>• Alprazolam</li><li>• Chlordiazepoxide</li><li>• Clobazam</li><li>• Clonazepam</li><li>• Diazepam</li><li>• Loprazolam</li><li>• Lorazepam</li><li>• Midazolam</li><li>• Nitrazepam</li><li>• Oxazepam</li><li>• Temazepam</li></ul>
<b>Neuroleptics/Antipsychotics</b>	<ul style="list-style-type: none"><li>• Chlorpromazine</li><li>• Haloperidol</li><li>• Levomepromazine/Methotrimeprazine</li></ul>
<b>Non-benzodiazepine hypnotics and sedatives</b>	<ul style="list-style-type: none"><li>• Clomethiazole</li><li>• Dexmedetomidine</li><li>• Melatonin</li><li>• Meprobamate</li><li>• Zolpidem tartare</li><li>• Zopiclone</li></ul>
<b>Opioids</b>	<ul style="list-style-type: none"><li>• Alfentanil</li><li>• Buprenorphine</li><li>• Diamorphine</li><li>• Fentanyl</li><li>• Methadone</li><li>• Morphine</li><li>• Oxycodone</li><li>• Tapentadol</li><li>• Tramadol</li></ul>
<b>Sedating antihistamines</b>	<ul style="list-style-type: none"><li>• Chlorphenamine</li><li>• Cinnarizine</li><li>• Clemastine</li><li>• Hydroxyzine</li><li>• Ketotifen</li><li>• Promethazine</li></ul>

## **Clinical information**

Prior to each monitoring phase, in order to characterise the study population, clinicians were asked to record each participant's performance status and to estimate their prognosis using the Palliative Performance Scale version 2 (Anderson, Downing, Hill, Casorso, & Lerch, 1996) and a Clinician Prediction of Survival.

### **Palliative Performance Scale version 2 (PPSv2)**

The PPS is a modification of the Karnofsky Performance Scale (Karnofsky, Abelmann, Craver, & Burchenal, 1948). It measures the performance status of palliative care patients through the assessment of five functional dimensions: ambulation, activity level and evidence of disease, self-care, oral intake, and level of consciousness. PPS scores are divided into 11 levels from 0% (death) to 100% (no evidence of disease), in 10% increments, with higher levels representing better functional status (Anderson et al., 1996). Since its development, the PPS has been translated into several languages and it is currently used in various palliative care settings across different countries (Downing et al., 2007; Ho, Lau, Downing, & Lesperance, 2008).

### **Clinician Prediction of Survival (CPS)**

Clinicians provided estimates of patients' expected survival by choosing from pre-specified time frames: "days" (0–13 days), "weeks" (14–55 days), or "months+" (56 days or more). This is the most prevalent method for the estimation of prognosis in palliative care (Glare, 2005; Hui, 2015).

## **Patient-reported pain and alertness**

During each monitoring period patients rated their level of pain and alertness using two 11-point Numerical Rating Scales (NRSs). The pain NRS ranged from 0 (no pain) to 10 (worst possible pain). Similarly, the alertness NRS ranged from 0 (very drowsy) to 10 (very alert). The NRSs were completed at five time points at hourly intervals [t0=baseline; t1=1 hour ( $\pm 15$  min); t2=2 hours ( $\pm 15$  min); t3=3 hours ( $\pm 15$  min); t4=4 hours ( $\pm 15$  min)].

NRSs were chosen to measure pain and alertness for several reasons. NRSs are quick and easy to complete (Iohom, 2006) and, therefore, minimise the research burden on study participants. They are sensitive to change (Williamson & Hoggart, 2005) and were, therefore, regarded as being more appropriate for use in this study in which repeated measures were required over a short period of time. NRSs are widely used in health services across the UK (British Pain Society,

2019; Schofield, 2018) and are extensively used within palliative care (Hjermstad et al., 2008; Wade et al., 2017), most notably as part of the Edmonton Symptom Assessment Schedule (ESAS) (Bruera et al., 1991; Hui & Bruera, 2017). Alternative patient-reported pain and alertness measures, such as the Brief Pain Inventory (Cleeland & Ryan, 1994) or the Toronto Hospital Alertness Test (C. M. Shapiro et al., 2006), were considered unsuitable for this study because, although better validated, they were felt to be too burdensome to use repeatedly and were less likely to respond to changes in patients' condition on an hour-to-hour basis.

## **Observational assessments of pain and alertness**

### **Numerical Rating Scales (NRSs)**

To enable direct comparisons with patient scores, a member of the clinical team and the researcher also independently scored the two NRSs based on their observations of patients' levels of pain and alertness at five time points (t0 to t4). The researcher and clinicians were blinded to participants' ratings and BIS values at the time of scoring.

### **Richmond Agitation-Sedation Scale – Palliative version (RASS-PAL)**

The RASS-PAL (Bush et al., 2014) was employed for assessing patients' level of consciousness. RASS-PAL is a modified version of a well-validated instrument, the RASS (Sessler et al., 2002), specifically developed for palliative care populations. It identifies and evaluates sedation and agitation levels on a 10-point scale consisting of four levels for agitation (ranging from +1 to +4), one level to represent an alert and calm state (0), and five levels of sedation assessed by patients' responses to stimulation of increasing intensity (ranging from -1 to -5) (see **Figure 5.3**).

RASS-PAL was one of the observational measures of level of consciousness identified by the systematic review described in Chapter 2 (Krooupa, Vivat, McKeever, Marcus, et al., 2020). It is a more reliable way of recording level of consciousness than using an NRS, but it relies on completion by a trained observer and is not suitable for self-assessment. Moreover, although relatively quick to complete, it was deemed to be too burdensome to ask clinicians to complete the measure on five separate occasions. For this reason, it was only recorded at baseline, after two hours and at study completion (i.e. t0, t2, t4). The researcher also scored the RASS-PAL at the same time points.

Since one of the study's secondary objectives was to evaluate the inter-rater reliability of this measure, RASS-PAL was simultaneously, but independently, completed by two members of the clinical team, where possible. All health care professionals involved in the rating of outcome measures received an educational session on the administration and scoring of instruments before the study commenced to ensure consistency of data collection.

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff (e.g. throwing items); +/- attempting to get out of bed or chair	
+3	Very agitated	Pulls or removes lines (e.g. IV/SQ/Oxygen tubing) or catheter(s); aggressive, +/- attempting to get out of bed or chair	
+2	Agitated	Frequent non-purposeful movement, +/- attempting to get out of bed or chair	
+1	Restless	Occasional non-purposeful movement, but movements not aggressive or vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to <i>voice (10 seconds or longer)</i>	} Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to <i>voice (less than 10 seconds)</i>	
-3	Moderate sedation	Any movement (eye or body) or eye opening to <i>voice (but no eye contact)</i>	
-4	Deep sedation	No response to voice, but any movement (eye or body) or eye opening to <i>stimulation by light touch</i>	} Gentle Physical Stimulation
-5	Not rousable	No response to <i>voice or stimulation by light touch</i>	

**Figure 5.3:** Richmond Agitation-Sedation Scale – Palliative version (RASS-PAL; adapted from Bush at al., 2014)



### **BIS monitoring information**

BIS readings were recorded continuously throughout the four hours of monitoring. In addition, SQI and EMG values were recorded. At the end of each monitoring period, data were downloaded and transferred to a password-protected laptop. The minute-by-minute output was used to obtain BIS, SQI, and EMG values for each data collection time point (t0 to t4) and to acquire readings for the full four-hour monitoring period for each participant. The time for which the BIS monitor was used was also recorded. This included any times at which BIS was paused or detached, and the reasons for this.

### **Participant experience questionnaires**

At the end of each monitoring period, participants from both phases, irrespective of the extent of monitoring achieved, completed a short questionnaire about their experiences of using BIS (see **Appendix 3.5**). The questionnaires comprised six primary and two follow-up close-ended questions and participants were able to choose the answer that best described their opinion/experience from pre-specified options. The follow-up questions (questions three and five) were designed to elicit more detailed responses on issues previously identified by respondents. Hence, these were only answered by respondents who had positively indicated the presence of relevant issues in previous questions. For these questions, respondents were able to select more than one response from the options provided. The questionnaire was common to both study phases, apart from the last question, which asked participants to indicate their willingness either to be further monitored as part of the study (Phase 1) or to participate in potential future research with BIS (Phase 2).

### **Monitoring completion data**

Completion rates and reasons for early termination of monitoring were documented. When monitoring stopped before the pre-specified endpoint (i.e. t4), the reasons for this and the time when monitoring was stopped was recorded. Reasons for non-completion were categorised according to whether early termination was requested by patients or it occurred for other reasons. A list of potential reasons for early monitoring termination was generated prior to data collection to enable systematic documentation (see **Table 5.6**).

**Table 5.6:** Reasons for early monitoring termination

<b>Patient-initiated early termination</b>	<ul style="list-style-type: none"><li>• Patient in distressing pain and/or fatigue</li><li>• Monitor-related reasons (e.g. restriction of movement, BIS sensor)</li><li>• Study-related procedures/activities (e.g. questionnaires, researcher’s presence)</li><li>• No reason volunteered</li><li>• Other reason(s)</li></ul>
<b>Other reasons</b>	<ul style="list-style-type: none"><li>• Patient died</li><li>• Patient lost capacity</li><li>• Patient too unwell (as deemed by the clinical team)</li><li>• Study procedures too distressing (as deemed by the clinical team)</li><li>• Other reason(s)</li></ul>

## 5.8 Data handling and management

All data collected were handled in accordance with the General Data Protection Regulation (GDPR) (European Parliament and Council of European Union, 2016) and UCL Research Data Policy (Ayriss, 2013). Only the clinical team reviewed potential participants’ personal data. The researcher did not have access to patients’ medical records until participants provided signed informed consent. Once data collection concluded, all paper-based data were securely stored in a locked cabinet in the Division of Psychiatry, UCL. Participants’ consent forms were stored separately from other study documentation. In line with UCL Research Data Policy (Ayriss, 2013), all participant data will be retained for 10 years.

Data were initially collected in the form of two types of paper-based records; a screening log for all inpatients (regardless of whether or not they were recruited) and case report forms for all study participants. The screening log provided a unique study identifier for each participant. This study number was used on the case report form together with the patient’s initials and date of birth. Case report forms were thus pseudo-anonymised. Case report forms included all data collected for each patient. During data collection, the screening log and case report forms were stored in a secure cabinet at the recruitment site.

When data collection ended, data from the screening log and case report forms were fully anonymised before being transferred to a password-protected university desktop and stored on a UCL networked drive. Only members of the research team had access to the electronic database. Patient identifiers and details of personal consultees (where provided) were not

transferred from the paper log to the electronic database; hence, it was impossible to link data to identifiable individual patients.

## **5.9 Data checking, input, and analysis**

Paper-based socio-demographic and medical data were checked against patients' medical records for accuracy at the end of each monitoring period. Data from research logs and case report forms were entered into an Excel spreadsheet. All electronic data were checked for accuracy against paper records twice: once after entry and once after the spreadsheet was complete, but prior to the start of analyses.

The data analysis plan was created after discussion with PhD supervisors and in consultation with Federico Ricciardi, a statistician based in the Marie Curie Palliative Care Research Department. I performed all statistical analyses using IBM Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp., 2016). However, where more complex analyses were required, the statistician conducted the same analyses independently, and both sets of results were compared to ensure their accuracy.

### **Missing data**

Due to the nature of the participant population and the practical difficulties of conducting research in a busy clinical environment, it was recognised that it might not be feasible to apply strict time frames to data collection periods. Therefore, a 15-minute grace period either side of the scheduled assessment points was permitted for data collection. This 15-minute "window" was also applied for the collection of all other data (clinician- and researcher-rated observational measures, and BIS values). For these latter data, the reference point was the time at which the patients completed their own self-assessments. In this way, the data collection periods were defined by the time at which the patient-rated outcome measures were recorded rather than at strict hourly intervals. This approach was adopted to ensure that, when comparing data obtained from different sources, there would be a time lag of no more than 15 minutes on each occasion. Data falling outside the allowed 15-minute time frame were treated as missing for the purposes of analyses. On those occasions when patients did not complete self-assessment measures (to act as a reference point), the data collection time points were defined by the timings of clinicians' scores.

The reliability of BIS readings was assessed by using SQI and EMG values (see Chapter 1). In line with other research (Bhargava et al., 2004; J. M. LeBlanc et al., 2006; Musialowicz et al., 2010), SQI values >50 and EMG values <50 dB were adopted as cut-off points for assessing the reliability of BIS readings in this study. BIS values which were judged not reliable by this standard were removed from the data set prior to analysis.

The proportion of missing data for all variables included in analyses was calculated. Missing data were handled through pairwise deletion (available case analysis), a method that uses only values that are present in statistical testing by separately eliminating pairs of values for which at least one value is missing (Kang, 2013).

## **Description of sample**

### **Socio-demographic, medical, and clinical information**

Descriptive statistics were used to summarise the characteristics of the study population. Described characteristics comprised socio-demographic, medical and clinical information (i.e. age, gender, ethnicity, principal diagnosis, presence of comorbidities, functional status, prognosis). Categorical and binary variables were presented as frequency counts and relative frequencies.

In keeping with recommendations for assessing the normality of continuous variables (Ghasemi & Zahediasl, 2012), both histograms and the Shapiro-Wilk test (S. S. Shapiro & Wilk, 1965), a normality test based on the correlation between given observations and associated normal scores (Das & Imon, 2016), were employed to explore whether data were normally distributed. Continuous variables that were approximately normally distributed were presented as means and standard deviations (SD). For non-normally distributed continuous variables, medians and inter-quartile ranges (IQR) were used.

### **Medication use**

The total number and percentage of participants receiving regular or PRN medication with sedative effects at the time of assessment was calculated. For each drug, median doses and IQRs were recorded. Indications for administration of PRN medication with sedative effects were recorded and summarised using frequency counts.

Opioid doses were converted to equi-analgesic doses of oral morphine. Given the lack of consensus in the existing literature on appropriate methods and equivalence ratios for opioid conversion (Rennick et al., 2016; Shaheen, Walsh, Lasheen, Davis, & Lagman, 2009), the Palliative Care Formulary (Twycross et al., 2017), British National Formulary (National Institute for Health and Care Excellence, 2017) and Royal College of Anaesthetists (2017) recommendations for opioid conversion were reviewed to identify acceptable equi-analgesic ratios. **Table 5.7** presents opioid conversions employed in this study. The calculation of total daily opioid use included oral, subcutaneous, intramuscular, intravenous, and transdermal opioid medications.

**Table 5.7:** Equivalent opioid doses

Opioid (route)	Equivalent dose to 10mg oral morphine
Alfentanil (subcutaneous)	0.3
Diamorphine (intramuscular, intravenous, subcutaneous)	3
Methadone (oral)	1
Methadone (subcutaneous)	0.5
Morphine (intramuscular, intravenous, subcutaneous)	5
Oxycodone (oral, intravenous, subcutaneous)	5
Tapentadol (oral)	25
Tramadol (oral)	100
Equivalent dose to oral morphine(mg/day)	
Fentanyl 12mcg/hour patch (transdermal)	30
Fentanyl 25mcg/hour patch (transdermal)	60
Fentanyl 50mcg/hour patch (transdermal)	120
Buprenorphine 5mcg/hour patch (transdermal)	12
Buprenorphine 10mcg/hour patch(transdermal)	24
Buprenorphine 52.5mcg/hour patch (transdermal)	126

### Description of outcome data

Outcome data were checked for normality and were subsequently summarised using means and SDs or medians and IQRs depending on whether they were normally distributed or not. Outcome data comprised:

- BIS values
- Patient-reported pain NRS and alertness NRS scores
- Clinician-reported pain NRS, alertness NRS, and RASS-PAL scores
- Researcher-reported pain NRS, alertness NRS, and RASS-PAL scores

### **Assessment of study outcomes**

*A priori* criteria were employed for the assessment of study outcomes which were directly linked to research objectives. Since no other studies had previously investigated the use of BIS in this population, there were no precedents to guide the development of assessment criteria. Where relevant information was available, criteria were informed by the outcomes of other research with a similar focus (Barbato et al., 2018; Barbato et al., 2017; Masman et al., 2016; Monreal-Carrillo et al., 2017). The data sets, assessment criteria and methods of analyses used for addressing each of the study objectives are presented in the sections below. A summary of this information is provided in **Table 5.8**.

**Table 5.8:** Overview of data analysis plan

Objective	Data set	Analysis method	Assessment criteria
<b>Primary objectives</b>			
1. BIS acceptability in practice	<ul style="list-style-type: none"> <li>• Participant experience questionnaires</li> <li>➢ Qualitative interview data (patients, relatives, clinicians) *</li> </ul>	<ul style="list-style-type: none"> <li>• Relative frequencies</li> <li>➢ Framework analysis *</li> </ul>	<ul style="list-style-type: none"> <li>• Percentage of patients reporting no/minor discomfort from BIS sensor <math>\geq 80\%</math></li> <li>• Percentage of patients having a good overall experience of BIS monitoring <math>\geq 80\%</math></li> <li>• Percentage of patients having no issues or concerns about having BIS sensor attached <math>\geq 80\%</math></li> <li>• Percentage of patients willing to be monitored again as part of Phase 2 <math>\geq 80\%</math></li> <li>• Percentage of patients willing to participate in potential future research with BIS <math>\geq 80\%</math></li> </ul>
2. BIS feasibility	<ul style="list-style-type: none"> <li>• Recruitment data</li> <li>• Monitoring completion data</li> </ul>	<ul style="list-style-type: none"> <li>• Relative frequencies</li> </ul>	<ul style="list-style-type: none"> <li>• Overall recruitment rate <math>\geq 15\%</math></li> <li>• Percentage of eligible patients refusing to be approached due to monitor-related reasons <math>\leq 10\%</math></li> <li>• Percentage of eligible patients refusing consent to participate for monitor-related reasons <math>\leq 10\%</math></li> <li>• Percentage of participants requesting early monitoring termination due to monitoring intolerance <math>\leq 10\%</math></li> <li>• Percentage of reliable BIS values collected for less responsive/unresponsive patients (RASS-PAL=-3 to -5) <math>\geq 80\%</math></li> </ul>
3. BIS clinical usefulness	<ul style="list-style-type: none"> <li>• BIS values</li> <li>• Patient-rated alertness NRS scores</li> <li>• Clinician-rated alertness NRS and RASS-PAL scores</li> </ul>	<ul style="list-style-type: none"> <li>• Bland &amp; Altman correlation coefficients</li> <li>• Wilcoxon signed-rank test</li> </ul>	<ul style="list-style-type: none"> <li>• High correlation between BIS and patients' self-reported alertness (<math>r \geq 0.7</math>)</li> <li>• BIS to perform at least as well as clinicians' structured level of consciousness observations</li> <li>• Median BIS scores to decrease after administration of sedative medication</li> </ul>
<b>Secondary objectives</b>			
1. Use of BIS as a measure of pain detection	<ul style="list-style-type: none"> <li>• BIS values</li> <li>• Patient-rated pain NRS scores</li> <li>• Clinician-rated pain NRS scores</li> </ul>	<ul style="list-style-type: none"> <li>• Bland &amp; Altman correlation coefficients</li> </ul>	

2. Relationship between BIS values and clinician-reported outcomes	<ul style="list-style-type: none"> <li>• BIS values</li> <li>• Clinician-reported pain NRS and alertness NRS scores</li> </ul>	<ul style="list-style-type: none"> <li>• Bland &amp; Altman correlation coefficients</li> </ul>
3. Inter-rater reliability of clinician-rated RASS-PAL and convergent validity of clinician-rated RASS-PAL and alertness NRS	<ul style="list-style-type: none"> <li>• Clinician-rated RASS-PAL scores</li> <li>• Clinician-rated alertness NRS scores</li> </ul>	<ul style="list-style-type: none"> <li>• Bland &amp; Altman correlation coefficients</li> <li>• Intra-class correlation coefficient (ICC)</li> </ul>
4. Relationship between researcher-reported and other outcomes	<ul style="list-style-type: none"> <li>• BIS values</li> <li>• Patient-, clinician-, researcher-reported data</li> </ul>	<ul style="list-style-type: none"> <li>• Bland &amp; Altman correlation coefficients</li> </ul>

\*Presented in Chapters 8 and 9

## Primary objectives

### Objective 1: Acceptability in practice of BIS monitoring

In line with recommendations for assessing the acceptability of research interventions in palliative care populations, the acceptability of BIS monitoring was evaluated by examining participants' views on the burden and satisfaction with the intervention, and of study procedures (Hagen, Biondo, Brasher, & Stiles, 2011; T. A. Jones, Olds, Currow, & Williams, 2017). Data obtained from participant experience questionnaires were used to examine the acceptability in practice of BIS monitoring. Questionnaire data were analysed by calculating the relative frequencies of responses to each question. The following benchmarks were used to determine whether trialling BIS was acceptable as a research tool to the study population:

- Percentage of patients reporting no or minor discomfort from the BIS sensor (responses 0 to 1 on 5-point scale where 0= no, not at all uncomfortable, 4= extremely uncomfortable) ≥80%
- Percentage of patients reporting having a good overall experience of BIS monitoring (responses 0 to 1 on 5-point scale where 0= good experience, 4= bad experience) ≥80%



- Percentage of patients reporting having no issues or concerns about having the BIS sensor attached  $\geq 80\%$
- Percentage of patients who would be willing to be monitored again as part of Phase 2  $\geq 80\%$
- Percentage of patients who would be willing to participate in potential future research with BIS  $\geq 80\%$

In the absence of “gold standard” benchmarks for assessing patient acceptability, these criteria were selected *a priori* as having reasonable face validity. Combined Phase 1 and Phase 2 questionnaire data were used to calculate percentages for the first three criteria. For criterion four, corresponding data were obtained from Phase 1 questionnaires. Similarly, related Phase 2 questionnaire data were employed for the assessment of the fifth criterion.

The acceptability in practice of BIS monitoring was further explored by holding qualitative interviews with a subset of patients who had previously been monitored with BIS, their relatives, and hospice clinicians. Interviews provided richer data which added depth and context to questionnaire findings. The methods and results of the qualitative exploration of BIS acceptability in practice are presented in Chapters 7 and 8.

### **Objective 2: Feasibility of conducting research with BIS in hospice inpatients**

The National Institute for Health Research (NIHR) has defined feasibility studies as pieces of research undertaken before a main study with the aim of estimating parameters that are integral for designing the main study (National Institute for Health Research, 2019). Although the present study was not conducted in preparation for a larger definitive trial, given the scarcity of research evidence on BIS monitoring in palliative care, it was considered appropriate to investigate certain feasibility parameters to provide information that could be used in designing any potential future research of BIS monitoring in this context. This study adopted recruitment rates, compliance rates, and characteristics of proposed outcome measures, all of which are common feasibility parameters (T. A. Jones et al., 2017). The following criteria were set for the assessment of BIS feasibility:

- Overall recruitment rate  $\geq 15\%$
- Percentage of eligible patients refusing to be approached by the researcher due to monitor-related reasons  $\leq 10\%$

- Percentage of eligible patients refusing consent to participate for monitor-related reasons  $\leq 10\%$
- Percentage of participants requesting early monitoring termination due to monitoring intolerance  $\leq 10\%$
- Percentage of reliable BIS values collected for patients who were less responsive/unresponsive (RASS-PAL=-3 to -5)  $\geq 80\%$

As with objective 1, these benchmarks were set *a priori*, because, in the absence of universally agreed criteria for assessing feasibility, the supervisory team agreed that they had reasonable face validity. The overall recruitment rate was calculated by dividing the total number of patients recruited by the number of those screened for eligibility from the commencement of the study until the end of recruitment. The ability of BIS to provide reliable readings (i.e. BIS values for which SQI  $> 50$  and EMG  $< 50$  dB) in patients who were moderately to deeply sedated, as assessed by clinicians' observations using the RASS-PAL, was determined by considering the presence of at least one reliable BIS value at associated assessment time points, then percentages were calculated.

### **Objective 3: Preliminary evaluation of clinical usefulness of BIS monitoring**

This research was exploratory in nature and was not adequately powered to determine the effectiveness of BIS monitoring in palliative care. Instead, considering the study design and resources available, a preliminary exploration of clinical usefulness was undertaken. Clinical usefulness was investigated by : i) examining the ability of BIS to provide valid assessments of hospice inpatients' level of consciousness, ii) comparing the performance of BIS to that of clinicians' structured observations of level of consciousness, and iii) exploring the sensitivity of BIS to changes in patients' consciousness levels following administration of medication with sedative effects. Certain *a priori* minimum performance criteria were set:

- High correlation between BIS and patients' self-reported alertness ( $r \geq 0.7$ )
- BIS to perform at least as well as clinicians' structured observations of level of consciousness
- Median BIS scores to decrease after administration of medication with sedative effects

Patients' self-reported assessments were used as the standard against which other outcomes were compared. This is in line with outcomes collected directly from patients being generally considered to be the "gold standard" in palliative care and with recommendations stating that, where possible, patient-reported outcome measures should take precedence over proxy measures (Bausewein, Daveson, Benalia, Simon, & Higginson, 2011; Bausewein et al., 2016; Evans et al., 2013). For assessing the validity of BIS, therefore, the relationship between BIS values and patients' scores on the 11-point alertness NRS was examined by using the method developed by Bland and Altman (1995) for calculating correlation coefficients with repeated within-participant observations. This method accounts for non-independence among observations by adjusting for inter-individual variability. The probability (p) value was obtained from the F-test in the analysis of variance undertaken as part of the calculation of the correlation coefficient.

The same approach was followed for exploring the relationship between patients' self-reported alertness (using NRS) and clinicians' observations of patients' consciousness levels (using NRS and RASS-PAL). To determine whether BIS performed as well as clinicians' observations of consciousness levels, correlation coefficients for paired data (BIS values – patient-rated alertness NRS scores, patient-rated alertness NRS scores – clinician-rated alertness NRS scores, patient-rated alertness NRS scores – clinician-RASS-PAL scores) were compared.

Correlation coefficients can take any value from -1 to +1, where 0 indicates the absence of correlation and +1 or -1 represent a perfect positive or inverse correlation between two variables (Swinscow, 1997). Coefficients of less than 0.3, between 0.3 and 0.5, between 0.5 and 0.7, and greater than 0.7 are generally considered to represent negligible, low, moderate, and high correlations, respectively (Mukaka, 2012). These cut-off points were broadly adopted in this study.

For the sensitivity to change analysis, paired BIS scores just before and 60 minutes after the administration of breakthrough medication with sedative effects were compared using the Wilcoxon signed-rank test. BIS values for this analysis were obtained from participants in Phase 2 (who had all received a dose of sedative medication) and from those patients whom by chance also happened to receive PRN sedative medication during Phase 1. To enable the interpretation of findings, paired clinician-rated alertness NRS scores for the before-60min intervals were also compared using the Wilcoxon signed-rank test. In addition, before and after data were

graphically presented using scatter plots for all cases included in the sensitivity to change analysis.

### **Secondary objectives**

Secondary research objectives were predominantly exploratory. Therefore, no predetermined benchmark criteria were set.

#### **Objective 1: Relationship between BIS and clinician-rated measures**

The primary comparisons in this study were between patient-reported outcomes and BIS values. However, it was also decided to evaluate how well BIS values compared to observational measures undertaken by clinicians in order to aid the interpretation of findings from primary analyses and allow comparisons with other studies of BIS monitoring.

The same method for computing correlation coefficients (Bland & Altman, 1995) described previously was employed. The following pairs of variables were included in the analyses:

- BIS and clinician-rated pain NRS
- BIS and clinician-rated alertness NRS
- BIS and clinician-rated RASS-PAL

#### **Objective 2: Inter-rater reliability of clinician-rated RASS-PAL and convergent validity of clinician-rated RASS-PAL and alertness NRS**

As noted in Chapter 2, no observational level of consciousness measures have been fully validated for use in palliative care (Krooupa, Vivat, McKeever, Marcus, et al., 2020). In order to add to the limited evidence available on the psychometric performance of these measures, therefore, the inter-rater reliability of clinician-rated RASS-PAL and the convergent validity of clinician-rated RASS-PAL and alertness NRS were evaluated as part of secondary analyses.

For the assessment of convergent validity, the relationship between pairs of clinician-rated RASS-PAL and alertness NRS scores was explored using the Bland and Altman (1995) method. The inter-rater reliability of RASS-PAL was assessed using the intra-class correlation coefficient (ICC) for paired assessments obtained from two clinicians who rated the scale at three time points (t0, t2, t4) during each monitoring phase. The ICC has been described as the most appropriate and frequently employed reliability parameter for ordinal and continuous measures (Terwee et al., 2007). As, on each occasion, the scale was scored by clinicians who were on site and available to

complete assessments, a random effect, two-way ICC model was used to account for the random sampling of raters (Hallgren, 2012; Koo & Li, 2016). An ICC of 0.7 or above is generally considered to be acceptable (Fitzpatrick et al., 1998; Terwee et al., 2007).

The feasibility of clinician-rated measures used in this study was also evaluated. Findings of this evaluation are presented in Chapter 8.

### **Objective 3: Use of BIS in the assessment of pain in hospice inpatients**

Evidence from research in non-palliative care settings suggests that BIS could be a potentially useful indicator of the presence of pain (Faritous et al., 2016; Gelinas, Tousignant-Laflamme, Tanguay, & Bourgault, 2011; Li, Miaskowski, Burkhardt, & Puntillo, 2009). To explore therefore whether BIS could have a role as a measure of pain detection in hospice patients, the relationship between BIS values and patient-reported pain NRS scores, and patient- and clinician-reported pain NRS scores were examined using the Bland and Altman (1995) method for calculating correlation coefficients. Correlation coefficients were compared to explore how BIS performs in assessing pain severity in relation to clinicians' structured observations.

### **Objective 4: Relationship between researcher-rated and other outcome measures**

Researcher-reported scores were compared to those of patients and clinicians, as well as to BIS values. This was to explore whether observational assessments undertaken by non-clinical researchers could be used in future studies, rather than relying on assessments by clinical staff.

Relationships between outcomes were evaluated for the following pairs of variables:

- Researcher-rated alertness NRS and patient-rated alertness NRS
- Researcher-rated alertness NRS and BIS values
- Researcher-rated alertness NRS and clinician-rated alertness NRS
- Researcher-rated alertness NRS and clinician-rated RASS
- Researcher-rated RASS and patient-rated alertness NRS
- Researcher-rated RASS and BIS values
- Researcher-rated RASS and clinician-rated RASS
- Researcher-rated RASS and clinician-rated alertness NRS
- Researcher-rated pain NRS and patient-rated pain NRS
- Researcher-rated pain NRS and BIS values
- Researcher-rated pain NRS and clinician-rated pain NRS

Associations between paired outcomes were analysed by calculating correlation coefficients for multiple within-subject observations (Bland & Altman, 1995). No adjustment was made to account for multiple comparisons. This is in keeping with recommendations that in exploratory studies statistical adjustment for multiple testing is not critical and may even be undesirable (Althouse, 2016; Bender & Lange, 2001). Therefore, any statistically significant findings presented in this thesis should be treated with caution as there is an increased probability of false-positive results (Althouse, 2016).

## **5.10 Chapter summary**

This chapter has described the methodology of the exploratory study of BIS monitoring. The study involved two phases during which participants were monitored with the BIS technology for four hours (+15 minutes, if required). Separate informed consent was sought for each monitoring phase. Eligible and consenting Phase 2 patients were additionally asked to verbally reconfirm their consent just before the commencement of data collection activities. During each monitoring period participants self-reported their level of pain and alertness using two 11-point NRSs at five time points at hourly intervals (t0 to t4). Clinical staff and the researcher also completed the same measures at five (t0 to t4), and the RASS-PAL at three (t0, t2, t4), time points. At the end of each monitoring period, patients completed a short questionnaire about their experiences of using BIS. Data on the progress of patients through the different stages of the study as well as information on participant retention were also collected. *A priori* criteria were set for the assessment of study outcomes which were directly linked to research objectives.

## Chapter 6 Exploratory study of Bispectral index monitoring with hospice inpatients: Results

### 6.1 Chapter outline

This chapter reports on findings from the exploratory study of BIS monitoring with hospice inpatients. The chapter begins by presenting the recruitment and flow of participants through the study. Then, demographic and clinical characteristics of the study sample are described. Section 6.4 covers the prescribing patterns of medication with sedative effects. Following this, a description of the outcome data collected during the study monitoring periods is provided in section 6.5. Finally, the results of primary and secondary analyses are presented in section 6.6.

### 6.2 Recruitment and flow of participants through the study

#### Participant recruitment

**Figure 6.1** illustrates the flow of participants through the study. Overall, 332 patients were screened for inclusion. Of the screened patients, 155/332 (46.7%) were deemed ineligible. The main reasons for ineligibility were lack of capacity (66/155; 42.6%) or patients being too unwell at the time of screening (53/155; 34.2%). Of the eligible patients, almost all were approached for participation by the clinical team (162/177; 91.5%) and the majority of those approached were subsequently seen by the researcher (142/162; 87.6%). Three patients refused to see the researcher (3/162; 1.8%). Of these three patients, one refused for reasons relating to the BIS monitor. Of the patients accessed by the researcher, 40/142 (28.2%) consented to take part and 72/142 (50.7%) declined to do so. The most common reasons for refusing consent were that patients were experiencing distressing pain and/or fatigue (35/72, 48.6%). Six patients (6/72; 8.3%) refused to take part in the study for reasons associated with BIS monitoring (either concerns about restriction of movement or possible discomfort from the BIS sensor).

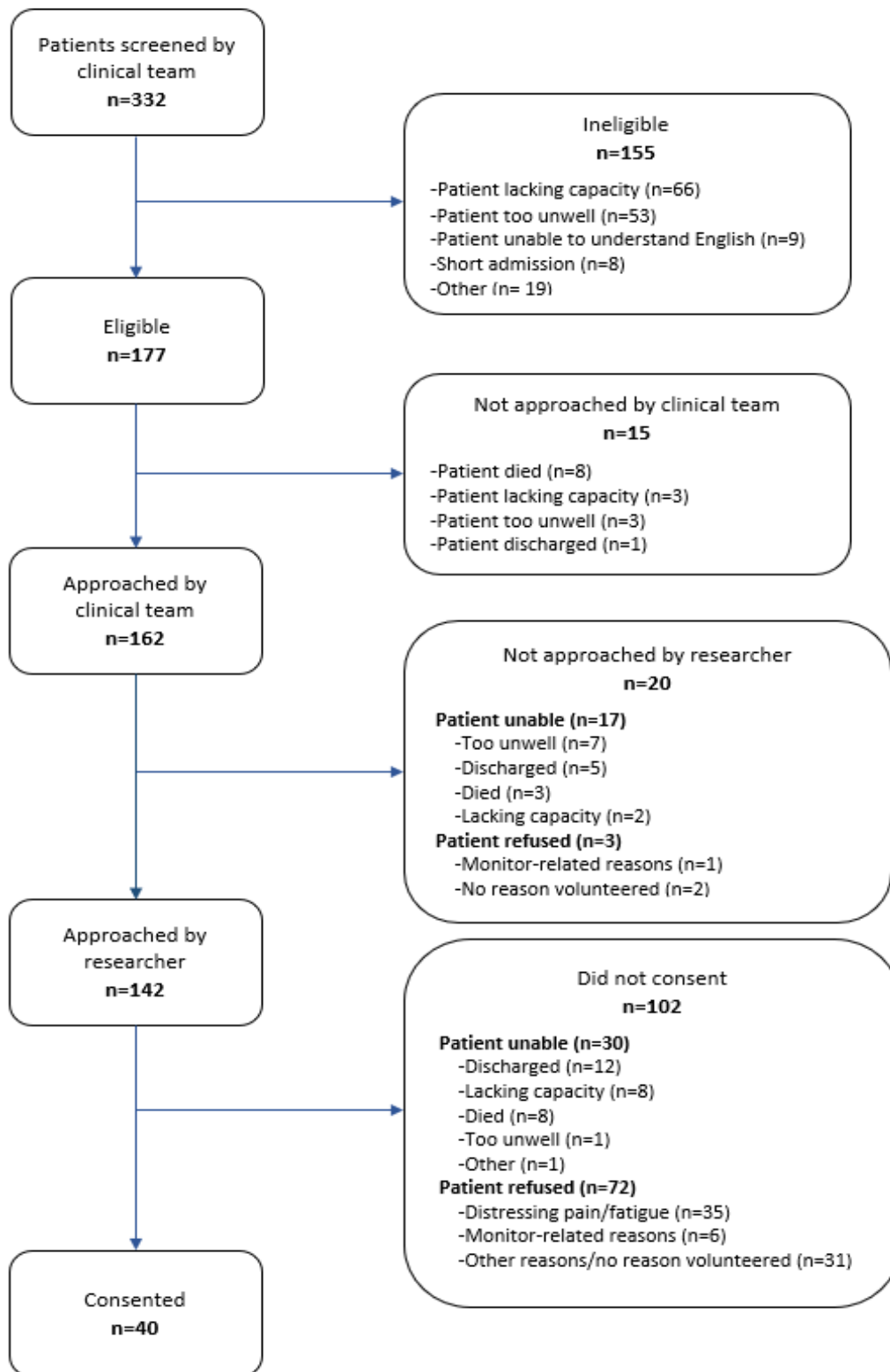
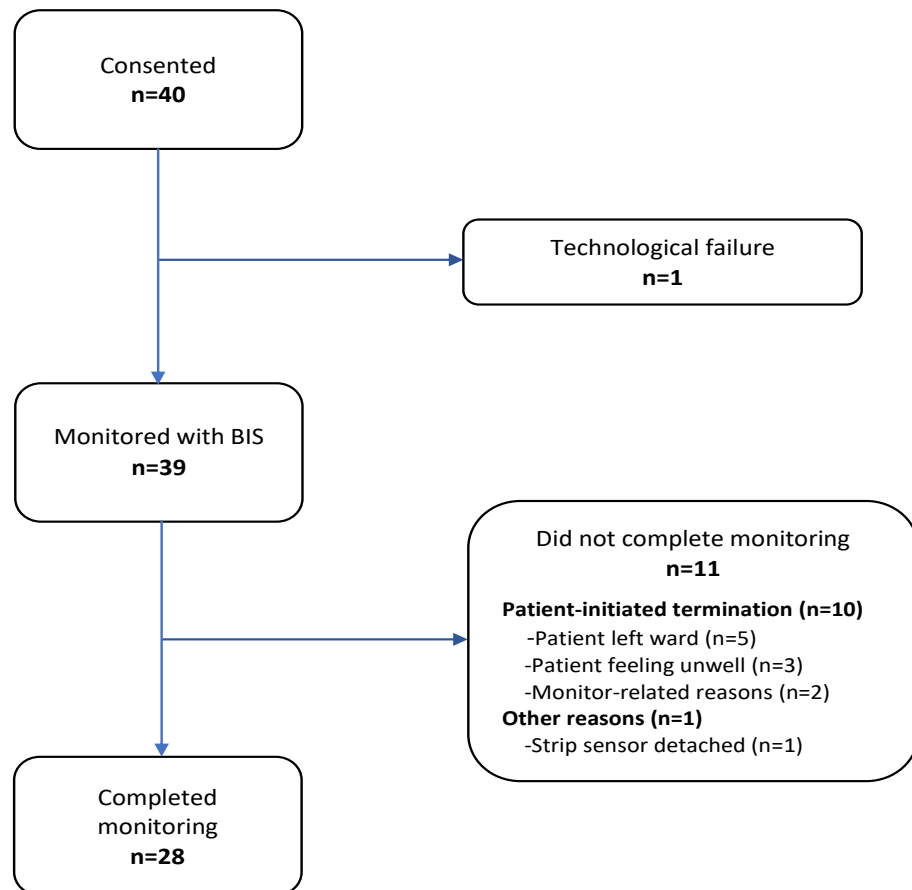


Figure 6.1: Recruitment flow chart



## Phase 1

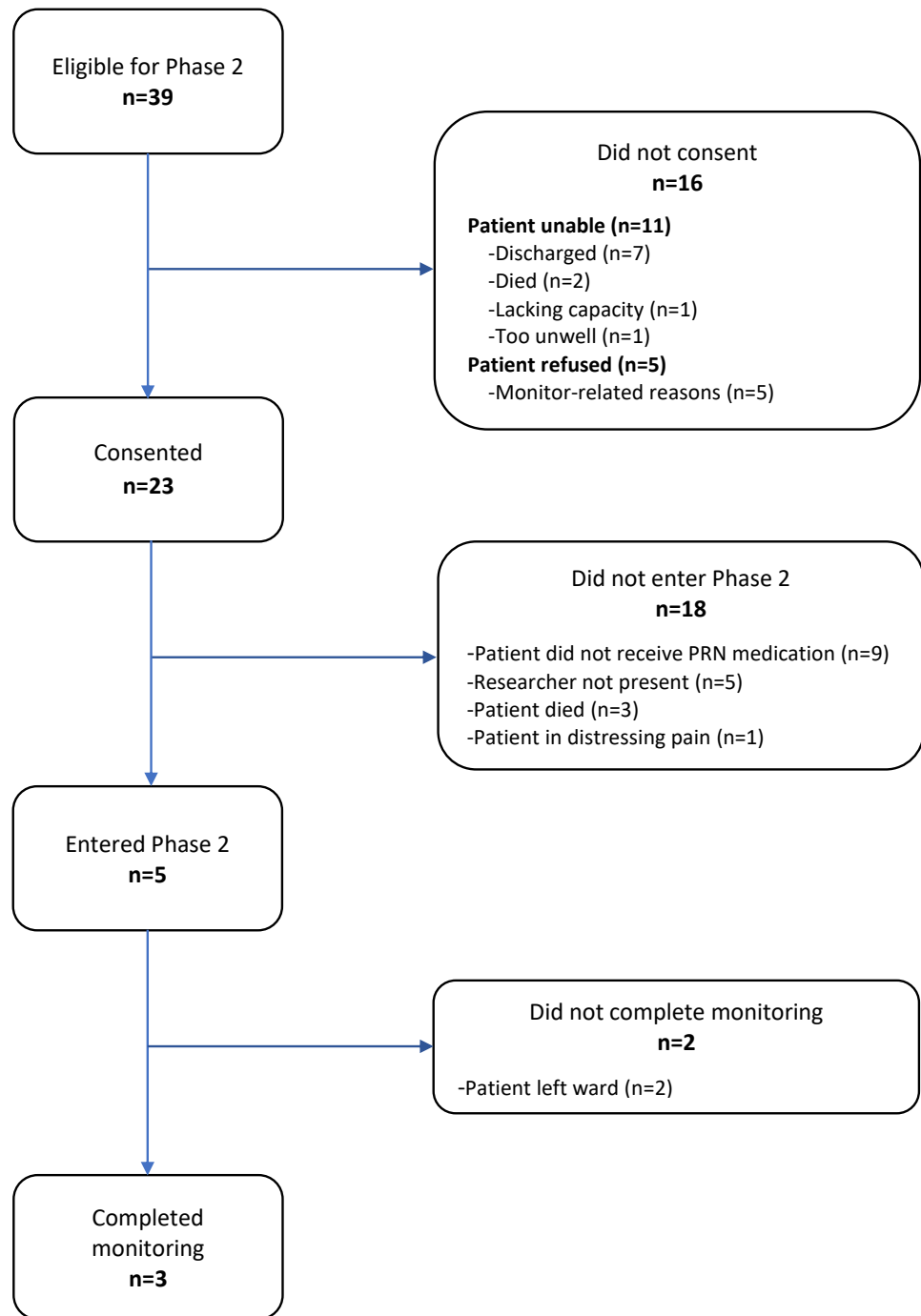
All patients who consented to take part in the study (n=40) entered Phase 1 of monitoring. BIS data could not be obtained for one patient (1/40; 2.5%) due to technological failure (the device could not establish reliable connection to the sensor). For this participant, only data from self-reported and observational assessments were collected. Of the remaining patients, 11/39 (28.2%) did not complete a full four hours of monitoring. The main reason for non-completion was patients requesting to leave the ward (5/11; 45.5%). Only two (2/39; 5.1%) of the patients monitored with BIS requested that the monitoring be stopped before the pre-specified endpoint due to monitor-related reasons. Four hours of BIS monitoring were completed for 28/39 (71.8%) patients. None of the patients were withdrawn from the study after written consent was obtained. Full details of participation in Phase 1 are presented in **Figure 6.2** below.



**Figure 6.2:** Phase 1 participation flow chart

## Phase 2

All patients who were monitored with BIS in Phase 1 (n=39) were eligible for participation in Phase 2. Of the eligible patients, 16/39 (41%) did not consent to participate. The most common reason was that potential Phase 2 participants were unable to provide consent at the time of approach (11/16; 68.8%), mainly due to being discharged from the hospice soon after participating in Phase 1 (7/11; 63.6%). Five patients (5/16; 32.3%) refused to consent for reasons related to the BIS monitor. These were mainly associated with the restriction of movement experienced by participants during Phase 1. Of the 23/39 (59%) who consented to participate, 18/23 (78.3%) did not actually enter Phase 2. The main reasons for not entering Phase 2 were that the patients did not go on to receive any additional medication with sedative effects during their remaining time in the hospice (9/18; 50%), or that the researcher was not available at the time that such medication was administered (5/18; 27.8%). As a result, only 5/39 eligible patients (12.8%) entered Phase 2. All five patients verbally reconfirmed consent to data collection, hence the input of consultees was not required. Of these five patients, three (3/5; 60%) completed the full four hours of monitoring. **Figure 6.3** shows the flow of participants through Phase 2.



**Figure 6.3:** Phase 2 participation flow chart

### 6.3 Participant characteristics

A summary of socio-demographic, medical and clinical characteristics of study participants is provided in **Table 6.1**. The median age of participating patients was 64 (IQR 55.3 to 73.3) years. The majority of participants were male (22/40; 55%), White British or Northern Irish (25/40; 62.5%) and had a principal diagnosis of cancer (30/40; 75%). Most participants (31/40; 77.5%) had one or more comorbid conditions. Of these, the most frequently recorded were hypertension (5/31; 16.1%), type 2 diabetes mellitus (5/31; 16.1%) and chronic obstructive pulmonary disease (4/31; 12.9%).

Most participants had PPSv2 scores of 40% (11/40; 27.5%) or 50% (11/40; 27.5%), indicating moderate functional ability. None of the participants had a PPSv2 score lower than 30%. Most participants (26/40; 65%) had an expected prognosis of “months” (i.e. 56 days or more). Only one patient (1/40; 2.5%) had an expected survival of “days” (i.e. fewer than 14 days).

The clinical characteristics (i.e. PPSv2 score and estimated prognosis) of the five patients who participated in both Phase 1 and Phase 2 were unaltered between the two phases. The median time between Phase 1 and Phase 2 data collection was 5 (IQR 4.5 to 10.5) days.

**Table 6.1:** Participant characteristics (n=40)

Characteristic	Median	IQR
<b>Age (years)</b>	64	55.3–73.3
	<b>n</b>	<b>%</b>
<b>Gender</b>		
Male	22	55
Female	18	45
<b>Ethnic group</b>		
White English/ Welsh/ Scottish/ Northern Irish/ British	25	62.5
White Irish	4	10
Any other White background	4	10
Black Caribbean	2	5
Any other Black/ African/ Caribbean background	1	2.5
Any other Mixed/ Multiple ethnic background	2	5
Asian Bangladeshi	1	2.5
Any other Asian background	1	2.5
<b>Principal diagnosis</b>		
Cancer	30	75
Cardiovascular disease	2	5
Multiple Sclerosis	2	5
Chronic respiratory disease	1	2.5
Chronic liver disease	1	2.5
Chronic pain	1	2.5
Chronic pancreatitis	1	2.5
Kidney Failure	1	2.5
Motor neurone disease	1	2.5
<b>Presence of comorbidities</b>		
Yes	31	77.5
No	9	22.5
<b>Functional status *</b>		
0%	0	0
10%	0	0
20%	0	0
30%	2	5
40%	11	27.5
50%	11	27.5
60%	5	12.5
70%	6	15
80%	5	12.5
90%	0	0
100%	0	0
<b>Predicted survival **</b>		
Days (0–13 days)	1	2.5
Weeks (14–55 days)	13	32.5
Months (56 days or more)	26	65

\*Assessed by PPSv2(Anderson et al., 1996), \*\*Assessed by Clinician Prediction of Survival (CPS)

## 6.4 Medication use

Medications with sedative effects were prescribed for 36/40 (90%) patient participants. Twenty-six participants (65%) were prescribed both regular and PRN medication with sedative effects. Eight participants received medication on a PRN basis only (20%), while two patients (5%) were on regular dosing only.

Twenty-eight participants (70%) were prescribed regular medication with sedative effects. Fifteen participants (37.5%) were prescribed one regular medication, eight (20%) were prescribed two medications and five patients (12.5%) were prescribed three medications. Similarly, 23/40 (57.5%) participants were prescribed one PRN medication, whilst 11/40 (27.5%) participants had PRN prescriptions for two or more medications (see **Table 6.2**).

Opioids were the most commonly used medications both as regular (23/40; 57.5%) and PRN (29/40; 72.5%) prescriptions. Oxycodone was the most frequently prescribed drug in this class. The median daily oral morphine equivalent dose for regularly prescribed opioids was 120 (IQR 30 to 280) mg. For opioids prescribed on a PRN basis, the median oral morphine equivalent dose was 15 (IQR 4 to 50) mg.

Benzodiazepines were more likely to be prescribed PRN (13/40; 32.5%) than regularly (8/40; 20%). Conversely, participants were more likely to receive regular doses of antipsychotic medications (7/40; 17.5%) than PRN (1/40; 2.5%). Median doses and frequencies for all prescribed medications with sedative effects are shown in **Table 6.3**.

**Table 6.2:** Frequency of prescribed medication with sedative effects by category and class

Medication	n	%
<b>Regular</b>	<b>28</b>	<b>70</b>
<b>One</b>	<b>15</b>	<b>37.5</b>
Opioid	11	27.5
Benzodiazepine	2	5
Neuroleptic/Antipsychotic	1	2.5
Non-benzodiazepine hypnotic/sedative	1	2.5
<b>Two</b>	<b>8</b>	<b>20</b>
Opioid + benzodiazepine	3	7.5
Opioid + neuroleptic/antipsychotic	4	10
Opioid + opioid	1	2.5
<b>Three</b>	<b>5</b>	<b>12.5</b>
Opioid + opioid + benzodiazepine	1	2.5
Opioid + opioid + neuroleptic/antipsychotic	2	5
Opioid + sedating antihistamine + benzodiazepine	1	2.5
Sedating antihistamine + sedating antihistamine + benzodiazepine	1	2.5
<b>PRN</b>	<b>34</b>	<b>85</b>
<b>One</b>	<b>23</b>	<b>57.5</b>
Opioid	18	45
Benzodiazepine	4	10
Non-benzodiazepine hypnotic/sedative	1	2.5
<b>Two</b>	<b>9</b>	<b>22.5</b>
Opioid + benzodiazepine	7	17.5
Opioid + opioid	1	2.5
Opioid + non-benzodiazepine hypnotic/sedative	1	2.5
<b>Three</b>	<b>1</b>	<b>2.5</b>
Opioid + neuroleptic/antipsychotic + benzodiazepine	1	2.5
<b>Five</b>	<b>1</b>	<b>2.5</b>
Three opioids + 2 benzodiazepines	1	2.5

**Table 6.3:** Frequency and median doses of prescribed regular and PRN medication with sedative effects

Medication	n (%)	Median dose (IQR) unless otherwise stated, mg
<b>Regular</b>		
<b>Opioids *</b>	<b>23 (57.5)</b>	<b>120 (30–280) <sup>a</sup></b>
Oxycodone	7 (17.5)	240 (80–320) <sup>a</sup>
Fentanyl patch	7 (17.5)	120 (90–240) <sup>a</sup>
Morphine	4 (10)	50 (25–315) <sup>a</sup>
Methadone	3 (7.5)	400 (50–1000) <sup>a</sup>
Alfentanil	3 (7.5)	30 (30–120) <sup>a</sup>
Buprenorphine patch	3 (7.5)	24 (12–24) <sup>a</sup>
<b>Benzodiazepines</b>	<b>8 (20)</b>	
Clonazepam	2 (5)	1.5 (1–2) <sup>b</sup>
Diazepam	2 (5)	21 (2–40) <sup>b</sup>
Clobazam	1 (2.5)	60 <sup>c</sup>
Chlordiazepoxide	1 (2.5)	40 <sup>c</sup>
Lorazepam	1 (2.5)	1 <sup>c</sup>
Temazepam	1 (2.5)	10 <sup>c</sup>
<b>Neuroleptics/Antipsychotics</b>	<b>7 (17.5)</b>	
Haloperidol	6 (15)	1.75 (1–3)
Levomepromazine	1 (2.5)	6 <sup>c</sup>
<b>Sedating antihistamines *</b>	<b>2 (5)</b>	
Chlorphenamine	2 (5)	18 (12–24) <sup>b</sup>
Promethazine	1 (2.5)	25 <sup>c</sup>
<b>Non-benzodiazepine hypnotics</b>	<b>1 (2.5)</b>	
Zopiclone	1 (2.5)	7.5 <sup>c</sup>
<b>PRN</b>		
<b>Opioids *</b>	<b>29 (72.5)</b>	<b>15 (4–50) <sup>a</sup></b>
Oxycodone	20 (50)	21.3 (7.4–70) <sup>a</sup>
Morphine	10 (25)	7.5 (3.8–20.6) <sup>a</sup>
<b>Benzodiazepines *</b>	<b>13 (32.5)</b>	
Lorazepam	13 (32.5)	<b>0.75 (0.5–2)</b>
Chlordiazepoxide	1 (2.5)	30 <sup>c</sup>
<b>Neuroleptics/Antipsychotics</b>	<b>1 (2.5)</b>	
Haloperidol	1 (2.5)	0.75 <sup>c</sup>
<b>Non-benzodiazepine hypnotics</b>	<b>2 (5)</b>	
Zopiclone	2 (5)	5.625 (3.75–7.5) <sup>b</sup>

\*Some patients received more than one medication from this category; therefore, individual medication totals do not sum to overall category total, <sup>a</sup>Median oral morphine equivalent dose, <sup>b</sup>Mean dose (range), <sup>c</sup>Actual dose



## **6.5 Description of patient-, clinician-, researcher-reported pain and alertness outcome data, and BIS data**

The completeness with which outcome data were collected, median scores and the time difference in the collection of data from different sources were calculated for each outcome measure. **Table 6.4** provides a summary of this information for each monitoring phase.

### **Patient-reported pain and alertness outcome data**

#### **Phase 1**

A maximum of 200 patient-reported pain and alertness NRS assessments could have been undertaken by the 40 participants in Phase 1 of the study (i.e. 5 assessments per patient). In fact, 160/200 (80%) completed sets of patient-reported pain and alertness NRS data were obtained. The median patient-reported alertness NRS score was 8 (IQR 5 to 10). This indicates a high degree of alertness. The median patient-reported pain NRS score was 2 (IQR 0 to 5), indicating a low level of pain.

#### **Phase 2**

A maximum of 25 patient-reported pain and alertness NRS assessments could have been undertaken by the 5 participants in Phase 2 of the study (i.e. 5 assessments per patient). In fact, 23/25 (92%) completed sets of patient-reported pain and alertness NRS data were obtained. The median patient-reported alertness NRS score was 9 (IQR 6 to 10). This indicates a high degree of alertness. The median patient-reported pain NRS score was 6 (IQR 4 to 10), indicating a moderate degree of self-reported pain.

### **Clinician-reported pain and alertness outcome data**

#### **Phase 1**

A maximum of 200 clinician-reported pain and alertness NRS assessments could have been undertaken for the 40 participants in Phase 1 of the study (i.e. 5 assessments per patient). In fact, 170/200 (85%) completed sets of clinician-reported pain and alertness NRS data were obtained. The median clinician-reported alertness NRS score was 10 (IQR 8 to 10). This represents

a high degree of alertness. The median clinician-reported pain NRS score was 0 (IQR 0 to 2), representing a low level of clinician-reported pain.

A maximum of 120 clinician-reported RASS-PAL assessments could have been undertaken for the 40 participants in Phase 1 of the study (i.e. 3 assessments per patient). In fact, 99/120 (82.5%) completed sets of clinician-reported RASS-PAL data were obtained. The median clinician-rated RASS-PAL score was 0 (IQR 0 to 0), indicating that patients were observed to be in an alert and calm state at the time of assessments.

## **Phase 2**

A maximum of 25 clinician-reported pain and alertness NRS assessments could have been undertaken for the 5 participants in Phase 2 of the study (i.e. 5 assessments per patient). In fact, 22/25 (88%) completed sets of clinician-reported pain and alertness data were obtained. The median score for clinician-reported alertness NRS was 10 (IQR 9 to 10). This represents a high degree of alertness. The median score for clinician-reported pain NRS was 3 (IQR 0 to 4), representing a low level of clinician-reported pain (in contrast to the moderate levels of patient self-reported pain in Phase 2).

A maximum of 15 clinician-reported RASS-PAL assessments could have been undertaken for the 5 participants in Phase 2 of the study (i.e. 3 assessments per patient). In fact, 12/15 (80%) completed sets of clinician-reported RASS-PAL data were obtained. The median clinician-rated RASS-PAL score was 0 (IQR 0 to 0), indicating that, as in Phase 1, patients were observed to be in an alert and calm state at the time of assessments.

## **Researcher-reported pain and alertness outcome data**

The same outcome measures as described above were also completed by the researcher for the 40 participating patients.

### **Phase 1**

Researcher pain and alertness NRS scores were available for 172/200 (86%) assessments. The median researcher-reported alertness NRS score was 9 (IQR 8 to 9), indicating a high degree of alertness. The median researcher-reported pain NRS score was 0 (IQR 0 to 0), indicating no pain.

Researcher-rated RASS-PAL scores were available for 102/120 (85%) assessments. The median researcher-rated RASS-PAL score was 0 (IQR 0 to 0), indicating that patients were observed to be in an alert and calm state at the time of assessments.

## **Phase 2**

Researcher pain and alertness NRS scores were available for 23/25 (92%) assessments. Similar to Phase 1, the median researcher-reported alertness NRS score was 9 (IQR 8 to 9), indicating a high degree of alertness. The median researcher-reported pain NRS score was 0 (IQR 0 to 1.5), indicating no pain.

Researcher-rated RASS-PAL scores were available for 12/15 (80%) assessments. The median researcher-rated RASS-PAL score was 0 (IQR 0 to 0) indicating that, as in Phase 1, patients were observed to be in an alert and calm state at the time of assessments.

## **BIS data**

During each monitoring period BIS values were recorded every minute. BIS readings were time-matched to assessment time points. Full four-hourly outputs were also collected for all participants.

### **Phase 1**

The median duration of BIS monitoring was 241 (IQR 193.8 to 247.5) minutes in Phase 1 of the study. Reliable time-matched BIS values (i.e. those for which SQI >50 and EMG <50 dB) were available for 116/200 (58%) assessments. The median BIS score was 91 (IQR 77.2 to 95), indicating a high level of consciousness for patients in Phase 1. BIS values were collected within a median of 2.5 (IQR 0 to 7) minutes from the collection of patient self-reported data.

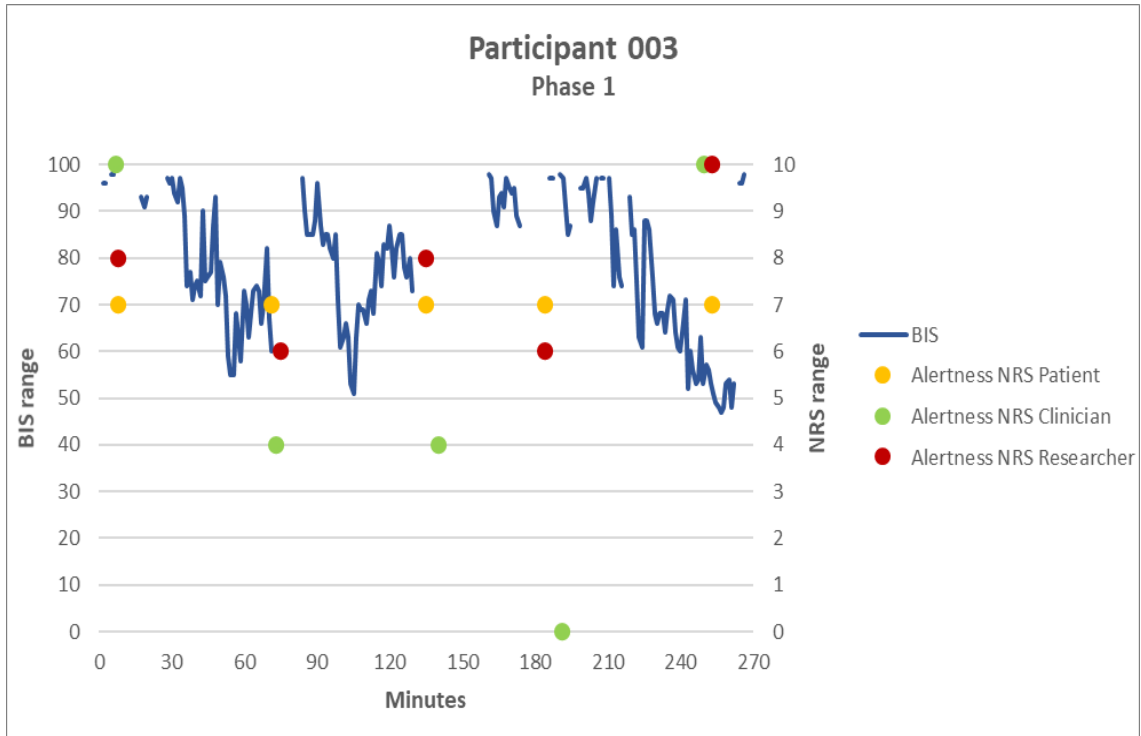
### **Phase 2**

The median duration of BIS monitoring was 234 (IQR 179.5 to 248.5) minutes in Phase 2 of the study. Reliable time-matched BIS values were available for 17/25 (68%) assessments. The median BIS score was 94 (IQR 90 to 94), indicating, as in Phase 1, a high level of consciousness for patients in this phase. BIS values were collected within a median of 4 (IQR 0 to 10) minutes from the collection of patient self-reported data.

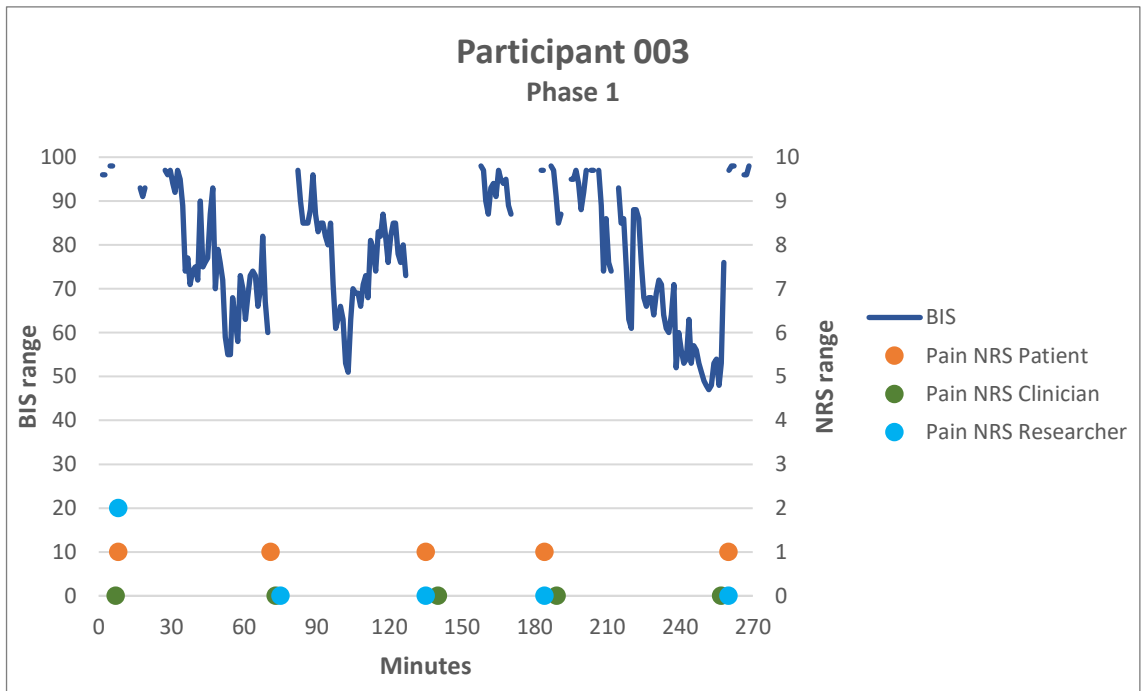
Four-hourly BIS outputs and alertness NRS data, plus BIS and pain NRS data were plotted for a selection of cases (see **Figures 6.4–6.5 and Appendix 4**). None of the datasets for individual patient cases were complete (mainly due to patients' being mostly alert during monitoring). Presented cases had the lowest proportion of missing data.

**Table 6.4:** Summary of patient-, clinician-, researcher-reported pain and alertness data, and BIS data

Outcome measures	Phase 1	Phase 2
<b>Patient-reported</b>		
<b>Alertness NRS</b>		
Collected data, n (%)	160 (80)	23 (92)
Missing data, n (%)	40 (20)	2 (8)
Median score (IQR)	8 (5–10)	9 (6–10)
<b>Pain NRS</b>		
Collected data, n (%)	160 (80)	23 (92)
Missing data, n (%)	40 (20)	2 (8)
Median score (IQR)	2 (0–5)	6 (4–10)
<b>Clinician-reported</b>		
<b>Alertness NRS</b>		
Collected data, n (%)	170 (85)	22 (88)
Missing data, n (%)	30 (15)	3 (12)
Median score (IQR)	10 (8–10)	10 (9–10)
Median time difference from patient self-report (IQR)	0 (0–5)	0 (0–5)
<b>Pain NRS</b>		
Collected data, n (%)	170 (85)	22 (88)
Missing data, n (%)	30 (15)	3 (12)
Median score (IQR)	0 (0–2)	3 (0–4)
Median time difference from patient self-report (IQR)	0 (0–5)	0 (0–5)
<b>RASS-PAL</b>		
Collected data, n (%)	99 (82.5)	12 (80)
Missing data, n (%)	21 (17.5)	3 (20)
Median score (IQR)	0 (0–0)	0 (0–0)
Median time difference from patient self-report (IQR)	0 (0–5)	0 (0–5)
<b>Researcher-reported</b>		
<b>Alertness NRS</b>		
Collected data, n (%)	172 (86)	23 (92)
Missing data, n (%)	28 (14)	2 (8)
Median score (IQR)	9 (8–9)	9 (8–9)
Median time difference from patient self-report (IQR)	0 (0–0)	0 (0–1.5)
<b>Pain NRS</b>		
Collected data, n (%)	172 (86)	23 (92)
Missing data, n (%)	28 (14)	2 (8)
Median score (IQR)	1.5 (0–2)	3 (2–4)
Median time difference from patient self-report (IQR)	0 (0–0)	0 (0–1.5)
<b>RASS-PAL</b>		
Collected data, n (%)	102 (85)	12 (80)
Missing data, n (%)	18 (15)	3 (20)
Median score (IQR)	0 (0–0)	0 (0–0)
Median time difference from patient self-report (IQR)	0 (0–0)	0 (0–1.5)
<b>BIS data</b>		
<b>Time-matched values</b>		
Collected data, n (%)	116 (58)	17 (68)
Missing data, n (%)	84 (42)	8 (32)
Median score (IQR)	91 (77.2–95)	94 (90–94)
Median time difference from patient self-report (IQR)	2.5 (0–7)	4 (0–10)



**Figure 6.4:** BIS and alertness NRS data collected for participant 003 in Phase 1



**Figure 6.5:** BIS and pain NRS data collected for participant 003 in Phase 1

## Participant experience questionnaires

Of the 39 patients monitored with BIS in Phase 1, 36/39 (92.3%) completed the participant experience questionnaire. At the end of Phase 2, 4/5 (80%) completed the questionnaire. The majority of respondents in both phases (Phase 1: 31/36; 86.1%, Phase 2: 3/4; 75%) reported experiencing no or minor discomfort (responses: 0 to 1) from the BIS sensor. However, 2/36 (5.5%) participants in Phase 1 and 1/4 (25%) in Phase 2, reported feeling very or extremely uncomfortable from the application of BIS sensor (responses: 3 to 4). Almost all respondents in Phase 1 (34/36; 94.4%) and all respondents in Phase 2 (n=4) indicated having no issues or concerns about having the sensor attached during BIS monitoring. One Phase 1 respondent (1/36; 2.8%) reported experiencing skin irritation from having the sensor attached, and a further participant (1/36; 2.8%) identified the duration of time for which the sensor was attached as an issue.

Half of Phase 1 (18/36; 50%) and three Phase 2 respondents (3/4; 75%), reported that their movement or activity had been affected by the monitoring to different extents (responses: 1 to 4). Moving inside the room was the most common activity affected by monitoring (Phase 1: 13/36; 36.1%, Phase 2: 3/4; 75%), followed by moving outside the room (Phase 1: 6/36; 16.6%, Phase 2: 3/4; 75%), and turning/moving in bed (Phase 1: 5/36; 13.8%, Phase 2: 3/4; 75%).

In Phase 1, 30/36 (83.3%) respondents reported having a mostly good overall experience of BIS monitoring (responses: 0 to 1), 4/36 (11.1%) had a moderate (response: 2) and 2/36 (5.5%) had a mostly bad experience of using the BIS technology (responses: 3 to 4). In Phase 2, all participants (n=4) reported having a good overall experience of BIS monitoring. **Table 6.5** provides a summary of responses to participant experience questionnaires.

**Table 6.5:** Responses to Phase 1 (n=36) and Phase 2 (n=4) participant experience questionnaires

Responses	Phase 1		Phase 2	
	n	%	n	%
<b>BIS sensor causing discomfort</b>				
0: No, not at all	21	58.3	2	50
1	10	27.8	1	25
2	3	8.3	0	0
3	1	2.8	0	0
4: Extremely	1	2.8	1	25
<b>Monitoring affected movement/activity</b>				
0: No, not at all	18	50	1	25
1	4	11.1	0	0
2	9	25	2	50
3	3	8.3	1	25
4: Extremely	2	5.6	0	0
<b>Activity affected by monitoring *</b>				
Moving inside room	13	36.1	3	75
Moving outside room	6	16.6	3	75
Turning/moving in bed	5	13.8	3	75
Performing daily activities	4	11.1	2	50
<b>Concerns/issues about wearing BIS sensor</b>				
No	34	94.4	4	100
Yes	2	5.6	0	0
<b>Reported concerns/issues about wearing BIS sensor</b>				
Amount of time spent being monitored	1	2.8	–	–
Skin irritation caused by BIS sensor	1	2.8	–	–
<b>Overall experience of using BIS monitor</b>				
0: Good experience	23	63.9	4	100
1	7	19.4	0	0
2	4	11.1	0	0
3	2	5.6	0	0
4: Bad experience	0	0	0	0
<b>Willing to be further monitored</b>				
Yes	32	88.8	–	–
Need more time/to discuss with others to decide	2	5.6	–	–
I prefer not to say/I am not sure	1	2.8	–	–
No	1	2.8	–	–
<b>Willing to participate in future randomised study</b>				
Yes	–	–	4	100
Need more time/to discuss with others to decide	–	–	0	0
I prefer not to say/I am not sure	–	–	0	0
No	–	–	0	0

\*Respondents selected multiple categories

## 6.6 Assessment of study outcomes

### Primary outcomes

#### Acceptability in practice of BIS monitoring

##### **Criterion 1: Percentage of patients reporting no or minor discomfort from the BIS sensor $\geq 80\%$**

Overall, 34/40 patients (85%) who completed the participant experience questionnaire in both phases of the study reported experiencing no or minor discomfort from the application of the BIS sensor (responses: 0 to 1).

##### **Criterion 2: Percentage of patients reporting having a good overall experience of BIS monitoring $\geq 80\%$**

Overall, 34/40 (85%) of respondents who completed the participant experience questionnaire in both phases of the study reported a mostly good or good experience of using the BIS monitor (responses: 0 to 1).

##### **Criterion 3: Percentage of patients reporting having no issues or concerns about having the BIS sensor attached $\geq 80\%$**

Overall, 38/40 (95%) of respondents who completed the participant experience questionnaire in both phases of the study reported having no issues/concerns with having the BIS sensor attached during the study monitoring periods.

##### **Criterion 4: Percentage of patients who would be willing to be monitored again as part of Phase 2 $\geq 80\%$**

Of the patients for whom Phase 1 questionnaire data were available, 32/36 (88.8%) reported that they would be willing to take part in a further four-hour period of monitoring.

##### **Criterion 5: Percentage of patients who would be willing to participate in potential future research with BIS $\geq 80\%$**

All four patients who completed Phase 2 questionnaires (4/4; 100%), responded positively to a question regarding their willingness to participate in a potential future randomised study of BIS monitoring. Participants were informed prior to completing the questionnaires that this was a hypothetical question and that their consent to be approached for such research was not sought at that point.



Questionnaire response data and the acceptability in practice of BIS monitoring are further explored with data from the interviews undertaken with patients, relatives and clinicians presented in Chapter 8.

### **Feasibility of conducting research with BIS in hospice inpatients**

#### **Criterion 1: Overall recruitment rate $\geq 15\%$**

In 12 months (November 2017 to November 2018), 332 hospice inpatients were screened for eligibility. Of these, 40/332 (12%) agreed to participate.

#### **Criterion 2: Percentage of eligible patients refusing to be approached by the researcher due to monitor-related reasons $\leq 10\%$**

Only one of the eligible patients approached (1/162; 0.6%), refused to be seen by the researcher for reasons related to BIS. This patient had viewed the research materials (which included a photograph of a member of the research team wearing the BIS sensor) and had been concerned that its appearance may upset their family.

#### **Criterion 3: Percentage of eligible patients refusing consent to participate for monitor-related reasons $\leq 10\%$**

Of patients approached to participate in Phase 1, 6/142 (4.2%) refused to consent due to reasons associated with the use of BIS. Of the patients who were eligible to participate in Phase 2, 5/39 (12.8%) refused to consent due to reasons associated with the use of BIS. As a result, the total rate of monitor-related refusal to participation was 11/181 (6.1%). For 7/11 (63.6%) the reason for refusing was the perceived potential restriction of movement that monitoring would entail. For the remaining 4/11 (36.4%) the reason for refusal was the possible (n=2; approached for Phase 1) or actual (n=2; approached for Phase 2) discomfort caused by the BIS sensor.

#### **Criterion 4: Percentage of participants requesting early monitoring termination due to monitoring intolerance $\leq 10\%$**

Of the patients monitored with BIS in both study phases, 2/44 (4.5%) requested monitoring to stop before the end of the four hours for reasons relating either to the monitoring procedure or to the BIS sensor. These two patients were monitored for 188 and 70 minutes, respectively.

#### **Criterion 5: Percentage of reliable BIS values collected for patients who were less responsive/unresponsive (RASS-PAL=-3 to -5) $\geq 80\%$**

Since most patients in both phases of the study were predominantly in an alert and calm state at the times when clinicians completed their assessments (median RASS-PAL score 0, IQR 0 to 0),

there were not enough data available to assess this criterion. There was only one occasion on which a patient was observed being less responsive (RASS-PAL=-3) at the time of assessment. On this occasion, a time-matched BIS value which met the reliability parameters (SQI >50 and EMG <50 dB) was not available in the data set.

### **Preliminary evaluation of clinical usefulness of BIS monitoring**

#### **Criterion 1: High correlation between BIS and patients' self-reported alertness ( $r \geq 0.7$ )**

For Phase 1, 96 pairs of patient-reported alertness NRS and BIS data were included in the analysis. No correlation between the two variables was found ( $r=-0.04$ ; 95% CI -0.28 to 0.21).

For Phase 2, 17 pairs of patient-reported alertness NRS and BIS data were included in the analysis. As in Phase 1, no correlation was found ( $r=0.17$ ; 95% CI -0.48 to 0.70).

#### **Criterion 2: BIS to perform at least as well as clinicians' structured observations of level of consciousness**

As discussed in Chapter 5, patient self-reports were used as the “gold standard” against which other outcomes were compared. Therefore, to examine how BIS performs in relation to clinicians' structured observations of consciousness levels, the correlation coefficient for paired BIS and patient alertness NRS data was compared to those of patient alertness NRS scores and clinician alertness NRS and RASS-PAL scores.

For Phase 1, 149 pairs of patient and clinician alertness NRS data, and 59 pairs of patient alertness NRS and clinician RASS-PAL data were included in the analyses. No evidence of association between patient- and clinician-rated alertness NRSs ( $r=-0.03$ ; 95% CI -0.22 to 0.16), or patient-rated alertness NRS and clinician-rated RASS-PAL scores ( $r=-0.05$ ; 95% CI -0.32 to 0.24) was found.

For Phase 2, 22 pairs of patient and clinician alertness NRS data, and 12 pairs of patient alertness NRS and clinician RASS-PAL data were included in the analyses. As in Phase 1, no evidence of association between patient- and clinician-rated alertness NRSs ( $r=0.31$ ; 95% CI -0.21 to 0.70), or patient-rated alertness NRS and clinician-rated RASS-PAL scores ( $r=0.34$ ; 95% CI -0.65 to 0.90) was found (see **Table 6.6**).

Since no correlation was found between BIS and patient self-reported alertness data or patient- and clinician-reported alertness data, it was not possible to assess whether this criterion had been met.

**Table 6.6:** Correlation coefficients for BIS, patient- and clinician-rated alertness NRSs by study phase

Variables	Number of paired data	r	95% CI	p-value
<b>Phase 1</b>				
BIS and patient-rated alertness NRS	96	-0.04	-0.28–0.21	0.76
Patient-rated alertness NRS and clinician-rated alertness NRS	149	-0.03	-0.22–0.16	0.77
Patient-rated alertness NRS and clinician-rated RASS-PAL	59	-0.05	-0.32–0.24	0.74
<b>Phase 2</b>				
BIS and patient-rated alertness NRS	17	0.17	-0.48–0.70	0.57
Patient-rated alertness NRS and clinician-rated alertness NRS	22	0.31	-0.21–0.70	0.20
Patient-rated alertness NRS and clinician-rated RASS-PAL	12	0.34	-0.65–0.90	0.40

Number of participants: Phase 1 n=40, Phase 2 n=5; BIS: Bispectral index; NRS: Numerical Rating Scale; RASS-PAL: Richmond Agitation-Sedation Scale – Palliative version.

### Criterion 3: Median BIS scores to decrease after administration of medication with sedative effects

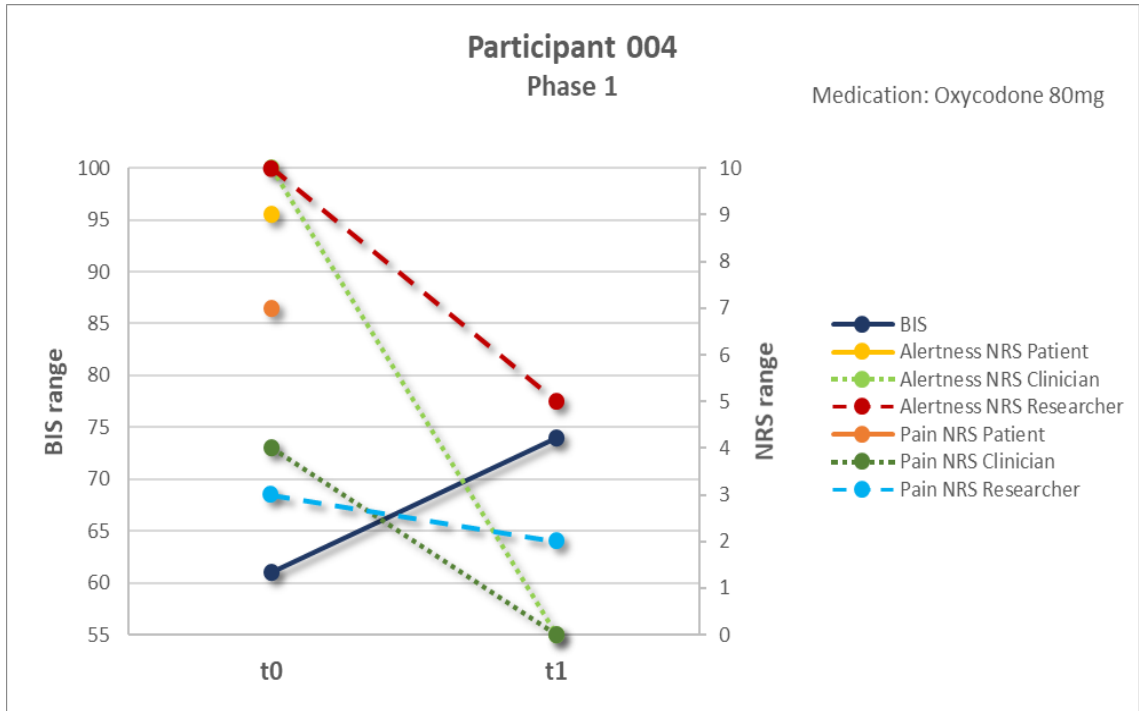
The ability of BIS to detect changes in patients' level of consciousness following the administration of medication with sedative effects was explored by comparing paired BIS scores before and 60 minutes after patients received such medication. Overall, 17 patients (Phase 1: n=12, Phase 2: n=5) received 21 doses of PRN medication with sedative effects.

Participants received breakthrough doses of either oxycodone (n=16) or morphine (n=5) administered predominantly orally (18/21, 85.7%). In three cases (3/21; 14.3%) patients received breakthrough medication subcutaneously. None of the participants received medication with sedative effects via a syringe driver for the first time during the study monitoring periods. The median oral morphine equivalent dose for breakthrough medication was 60 (IQR 20 to 90) mg.

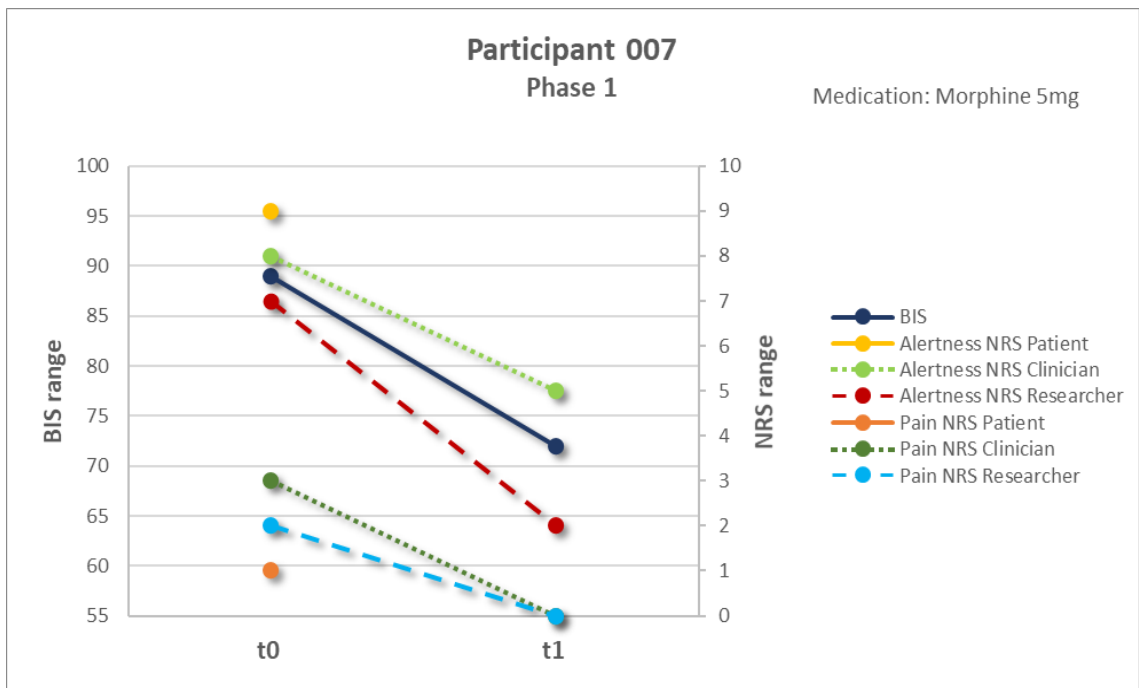
Indications for the administration of medication with sedative effects were recorded for 19/21 (90.5%) occasions on which patients received such medication. In all cases, hospice clinicians documented more than one indication for administering breakthrough medication. Reported indications were pain (n=19), anxiety (n=9), restlessness (n=5), and agitation (n= 1).

Reliable BIS values just before (t0) and 60 minutes after breakthrough administration (t1) were available for 12/21 (57.1%) of the occasions when breakthrough doses of medication with sedative effects were administered. Of these, eight occurred in Phase 1 and four in Phase 2. Thus, 12 pairs of BIS values were included in the sensitivity to change analysis.

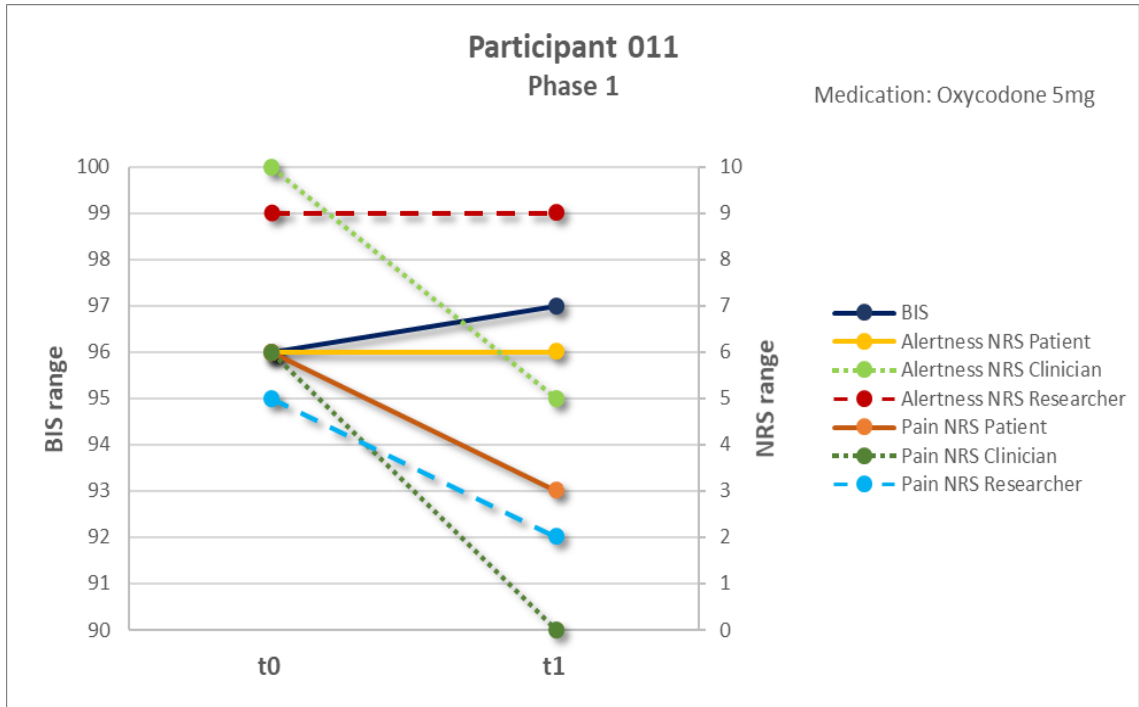
The median BIS value just before administration was 90.5 (IQR 78 to 95.75) and this was slightly higher than the median BIS value 60 minutes after administration (88.5; IQR 72.5 to 95). However, this reduction in BIS values was not statistically significant ( $Z=-0.62$ ;  $p=0.53$ ). Similarly, the median clinician-rated alertness NRS score just before administration was 10 (IQR 6.75 to 10), and this was marginally higher than the equivalent median score 60 minutes post administration (9.5; IQR 5 to 10). However, as with BIS values, this change was not statistically significant ( $Z=-0.94$ ;  $p=0.35$ ). Changes in BIS scores and other outcome data in the 60-minute intervals following breakthrough administration are graphically presented for the 12 occasions on which patients received such medication in **Figures 6.6 to 6.17**.



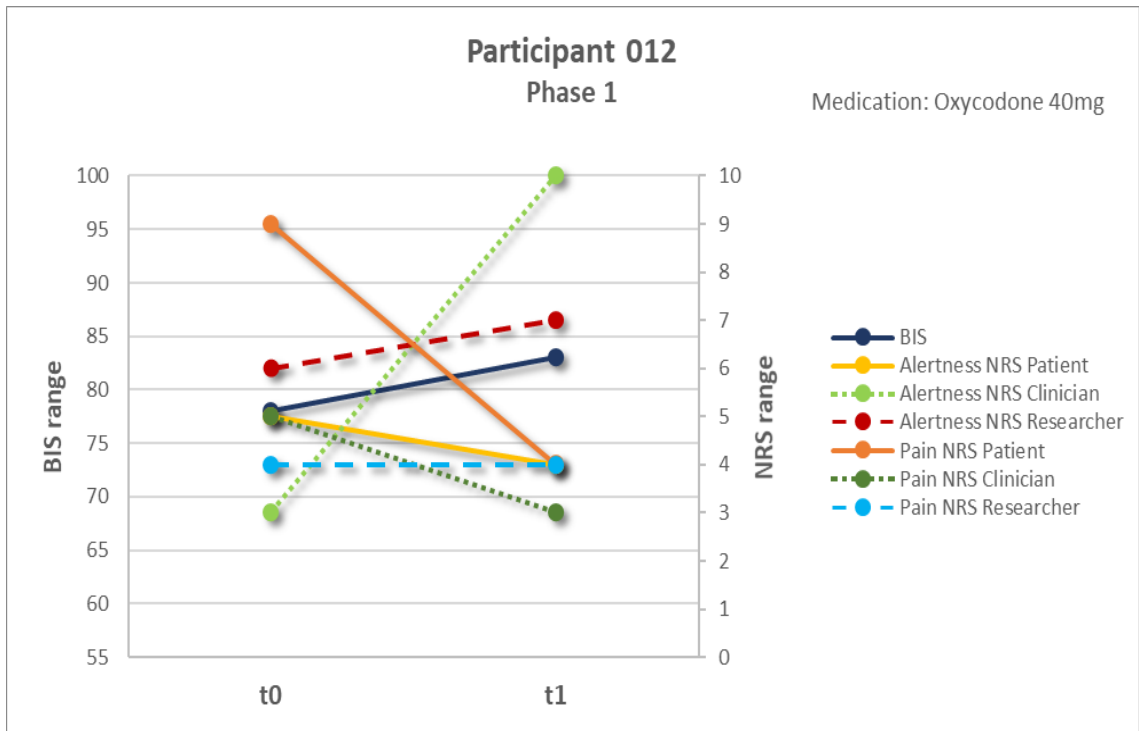
**Figure 6.6:** Outcome data before and after breakthrough administration for Participant 004 in Phase 1



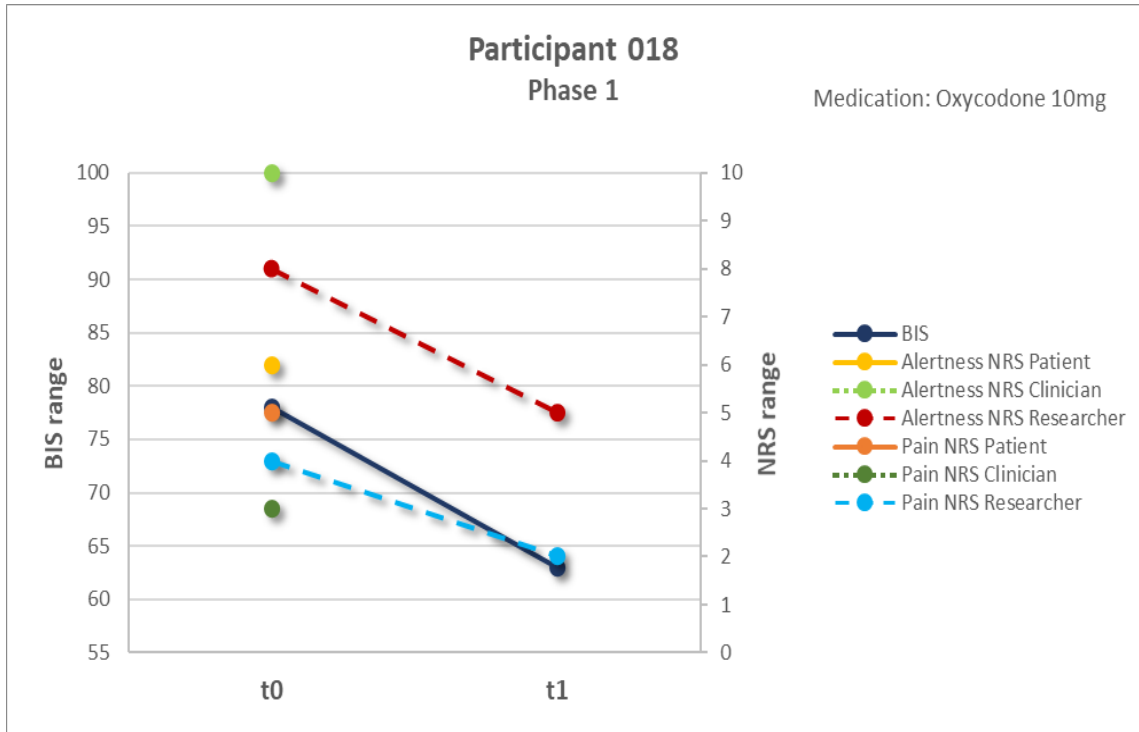
**Figure 6.7:** Outcome data before and after breakthrough administration for Participant 007 in Phase 1



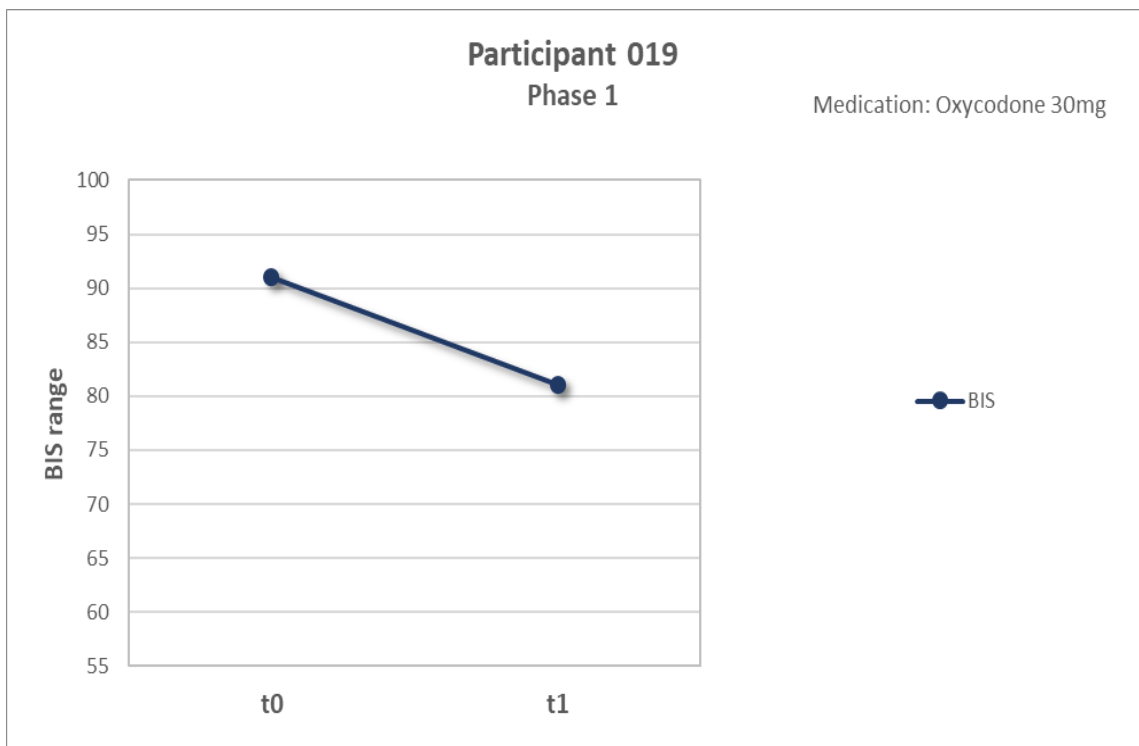
**Figure 6.8:** Outcome data before and after breakthrough administration for Participant 011 in Phase 1



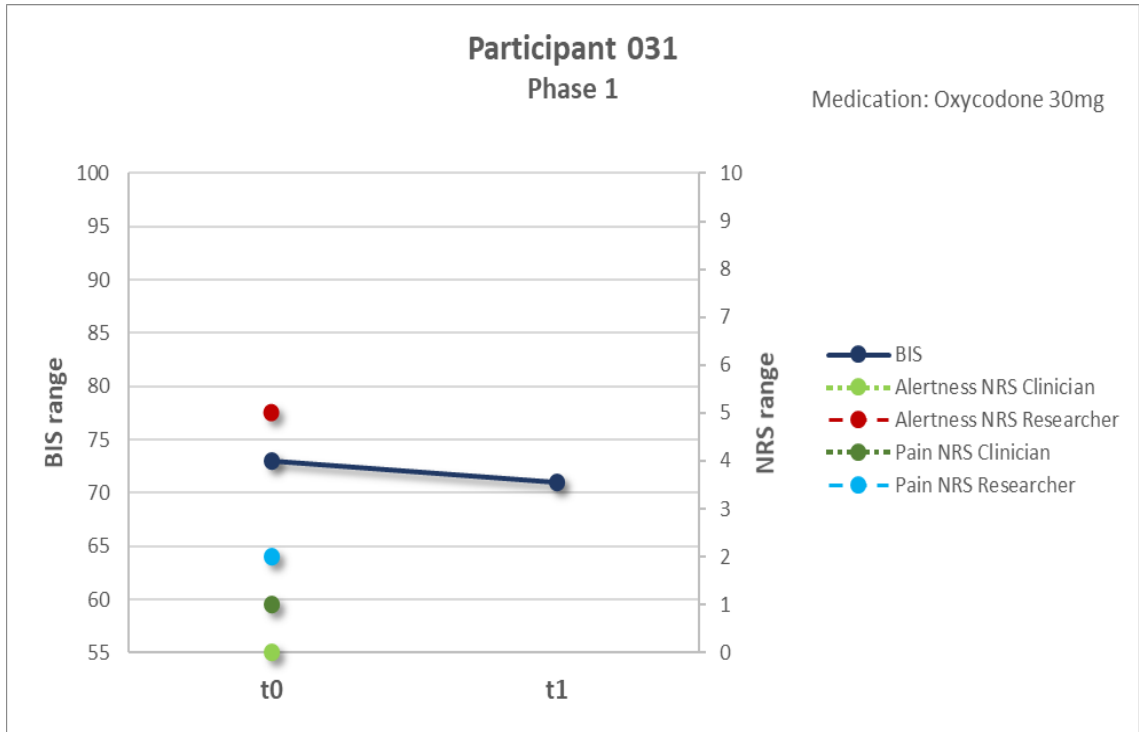
**Figure 6.9:** Outcome data before and after breakthrough administration for Participant 012 in Phase 1



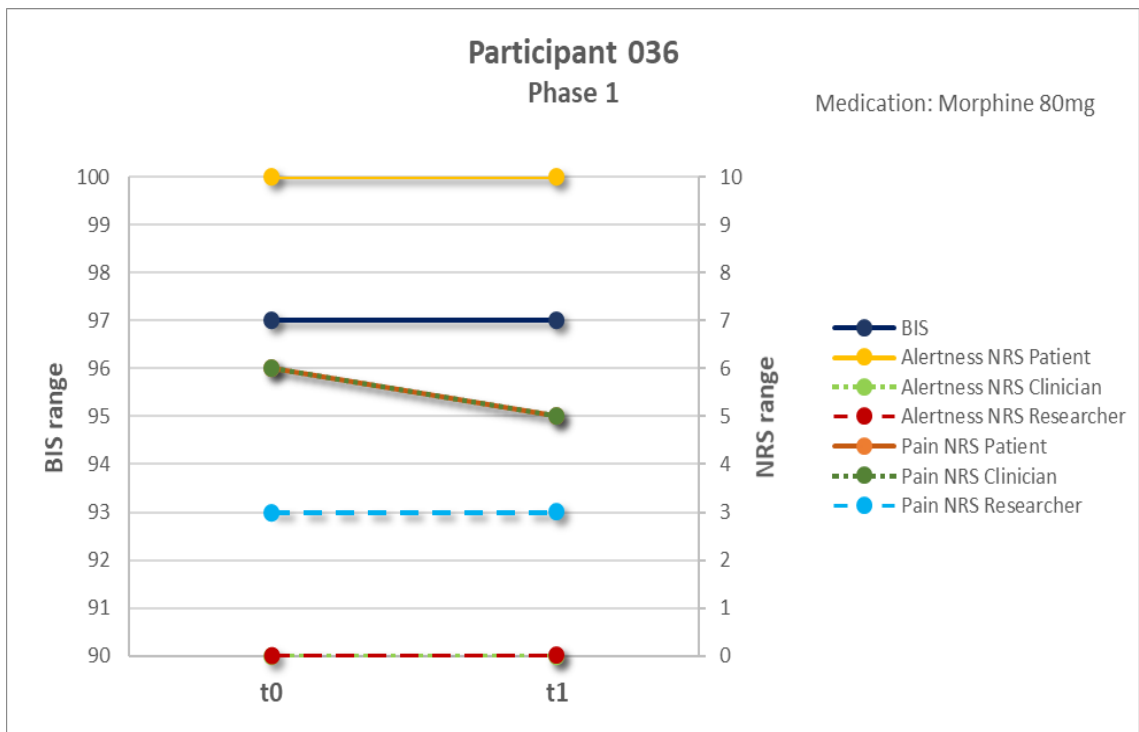
**Figure 6.10:** Outcome data before and after breakthrough administration for Participant 018 in Phase 1



**Figure 6.11:** Outcome data before and after breakthrough administration for Participant 019 in Phase 1

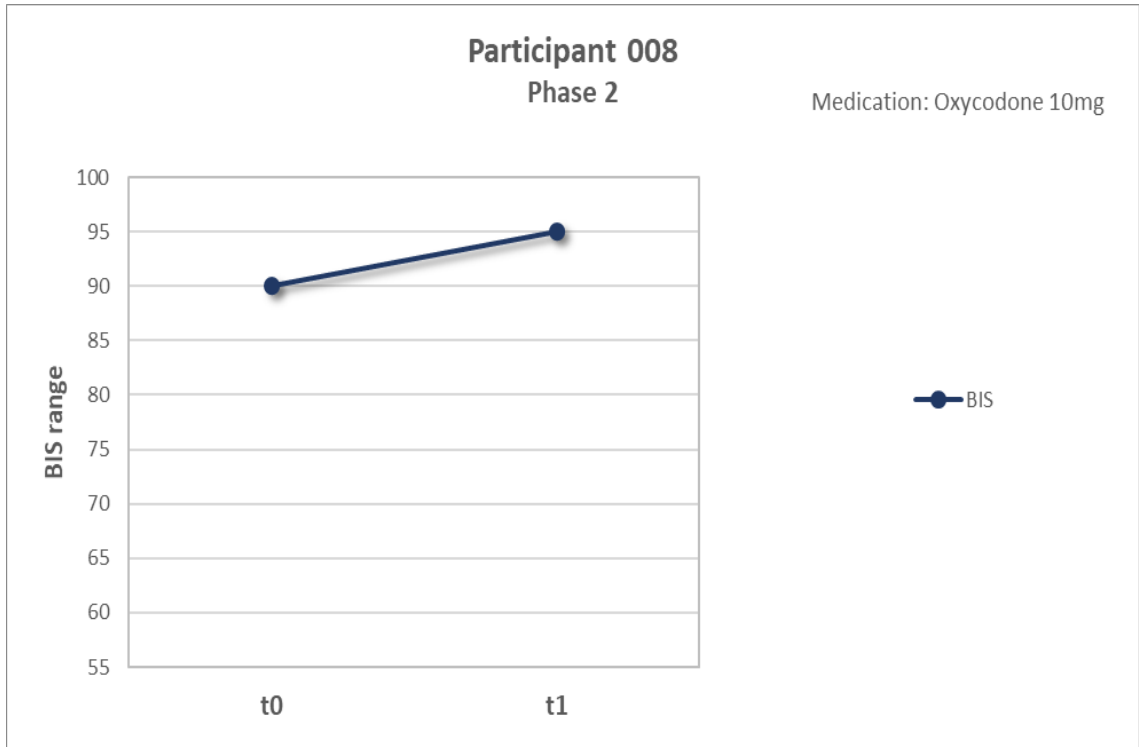


**Figure 6.12:** Outcome data before and after breakthrough administration for Participant 031 in Phase 1

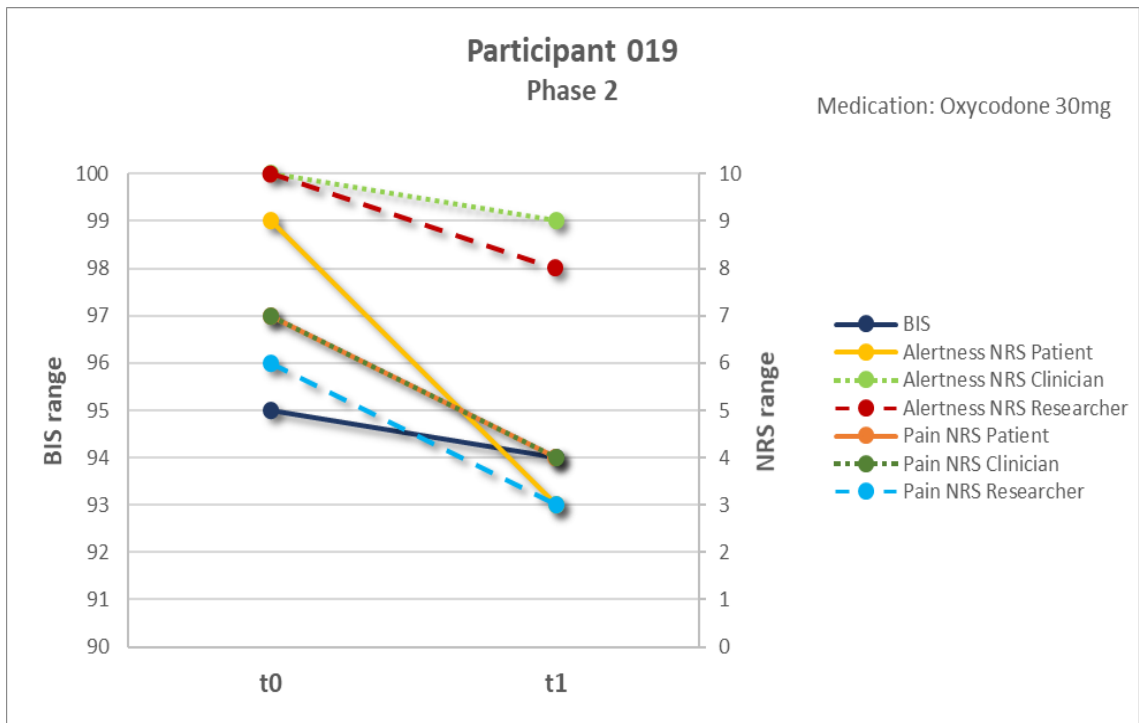


**Figure 6.13:** Outcome data before and after breakthrough administration for Participant 036 in Phase 1

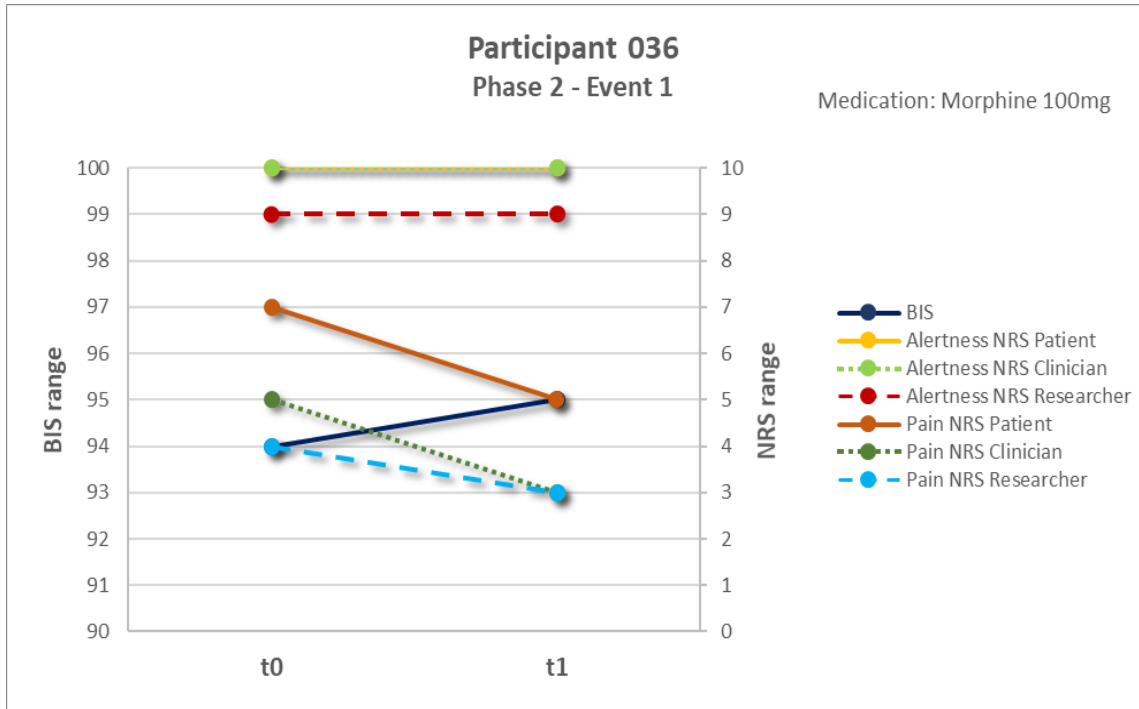




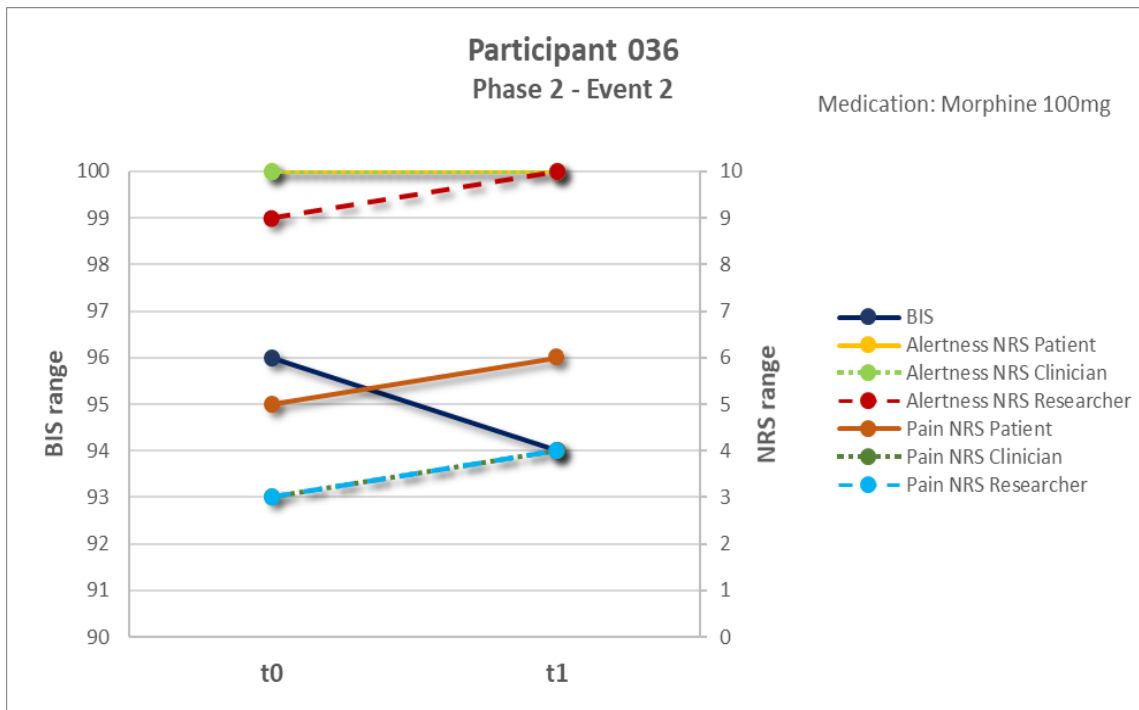
**Figure 6.14:** Outcome data before and after breakthrough administration for Participant 008 in Phase 2



**Figure 6.15:** Outcome data before and after breakthrough administration for Participant 019 in Phase 2



**Figure 6.16:** Outcome data before and after breakthrough administration for Participant 036 in Phase 2 (Event: 1/2)



**Figure 6.17:** Outcome data before and after breakthrough administration for Participant 036 in Phase 2 (Event: 2/2)

## Secondary outcomes

### Relationship between BIS and clinician-rated measures

For Phase 1, 107 pairs of BIS and clinician pain and alertness NRS data, and 59 pairs of BIS and clinician RASS-PAL data were included in the analyses. No evidence of association between BIS and clinician pain NRS data ( $r=0.08$ ; 95% CI -0.16 to 0.30), or BIS and clinician RASS-PAL data ( $r=0.18$ ; 95% CI -0.20 to 0.52) was found. However, a low correlation was found between BIS and clinician alertness NRS scores for Phase 1 data ( $r=0.42$ ; 95% CI 0.21 to 0.59).

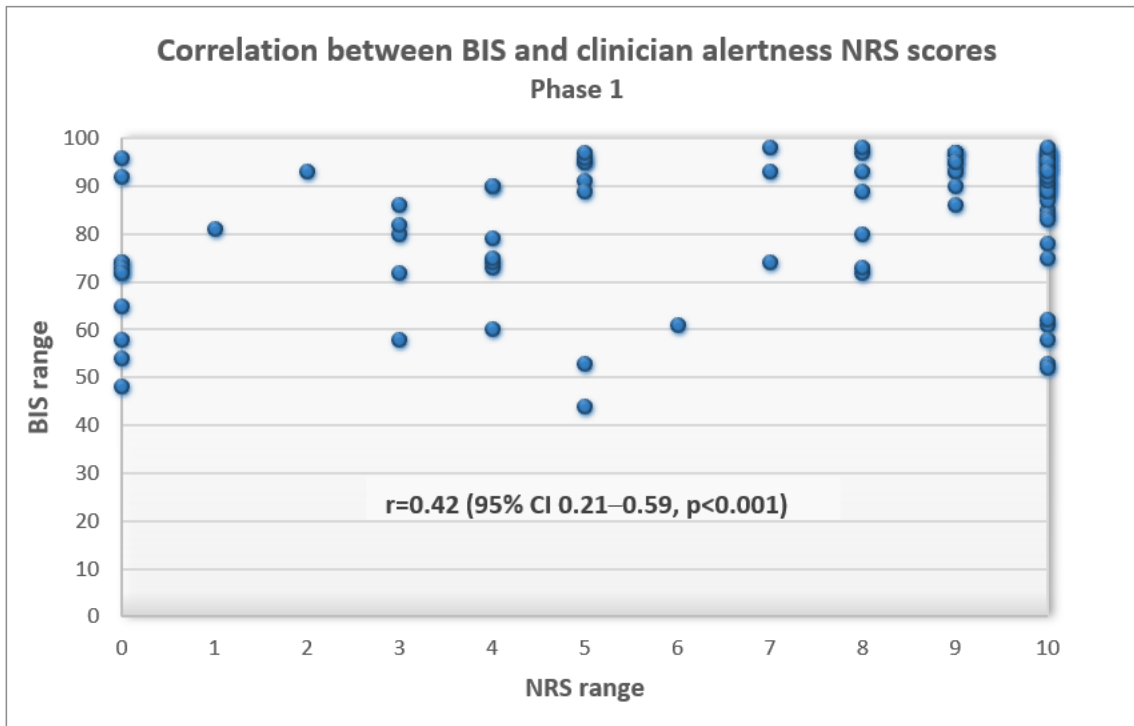
For Phase 2, 17 pairs of BIS and clinician pain and alertness NRS data, and 11 pairs of BIS and clinician RASS-PAL data were included in the analyses. No evidence of association between BIS and clinician pain NRS data ( $r=0.56$ ; 95% CI -0.06 to 0.87), or BIS and clinician RASS-PAL data ( $r=0.25$ ; 95% CI -0.81 to 0.93) was found. However, a high correlation was found between BIS and clinician alertness NRS scores for Phase 2 data ( $r=0.84$ ; 95% CI 0.49 to 0.96).

**Table 6.7** below provides a summary of correlation coefficients for pairs of BIS and clinician-reported outcomes for each study phase. Scatter plots of statistically significant correlations are presented in **Figures 6.18** and **6.19**.

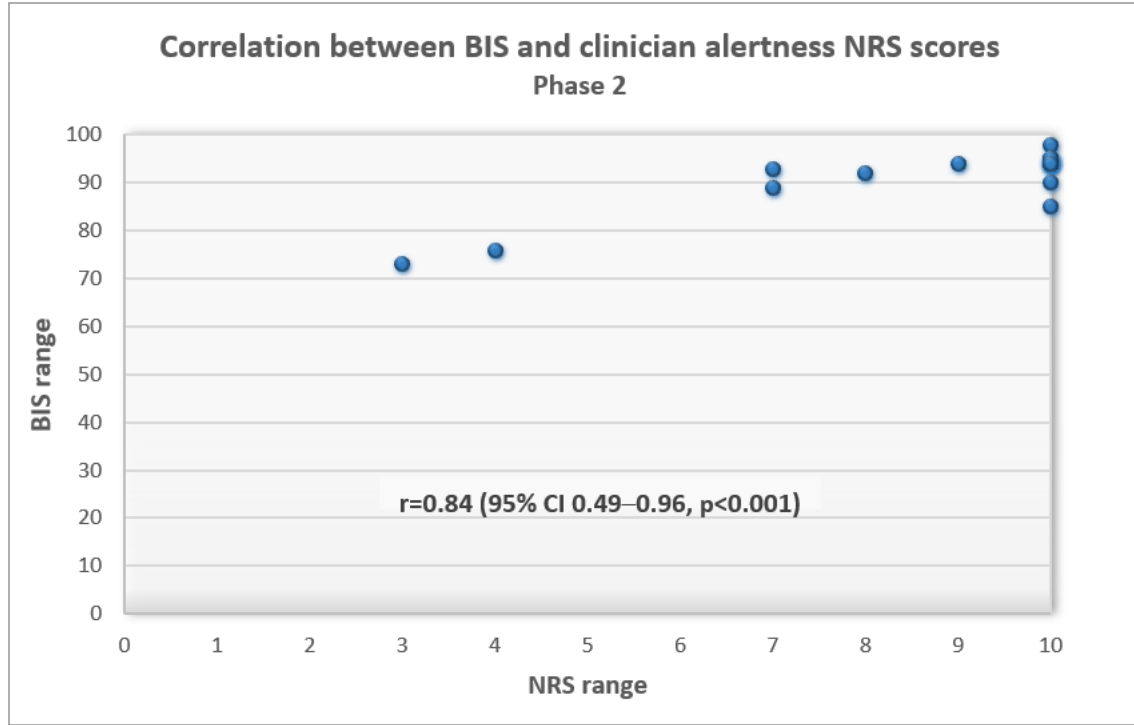
**Table 6.7:** Correlation coefficients for BIS and clinician-rated measures by study phase

Variables	Number of paired data	r	95% CI	p-value
<b>Phase 1</b>				
BIS and clinician-rated alertness NRS	107	0.42	0.21–0.59	<0.001
BIS and clinician-rated pain NRS	107	0.08	-0.16–0.30	0.51
BIS and clinician-rated RASS-PAL	59	0.18	-0.20–0.52	0.33
<b>Phase 2</b>				
BIS and clinician-rated alertness NRS	17	0.84	0.49–0.96	<0.001
BIS and clinician-rated pain NRS	17	0.56	-0.06–0.87	0.06
BIS and clinician-rated RASS-PAL	11	0.25	-0.81–0.93	0.58

Number of participants: Phase 1 n=40, Phase 2 n=5; BIS: Bispectral index; NRS: Numerical Rating Scale; RASS-PAL: Richmond Agitation-Sedation Scale – Palliative version.



**Figure 6.18:** Scatter plot of BIS and clinician alertness NRS scores in Phase 1



**Figure 6.19:** Scatter plot of BIS and clinician alertness NRS scores in Phase 2

### **Inter-rater reliability of clinician-rated RASS-PAL and convergent validity of clinician-rated RASS-PAL and alertness NRS**

The convergent validity of the clinician-rated alertness NRS and RASS-PAL was assessed using correlation coefficients. In total, data for 98 paired observational assessments of patients' consciousness levels were available for comparison. A correlation coefficient of 0.58 (95% CI 0.37 to 0.73) was found, indicating a moderate association between the two measures.

For the assessment of the interrater reliability of the RASS-PAL, 56 hospice clinicians (nurses: 48/56; 85.7%, physicians: 8/56; 14.3%) completed the RASS-PAL for patients in both study phases. Overall, 93 paired RASS-PAL scores were included in the analysis. Assessments were performed almost simultaneously by the two clinicians who rated the scale on each occasion (median time difference between assessments 0 [IQR 0 to 2.5] minutes). The results of the analysis of clinicians' independent assessments of patients' consciousness levels using the RASS-PAL suggested low agreement between raters, with an ICC of 0.34 (95% CI 0.29 to 0.41).

### **Use of BIS in the assessment of pain in hospice inpatients**

To investigate how well BIS performs as a measure of pain assessment compared to clinicians' observational assessments, the correlation coefficient for paired BIS and patient pain NRS data was compared to that of paired patient and clinician NRS pain scores (see **Table 6.8**).

For Phase 1, 96 pairs of BIS and patient pain NRS data, and 149 pairs of patient and clinician pain NRS data were included in the analyses. No evidence of association between BIS and patient pain NRS scores was found ( $r=-0.08$ ; 95% CI -0.33 to 0.17). However, a weak correlation was found between clinician and patient pain NRS scores for Phase 1 data ( $r=0.24$ ; 95% CI 0.05 to 0.41).

For Phase 2, 17 pairs of BIS and patient pain NRS data, and 22 pairs of patient and clinician pain NRS data were included in the analyses. No evidence of association between BIS and patient pain NRS scores was found ( $r=0.28$ ; 95% CI -0.38 to 0.75). However, a moderate correlation was found between clinician and patient pain NRS scores for Phase 2 data ( $r=0.52$ , 95% CI 0.03 to 0.80).

**Table 6.8:** Correlation coefficients for BIS, patient- and clinician-rated pain NRSs by study phase

Variables	Number of paired data	r	95% CI	p-value
<b>Phase 1</b>				
BIS and patient-rated pain NRS	96	-0.08	-0.33–0.17	0.50
Patient-rated pain NRS and clinician-rated pain NRS	149	0.24	0.05–0.41	0.01
<b>Phase 2</b>				
BIS and patient-rated pain NRS	17	0.28	-0.38–0.75	0.36
Patient-rated pain NRS and clinician-rated pain NRS	22	0.52	0.03–0.80	0.03

Number of participants: Phase 1 n=40, Phase 2 n=5; BIS: Bispectral index; NRS: Numerical Rating Scale.

### Relationship between researcher-rated and other outcome measures

For investigating how observational assessments undertaken by staff with no clinical training in palliative care compared to those made by clinicians, the relationship between researcher-reported and all other outcomes was explored. **Table 6.9** shows the correlation coefficients for all pairs of analysed variables for each study phase.

Correlations for Phase 1 assessments varied from low to high, with the highest correlation found being between researcher- and clinician-rated alertness NRS ( $r=0.73$ , 95% CI 0.64 to 0.80). Low to moderate correlations ranging from 0.26 to 0.56 were found for all other paired researcher and clinician assessments. Similarly, researcher assessments correlated weakly with patient self-reported measures ( $r=0.30$  to 0.36), and weakly to moderately with BIS values ( $r=0.36$  to 0.58).

The majority of correlations for Phase 2 assessments were not statistically significant. Of those that reached statistical significance, the highest correlations were between researcher- and patient-rated alertness NRS ( $r=0.79$ , 95% CI 0.50 to 0.92), and researcher- and clinician-rated pain NRS ( $r=0.71$ , 95% CI 0.32 to 0.89). Researcher pain NRS scores also correlated moderately to those self-reported by patients ( $r=0.64$ , 95% CI 0.22 to 0.85).

**Table 6.9:** Correlation coefficients between researcher-rated and other measures by study phase

Variables	Number of paired data	r	95% CI	p-value
<b>Phase 1</b>				
Researcher-rated alertness NRS and patient-rated alertness NRS	150	0.30	0.12–0.46	0.001
Researcher-rated alertness NRS and BIS values	116	0.58	0.42–0.71	<0.001
Researcher-rated alertness NRS and clinician-rated alertness NRS	160	0.73	0.64–0.80	<0.001
Researcher-rated alertness NRS and clinician-rated RASS	93	0.46	0.22–0.65	<0.001
Researcher-rated RASS and patient-rated alertness NRS	92	0.30	0.04–0.53	0.02
Researcher-rated RASS and BIS values	65	0.48	0.17–0.70	0.003
Researcher-rated RASS and clinician-rated RASS	93	0.54	0.32–0.70	<0.001
Researcher-rated RASS and clinician-rated alertness NRS	93	0.56	0.34–0.72	<0.001
Researcher-rated pain NRS and patient-rated pain NRS	150	0.36	0.19–0.51	<0.001
Researcher-rated pain NRS and BIS values	116	0.36	0.16–0.54	0.001
Researcher-rated pain NRS and clinician-rated pain NRS	160	0.26	0.08–0.42	0.004
<b>Phase 2</b>				
Researcher-rated alertness NRS and patient-rated alertness NRS	23	0.79	0.50–0.92	<0.001
Researcher-rated alertness NRS and BIS values	17	0.21	-0.44–0.72	0.48
Researcher-rated alertness NRS and clinician-rated alertness NRS	22	0.18	-0.34–0.62	0.46
Researcher-rated alertness NRS and clinician-rated RASS	12	0.35	-0.64–0.90	0.39
Researcher-rated RASS and patient-rated alertness NRS	13	0.34	-0.56–0.87	0.37
Researcher-rated RASS and BIS values	11	-0.20	-0.92–0.83	0.67
Researcher-rated RASS and clinician-rated RASS	12	0.67	-0.31–0.96	0.07
Researcher-rated RASS and clinician-rated alertness NRS	12	-0.26	-0.88–0.70	0.53
Researcher-rated pain NRS and patient-rated pain NRS	23	0.64	0.22–0.85	0.003
Researcher-rated pain NRS and BIS values	17	0.53	-0.11–0.86	0.06
Researcher-rated pain NRS and clinician-rated pain NRS	22	0.71	0.32–0.89	0.001

Number of participants: Phase 1 n=40, Phase 2 n=5; BIS: Bispectral index; NRS: Numerical Rating Scale; RASS-PAL: Richmond Agitation-Sedation Scale – Palliative version.

## 6.7 Chapter summary

This chapter has presented the characteristics and flow of participants through the exploratory study of BIS monitoring, provided a description of outcome data, and detailed the results of the primary and secondary analyses undertaken. Findings suggest that conducting research with BIS in an inpatient palliative care unit was mostly feasible (three out of the five feasibility criteria were met; there were insufficient data for the assessment of one criterion) and acceptable to study participants (all acceptability criteria were met). There was insufficient preliminary evidence to support the clinical usefulness of BIS monitoring in this population.

Results of secondary analyses were mixed. The assessment of the convergent validity of clinician-rated RASS-PAL and alertness NRS indicated a moderate association between the two measures. The inter-rater reliability of RASS-PAL could not be supported as findings indicated only a weak agreement between RASS-PAL scores from independent raters. Regarding the analyses undertaken to explore the use of BIS in pain assessment, findings suggest that clinicians' observational assessments performed better than BIS in assessing participants' level of pain, although clinicians' pain assessments correlated only weakly to moderately with patients' own self-assessments. Nonetheless, mostly moderate to high correlations were found between BIS and the clinician-rated alertness NRS. Researcher-reported assessments correlated significantly with patient self-reports of pain and alertness, and clinicians' observational assessment of pain (using NRSs) across both study phases. However, due to the lack of adjustment for multiple comparisons, the statistically significant findings presented in this chapter should be interpreted with caution.



# **Chapter 7 Patients', relatives', and hospice clinicians' direct experiences and perceptions of Bispectral index monitoring: Methodology**

## **7.1 Chapter outline**

This chapter discusses the methodology of the qualitative study conducted with palliative care patients, patient relatives, and hospice clinicians who had a direct experience of BIS monitoring. The study design, aim, and objectives are described first; then, participant selection, recruitment, and consent processes. Finally, the chapter describes the data collection and analysis procedures employed. Regulatory approvals for this research were obtained as part of the exploratory study of BIS monitoring (see **section 5.3**).

## **7.2 Study design, aim, and objectives**

This was a qualitative study using face-to-face, semi-structured interviews with palliative care patients, patient relatives, and hospice clinicians who had used or witnessed the use of BIS in the exploratory study. The aim was to explore participants' views on, and direct experiences of, BIS monitoring.

The objectives of this study were to: i) gain insight into participants' direct experiences of BIS monitoring, ii) validate, add clarity and depth, and enable the interpretation of participant experience questionnaire findings, iii) explore the feasibility of clinician-rated pain and alertness measures, iv) identify contextual and design issues that could affect participation in future research with BIS, and v) identify potential facilitators and barriers to the introduction of BIS monitoring into clinical practice.

## **7.3 Setting and participants**

Study participants were recruited from the inpatient unit of the MCHH. All interviews took place in private rooms at the recruitment site.

## Eligibility criteria

Patients, relatives, and hospice clinicians were eligible to take part in the study if they met the criteria outlined in **Table 7.1** below.

**Table 7.1:** Eligibility criteria for study participants

Inclusion criteria
<ul style="list-style-type: none"><li>• Adults (i.e. <math>\geq 18</math> years of age)</li><li>• Patients who had participated in Phase 1 of the exploratory study, irrespective of the extent of monitoring achieved OR relatives of patient participants who had witnessed their relative being monitored with BIS OR hospice clinicians who had witness patients under their care being monitored with BIS</li><li>• People who are able to provide fully informed consent</li></ul>
Exclusion criteria
<ul style="list-style-type: none"><li>• People who cannot communicate verbally in English</li><li>• Patients OR relatives for whom the nature and/or procedures of the study might be too distressing (as deemed by the attending clinical team)</li></ul>

## Sample size

The overall research aim in this study was broadly similar to that of the previous qualitative study undertaken as part of this doctoral project (see Chapter 3) and so the aim was to recruit 10-12 participants in each of the three participant groups. It was anticipated that this number would be adequate to achieve a comprehensive exploration of key themes across all participants and would also enable comparisons between participant groups.

## Sampling strategy

Participants were selected using a combination of convenience and purposive sampling strategies. Purposive sampling has been defined as the selection of participants based on specific criteria in order to obtain rich and relevant information which can provide answers to research questions (Mack, Woodsong, MacQueen, Guest, & Namey, 2005; Yin, 2011).

Numerous different techniques for purposefully selecting study participants have been described in the literature, each serving distinct research purposes (Palinkas et al., 2015; Patton, 1990; Teddlie & Yu, 2007). As this study endeavoured to gain a comprehensive understanding of patient participants' differing perceptions and experiences regarding the use of BIS technology, a maximum variation sampling method was chosen (Palinkas et al., 2015).

The inclusion of participants with a broad range of characteristics and/or experiences in the sample can promote the investigation of both individual variations and shared patterns that cut across cases (Patton, 1990). In order to ensure the inclusion of patient participants with diverse perspectives and experiences, a log of the characteristics of recruited patients was maintained. The log was used to help identify suitable participants. Patients were purposively selected based on their responses to the participant experience questionnaire, including their overall experience of using BIS and willingness to be further monitored.

No additional criteria were employed for selecting relatives and hospice clinicians for participation in qualitative interviews. Relatives and clinicians were included solely based on their willingness to participate and availability at the time of data collection (i.e. convenience sampling). Although convenience sampling is more prone to bias than other non-probability sampling techniques (Etikan et al., 2016), it is probably the most commonly employed sampling strategy in qualitative research due to being cost-effective and simple to implement (Jager et al., 2017; Patton, 1990). Given the challenges encountered in recruiting relatives of current patients for the qualitative study exploring the potential use of BIS monitoring (see Chapter 4), the limited availability of hospice staff, and the limited resources available for recruitment in the present research (i.e. one researcher), convenience sampling was deemed the most appropriate method for selecting relatives and clinicians in this study. However, as previously discussed (see Chapter 3), descriptive qualitative studies using non-purposively selected samples sit lower in the hierarchy of qualitative research designs and, therefore, are less likely to produce generalisable, high-quality evidence (Daly et al., 2007).

## **7.4 Participant recruitment and consent processes**

### **Hospice patients**

Patients who entered Phase 1 of the exploratory study were asked to indicate their willingness to be contacted by the researcher to discuss participation in a qualitative interview. Only patients who agreed to be approached and met the sampling criteria, were further contacted. Patients approached for participation were given an information sheet (**Appendix 5.1**) detailing the aim and procedures of the study and had the opportunity to ask questions.

### **Relatives of patient participants**

A member of the clinical team approached eligible relatives and provided a brief description of the study. Relatives who expressed interest in being interviewed, were subsequently contacted by the researcher for a comprehensive description of the interview procedure, were given an information leaflet and had the opportunity to ask questions.

### **Hospice clinicians**

An electronic invitation and information leaflet were circulated to all clinicians who took part in data collection for the exploratory study. Additional information on the nature and procedures of the study and the opportunity to ask study-related questions were given to all clinicians who responded to the invitation.

Informed consent was obtained from all participants who took part in qualitative interviews. Patients, relatives, and clinicians who expressed willingness to take part in the study, after being allowed at least 24 hours to consider participation, were asked to sign a consent form in the presence of the researcher (patient participants were asked sign an additional, separate consent form to that used for the exploratory study).

## **7.5 Data collection**

Individual, face-to-face interviews were conducted with a subset of patients who had been monitored with BIS as part of the exploratory study, their relatives, and hospice clinicians. The interviews were semi-structured and were conducted by means of a topic guide tailored to each participant group (see **Appendix 5.2**).

Interview topic guides drew on those used in the previous qualitative study (see **section 3.7**). They were initially drafted by the researcher, reviewed by the project Advisory Group, and refined based on feedback. Topic guides aimed to elicit information about:

- Participants' perceptions and direct experiences of BIS monitoring
- Their thoughts about the potential use of BIS as part of routine clinical care
- Patients' and relatives' overall experience of participation in the exploratory study
- Clinicians' experiences of completing observational measures of pain and alertness and their views about the potential integration of these into usual care
- Patients' and relatives' thoughts regarding participation in future randomised research with BIS (it was explained to participants that this was a hypothetical question to identify factors that could affect participation in a potential subsequent study with BIS, rather than asking participants to volunteer to take part in such research)

Data relevant to clinicians' views on, and experiences of, using observational pain and alertness measures were used for the assessment of the feasibility of these tools. Feasibility was defined as the user-friendliness of a measure in terms of administration and processing (Fitzpatrick et al., 1998).

All interviews were audio-recorded, with participants' permission. To supplement interview data, short notes of the overall demeanour of participants, pertinent non-verbal behaviours, and relevant comments not captured by audio recording, were taken during the interviews. These were developed into detailed field notes after the end of each interview.

A brief form was used to collect key socio-demographic information (age, gender and ethnicity) from relatives and clinicians who participated in interviews. For relatives, data were also collected on their relationship to participants and their living and employment circumstances. For clinicians, job title, years of professional experience and years spent working in palliative care, were also recorded.

## **7.6 Data analysis**

The research aim and type of collected data in this study were similar to those of the qualitative study presented in Chapter 3. The same data analysis method was therefore applied across the

two studies. Interview data were analysed following the five key stages of the framework approach (Ritchie & Spencer, 1994). A detailed description of the rationale for choosing this method and of the analytical procedure followed have been provided in Chapter 3.

## **7.7 Chapter summary**

This chapter has presented the research design and methodology of the interview study investigating patients', relatives', and hospice clinicians' perceptions and direct experiences of BIS monitoring in palliative care clinical practice. Potential participants were identified from those who had previously experienced or witnessed the use of BIS (as part of the exploratory study) employing a combination of convenience and purposive sampling strategies. Data were collected through holding face-to-face, semi-structured interviews with study participants and were subsequently analysed following the five key stages of the framework approach.

# **Chapter 8 Patients', relatives', and hospice clinicians' direct experiences and perceptions of Bispectral index monitoring: Results**

## **8.1 Chapter outline**

This chapter discusses the results of the qualitative study exploring the perceptions and direct experiences of patients, relatives, and hospice clinicians about BIS monitoring. Section 8.2 describes participant recruitment processes. Next, characteristics of the study population are presented. Lastly, section 8.4 presents the themes and subthemes generated from the analysis of interview data.

## **8.2 Recruitment of study participants**

### **Hospice patients**

All hospice patients (40/40) who took part in Phase 1 of the exploratory study (see Chapters 5–6) indicated their willingness to be approached for participation in qualitative interviews. Of these, 14 who met pre-specified selection criteria were approached, and 10 consented to participate. Three of the fourteen approached for participation refused to be interviewed due to experiencing pain and/or other symptoms, and the fourth left the hospice before being approached for consent.

### **Relatives of patient participants**

The target of 10-12 participants was not reached for the relatives' group. This was mainly because patients chose to be monitored with BIS technology during less busy times when their relatives were not present at the hospice and/or when they were not participating in other activities, such as complementary therapies or social groups. Only two patients' relatives were identified as eligible for inclusion and were subsequently approached. Both agreed to participate in an interview.

### **Hospice clinicians**

Overall, 51 hospice clinicians were contacted to take part in qualitative interviews via an electronic invitation. Of these, 26 responded to the invitation, and 10 were present at the hospice and available to participate in an interview at the time of data collection.

## **8.3 Characteristics of interview participants**

### **Hospice patients**

The median age of the ten patients who participated in qualitative interviews was 69 (IQR 58.3 to 74.5) years. Patient participants were predominantly male (6/10), White British/Northern Irish (6/10), had a principal diagnosis of cancer (8/10), and a predicted survival of “months” (i.e. 56 days or more) (9/10). This broadly reflected the distribution of characteristics of the entire group of participants who took part in the exploratory study. **Table 8.1** provides a full description of characteristics of interview participants.

Patient participants were purposively selected based on their responses to the participant experience questionnaire. Thus, interview participants were more likely to have reported a broader range of perspectives and experiences regarding BIS monitoring compared to the whole group of Phase 1 questionnaire respondents (see **Table 8.2**).

### **Relatives of patient participants**

One female (White British and aged 35 to 44 years) and one male (White British and aged 45 to 54 years) participated in one interview each. Their relationship to patient participants was that of adult child and spouse/partner, respectively.

### **Hospice clinicians**

Nine of the ten clinicians who were interviewed were female, one male. The majority were White British/Northern Irish (6/10) and were between the ages of 18 and 34 (8/10). Six were staff nurses, three senior nurses, and the tenth a senior house officer. Clinicians had a median professional experience of 5.5 (IQR 2.5 to 10) years in health care, and 2.5 (IQR 1.5 to 4) years in palliative care, at the time of participation.



**Table 8.1:** Interview participant characteristics

Characteristics	Patients (n=10)	Relatives (n=2)	Clinicians (n=10)
<b>Age (years)</b>			
<b>Median (IQR)</b>	69 (58.3–74.5)		
18–34		–	8
35–44		1	2
45–54		1	–
55–64		–	–
65–74		–	–
75–84		–	–
<b>Gender</b>			
Female	4	1	9
Male	6	1	1
<b>Ethnic group *</b>			
White English/ Welsh/ Scottish/ Northern Irish/ British	6	2	6
Any other White background	1	–	2
Any other Mixed/ Multiple ethnic background	1	–	–
Asian/Asian British Bangladeshi	1	–	–
Any other Asian background	1	–	2
<b>Primary diagnosis</b>			
Cancer	8	–	–
Kidney failure	1	–	–
Motor neurone disease	1	–	–
<b>Predicted survival **</b>			
Days (0–13 days)	1	–	–
Weeks (14–55 days)	–	–	–
Months (56 days or more)	9	–	–
<b>Relationship to patient</b>			
Spouse/Partner	–	1	–
Adult child	–	1	–
<b>Professional role</b>			
Staff nurse	–	–	6
Senior staff nurse	–	–	3
Senior house officer	–	–	1
<b>Clinical experience (years; median [IQR])</b>	–	–	5.5 (2.5–10)
<b>Palliative care experience (years; median [IQR])</b>	–	–	2.5 (1.5–4)

\*Ethnic group categories as recommended by the Office for National Statistics (2015), \*\*Assessed by Clinician Prediction of Survival (CPS)

**Table 8.2:** Responses to participant experience questionnaire of interviewed patients (n=10) compared to the whole group of Phase 1 questionnaire respondents (n=36)

Responses to participant experience questionnaire	Interviewed patients		All questionnaire respondents	
	n	%	n	%
<b>BIS sensor causing discomfort</b>				
0: No, not at all	7	70	21	58.3
1	0	0	10	27.8
2	2	20	3	8.3
3	0	0	1	2.8
4: Extremely	1	10	1	2.8
<b>Monitoring affected movement/activity</b>				
0: No, not at all	5	50	18	50
1	1	10	4	11.1
2	3	30	9	25
3	1	10	3	8.3
4: Extremely	0	0	2	5.6
<b>Overall experience of using BIS monitor</b>				
0: Good experience	7	70	23	63.9
1	1	10	7	19.4
2	0	0	4	11.1
3	2	20	2	5.6
4: Bad experience	0	0	0	0
<b>Willing to be further monitored</b>				
Yes	8	80	32	88.9
Need more time/to discuss with others to decide	1	10	2	5.5
I prefer not to say/I am not sure	0	0	1	2.8
No	1	10	1	2.8

## 8.4 Framework analysis of interview transcripts

Interviews were conducted between November 2017 and November 2018 in patients' rooms or other private rooms at MCHH. Interviews lasted between 11 and 22 minutes. The framework analysis identified three main themes incorporating eight subthemes. Main themes were: (1) perceptions and experiences of BIS monitoring, (2) perceptions regarding participation in the exploratory study, and (3) clinician interviewees' views and experiences of observational pain and alertness measures. The first two themes arose from interviews held with all participant groups. The third theme emerged from interviews conducted only with hospice clinicians (nine nurses plus one senior house officer). As discussed in Chapter 5, clinicians' perceptions regarding the user-friendliness of pain and alertness measures informed the evaluation of the feasibility of using these tools in the palliative care setting.

**Table 8.3** provides an overview of core themes, subthemes, and categories. Similar to Chapter 4, in order to aid comparison, patient, relative, and hospice clinician views are discussed side by side throughout the following sections. Patient quotes are presented in blue, quotes from the two interviewed relatives in purple, and hospice clinician quotes are presented in brown. All names presented with quotes, other than mine (AMK), are pseudonyms.

**Table 8.3:** Overview of core themes, subthemes, and categories

Themes	Subthemes and main categories
<p><b>Perceptions and experiences of BIS monitoring</b></p>	<p><b>1. Direct experiences of BIS monitoring</b></p> <ul style="list-style-type: none"> <li>• Non-intrusive</li> <li>• Pain/discomfort caused by BIS sensor</li> <li>• Skin irritation</li> <li>• Monitoring duration</li> </ul> <p><b>2. Appearance of BIS sensor and monitor</b></p> <ul style="list-style-type: none"> <li>• Acceptable appearance</li> <li>• Visual impact of BIS sensor</li> <li>• “Unusual” appearance</li> </ul> <p><b>3. Incorporation of BIS monitoring into clinical practice</b></p> <ul style="list-style-type: none"> <li>• As long as it is clinically useful</li> <li>• As long as patient and/or family consent to its use</li> <li>• As long as appropriate training is available</li> <li>• As long as it doesn’t cause discomfort</li> <li>• Time and resource implications</li> <li>• Monitoring duration</li> </ul> <p><b>4. Participation in future research with BIS</b></p> <ul style="list-style-type: none"> <li>• Agreeable to take part in future research</li> <li>• As long BIS is additional to usual care</li> </ul>
<p><b>Perceptions regarding participation in the exploratory study</b></p>	<p><b>1. Contribution to research</b></p> <ul style="list-style-type: none"> <li>• Study-specific aim and objectives</li> <li>• Broader sense of altruism</li> </ul> <p><b>2. Useful distraction</b></p> <ul style="list-style-type: none"> <li>• Breaking hospice routine monotony</li> <li>• Additional interaction</li> </ul>
<p><b>Clinician interviewees’ views and experiences of observational pain and alertness measures</b></p>	<p><b>1. Experiences of using observational measures</b></p> <ul style="list-style-type: none"> <li>• Feasibility of measures</li> <li>• Subjective interpretation of observable signs and responses</li> </ul> <p><b>2. Integration of observational measures into usual care</b></p> <ul style="list-style-type: none"> <li>• Potential for improving patient care</li> <li>• Monitoring of effects of interventions</li> <li>• Possible challenges</li> </ul>

## Perceptions and experiences of BIS monitoring

This theme was the main focus of interviews, and therefore was discussed with all participant groups. Interview participants' thoughts and views about the BIS technology and their experiences of BIS monitoring were categorised into four subthemes: (1) participants' direct experiences of BIS monitoring, (2) their views about the appearance of BIS sensor, (3) their thoughts about the potential use of BIS as part of routine clinical care, and (4) patient and relative participants' thoughts regarding participation in future research with BIS. The first and latter two subthemes were developed deductively from topics included in the interview guide while the subtheme regarding the appearance of the BIS sensor was identified through inductive analysis.

### Direct experiences of BIS monitoring

All interviewed patients felt that the BIS device and sensor were small and easily handled. These characteristics and the application of the sensor on patients' foreheads, rather than on other body parts, contributed towards BIS monitoring being perceived as non-intrusive. Two patient participants specifically commented that after the sensor had been applied to their foreheads, they "hardly knew it was there". Most felt that BIS monitoring did not markedly affect their daily routines or care activities overall, despite finding that it somewhat restricted their movement.

It [*my care*] was status quo as normal but I had something attached to my forehead, so I didn't find any problem with it. I didn't find that it interfered with anything, and I certainly didn't find it intrusive. I was just relaxing, watching TV while it was happening, no impact at all. (Scott, patient)

It [*sensor*] was just on my forehead, so I couldn't really see it and it didn't affect me that much. And the screen and all was light and small... I could move it around when I wanted to get up and do stuff. That said, I couldn't move as I would without this [*monitoring*] being in place, but it was easy to have it on and reach something, go to the toilet and things... Really it [*monitoring*] was not much of an issue at all. (Robert, patient)

AMK: And how did you find having the monitor attached during the study?

Mary (patient): I hardly knew that it was on. I didn't really even know it was there to be honest.

AMK: Did you find that it affected your movement or usual activities while it was on?

Mary: No, it didn't. I wasn't up to too much anyway...

Clinicians and relatives were not directly monitored with BIS, so their experiences were distinct to those of patients. However, all clinicians and both relatives expressed similar views to those of patient interviewees regarding the non-intrusiveness of BIS monitoring, based on their experiences of witnessing patients using the technology. Nurse interviewees additionally commented that BIS monitoring did not interfere with providing patient care.

I thought it [*BIS monitoring*] was unobtrusive and thought that it was very acceptable. For my mum really, it didn't seem to affect her in any way. So, I didn't think that it was intrusive or obtrusive at all. (Cristy, adult child)

It doesn't really get in our way, so when it's just on the forehead the patients don't seem to be bothered by it, they don't even know if it's there really, which is nice... If it was something, like, on maybe their arms or fingers, it would be more hindering if they wanted to try and do something, I think they'd be more aware it was there. (Bowe, staff nurse)

It was quite compact and out of the way, so it didn't affect any care that we were giving, so it wasn't in any way an issue... Patients were still getting up and going to the bathroom, being independent as at their baseline with the monitoring in place. (James, staff nurse)

Most patients said that they felt no pain or discomfort from having the BIS sensor attached during the monitoring period or after it was removed.

AMK: So, how did you find using the monitor, the BIS, as part of this research project?

Sophia (patient): I found it fine, it was not painful, it was not intrusive in any way, it was fine... I just found it very straightforward, there was no pain or anything, I wasn't worried about anything.

AMK: Mm hmm... could you feel the sensor on your forehead whilst it was there, during the monitoring?

Sophia: I think once you put it, I didn't really think about it.

However, three patients expressed experiencing minor discomfort either during initial application of the sensor (until connection between the sensor and the monitor was established),

or during monitoring itself. Nevertheless, overall they did not feel that BIS monitoring was invasive.

AMK: And how did you find having the strip sensor applied on your forehead?

Mary (patient): That wasn't so comfortable, but it was alright.

AMK: I remember that you mentioned when you were completing the questionnaire that I gave you that it was uncomfortable when I was putting it on, when I was attaching it.

Mary: Yes, that's true. It wasn't bad but it wasn't that comfortable.

AMK: Was this when I first tried to apply it on your forehead?

Mary: Yes, but afterwards I couldn't feel it really.

AMK: So, it felt initially uncomfortable but then, during the monitoring, you were not as aware of it?

Mary: No, exactly.

One of the two relatives interviewed said that the sensor had caused some skin irritation on the area of their family member's forehead where it was applied. This resolved a few hours after the sensor was removed.

It [*BIS monitoring*] seemed to be non-invasive. There was a slight problem with irritation of the skin afterwards, but I think that's just the stickiness of the thing [*sensor*]. Her skin is sensitive anyway and it's thin, one of the side effects of the condition has been the skin thinning which has been going on for a while. But apart from that, it seemed non-invasive. (Homer, spouse/partner)

When asked about the duration of BIS monitoring, the majority of participants felt that four hours was an appropriate amount of time for the patient group with whom the monitor was being used (i.e. patients who were mostly able to mobilise and engage with hospice activities). Participants mostly expressed that the monitoring time frame was acceptable as it did not interfere with patients' activities, such as mealtimes and personal hygiene routines. However, when initially approached about the exploratory study some patients had felt that having the monitor attached for four hours could be bothersome given the anticipated movement restriction.

I think that's a reasonable amount of time. Because, I think, any more and then you'd be pushing into lunch times, dinner times, then they're going to bed, toilet and things like that so I think that's a good time slot. I don't think it's too much or too short. (Kim, senior staff nurse)

Well, when I was first approached and I was told that it's going to be four hours, I thought that that would be a bit long. But as it happened, it wasn't a constant intrusion and basically, I was able to continue doing what I normally did. So, if a similar situation arose, for up to four hours or anything like that, I don't anticipate any problem with it. (Scott, patient)

Prior to the beginning of each monitoring period, clinicians, patients, and relatives were shown how to attach and detach the sensor from the BIS monitor. Being able to disconnect the sensor and take a break from monitoring, if needed, mitigated movement restriction and contributed towards the monitoring time frame being perceived as acceptable.

I think four hours it's fine because the patients can be disconnected so this is not an issue. They are fine and I haven't had any issue or negative feedback on this by any of the patients. (Laura, senior staff nurse)

Nevertheless, three nurse interviewees felt that four hours was a lengthy period for patients who wanted to leave the ward (e.g. patients who wanted to visit the garden).

AMK: Do you have any thoughts about the amount of time that we were asking patients to use the monitor for? It was four hours.

Maria (staff nurse): I think for patients who like to go outside, it's a bit too long. This is my feeling. I think that it's a bit too long for those who are mobile and like to go outside.

### **Appearance of BIS sensor and monitor**

Overall, participants found that the appearance of the BIS sensor and monitor was acceptable, although a few clinician interviewees raised the issue of the visual impact of the BIS sensor. This mainly related to its perceived "medical" appearance and the presumed invasiveness of the technology when it was initially seen. These concerns mostly subsided after witnessing patients using BIS in practice.



I think when I first saw it, it looked... a little bit scary, like it looked very invasive, but it's not actually. It kind of looked like electric shocks, but you know that it doesn't actually do that. When I first saw it, I thought that it would be a burden for the patients being on it for hours, they wouldn't be able to go to the toilet, or do other things while they were on it. But as I've got to know it, I discovered that that wasn't the case, it doesn't affect them that much and it doesn't cause them any harm or anything. (Harriet, senior staff nurse)

Two clinician interviewees said that seeing patients using the BIS monitor was "unusual" as the use of medical devices in palliative care in general is uncommon:

It was unusual I guess [*seeing patients using BIS*] because we're used to them not being attached to monitors or anything. That was unusual, that something is being measured because we don't even do observations on the patients. (Olivia, senior house officer)

One nurse interviewee expressed concerns about the potential reaction of relatives when seeing BIS used with their family member:

I think I'm kind of biased when you ask me "Does it look okay?" I think it looks fairly normal. Sometimes when people aren't used to medical things, if you haven't come from a medical background, just seeing that can be quite daunting. I don't know, that's what I think just because to me it looks quite standard, it's not even... it doesn't get in the way. But I'm used to seeing different like machines being used on people whereas a family member seeing that on their mum or dad may think "Oh gosh, it's on their head and it's attached to a machine" thinking that it makes them look sicker in a way. (Bowe, staff nurse)

In contrast, none of the patients or relatives interviewed expressed concerns regarding the appearance of the BIS sensor or monitor. Although, similar to clinicians, a few found its appearance unusual, they mostly used humour to describe their experience of BIS monitoring.

It was just interesting to have a strip around your head like an Indian, but it wasn't really strange at all. (Milo, patient)

AMK: How do you think that your family would find seeing you having the sensor on your forehead?

Oprah (patient): They would laugh at it probably, like they would come in and say “Hell, I didn’t know that you were pretending to be a robot!” [*laughter*].

Well, I took some pictures, because it’s an unusual situation and worth photographing, and in fact we sent the pictures to some people and told them a variety of humorous things about what was actually going on, none of which were true. (Homer, spouse/partner)

### **Incorporation of BIS monitoring into clinical practice**

Interview participants in general had no objections to the potential incorporation of BIS into palliative care clinical practice. However, they highlighted that certain conditions would need to be met. The clinical benefit of BIS was identified as a main requirement by all participant groups. Specifically, participants expressed the opinion that BIS would be acceptable to use in clinical practice if it provided useful information that could improve patient care and comfort.

If research shows that it does improve patient care, then that would obviously be a massive benefit. But we have to be sure that this can be useful for patients first, before we start using it. (Harriet, senior staff nurse)

AMK: So, we’ve used the BIS technology as part of this research project, that your relative kindly participated in, and I was wondering how would you feel if it was to be used as part of patients’ routine care here at the hospice?

Cristy (adult child): If it’s proven to be valuable, then absolutely... I can’t think of any valid objection because it’s so non-intrusive and acceptable in my opinion.

I wouldn’t mind [*being monitored*] as long as it was useful. You can’t feel the thing, the electrodes on your head anyway, but it would have to be useful to me, to give useful information which could help with my situation. (Kumar, patient)

Other conditions identified specifically by clinician interviewees were: patient consent, training in handling and interpreting BIS, and a requirement that monitoring should not cause discomfort to patients. Most clinician interviewees felt that patients and their families should be given the

option to decide whether they would be willing to use BIS technology after being informed about how BIS operates and the potential benefits of including BIS monitoring in patients' care. They suggested that consent should be sought in advance, particularly in cases where patients are expected to become less conscious during their admission. Interviewed clinicians commented that providing information and gaining consent from patients or their families prior to BIS use could reassure family members about the appropriateness of BIS monitoring, especially if BIS was to be used with unconscious patients.

If it [*BIS monitoring*] was just something we did all the time, it might be more impacting on [*patients*]. So, I think they'd need to get a say in it, to say yes or no if they want it. I think that family members or actual patients would have to consent to it before it being used and maybe just giving them like a brief of things not to worry about. Because it's not a big deal for people that have capacity, but sometimes if the person is unconscious you might get families that are like "What's that?", people are just overanxious maybe. But if you explain it to them, I don't see why there would be a problem [*using BIS*]. (Bowe, staff nurse)

AMK: Do you have any thoughts about potentially using BIS with people who are less conscious or unconscious?

Harriet (senior staff nurse): They'd either have to consent to it before they lose consciousness or otherwise if someone else, like a next of kin, would be allowed to consent for them. Yes, because my only issue would be advance consent.

Clinician interviewees felt that for BIS to be used as part of routine practice, clinical teams should first receive information and training in handling and operating the monitor, and in the interpretation and appropriate use of BIS data. In relation to this point, a few nurse interviewees voiced concerns regarding the time and resource implications of incorporating BIS into clinical practice. In particular, they said that it might increase the workload of nursing staff and, given the limited time and resources available, may affect quality of care.

AMK: And are there any other challenges that you can think of that could possibly occur if this technology was to be used as part of patients' routine care?

Olivia (senior house officer): I think explaining to all the medical team and the nurses what it is and why we're doing it, and knowing what to do with the information. Like if I know someone's

slightly less conscious, does that mean that I should give them less benzodiazepines? I don't know. So, yeah, what to do with the information when we've got it, I guess.

Time constraints [*would be a potential challenge*] because it'd kind of be like another thing, you know, on our list of things to do. And another concern would be whether I'm putting it on properly, I'm doing it right. But obviously if I had adequate training then that wouldn't be a problem. (Harriet, senior staff nurse)

I think that this would be kind of different from a nursing perspective because of the job roles that we already have, the amount of work that is... I think our jobs are kind of being stretched and we're getting more work to do and I think that might affect the quality of work that we do with patients if we also have an additional thing to do as well as all the other aspects of nursing so I think that it may affect our workload. (James, staff nurse)

Patient comfort was another condition to BIS use in routine practice identified by interviewed clinicians. Some expressed that using BIS would be acceptable provided that patients were comfortable having it attached and suggested that patients should be monitored by clinical staff when initially using the technology to ensure that it is not causing undue discomfort.

I think it really does depend on the individual, how comfortable they are. I think that's a big one because everybody is so unique in terms of what they need. So, I think probably it very much depends on how comfortable that person is with it but also how much of a use it is. I think also with any sort of extra addition then you'd have to monitor how well the patient is getting on with it. (Aaliyah, staff nurse)

One nurse interviewee additionally commented that it may be inappropriate to use BIS with patients who are experiencing restlessness or agitation:

Maybe if you get someone who's got like agitation or something, I don't think they'd cope with that [*sensor*] on their head. (Bowe, staff nurse)

Patient and relative interviewees' views regarding the incorporation of BIS into clinical care mostly centred on the potential restriction of movement that could be experienced by patients if the technology was to be used routinely. They emphasised that the duration of BIS monitoring should be limited to a few hours on each occasion for patients who are able to mobilise, whilst continuous monitoring was regarded as appropriate for less conscious or unconscious patients.

I wouldn't mind having it on every day, but it would have to be for a short period, like three, four hours the most, I think. Otherwise, it could be an inconvenience because you can't just move around or go out as easily... If I was not conscious, that wouldn't be a problem because I wouldn't move [*laughter*] so I wouldn't mind having it on all the time really, if it was useful.  
(Kumar, patient)

I suppose as it stands then a few hours per use, if you will, would be acceptable, because perhaps more could restrict them [*patients*] from doing what they normally do... For people who are unconscious, using it all the time wouldn't be an issue I don't think, because it doesn't cause discomfort and it's not obtrusive. (Cristy, adult child)

### **Participation in future research with BIS**

All patients and both relatives interviewed expressed that they would agree to participate (or that they would agree for their family member to participate) in a possible future randomised study with BIS technology. Their willingness to take part in such research was mainly influenced by the fact that BIS was perceived as being non-intrusive, their overall experience of participating/witnessing their family member participate in the exploratory study, and their willingness to contribute to research.

I'm very willing to help research so yes, I would be happy to participate. Because I didn't notice it really, it was not intrusive. Therefore, why would I not help again? Why would I say no?  
(Mary, patient)

Although agreeable to their family member participating in future research, one of the two relatives stressed that any research intervention (i.e. either BIS monitoring or monitoring

through observation by clinical staff) would have to be additional to the standard care provided to their relative:

Cristy (adult child): How would I feel if my relative was to be involved [*in future research*]?

AMK: Yes

Cristy: Absolutely fine because if she's [*family member*] getting treatment as usual and the monitoring would be on top of this, an addition, then I think that's completely acceptable.

### **Perceptions regarding participation in the exploratory study**

Reflecting on all the procedures of the exploratory study, all ten patients and both relative interviewees expressed positive views about their/their family member's participation in the study. They generally felt that the study procedures were not overly burdensome, principally because BIS monitoring was not considered to be invasive or intrusive, and mostly attributed their positive views to a sense of contributing to research and getting a useful distraction from routine hospice activities through participating in the study.

### **Contribution to research**

All patient and both relative interviewees expressed positive feelings about having participated/their family member having participated in the study as they perceived participation as an opportunity to contribute to the advancement of scientific knowledge and they hoped that knowledge produced by the study could help other patients in the future. For some, engagement in the exploratory study was considered important because of its particular research aim and objectives, while others described a broader sense of altruism in contributing to research in general.

AMK: How did you find the overall experience of taking part in this study?

Anne (patient): It was good. Didn't feel much really as I said and if it helps some other people in the future, then that's very good. You have to help research if you can, you know, so that new things, treatments and technologies and stuff are tested and maybe they'll help some people later on.

I think that it was very good, I was happy to be involved because of the actual study and what you're trying to do. I think that it's important. Because sometimes people are drowsy, especially if they're receiving lots of pain medication and maybe they can't show how alert they are, and this is measuring that directly with the sensors so maybe it can help somebody else in the future. (Kumar, patient)

AMK: ...how did you find the overall experience of your relative taking part in the study?

Cristy (adult child): Um... I think it's valuable information that you're looking for and I consider it to be a positive thing... and I think it's measured in a pretty non-invasive and obtrusive way, so I was very happy for my mum to take part.

Even though clinician interviewees were not directly asked about their overall opinion of the exploratory study, their views emerged from the discussion. Most interviewed clinicians had positive views about the study and the involvement of patients under their care in it. These perceptions, similar to patient and relative participants, stemmed from the idea that research in general and the exploratory study in particular, could generate new knowledge that could contribute towards improving clinical practice and, therefore, patient care.

I feel quite positively about the study, about having it, being involved in Marie Curie. Because any kind of research or anything to make us do our jobs better or to benefit people is good, and I felt willing to have the patients participate. (James, staff nurse)

I think that it's good, the whole trial. I do think it's beneficial and once you have obviously your findings and go back and do some more research, it may be proved that this is very useful because we can't do this here right now, we just look at someone, assess, and we can just try and guess what's happening. So, it's nice to see that there is something that might help us get these assessments right, be a bit more confident about them, because this will impact the care that we're giving to patients. (Bowe, staff nurse)

## Useful distraction

Participants overall expressed that patients' involvement in the study and their interaction with the researcher provided a useful distraction from their hospice routine. This was considered a further advantage of participating in the exploratory study.

I know that some patients here have enjoyed being part of the study. They get quite bored, so it's nice to do something and feel that they're contributing to something. (Olivia, senior house officer)

I think that they [*patients*] get quite a lot of interaction from it [*participating in the study*]. So, it's something for them, a good distraction, they get a useful distraction like that. (Florence, staff nurse)

One patient specifically said that the data collection at hourly intervals broke the monotony of their usual hospice activities:

AMK: So, how did you find the overall experience of taking part in the study?

Milo (patient): It was quite good, yeah, and somebody coming every hour, that was all right. It breaks the monotony of just sitting here and watching the telly all the time.

Another patient commented that they enjoyed the researcher's company during their participation in the study:

It [*the experience of participation*] was fine, I had no pain, I had no concerns, and I met you which is very nice, I enjoyed your company. I don't think I had any worries at all. (Sophia, patient)

## Clinician interviewees' views and experiences of observational pain and alertness measures

After having used the 11-point NRSs for pain and alertness and RASS-PAL during data collection for the exploratory study, hospice clinicians were asked about their experiences of scoring the three measures, and their views about the potential integration of these into clinical practice.



## Experiences of using observational measures

Interviewed clinicians generally considered all three measures to be user-friendly, quick and easy to administer. They commented that using the measures was a straightforward process and that the scoring took only a few seconds to complete on each occasion.

AMK: ...so I was wondering how did you find using those scales?

Maria (staff nurse): It was okay, yes. They were very straightforward, and it was quick and easy to complete them.

It [*using the measures*] was fine. They were fairly easy to follow and score, really. It took like two seconds to score each of them. So, it wasn't an issue at all. (Laura, senior staff nurse)

Clinician interviewees expressed that the pain NRS was the easiest of the three measures to score. This was mainly because the 11-point NRS already formed part of usual hospice practice for the assessment of patients' pain, and although pain scores were not systematically recorded and the scale was mostly used as a patient self-report measure, rather than an observational one, clinician interviewees felt that their familiarity with this particular scale aided the scoring process.

I think that the numerical one for pain was the easiest [*to use*]. We use the zero to ten scoring for our pain score anyway. The only difference is that we use it to ask patients to score their pain instead of us doing it. But it's one that everyone is familiar with here, so it makes it very easy to use. (Kim, senior staff nurse)

I think we're quite used to zero to ten scales, especially for pain. And we ask patients quite often to score their pain so we're quite used to these. The alertness and the sedation ones are a bit more complicated because trying to think how alert someone is, we don't normally do such assessments. So, pain was easier to score, the other two were also quite straightforward but had to think more. (Olivia, senior house officer)

One challenge to the administration of measures identified by clinicians was the subjective element of scoring which was considered to be an inherent issue with the use of observational

measures in general. Three nurse interviewees specifically said that scoring patients' symptoms based on their own interpretation of observable signs and responses could be difficult, especially when using the measures with patients that they did not know well.

I think sometimes scales generally can be a bit difficult though, especially when you don't know the patient really well, because you're not really aware what they normally look like when they are in pain or experiencing some other symptom. Because there are some where it just doesn't show and there are some people where it does, and you have to make a judgement based on what you see. (Aaliyah, staff nurse)

I thought that they [*measures*] were really good and easy to use... I just think that sometimes it's hard to like do the scoring because of the way the patient is. You can't really tell if they are ok or have any symptoms or if they are a bit drowsy. Because it's quite subjective and I don't know how you'd get around that, you can only base your score on what you see but maybe this doesn't reflect how the patient actually feels or is. (Harriet, senior staff nurse)

Comparing the alertness NRS and RASS-PAL, clinician interviewees felt that RASS-PAL was easier to score due to the presence of clear administration instructions with descriptions about how responses to stimulation should be assigned to each score (as opposed to the NRS where descriptors are available only for the scale ends). Interviewed clinicians said that these clear instructions reduced the subjective element of scoring and increased their confidence in the accuracy of assessments.

Between this [*alertness NRS*] and the other scale for sedation [*RASS-PAL*], I think the other was easier to score because it had the instructions next to each number and it helped you assess the patient better, and make sure that you chose the right score for how sedated they are. Perhaps having these instructions there to guide you when you do the scoring, can help so that different people, nurses and doctors, can do it more consistently, if you know what I mean. This scale gives you more clarification as to what you should expect to see from the patient for each score so it helps people to give more accurate scores, I think, and they would have the same idea as to what each score means. (Kim, senior staff nurse)

## Integration of observational measures into usual care

Interviewed clinicians overall had positive views about the potential integration of the pain and alertness NRSs, and RASS-PAL, into routine clinical practice. They viewed these measures as means to enable the systematic and consistent assessment and recording of patients' conditions which could help towards providing better care.

I think it's good, you should have them, a pain assessment score and alertness scores anyway really. We do it, but we don't really record it. We're doing it subconsciously. So, I think that it'd be helpful to have a more structured way of doing it. Because then you have comparisons, and you can see how they [*symptoms*] fluctuate against a scale. (Florence, staff nurse)

I think they are useful. I think that when the patient not always tells you everything and you can see that they are in pain for example, even if they are unconscious, you can see them groaning, grimacing, and reporting this is quite important. So, having these little tools may help us in reporting these, I think it's quite useful. (Laura, senior staff nurse)

I guess it allows you to figure out what's causing the pain or how the symptoms change over time. So, it allows you to give better care then as well. (Aaliyah, staff nurse)

One nurse interviewee emphasised that observational measures should only be used in cases where the information would be helpful for monitoring the effects of specific clinical interventions, rather than being used routinely with all patients:

If using these can be helpful for some patients, then absolutely, it's a good idea [*to use them in clinical practice*]. But I wouldn't necessarily say we should do things for the sake of doing them. You know, like we wouldn't do observations on somebody if we're not gonna use it, or react to it, or change something because of that. If it's gonna benefit the patient to see how their pain or alertness changes after we've done something, like given them medication, then fine. But I don't think we should use them with all the patients or all the time. (Kim, senior staff nurse)

Considering the possible challenges of integrating observational measures into usual hospice care, interviewed clinicians felt that there was potentially a large degree of subjectivity about

the interpretation of patients' symptoms and that this had implications for the consistency of scores between observers.

Challenges there would be because to every nurse the patient looks a bit different. To me, they may look as if they're not in pain. To another nurse, they may look as if they're in a bit of pain. Same with alertness, really. It's quite subjective. So, we can be looking at the same patient and have different ideas as to what their symptoms really are. (Maria, staff nurse)

As with the potential inclusion of BIS monitoring into usual care, some nurse interviewees felt that introduction of observational measures to clinical practice would add to their workload. Although brief and easy to complete, these nurses considered routine use of such measures as an additional task to fit in their already busy schedules.

The tools are simple, straightforward, they take just a few seconds to complete. But probably using them all the time may be a bit hard as there might be a little bit more work to do for the assessments to be carried out. It will add to the workload and we're already quite busy... It's like one more work to do. (Sunny, staff nurse)

## **8.5 Chapter summary**

The findings discussed in this chapter have provided an insight into patients', relatives' and hospice clinicians' direct experiences and perceptions of BIS monitoring, as well as into interviewed clinicians' thoughts and views about the use of observational pain and alertness measures in palliative care. Ten palliative care patients, two patient relatives, and ten hospice clinicians (nine nurses and a senior house officer) participated in individual interviews.

Participants' experiences of using/witnessing patients using BIS in clinical practice were overall positive. Interviewed patients, relatives, and hospice clinicians mostly perceived BIS monitoring as non-intrusive. They felt that the BIS device and sensor were small and easily handled, and felt that, although the monitoring somewhat restricted patients' movement, it did not markedly affect their daily routines or care activities.

After trialling BIS monitoring, patient and relative interviewees expressed that they would be willing to take part/their family member to take part in future research with BIS technology. Furthermore, all participants felt that incorporating BIS into hospice practice would be acceptable, provided that it was beneficial for patients and that patients and/or family members would consent to its use.

In spite of the inherent difficulties to the use of observational measures as a whole, hospice clinicians found that the pain and alertness measures considered in this study were feasible to use and, similar to BIS technology, felt that their potential inclusion into routine clinical practice could possibly improve patient care.

## **Chapter 9 Discussion, implications, and conclusions**

### **9.1 Chapter outline**

This chapter discusses key findings of the doctoral research with an emphasis on how this work contributes to and develops existing knowledge. Main findings of the empirical studies presented in this thesis are summarised, discussed in relation to the published literature, and possible explanations for principal findings are offered in the first part of the chapter. The strengths and limitations of each study, and the contribution of this research to the evidence base are considered next. Implications for clinical practice and directions for future research are discussed last.

### **9.2 Summary, discussion, and interpretation of main findings**

#### **Acceptability of BIS monitoring in palliative care**

##### **Summary of findings**

##### **Acceptability in principle**

Interviewed patients, relatives of current patients, and bereaved relatives generally considered that BIS technology would be acceptable in principle for monitoring palliative care patients' consciousness levels (Chapter 4). No major differences in perspectives were observed between the three participant groups. However, individual views on BIS monitoring appeared to be influenced by participants' prior knowledge and/or experiences of using sedative medication, and their overall attitude towards the use of medical/technological interventions in palliative care.

Most participants expressed that they would be willing to use BIS if it was offered to themselves or to a family member after receiving sedative medication in a palliative care setting. Participants' positive attitudes towards BIS mostly stemmed from the perceived potential benefits of the technology to patient care. Some participants, although positively disposed towards the potential use of BIS in general, expressed that certain conditions would need to be met for BIS to be considered acceptable for use in palliative care, such as: (i) monitoring being

beneficial to patients; (ii) complementing, rather than replacing, usual care and practice, and (iii) ensuring that patients and/or relatives consented to BIS use.

Some participants voiced further concerns about certain aspects of BIS monitoring and how it might be implemented in palliative care. Specifically, a few participants viewed BIS as an additional intervention, which, like other medical interventions, could potentially increase the medicalisation of palliative and end-of-life care. Relating to this point, some participants expressed that the placement of the sensor on patients' foreheads made BIS monitoring more noticeable than other medical interventions. These views, however, were distinct from those of most participants who considered that, unlike other medical interventions, BIS was minimally intrusive and hence less likely to negatively affect patients' care experiences. Similarly, most participants found that the BIS sensor was small and discreet, and therefore acceptable for use with palliative care patients. Despite expressing some reservations, patient and relative participants mostly expressed positive views about BIS monitoring, and none raised objections to its potential use in palliative care.

#### **Acceptability in practice**

Data from questionnaires (Chapter 6) and interviews (Chapter 8) indicated that BIS monitoring was acceptable to patients, relatives, and hospice clinicians who directly experienced or witnessed using the technology. Most questionnaire respondents reported having a good overall experience with BIS (34/40; 85%), experienced no or minor discomfort from the BIS sensor (34/40; 85%), and had no other concerns or issues relating to the sensor (38/40; 95%). In addition, most said that they would be willing to be monitored with BIS again (32/36; 88.8%), and all respondents who completed both monitoring phases indicated that they would be willing to take part in potential future research with BIS (4/4; 100%).

Interviews with patients, relatives, and hospice clinicians corroborated questionnaire findings, with most attributing their positive experiences of using BIS to the perceived non-intrusiveness of the technology. In line with quantitative findings, interviewed patients described mainly experiencing no discomfort from having the BIS sensor attached during study monitoring periods, with some patients commenting that after the sensor had been applied to their foreheads, they "hardly knew that it was there". Likewise, participants overall described having no concerns or issues relating to the appearance of the BIS sensor and device, although a few

clinicians expressed some initial concerns about the visual impact of the technology and its presumed invasiveness.

Patients' willingness to take part in future research with BIS was predominantly influenced by the perceived non-intrusiveness of the technology, their overall experience of participation in the exploratory study, and their general willingness to contribute to research. Furthermore, interview participants felt that incorporating BIS into routine hospice practice would be acceptable if it was beneficial for patients, patients and/or family members would consent to its use, and clinicians would receive appropriate training in operating the device and interpreting BIS data.

### **Discussion and interpretation of main findings**

#### **Contributing factors to the acceptability of conducting research with BIS in hospice inpatients**

Findings from the exploration of the acceptability of BIS monitoring in practice are largely consistent with previous research. Other studies of BIS monitoring in palliative care found that BIS was an acceptable research tool for patients, family caregivers, and clinical staff (Barbato, 2001; Masman et al., 2016; Monreal-Carrillo et al., 2017). The analysis of interview data indicated a number of contributing factors to the acceptability of conducting research with BIS in palliative care. These were: the non-invasiveness/non-intrusiveness of BIS monitoring, the appearance of BIS sensor and monitoring system, the opportunity for social interaction, and a sense of contributing to research.

#### **Non-invasiveness/non-intrusiveness of BIS monitoring**

Interview participants generally perceived BIS as being non-invasive or non-intrusive. Using the BIS sensor did not cause patient participants pain or discomfort, or raise other concerns. Patient participants were predominantly conscious and able to mobilise, but BIS monitoring did not markedly hinder their activities. This was mainly because the BIS device was small and easily handled in terms of moving and attaching/detaching the sensor from the monitor. Patients could therefore be in control of the monitoring process and, if needed, manipulate it if they wished to perform certain activities. For the same reasons, hospice clinicians felt that, unlike other medical interventions, BIS monitoring was not obstructive to the provision of patient care.



### Appearance of BIS sensor and monitoring system

A few patients and relatives found the appearance of BIS unusual and were interested in the novelty of seeing and using a brain monitoring device, but none had issues with the visibility of the forehead sensor and found the appearance of the monitoring system acceptable. Other studies exploring the use of BIS in palliative care have also found that family caregivers were not deterred or distracted by the appearance of the BIS sensor and monitor (Barbato, 2001; Masman et al., 2016; Monreal-Carrillo et al., 2017).

### Opportunity for social interaction

Patient participants did not consider participation in the exploratory study overly burdensome. In fact, patients expressed enjoying the interaction with the researcher and felt that taking part in the study provided a useful distraction from their hospice routine. Other research has identified the opportunity for social interaction and developing a personal relationship with research teams as important contributors to participants' positive perceptions and experiences of participation in clinical research (Kost, Lee, Yessis, Coller, & Henderson, 2011; Pessin et al., 2008). Interaction with research staff was the most commonly reported benefit of research participation in a study assessing the burden and benefits of participation in research addressing end-of-life issues among patients receiving inpatient palliative care (Pessin et al., 2008). Similarly, a study exploring participants' perceptions of their clinical research experiences found that developing a close relationship with research staff was the factor most frequently identified as contributing to a positive experience of participation (Kost et al., 2011).

### Contribution to research

Patients' and relatives' positive experiences of participation in the exploratory study were, at least partly, attributed to a feeling of contributing towards the generation of important new knowledge that could benefit future patients. Likewise, hospice clinicians viewed their own/their patients' participation in the study as an opportunity to engage in research that could potentially improve clinical practice, and, ultimately, patient care. Altruism has been described as an important value for people faced with terminal illness (Institute of Medicine, 1997). Numerous studies have reported that palliative care patients consider altruism as a key motive for taking part in research and one of the main perceived benefits of research participation (Abernethy et

al., 2014; Bloomer, Hutchinson, Brooks, & Botti, 2018; Harrop et al., 2016; Truong, Weeks, Cook, & Joffe, 2011; White & Hardy, 2010).

### **Integration of BIS monitoring into routine practice**

Qualitative data obtained through the studies exploring the acceptability of BIS monitoring in principle (Chapter 4) and in practice (Chapter 8) and particularly participants' views on the potential use of BIS, were used to identify preliminary barriers and facilitators to incorporating BIS into routine clinical care. Overall, participants in both studies had no objections to possible integration of BIS monitoring into usual hospice care. However, some participants expressed concerns about certain aspects of BIS monitoring before using it/witnessing patients using it in practice. These concerns were mostly mitigated after trialling BIS in practice, highlighting the important role of experiential learning in increasing acceptance of BIS monitoring.

### Potential benefits of BIS monitoring

Patients and relatives considered that information obtained through BIS monitoring could assist clinicians in adjusting sedative and analgesic medication according to each patient's individual needs. This potential benefit of BIS monitoring was perceived to contribute to what was regarded by patients and relatives as the main objective of hospice care; that is, ensuring patient comfort, especially towards the end of life. Patients' relatives in particular thought the close monitoring of patients for possible signs of discomfort would be reassuring. Hospice clinicians expressed similar views, acknowledging the uncertainty of observational assessments in patients who are less responsive. They felt that the additional information from BIS could increase the reliability of observational assessments and, therefore, clinician confidence in making decisions regarding the care provided to patients.

These findings largely agree with those of a recently published Belgian study exploring the use of two monitoring devices assessing level of consciousness and pain severity in the context of continuous palliative sedation (Six, Van Overmeire, et al., 2020). The study found that family members of patients who had previously been monitored with those devices perceived them as a useful addition to existing care and felt that their use could improve patient comfort at the end of life. Healthcare professionals in the same study expressed that using state-of-the-art monitoring methods could reduce the risk of over- or under- sedation and help to provide the best possible care to patients (Six, Van Overmeire, et al., 2020). Research suggests that in order for the implementation of any technological intervention in palliative care to be successful, it

needs to meet the needs and expectations of key stakeholders (Allsop et al., 2019; Demiris, Parker Oliver, & Wittenberg-Lyles, 2011; Oliver & Demiris, 2004). If, therefore, BIS proves to be a useful supplement to existing care, the anticipated benefits of BIS could aid its uptake and incorporation into routine practice.

#### Perceptions regarding the invasiveness of BIS monitoring

Patients and relatives across both studies considered BIS to be non-invasive, with some patients comparing it to other wearable technologies that are minimally intrusive. In contrast to patients' and relatives' perceptions, some clinicians, on first seeing the technology, expressed concerns about its presumed invasiveness and the risk of negative effects on patients (mainly pain or discomfort). Similar reservations were expressed by a different sample of clinicians from the same hospice who had participated in a qualitative study undertaken as part of the I-CAN-CARE programme prior to the trialling of BIS in clinical practice (Vivat et al., 2020). However, clinicians who observed the use of BIS with patients in practice were not concerned. After the trial, clinicians commented that BIS did not seem to have any negative effects on patients and, hence, felt that it would be acceptable to use as part of routine hospice care.

Clinicians' initial concerns may be explained by the over-protective stance that health care professionals sometimes assume towards patients with advanced illness, stemming from a general feeling of responsibility to protect patients from potential harm coupled with the perceived overall vulnerability of these patients (Kars et al., 2016). The shift in hospice clinicians' perceptions regarding the invasiveness of BIS monitoring suggests that concerns about the appropriateness of BIS can change as staff experiences confirm or reject initial perceptions about the use of the technology in clinical practice. These findings confirm the key role of experiential knowledge in addressing barriers and increasing acceptance among clinical staff about the adoption of new technologies for patient care in the palliative care setting (Taylor et al., 2015).

#### Possible medicalisation of end-of-life care

A concern expressed by some patients, relatives (Chapter 4) and hospice clinicians (Chapter 8) before trialling BIS monitoring in practice related to the potential for BIS monitoring to replace clinical observation and decision-making, and to increase the medicalisation of end-of-life care. This was opposed to some participants' understanding of palliative care as being associated with minimal intervention at the end of life. However, as with the issue of the perceived invasiveness

of BIS, none of the interviewed participants who had a direct experience of using BIS voiced analogous concerns.

The idea that using medical technologies in end-of-life care constitutes a departure from palliative care ideals for “holistic care” and a more “natural” course of dying has been extensively debated in the literature since the development of palliative medicine as an independent medical speciality (Clark, 2002; Field, 1994; Seymour, 1999). Nevertheless, Clark (2002) has pointed out that in light of the broadened boundaries of palliative care and the associated shift of emphasis from the achievement of the “good death” to pain and symptom management throughout the dying trajectory, it is more appropriate to view medicalisation as the expected, rather than unintended, outcome of the growth of palliative care. Building on this, and given that inadequate monitoring of physiological parameters of patients receiving sedative medication at the end of life may lead to substandard patient care, Six and colleagues (2020) proposed that the stipulation to avoid technology in palliative care is often misinterpreted and should be more nuanced to leave room for non-invasive monitoring technologies. Furthermore, Seymour (1999) suggested that it is not the presence or absence of technology alone, but a number of other factors that determine how the use of medical technologies at the end of life is perceived. These include the ability of medical technologies to deliver expected outcomes, being amenable to human manipulation, and being easy to understand. In this research, the factors discussed by Seymour (1999), and particularly the increased information on BIS monitoring and the opportunity to handle and operate the device in clinical practice, appeared to contribute towards mitigating concerns regarding the possible medicalisation of hospice care among patients, relatives, and hospice clinicians.

#### Burden on clinical staff

Clinician participants identified the potential impact on their workload from the use of BIS and its implications on the quality of care provided to patients as an additional barrier to the possible integration of BIS into clinical practice. Previous research has shown that clinical staff play a central role in the uptake and sustained use of new technologies (Collier et al., 2016; Whitten & Mackert, 2005). It has been therefore suggested that implementation efforts should be focused on fostering positive leadership approaches at an organisational level. Such approaches should incorporate the development of service structures that are motivational to the integration of new practices, while also making necessary provisions to minimise the additional burden on

clinical staff from the adoption of such practices (Collier et al., 2016; Rye, Rognmo, Aarons, & Skre, 2019; Whitten & Mackert, 2005).

## **Feasibility of conducting research with BIS in hospice inpatients**

### **Summary of findings**

Findings from the exploratory study (Chapter 6) demonstrated that it is possible to prospectively recruit and retain hospice inpatients in a study of BIS monitoring. Insufficient data were collected for assessing one of the five *a priori* feasibility criteria. Three of the four remaining criteria were met. The percentage of eligible patients refusing to be approached by the researcher (1/162; 0.6%) or refusing consent (11/181; 6%) for BIS-related reasons were below the predetermined limit of 10%. The percentage of patients requesting early termination due to monitoring intolerance (2/44; 4.5%) was also below the limit of 10%. However, the achieved overall recruitment rate (40/332; 12%) did not meet the benchmark of 15%. The criterion relating to the reliability of collected BIS data for patients observed to be less responsive/unresponsive (i.e. RASS-PAL=-3 to -5) could not be evaluated as patients were predominantly responsive and alert during the study monitoring periods (median RASS-PAL 0, IQR 0 to 0).

### **Discussion and interpretation of main findings**

#### **Participant recruitment**

The use of BIS itself was not found to significantly affect patient accrual to the exploratory study, but the target recruitment rate of 15% was not reached. Nevertheless, the achieved recruitment rate of 12% is similar to that found in previous research of BIS monitoring in palliative care (Barbato et al., 2017; Masman et al., 2016). Masman and colleagues (2016) reported assessing for eligibility a total of 516 patients, of whom 65 consented to participation (12.6%). In the study of Barbato et al. (2017) consent was obtained from 58/450 potentially eligible patients (12.9%).

Participant recruitment has been consistently identified as a significant challenge in palliative care clinical research, often resulting in studies failing to enrol a sufficient number of participants on schedule (Boland et al., 2015; Grande & Todd, 2000; Hanson et al., 2014; T. W. LeBlanc, Lodato, Currow, & Abernethy, 2013; Steinhauser et al., 2006). An online survey of principal investigators leading palliative care research projects found that 80% of those projects had encountered problems with participant accrual (O'Mara, St Germain, Ferrell, & Bornemann,

2009). Similarly, 10 of the 11 studies included in a systematic review of randomised controlled trials of palliative care interventions reported recruitment problems, while in two studies the numbers of recruited participants were so low that no results could be reported (Rinck et al., 1997).

Several different barriers to participant recruitment have been described by palliative care researchers in the literature. The most frequently reported of these include the physical and emotional vulnerability of the patient population, high rates of cognitive impairment, patients' limited life expectancy or prognostic uncertainty, the often unpredictable and rapid changes in patients' conditions, gatekeeping by clinical staff and/or family members, and the lack of infrastructure and resources to support research in clinical settings (Boland et al., 2015; Fischer, Burgener, Kavanaugh, Ryan, & Keenan, 2012; Hanson et al., 2014; T. W. LeBlanc et al., 2013; Steinhäuser et al., 2006; Stone et al., 2013). Similar recruitment difficulties were encountered in this research.

#### Patient health

The main reasons for patients being deemed ineligible for inclusion in the exploratory study were that they lacked capacity or were too unwell at the time of screening (119/155; 76.8%). Likewise, the most common reasons for eligible patients not being approached for participation were that they had lost capacity, become too unwell, or had died before being accessed by clinical staff (14/15; 93.3%) or the researcher (12/20; 60%). Of the patients who declined to consent, almost half (35/72; 48.6%) refused due to experiencing distressing pain or fatigue.

#### Gatekeeping by clinical staff

"Gatekeeping" is used to refer to the reluctance of clinical staff to refer or enter eligible patients into research studies (Aoun & Kristjanson, 2005; White & Hardy, 2008), and can significantly affect participant accrual (Ewing et al., 2004; Stone et al., 2013). Gatekeeping often stems from a desire to protect patients from research that is perceived to be burdensome, intrusive or potentially upsetting (Hudson, Aranda, Kristjanson, & Quinn, 2005; T. W. LeBlanc et al., 2013). Other clinician-related reasons for not referring eligible patients to palliative care research studies include forgetfulness, a lack of time, and research not being considered a priority especially in light of competing clinical demands (Kars et al., 2016; White & Hardy, 2008). It has been argued that clinicians' reluctance to refer eligible patients to research studies restricts the autonomy of patients by denying them the right to make an informed choice regarding research

participation (Hudson et al., 2005). Gatekeeping may also lead to selection bias; thus, threatening the representativeness of the study sample and the generalisability of research findings (Hudson et al., 2005; Stone et al., 2013).

Gatekeeping by clinical staff was not found to be a barrier to recruitment in this research. Clinical staff approached all eligible patients, and the only patients not approached were those deemed ineligible according to the study inclusion and exclusion criteria. This resulted from a number of strategies developed specifically to minimise potential gatekeeping, based on recommendations found in the literature (Cook, Finlay, & Butler-Keating, 2002; Hudson et al., 2005; T. W. LeBlanc et al., 2013; Segre, Buckwalter, & Friedemann, 2011; White & Hardy, 2008). These strategies were successfully implemented in two phases: at the design stage of the exploratory study and after recruitment had commenced. Firstly, senior hospice clinicians were involved in designing the study as members of the project Advisory Group. Their engagement from an early point in the research process ensured that the study protocol and procedures were perceived to be relevant to the hospice's clinical practice, acceptable to hospice staff, and not too demanding on patients. After ethical approval was obtained and before the study commenced, meetings were held with clinical staff at the hospice, during which the study was presented. Information posters were also hung in staff meeting rooms and nursing stations to inform and remind hospice clinicians about the study, raise its profile, and promote staff engagement. Once recruitment activities began and throughout the study, I was based at the hospice to oversee and aid the recruitment and data collection processes so that clinicians would not be overburdened by research demands, and to inform staff about the progress of the study. My daily presence at the hospice enabled the establishment of a good relationship with hospice clinicians which promoted staff enthusiasm and engagement with the study. These strategies collectively aided towards achieving increased staff involvement with, and commitment to, the study and, thus, in preventing clinician gatekeeping.

### Resources

One logistical difficulty encountered was that data collection was undertaken by a lone researcher. According to the study protocol, BIS monitoring needed to commence just before Phase 2 participants were about to receive an additional dose of medication with sedative effects. This meant that I needed to be available to attach the monitor and coordinate data collection activities whenever such occasions arose. Although it had been anticipated that some

patients would receive such medication outside of “office hours”, when I would not be available, the proportion of patients who did not enter Phase 2 due to this limitation was higher than originally expected (5/18; 27.7%).

#### Recruitment procedures and length of hospice stay

An additional difficulty (encountered mostly with potential Phase 2 participants) stemmed from the short length of stay of potential participants and the time lag between initial screening and start of data collection. The study protocol required at least 24 hours between each stage of the recruitment process (i.e. eligibility screening, approach by clinical staff, approach by researcher and consenting). Even after consent, a convenient time for the monitoring to take place needed to be agreed. This could be anytime up to three days after patients consented to take part in the study. As a result of this potentially considerable time lag between initial screening and participation, a number of patients (7/39; 17.9%) were discharged from the hospice soon after the end of Phase 1 of the research and before they could be approached for participation in Phase 2.

In summary, the use of BIS and gatekeeping by clinical staff did not adversely affect participant recruitment to the exploratory study. However, similar to other palliative care research studies, recruitment challenges were encountered which mostly related to the nature of the patient population. As a result of these difficulties, participant accrual was slow and the target recruitment proportion of 15% was not achieved.

#### **Participant retention**

Another methodological challenge in conducting palliative care research is that of participant retention (Chaiviboontham, 2011; McMillan & Weitzner, 2003). Although not a problem that is exclusive to palliative care trials, preventing drop-out and loss to follow-up is often more difficult in palliative care studies due to the high mortality rates and symptom burden in this population (Orani, Dunleavy, Sharples, Perez Algorta, & Preston, 2020). Like poor recruitment, high attrition can lead to sample bias and premature study closures (Chaiviboontham, 2011; Hui, Glitza, Chisholm, Yennu, & Bruera, 2013).

Recommended strategies for maintaining participation in palliative care research studies include efforts to minimise the research burden posed to study participants by reducing follow-up times, avoiding complex outcome measures, limiting participants’ overall time commitment to the



study, and incorporating close monitoring and support for patient participants (Hui, Glitza, et al., 2013; Mackin et al., 2009; Steinhauser et al., 2006). In congruence with these recommendations, the exploratory study was designed so that participation required patients to only participate in BIS monitoring for a period of four hours, but with the option for further involvement if desired (i.e. a further four-hour monitoring period and/or an interview with the researcher). Outcome measures were chosen on the basis of being brief and simple for patients to complete, and total contact time to obtain research data was kept to under 30 minutes.

The overall rate of non-completion for the exploratory study was 29.5% (13/44). This is comparable to the attrition rate reported by Barbato and colleagues (2017) in their study of BIS monitoring with palliative care patients and is consistent with the broader literature on participant retention in palliative care clinical research studies. Barbato et al. (2017) found that 18 of the 58 consenting patients (31%) dropped out due to a sudden deterioration of their condition. Similarly, a recently published systematic review of 119 palliative care trials reported that the weighted average attrition across all included studies was 29% (95% CI 28 to 30), with the main reasons for participant drop-out being death (weighted mean 31.6%; SD 27.4) and illness (weighted mean 17.6%; SD 24.5) (Oriani et al., 2020).

The main reason for attrition in this research was from patients requesting to leave the ward before the pre-specified monitoring endpoint (i.e. four hours) (7/13; 53.8%), followed by high symptom burden that was unrelated to BIS monitoring (3/13; 23.1%). Findings from the qualitative interviews conducted with patient participants, their relatives, and hospice clinicians suggested that the four-hour monitoring time frame was appropriate for the studied population as it could be scheduled so that it did not interfere with patients' routines and care activities, such as meal times and personal hygiene routines. However, during the study, unplanned events, such as visits from family members and friends, led participants to request early termination of monitoring. In the majority of cases, nevertheless, participants dropped out close to the point at which monitoring had been planned to end. Hence, participant attrition did not significantly affect data collection, with the overall proportion of collected patient-reported data across both study phases being relatively high (81.3%).

#### **Proportion of reliable BIS data**

It was expected that at least a proportion of patients in this study would experience fluctuations in their level of consciousness either as a result of disease and symptom progression or as an

effect of the administration of medication with sedative effects. However, patients across both study phases were predominantly responsive and alert (median RASS-PAL 0, IQR 0 to 0). Consequently, it was not possible to assess the feasibility criterion relating to the reliability of BIS data for less responsive/unresponsive patients (i.e. RASS-PAL=-3 to -5). Most patients had moderate functional ability (as measured by the PPSv2) and a prognosis of “months” at the time of participation. These characteristics remained unaltered between the two study phases. Moreover, the doses of medication prescribed to study participants were consistent with levels required to achieve symptom control (such as relief of anxiety), rather than doses that would be expected to result in significant sedation.

The overall proportion of available BIS values meeting reliability criteria (i.e. those for which SQI >50 and EMG <50 dB) was 58% (116/200) for Phase 1 assessments and 68% (17/25) for Phase 2 assessments. The proportion of missing BIS data due to poor quality was considerably higher than that found in other studies of BIS monitoring in palliative care where equivalent figures were reported to range between 3 and 12.5% (Barbato et al., 2018; Barbato et al., 2017; Masman et al., 2016). This discrepancy may be explained by the differing clinical characteristics of the participant population in this research. In previous studies, participants were at the end-stage of their disease and were being sedated to unconsciousness. Therefore, contamination of EEG signals due to increased facial or forehead muscle activity was less likely to affect the quality of BIS recordings and, thus, the proportion of reliable BIS data.

## **Preliminary evaluation of clinical usefulness of BIS monitoring**

### **Summary of findings**

There was insufficient evidence to support the clinical usefulness of BIS monitoring in the studied population (Chapter 6). There was no correlation between BIS and patients’ self-reported alertness scores in either of the two study phases; hence, the criterion pertaining to BIS validity was not met. Likewise, no evidence of association was found between patients’ self-reported alertness and clinicians’ structured observations. Given these findings and since patients’ self-reported alertness was used as the “gold standard” against which other outcomes were compared, it was not possible to evaluate the performance of BIS in relation to structured clinical observation, and, thus, the corresponding criterion was not assessed.

The criterion relating to the ability of BIS to detect changes in patients' level of consciousness following the administration of medication with sedative effects was also not achieved. The median BIS value before the administration of breakthrough medication was 90.5 (IQR 78 to 95.75). This was reduced to a median BIS value of 88.5 (IQR 72.5 to 95) 60 minutes post administration. However, this change in BIS values was not statistically significant ( $Z=-0.62$ ;  $p=0.53$ ).

### **Discussion and interpretation of main findings**

A possible explanation for the absence of any observed relationship between patients' alertness self-reports, BIS, and clinicians' structured observations is the likelihood that neither of these latter assessment methods is sensitive enough to reliably reflect patients' subjective experiences of alertness; especially when alterations in self-perceived alertness do not cause changes in clinical signs detectable to an observer or physiological changes that can be captured by the BIS monitor (Barbato et al., 2017; Klepstad et al., 2002). In this study, median scores for patient self-reported alertness (Phase 1: 8, IQR 5 to 10; Phase 2: 9, IQR 6 to 10), clinician-reported alertness (Phase 1: 10, IQR 8 to 10; Phase 2: 10, IQR 9 to 10), and BIS (Phase 1: 91, IQR 77.2 to 95; Phase 2: 94, IQR 90 to 94), indicated high levels of alertness, with patient median alertness scores being marginally lower than those reported by clinicians and BIS. Therefore, BIS and the clinician-rated NRS may not be able to discriminate well between small variations in a person's level of alertness, perceivable to the person concerned, particularly when these variations occur at the higher ends of respective measures.

Another plausible explanation for this absence of relationship is that patients' perceptions of their alertness levels may be influenced by other, related, symptoms, such as depression and fatigue, and/or by reduced functional status. A study comparing cancer patients' subjective reports with standard neuro-psychometric tests of concentration and memory found that patients reporting concentration and memory difficulties did not perform abnormally on neuro-psychometric tests, but had significantly higher scores on measures of anxiety, depression and fatigue (Cull et al., 1996). Likewise, Klepstad et al. (2002) found that cancer patients' self-reports did not correlate with observational assessments of level of sedation/standardised measures of cognitive function, but the majority of patients who scored highly for perceived sedation and cognitive dysfunction were also experiencing high levels of fatigue.

This study did not replicate findings from previous studies identifying BIS as sensitive in detecting changes in palliative care patients' consciousness levels following the administration of medication with sedative effects (Barbato et al., 2018; Masman et al., 2016). The exploratory study found a small reduction in median BIS values (90.5 to 88.5) in the 60-minute interval following the administration of single doses of breakthrough medication, but this was not statistically significant. However, a small reduction in median scores (10 to 9.5) that did not reach statistical significance was also noted in the same time interval for the clinician-rated alertness NRS. Drowsiness and sedation are among the most commonly reported opioid-associated side-effects in palliative care patients (Cherny et al., 2001; Vella-Brincat & MacLeod, 2007). Certain strategies such as dose reduction, opioid rotation, and altering the route of opioid administration, have been found to be effective in minimising, and sometimes even resolving, opioid-induced drowsiness (Cherny et al., 2001; Rogers, Mehta, Shengelia, & Reid, 2013). Furthermore, it has been suggested that drowsiness can be transient, occurring with opioid initiation or dose escalation and subsequently decreasing over time as opioid tolerance increases (National Institute for Health and Care Excellence, 2012b; Rogers et al., 2013). Patients included in the sensitivity to change analysis received breakthrough doses of either oxycodone or morphine. It is possible, therefore, that either as a result of the aforementioned approaches or due to increased opioid tolerance (or both), breakthrough opioids did not cause significant alterations in participants' consciousness levels which could be detected by clinical observation or BIS.

## **Relationship between BIS and clinician-rated alertness measures**

### **Summary of findings**

BIS correlated mostly moderately to highly with clinician-reported alertness NRS scores (Phase 1:  $r=0.42$ , 95% CI 0.21 to 0.59; Phase 2:  $r=0.84$ , 95% CI 0.49 to 0.96). However, no evidence of association was found between BIS and clinician-reported RASS-PAL scores (Phase 1:  $r=0.18$ , 95% CI -0.20 to 0.52; Phase 2:  $r=0.25$ , 95% CI -0.81 to 0.93).

### **Discussion and interpretation of main findings**

The observed associations between BIS and clinician-reported NRS alertness scores in this research are largely consistent with the previous studies of BIS monitoring in palliative care. In these studies, reported correlations between BIS and clinician-rated level of consciousness

measures ranged from 0.42 to 0.68 (Barbato et al., 2017; Masman et al., 2016; Monreal-Carrillo et al., 2017). As noted earlier, however, these findings were not replicated for BIS and clinician-reported RASS-PAL scores. This inconsistency may have arisen because of the limited range of scoring options of the RASS-PAL (6 points; -5 to 0) compared to the alertness NRS (11 points; 0 to 10). The high concentration of RASS-PAL scores around a single score (0) representing an alert and calm state, which was observed in both study phases (median RASS-PAL 0, IQR 0 to 0), suggests that RASS-PAL was not sensitive enough to discriminate between different levels of alertness in the studied population. Therefore, RASS-PAL may be a relatively insensitive instrument, particularly around its central scores, and may not be able to reflect small changes in patients' consciousness levels.

## **Psychometric properties of clinician-rated RASS-PAL, pain and alertness NRSs**

### **Summary of findings**

Clinician participants described all of RASS-PAL, pain NRS, and alertness NRS as user-friendly, brief and easy to complete (Chapter 8). Of the three, they considered the pain NRS the easiest to score and interpret as they had prior experience of using this measure for the assessment of patients' pain severity. Clinicians found that RASS-PAL was clearer and easier to use than the alertness NRS, mainly because the clear administration and scoring instructions of RASS-PAL increased their confidence in the accuracy of their assessments.

A correlation of 0.58 (95% CI 0.37 to 0.73) was found between the RASS-PAL and clinician-rated alertness NRS, providing moderate evidence of convergent validity for the two measures. The assessment of the inter-rater reliability of RASS-PAL indicated low agreement between hospice clinicians who scored the measure (ICC=0.34, 95% CI 0.29 to 0.41) (Chapter 6).

### **Discussion and interpretation of main findings**

#### **Inter-rater reliability of clinician-rated RASS-PAL and convergent validity of clinician-rated RASS-PAL and alertness NRS**

The pragmatic nature of the exploratory study and the predominantly alert and wakeful state of study participants limited the ability to make definitive statements about the psychometric properties of the appraised measures. A moderate correlation between the alertness NRS and the RASS-PAL was found, suggesting that these tools could either be valid measures of different,

but related, constructs, or invalid measures of similar constructs (Post, 2016). Data were highly concentrated on a limited range of scores representing an alert patient state. Given that the size of a correlation coefficient tends to reduce when the range of one or both variables is restricted (Bryant & Gokhale, 1972), it is uncertain whether the observed correlation represents the true degree of association between the two measures and, therefore, if these two measures can provide valid assessments of the same construct.

The same issue of limited variability in level of consciousness scores may also be, at least partly, responsible for the low level of agreement between hospice clinicians scoring the RASS-PAL. The degree of consistency between RASS-PAL scores may have been additionally affected by the opportunistic selection of raters from those clinicians who were on site and available to complete assessments, which resulted in a large number of clinicians with differing characteristics scoring the measure. In total, 56 clinicians with diverse training backgrounds (i.e. nurses or physicians) and varying levels of professional experience, provided 93 pairs of scores. Greater consistency might have been achieved if a smaller, more homogeneous group of raters had performed the scoring.

### **Integration of observational measures into routine hospice practice**

Routine data collection using outcome measures has been shown to consistently improve patient outcomes at a systems level (Barbera et al., 2010; Currow et al., 2015). Nevertheless, despite outcome measures being widely used in palliative care for research purposes, they are not yet frequently incorporated into routine clinical practice (Bausewein et al., 2016). Clinicians involved in the exploratory study expressed positive views about the possible integration of structured observational measures into usual hospice practice and considered that their routine use could improve patient care. However, even though they regarded the measures used in the exploratory study to be brief and easy to complete, clinicians identified the subjective element of scoring and its potential impact on the consistency of ratings as well as the burden of data collection and recording as possible barriers to uptake and implementation of such measures in routine practice.

A degree of subjectivity is intrinsic to all observational assessment methods based on individual interpretation, including well-validated and standardised outcome measures, but a number of strategies have sought to mitigate the subjectivity of the assessment process and improve the level of scoring consistency between different observers (Dateo, 2013; Liddy, Wiens, & Hogg,

2011; Shiloach et al., 2010). These include the education of observers in the constructs being evaluated, training in the administration and processing of assessment instruments, and the development of a support system for addressing difficulties associated with instrument use. For such strategies to be successfully implemented in practice, efforts that promote a culture of learning at an organisational level are needed (Law, 2014).

In agreement with hospice clinicians' concerns regarding the burden associated with routine use of observational measures, the additional time and work requirements on clinical staff from the administration, interpretation, and entry of outcome measures has been repeatedly recognised as a significant challenge to the uptake of routine outcome monitoring in clinical practice (Gleacher et al., 2016; Hall et al., 2014; Rye, Rognmo, et al., 2019; Wolpert, Fugard, Deighton, & Görzig, 2012). It has been proposed that the utility of outcome data may enhance clinical practice and, therefore, may, to an extent, offset clinicians' sense of burden (Wolpert et al., 2012). However, evidence from settings where routine outcomes have been introduced suggests that in order to facilitate the sustained use of routine outcome monitoring, the development of a supportive infrastructure offering appropriate technological solutions, and dedicated administrative and information technology support to reduce burden on clinicians' time is required (Batty et al., 2013; Boyce, Browne, & Greenhalgh, 2014; Hall et al., 2013).

As certain barriers are expected to arise with almost any effort to introduce new practices into routine care, the presence of key organisational conditions that support users to overcome these barriers has been identified as a critical point for successful implementation (Gleacher et al., 2016; Rye, Rognmo, et al., 2019). This entails the development of organisational environments that are supportive of the process of adopting new practices, whilst acknowledging the extended work demands placed on clinical staff and taking active measures to address their concerns (Rye, Rognmo, et al., 2019). Therefore, the success of efforts to incorporate the systematic use of observational outcome measures into routine hospice care is likely to depend on the role that organisations assume in creating conditions that are conducive to the introduction and sustained use of such measures in clinical practice.

## **Use of BIS in the assessment of pain in hospice patients**

### **Summary of findings**

No significant relationship was found between BIS and patients' self-reported pain scores or BIS and clinician-reported pain scores in either of the study phases. In contrast, low to moderate correlations were found between patient- and clinician-reported pain scores (Phase 1:  $r=0.24$ , 95% CI 0.05 to 0.41; Phase 2:  $r=0.52$ , 95% CI 0.03 to 0.80).

### **Discussion and interpretation of main findings**

This research did not replicate findings from previous studies which found weak correlations between BIS and clinician-rated measures of pain and comfort ( $r=0.11$  to  $0.30$ ) (Barbato et al., 2017; Masman et al., 2016). This may be due to differences in participants' consciousness status between this research and other studies. As noted earlier in this chapter, unlike previous research where samples consisted of patients who were palliatively sedated (Barbato et al., 2017; Masman et al., 2016), the observed level of consciousness of participants in the exploratory study was high at baseline and throughout the study monitoring periods. BIS is a depth of anaesthesia measure and could only potentially offer an indication of pain presence by reflecting changes in patients' arousal levels (Coleman et al., 2015). However, in a population that is primarily alert and conscious, such changes may be small and therefore less likely to be detected by BIS.

Significant correlations were found between patient self-reports and clinician structured pain assessments. Despite these correlations being low to moderate, they reached statistical significance in both study phases, suggesting that structured clinical observation may be a more reliable proxy measure of pain than BIS, at least in patients who are alert and can display behavioural signs of pain.

## **Relationship between researcher-rated and other outcome measures**

### **Summary of findings**

Findings from the exploratory analyses comparing researcher assessments with BIS, patient, and clinician assessments, were mixed. Statistically significant associations between researcher-rated and other outcome measures were found for all Phase 1 analyses. However, these findings were mostly not replicated in Phase 2 analyses. Correlations reaching statistical significance



across both study phases were found for researcher- and patient-reported alertness NRS scores (Phase 1:  $r=0.30$ , 95% CI 0.12 to 0.46; Phase 2:  $r=0.79$ , 95% CI 0.50 to 0.92), researcher- and patient-reported pain NRS scores (Phase 1:  $r=0.36$ , 95% CI 0.19 to 0.51; Phase 2:  $r=0.64$ , 95% CI 0.22 to 0.85), and researcher- and clinician-reported pain NRS scores (Phase 1:  $r=0.26$ , 95% CI 0.08 to 0.42; Phase 2:  $r=0.71$ , 95% CI 0.32 to 0.89). Correlation coefficients for all three pairs of variables varied from low to moderate and high between the two study phases, with correlations for Phase 2 assessments being higher compared to Phase 1 assessments.

### **Discussion and interpretation of main findings**

Both study phases identified statistically significant correlations between patient self-reports and researcher observational assessments of pain and alertness. These findings suggest that proxy assessments provided by non-clinical researchers may be a potential substitute for patient self-reports. The use of patient-reported outcome measures in palliative care is challenging, especially towards the end of life when symptom burden and cognitive difficulties tend to increase, so proxy assessments are often used as an alternative source of information on patients' conditions (Bausewein et al., 2016; Kutner, Bryant, Beaty, & Fairclough, 2006). Proxy assessments in palliative care are currently predominantly performed by healthcare professionals or family members (Bausewein et al., 2016; Kutner et al., 2006). Findings from this research suggest that non-clinical researchers trained in outcome measure assessment and scoring could potentially provide proxy pain and alertness data in future studies. Using researchers as proxies for data collection could reduce research-related burden on clinical staff and relatives/carers.

## **9.3 Strengths and limitations**

### **Qualitative studies**

#### **Strengths**

Findings from the literature review of BIS monitoring in palliative care (Chapter 1) indicated that although previous research had investigated its use in the context of palliative care, participants' perceptions about its acceptability had not been systematically explored. The qualitative studies undertaken as part of this doctoral project constitute the first comprehensive investigation of

key stakeholders' views on the acceptability in principle (Chapters 3–4) and in practice (Chapters 7–8) of using BIS technology in the palliative care setting.

Varied groups of participants (patients, current patient relatives, bereaved relatives, hospice clinicians) with a diverse range of backgrounds and professional/service use experiences took part in the two studies. Comparing and contrasting data from these different sources enabled the exploration of multiple perspectives and viewpoints, which contributed to the richness and relevance of the analysis, and enhanced the trustworthiness and credibility of findings (Carter, Bryant-Lukosius, DiCenso, Blythe, & Neville, 2014; Patton, 1999).

The rigorous methods and techniques employed for the collection and analysis of research data constitute a further strength of the qualitative studies presented in this thesis. Initial drafts of topic guides were refined based on feedback from the project Advisory Group, involving palliative care clinicians, researchers, and service user representatives. Initial codes and themes were reviewed by a PhD supervisor, Bella Vivat, and the emerging framework was discussed with members of the Advisory Group to minimise the potential for interpretive bias and ensure the relevance and credibility of the analysis (Noble & Smith, 2015; Patton, 1999). In addition, rich verbatim descriptions of participants' accounts, a clear description of the data collection and analysis processes followed, and key information on participant characteristics were provided to enhance the transferability and dependability of findings (Letts et al., 2007; Noble & Smith, 2015). These strategies collectively helped to improve the rigour of the qualitative studies and ensured the trustworthiness of reported findings.

### **Limitations**

Both studies included relatively small numbers of participants (25 and 22 respectively) recruited from a single hospice in London, England. The generalisability and transferability of findings beyond the study samples may be therefore limited. Despite these limitations, rich data were obtained, and recruitment continued until it was considered that collected data were adequate to allow for variations in the opinions expressed about the issue of BIS acceptability; thus, enabling research objectives to be comprehensively explored (Levitt, Motulsky, Wertz, Morrow, & Ponterotto, 2017). Furthermore, findings from the qualitative studies broadly agree with previous international work investigating the use of BIS, or other comparable technologies, with patients receiving end-of-life care in clinical settings (Barbato, 2001; Masman et al., 2016;

Monreal-Carrillo et al., 2017; Six, Van Overmeire, et al., 2020), and, hence, may be transferable to other settings or countries.

Considerable efforts were made to recruit comparable numbers of participants across all groups. However, there were challenges in accessing relatives of current patients, for reasons such as not being present at the hospice during recruitment/study monitoring periods or caring commitments. This resulted in a considerably smaller number of current patient relatives participating in both studies, compared to other participant groups. It is, therefore, possible that the views of current relatives may have been under-represented in the study samples. Nevertheless, the comparison of data obtained from different sources revealed a high level of congruence on views relating to the acceptability of BIS monitoring across participant groups.

A further limitation was the self-selection of study participants from among those who met the inclusion criteria. This may have led to a biased sample. It is possible that patients, relatives, and clinicians who agreed to take part in the qualitative studies had more positive attitudes towards the use of medical technologies in palliative care in general, thereby finding BIS monitoring more acceptable. Most participants, however, expressed a range of views, some of which were negative or neutral, about BIS technology and its use in palliative care. Nonetheless, it should be noted that study participants represented only a small part of hospice staff and service users.

## **Exploratory study**

### **Methodological strengths**

A three-stage approach to consent was adopted in the exploratory study presented in this thesis in line with the MORECare guidance on ethical issues in palliative and end-of-life care research (Gysels et al., 2013). The guidance recommends that consenting procedures should be dynamic to ensure sensitivity to changes in an individual's attitude and ability to participate, and suggests that seeking advance consent may be a solution to the issue of fluctuating capacity which is often prevalent among palliative care patients (Casarett, 2003; Gysels et al., 2013). In this study, consenting patients entered the first monitoring phase. Those willing to be further monitored, after the end of Phase 1, provided advance consent, as it was unpredictable how long the time gap between Phase 1 and Phase 2 would be. Just before entering Phase 2, patients were asked to verbally reconfirm their consent. In the event of patients losing capacity to reconfirm consent,

the input of a consultee would be sought for decisions regarding their continuation in the study. This comprehensive strategy, involving a staged approach and alternative procedures to obtaining informed consent (i.e. advance and surrogate consent), allowed consent to be revisited and renegotiated throughout the course of study participation, whilst making provisions for the anticipated potential loss of participants' decision-making capacity. By adopting this strategy, therefore, it was possible to mitigate some of the challenges relating to consent while also meeting the ethical requirement for actively promoting patients' autonomy.

A further strength of this study was the use of *a priori* minimum performance criteria for the assessment of primary research outcomes. There is increasing recognition that smaller studies that aim to provide evidence on parameters such as recruitment and compliance rates, and characteristics of proposed outcome measures to inform the planning of future large-scale investigations, should include clearly defined "criteria for success" that are stated in advance of data collection or analysis (Giangregorio & Thabane, 2015; T. A. Jones et al., 2017; Thabane et al., 2010). Outcome assessments are integral to study design to provide the basis for analyses and ensure the integrity of research findings (Giangregorio & Thabane, 2015; T. A. Jones et al., 2017). However, a recently published systematic review of feasibility and pilot studies conducted in palliative care settings found that only 3 of the 56 reviewed studies had used *a priori* criteria to measure success (T. A. Jones et al., 2017). The review authors concluded that a "gold standard" for feasibility study design in palliative care research that includes criteria for the assessment of feasibility as well as participant acceptability and burden parameters is needed (T. A. Jones et al., 2017). Although the present study had a broader scope than a feasibility study conducted solely in preparation for a randomised controlled trial (Eldridge et al., 2016), it shared similar characteristics, in terms of research design and methodology, with other palliative care feasibility studies (T. A. Jones et al., 2017). Therefore, it was considered appropriate to follow the recommendations of Jones and colleagues (2017). The minimum performance criteria employed in this research served as quality assurance standards for the robustness of the data analysis plan and the reliability of reported findings.

Another methodological strength was the use of multiple outcome measures, including patient-, clinician-, and researcher-rated measures. Given the need for proxy measures that accurately reflect palliative care patients' conditions and symptoms (Bausewein et al., 2011; Bausewein et al., 2016; Evans et al., 2013), researcher- and clinician-reported outcome data were compared

to that collected directly from patients. In spite of the mostly low to moderate associations found between patient-reported and proxy assessments, findings from these comparisons contribute to the limited evidence base on the validity of proxy measures in palliative care (Evans et al., 2013). Furthermore, the preliminary evidence found on the association between patient- and researcher-reported alertness and pain assessments suggests that non-clinical researchers might be used as alternative proxy assessors in future palliative care studies.

### **Limitations to the exploratory study**

The target sample size of 100 patients was not reached in this study, despite the overall recruitment rate of 12% being similar to that reported in other research of BIS monitoring in palliative care (Barbato et al., 2017; Masman et al., 2016). Sample size calculations may be of little value in early exploratory studies where scarce data are available (S. R. Jones, Carley, & Harrison, 2003), so the target sample size was determined on pragmatic grounds, considering senior hospice clinicians' estimates of usual hospice admission rates. These estimates were that 600 to 750 new patients would be admitted to the inpatient wards in the 12-month recruitment period. Due to various logistical difficulties however, such as staff shortages and hospice bed closures, only 332 new patients were actually admitted during this time. The substantially lower than anticipated rate of hospice admissions, therefore, hindered the ability to recruit to target.

Apart from the relatively low rate of admissions, as discussed earlier in this chapter, participation in the second phase of the study was also significantly affected by the limited resources for data collection (i.e. one researcher) and the considerable time lag, ranging from a minimum of four to seven days, between patient admission and completion of Phase 1 activities. Although efforts were made for patients to progress through the study without undue delays, the required 24-hour gap between the different recruitment stages together with the identification of an appropriate time for monitoring to take place, meant that a proportion of eligible Phase 2 patients could not be approached for participation before being discharged. Moreover, patients receiving PRN sedative medication outside of the times when the researcher was available also adversely affected participation in Phase 2. It is likely that training hospice staff on data collection and management procedures could have resulted in fewer patients being missed due to researcher unavailability. However, given the complexity of the study design (handling of BIS monitor, multiple data collection time points and outcome measures), it was felt that such a task would be overly burdensome for hospice staff to undertake in addition to their clinical duties.

The small participant numbers in both study phases limit the ability to extrapolate findings beyond the study sample. Furthermore, as small samples increase the likelihood of sampling bias resulting in spuriously inflated correlation coefficients (Sheskin, 2011), the results of correlation analyses in this study, and especially those relating to Phase 2 assessments, should be interpreted with caution.

The reliability of correlation outcomes reported in this thesis was further limited by the participants' primarily alert and responsive status during the study monitoring periods. The two-phase approach to data collection was designed with the expectation that a proportion of Phase 1 and all Phase 2 participants would experience, at least to some extent, fluctuations in their level of consciousness during monitoring periods. However, the consistently high scores on alertness outcome measures indicated that participants were predominantly alert and conscious across both study phases. This limited the amount of data variability which is likely to have adversely affected the size of correlation coefficients (Goodwin & Leech, 2006).

Acknowledging that it might not be feasible to apply strict time frames to data collection periods when conducting research in a busy clinical environment, a 15-minute "window" was allowed for the collection of clinician-, researcher-reported data, and BIS values using the time that patients completed self-reported assessments as a reference point. It is possible therefore that patients' symptoms could have changed within the 15-minute data collection "window", thus affecting the consistency of data obtained from different sources, and, subsequently, the quality of reported findings. Moreover, in line with recommendations (Althouse, 2016; Bender & Lange, 2001), no adjustments were made to account for the multiple analyses performed in this study. There is therefore an increased probability of false-positive results to have been presented in this thesis (Althouse, 2016).

A further limitation in this study was the necessity of using level of consciousness measures which had not been previously thoroughly validated in palliative care patients. Given the lack of an acceptable "gold standard" measure for assessing palliative care patients' consciousness levels (Arevalo et al., 2012), the selection of outcome measures was informed by the limited psychometric evidence available on existing observational measures (Krooupa, Vivat, McKeever, Marcus, et al., 2020), and by considering the burden on patients and clinical staff from completing multiple repeated measures over a short period of time. Therefore, level of

consciousness tools were not themselves fully validated for use in the palliative care setting, raising some difficulties with interpreting study findings.

Patient-reported outcomes are widely acknowledged as the “gold standard” in palliative care (Bausewein et al., 2011; Bausewein et al., 2016; Evans et al., 2013). Consistent with this, this research used patients’ self-reported assessments as the standard against which all other outcomes were compared. However, the subjective experience of consciousness has little relation to levels of consciousness, i.e. the measure of a contact a person has with the outside world based on perceptible signs (Overgaard & Overgaard, 2011). Moreover, as discussed earlier in this chapter, patients’ own perceptions of their consciousness levels may be influenced by other, related, symptoms, such as depression and fatigue (Cull et al., 1996; Klepstad et al., 2002). The use of outcome measures therefore which have not been developed based on correlations with patients’ reports of their subjective experience of consciousness, such as the measures used in this research, adds an additional level of complexity to the interpretation of findings reported in this thesis.

#### **9.4 Originality of research and contribution to the evidence base**

The present research is the first to investigate the acceptability, feasibility, and preliminary clinical usefulness of BIS monitoring in the UK palliative care context. The doctoral project overall comprised a number of studies; literature reviews, qualitative studies, and a prospective exploratory study, with findings from preceding studies guiding the uptake and design of subsequent ones. This systematic approach to the development of the overall project ensured the relevance of research objectives and the appropriateness of methods employed.

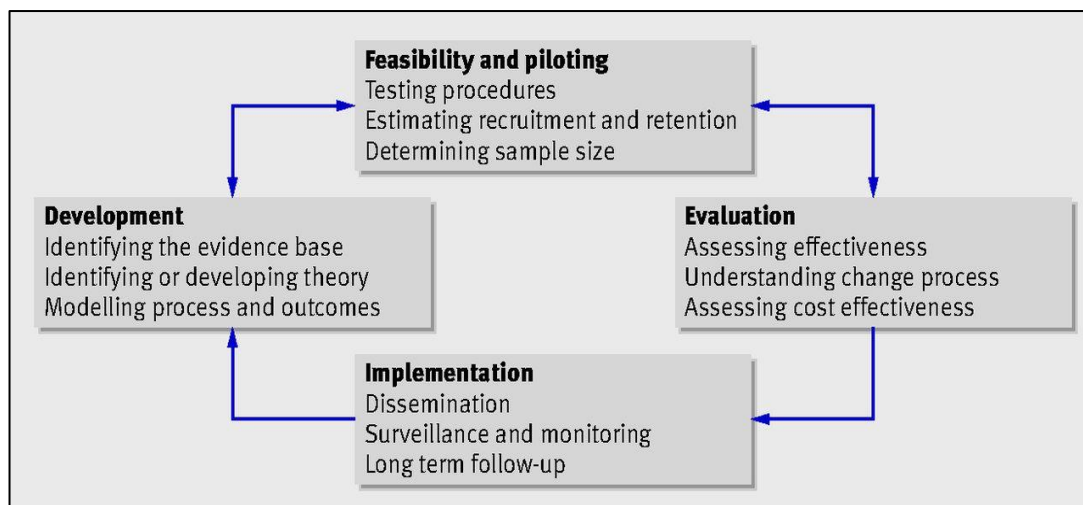
This research adds new understanding about the use of BIS monitoring in the palliative care setting. It provides new evidence on the factors affecting the acceptability of conducting research with BIS in palliative care by combining quantitative and qualitative data from key stakeholders who had a direct experience of using BIS in clinical practice. Furthermore, it is the first research to systematically document the recruitment and flow of participants in a prospective study of BIS monitoring in palliative care, and to identify the reasons influencing accrual and retention to such research, as well as strategies to minimise gatekeeping by clinical staff. It is also the first study to identify preliminary barriers and facilitators to the potential integration of BIS monitoring into routine palliative care clinical practice.

Despite the limitations noted, findings from this research contribute to the limited international evidence base on BIS monitoring in palliative care and offer important new evidence that could be used to inform the design and development of future research studies in this field.

## **9.5 Directions and recommendations for future research**

The sample participating in the exploratory study was small and designed to provide only preliminary evidence on the clinical usefulness of BIS monitoring. Furthermore, study participants were not patients with whom BIS would be used in practice, since they were conscious and able to comment on their experiences of using the technology. Future research should seek to develop an intervention of BIS monitoring and evaluate its effectiveness in larger samples of unconscious or semi-conscious palliative care patients. Ideally such research would take the form of a randomised controlled trial designed in accordance with the Medical Research Council (MRC) guidance for the development and testing of complex interventions in health care (Craig et al., 2008). The MRC framework proposes a systematic process for intervention development and testing, involving evaluating the existing evidence base and developing a theoretical approach to underpin the novel intervention, a period of feasibility testing and piloting, followed by the definitive evaluation of effectiveness and cost-effectiveness, and a period of implementation and dissemination (Craig et al., 2008). Much of the work done as part of this doctoral project could be used by researchers seeking to develop and test an intervention of BIS monitoring to inform elements of the “development” and “feasibility and piloting” stages of this process (see **Figure 9.1**).





**Figure 9.1:** Key elements of intervention development and evaluation process (reproduced with permission from Craig et al., 2008)

This research found significant correlations between patient self-reports and researcher-observed assessments of pain and alertness. Family members/caregivers and health professionals are currently mostly used as proxy assessors in palliative care clinical practice and research (Bausewein et al., 2016; Kutner et al., 2006). However, evidence on the validity of proxy assessments provided by family members and healthcare professionals is conflicting (Bausewein et al., 2016; Kutner et al., 2006), whilst research-related burden has been found to adversely affect participation in palliative care clinical studies (Mackin et al., 2009). Using researchers as alternative proxy assessors could reduce research-related burden on clinical staff and patient relatives/carers, and, therefore, potentially aid in promoting research engagement and participation. Given that the evidence on the validity of proxy researcher assessments provided in this research is preliminary, further research is needed to ascertain whether proxy assessments by non-clinical researchers could be used as fair substitutes for patient self-reports of pain and alertness.

Limited time often characterises palliative and end-of-life care research (Gysels et al., 2013). Given the adverse impact that the slow flow of patients through the recruitment process had on participation in the exploratory study, researchers should consider the time requirements of accessing and obtaining consent from potential participants at the design stage of future studies.

In some circumstances it may be advisable to seek permission from Research Ethics Committees to allow patients to participate without requiring a 24-hour gap to consider their decision. Such circumstances and accompanying alternative strategies to participant recruitment and consent would need to be clearly described in study protocols to avoid undue inducement or coercion (Gysels et al., 2013).

This research found moderate evidence of convergence between an 11-point alertness NRS and the RASS-PAL, and a low level of agreement between hospice clinicians scoring the RASS-PAL. However, these findings were limited by the high proportion of scores in a restricted range of respective scales and the large number of clinicians with differing characteristics performing the scoring. Future research should seek to further validate existing level of consciousness tools in diverse samples of palliative care patients using smaller and more homogeneous groups of clinicians for the administration and scoring of measures.

## **9.6 Implications for clinical practice**

Findings from this research suggest that the possible integration of BIS monitoring into usual clinical practice is acceptable to palliative care patients, their relatives, and clinical staff; thus, indicating its appropriateness in the palliative care context. Study participants expressed that using BIS as an adjunct to current clinical practice could aid in guiding the effective titration and delivery of sedative medication and so contribute towards improving patient care and comfort. These clinical benefits are in line with findings from research conducted in settings where sedative and anaesthetic drugs are commonly used, where the incorporation of BIS into standard practice has been found to improve patient outcomes (Punjasawadwong et al., 2014; Siddiqi et al., 2016). However, despite some preliminary evidence on the utility of BIS monitoring in palliative care (Barbato et al., 2018; Barbato et al., 2017; Masman et al., 2016; Monreal-Carrillo et al., 2017), the exploration of its use in this setting is still in its infancy and more evidence is needed to before its contribution to palliative care clinical practice is clear (Barbato et al., 2018). If future evidence supports the clinical usefulness of BIS in palliative care, efforts should be made for detailed implementation plans to be developed to aid its successful incorporation into existing care pathways. Such plans would benefit from being theory and evidence-driven, should systematically consider the effects of the novel intervention on existing systems and work

practices, and would need to make provisions for the ongoing training and education of all those involved with implementation (Ross et al., 2018).

Gaining insight into factors influencing the acceptance of novel interventions is essential in tailoring implementation strategies aiming to increase their uptake and sustainability in health care settings (Rye, Friberg, & Skre, 2019). By comparing key stakeholders' views on the acceptability of BIS monitoring before and after having a direct experience of using the technology in practice, preliminary barriers and facilitators to the potential uptake and implementation of BIS monitoring into routine hospice care were identified. Perceived barriers included the presumed invasiveness of the technology, the possibility for BIS to replace clinical observation and decision-making and to increase the medicalisation of end-of-life care, and the potential burden on clinical staff from routine BIS use. However, the observed shift in participants' perceptions regarding the appropriateness of BIS monitoring after using the technology in practice emphasises the key role of experiential knowledge and learning in increasing acceptance of novel interventions in palliative care (Taylor et al., 2015). If, therefore, BIS proves to be a useful adjunct to existing practice, the barriers identified could be overcome and its successful integration into routine clinical care achieved by providing clear information on its purpose and use (that it is designed to supplement, rather than replace, usual care), enabling key stakeholders to interact with technology before use in practice (for example in the form of trial monitoring sessions), and creating organisational environments that are conducive to the adoption of new practices.

## **9.7 Conclusions**

The research presented in this thesis contributes to the limited international evidence base on BIS monitoring in palliative care. Findings revealed that conducting research with BIS in adult palliative care patients in the UK is feasible and acceptable to key stakeholders, and provided new evidence on factors influencing the acceptability and feasibility of BIS as a research tool. This information could be used to guide the design and development of future studies in this field.

This research did not find evidence to support the clinical usefulness of BIS monitoring in hospice inpatients. However, the study sample was small and consisted of patients who were predominantly alert and conscious, therefore limiting the ability to draw firm conclusions on the utility of BIS in this setting. Further research in larger samples of semi-conscious or unconscious patients is needed to ascertain whether BIS could have a role in the assessment and monitoring of palliative care patients' consciousness levels in routine clinical practice.

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## Appendices

### Appendix 1 Published systematic review paper

Review Article



# Identification and evaluation of observational measures for the assessment and/or monitoring of level of consciousness in adult palliative care patients: A systematic review for I-CAN-CARE

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#### Abstract

**Background:** The use of observational measures to assess palliative care patients' level of consciousness may improve patient care and comfort. However, there is limited knowledge regarding the validity and reliability of these measures in palliative care settings.

**Aim:** To identify and evaluate the psychometric performance of observational level of consciousness measures used in palliative care.

**Design:** Systematic review; PROSPERO registration: CRD42017073080.

**Data sources:** We searched six databases until November 2018, using search terms combining subject headings and free-text terms. Psychometric performance for each identified tool was appraised independently by two reviewers following established criteria for developing and evaluating health outcome measures.

**Results:** We found 35 different levels of consciousness tools used in 65 studies. Only seven studies reported information about psychometric performance of just eight tools. All other studies used either *ad hoc* measures for which no formal validation had been undertaken ( $n = 21$ ) or established tools mainly developed and validated in non-palliative care settings ( $n = 37$ ). The Consciousness Scale for Palliative Care and a modified version of the Richmond Agitation–Sedation Scale received the highest ratings in our appraisal, but, since psychometric evidence was limited, no tool could be assessed for all psychometric properties.

**Conclusion:** An increasing number of studies in palliative care are using observational measures of level of consciousness. However, only a few of these tools have been tested for their psychometric performance in that context. Future research in this area should validate and/or refine the existing measures, rather than developing new tools.

#### Keywords

Analgesics, consciousness, hypnotics and sedatives, palliative care, psychometrics, surveys and questionnaires, systematic review, terminal care

#### What is already known about the topic?

- The European Association for Palliative Care (EAPC) framework for sedative use recommends that patients' level of consciousness should be evaluated as part of their periodical assessments during and after administering sedative medication.
- Observational measures are frequently employed for monitoring consciousness levels in settings where sedatives and analgesics are commonly used.

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- The use of observational measures to assess palliative care patients' level of consciousness may improve patient care and comfort; however, little is known about which measures are the most appropriate, valid and reliable to use in the palliative care setting.

#### What this paper adds?

- An increasing number of studies are using observational tools for the assessment of palliative care patients' level of consciousness.
- Only eight of these tools have been tested for their psychometric performance with palliative care patients in single validation studies, and none have been tested for all measurement properties.
- Most measures of level of consciousness used in primary studies are *ad hoc* tools for which no formal validation has been undertaken or tools developed and validated in non-palliative care settings.

#### Implications for practice, theory or policy

- Clinicians and researchers should be mindful of the limited evidence supporting the psychometric quality of existing level of consciousness measures, especially in terms of responsiveness, when using such scales in the palliative care setting.
- Future research should focus on validating and refining the existing measures for use in palliative care, rather than developing new tools.

## Background

Palliative care patients may experience alterations in their level of consciousness, either as a result of disease and symptom progression or as an effect of different pharmacological treatments.<sup>1</sup> Clinicians may intentionally reduce the consciousness of some patients, especially towards the end of life when symptom burden tends to increase, by administering sedative and/or analgesic medication. This practice aims to relieve patients' intractable distress resulting from one or more treatment-resistant symptoms.<sup>2</sup>

National and international palliative care organisations recommend using sedative medication for the alleviation of refractory symptoms at the end of life.<sup>3</sup> However, the prevalence and practice of sedative use vary considerably according to setting and country.<sup>4-6</sup> Nevertheless, the majority of clinical practice guidelines on the use of sedatives in palliative care agree that sedative medication should be used proportionately, to the extent that distressing symptoms for each individual patient are adequately addressed.<sup>2,7,8</sup>

Inappropriate use of sedative and analgesic medication may have considerable consequences for the care and experience of patients and family members. A survey among palliative care nurses found that sedative use was considered insufficiently effective by approximately 40% of the respondents,<sup>9</sup> while another study reported suboptimal use of palliative sedation performed by general practitioners in 11 of the 27 described cases.<sup>10</sup> Inadequate symptom palliation can be traumatic for patients and a significant source of emotional distress for their families.<sup>10,11</sup> Conversely, the use of disproportionately high doses of sedatives may be equally distressing for relatives due to the

impaired ability of the patient to interact with family members and the possible risk of hastening death.<sup>12,13</sup>

The European Association for Palliative Care (EAPC) framework for sedative use recommends that patients' level of consciousness should be evaluated as part of their periodical assessments during and after administering sedative medication. This is in order to avoid the effects of over- or under-sedation and fulfil the requirements of proportionality.<sup>2</sup> In settings where sedatives and analgesics are commonly used, observer-rated measures are frequently employed for monitoring consciousness levels.<sup>14-16</sup> A review of sedation instruments in intensive care units identified 25 studies describing relevant tools.<sup>14</sup> Similarly, another review found that numerous tools measuring sedation depth had been used in clinical research on procedural sedation.<sup>15</sup> Although the authors of these reviews concluded that further research into the psychometric performance of the identified measures is needed, a number of measures achieved high ratings for validity and reliability in the settings/populations in which they were tested. Most of the instruments in these studies comprise a single item with a categorical grading representing decreasing levels of consciousness, usually assessed by patients' response to stimulation of increasing intensity. This type of scale structure may create overlaps between different consciousness levels which are not necessarily mutually exclusive, but provides benefits in terms of simplicity and ease of use, so allowing for repeated administrations to be quickly performed and, consequently, enabling the close monitoring of responses to sedative and analgesic use.<sup>17</sup> Other advantages of using valid and reliable observational measures for the assessment of level of consciousness include improved consistency in



medication administration, better communication among healthcare professionals, enabling the development of sedation guidelines and protocols, and facilitating comparison between research data and findings.<sup>18–20</sup> Occasionally, level of consciousness scores may also provide an indication of disease progression and expected survival.<sup>21–23</sup>

Despite these benefits being highly applicable and relevant to the palliative care context, little is known about which measures are the most appropriate, valid and reliable to use with palliative care patients. The aim of the present systematic review, therefore, was to (1) identify all relevant observational levels of consciousness tools used in primary research studies, (2) describe their content and (3) critically appraise their psychometric performance. This review was undertaken as part of the sedation work package of I-CAN-CARE (Improving care, assessment, communication and training at the end of life), a Marie Curie-funded research programme on prognosis and sedative use in palliative care.

## Methods

This review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement<sup>24</sup> and the review protocol published in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42017073080).

### Search strategy

A four-step search strategy was employed (Table 1). An initial broad search was performed to identify primary research studies reporting the use of observational level of consciousness measures and produce a list of search terms. Six databases were then systematically searched using a combination of subject headings and free-text terms for palliative care, measurement instruments and sedative use, adjusted for each database. Subsequently, the reference lists of all included papers were hand-searched for relevant publications. When eligible articles were identified, the process of backward reference searching was repeated until no more relevant publications could be located. The same method was applied for finding newer studies citing the included papers. Finally, the authors of conference abstracts meeting inclusion criteria were contacted for full-text publications. Where relevant data were missing from included papers, authors were also contacted.

### Eligibility criteria

Full-text publications of primary studies (prospective or retrospective, patient-based or clinician-based) describing the use of observational measures (validated or ad

hoc) for the assessment and/or monitoring of level of consciousness/sedation depth in adult palliative care patients were included.

We excluded non-primary studies, such as systematic reviews, and studies providing no information about sample size. Due to resource constraints, non-English language publications were also excluded.

### Study selection

After removing duplicates 11,938 titles and abstracts were screened against eligibility criteria (A.M.K.). A second reviewer (E.M.) independently screened a random 10% selection. The inter-reviewer agreement for the initial title and abstract screening was  $\kappa = 0.71$ . Full-text publications which potentially met inclusion criteria after first screening were each independently assessed for eligibility by two reviewers from a group of six (A.M.K., J.S., E.M., S.M., B.V. and P.S.). Discrepancies at each stage of study selection were resolved through discussion.

### Data extraction

We extracted the following information for each included study into a standardised form: first author, date of publication, country of origin, study aim(s), setting, sample size and participant characteristics. For each measure identified, tool name, measurement aim/purpose, number of subscales and items and response options were extracted. Data on the psychometric performance of instruments, where available, were also extracted.

### Psychometric performance of included measures

We used a checklist (Table 2) to evaluate the psychometric performance of included measures. This checklist drew on that developed by Zwakhalen et al.<sup>25</sup> with some modifications, following discussion between A.M.K. and B.V., based on the established criteria for developing and evaluating health outcome measures.<sup>26–28</sup>

The psychometric properties appraised include the reported validity, reliability and responsiveness of measures. In addition, the feasibility and origin (source) of tool items were also evaluated.

Validity of an instrument was defined as an assessment of the extent to which it measures what it purports to measure.<sup>26</sup> It is generally understood that there are four types of validity; we assessed three of these: (1) content validity: the degree to which the construct of interest is comprehensively represented by the measure items, assessed through the extent of involvement of the target population in item selection and the provision of a clear description of the concept that the instrument is intended to measure;<sup>28</sup> (2) construct validity: correlation

**Table 1.** Search strategy and eligibility criteria.

Search strategy	Step 1: Broad search of relevant literature	1. Identification of relevant publications in PsycINFO and MEDLINE 2. Compilation of text words contained in title, abstract and authors' keywords, and database index terms, to produce a list of search terms
	Step 2: Systematic database search	Databases: (1) CENTRAL, (2) CINAHL, (3) Embase, (4) MEDLINE, (5) PsycINFO and (6) WoS Dates: Database inception – 14 November 2018 Restrictions: No language or other restrictions applied Search terms (used in MEDLINE and modified for other databases): 1. Self Report/ 2. Checklist/ 3. (tool* or assess* or survey* or question* or measur* or method* or scale* or checklist* or rating* or test* or instru* or inventor* or technique* or monitor* or observ* or rate* or function* or scoring system* or outcome*).mp. 4. 1 or 2 or 3 5. Palliative Care/ 6. exp Terminal Care/ 7. Hospices/ 8. (palliat* or terminal* or endstage or hospice*).mp. 9. (end adj3 life).mp. 10. (care adj3 dying).mp. 11. ((advanced or late or last or end or final) adj3 (stage* or phase*)).mp. 12. 5 or 6 or 7 or 8 or 9 or 10 or 11 13. ((continuous or deep or intermittent or intermediate or respite or mild) adj3 (sedat* or an?esthe*)).mp. 14. Deep Sedation/ 15. Conscious Sedation/ 16. sedat*.mp. 17. 13 or 14 or 15 or 16 18. 4 and 12 and 17
	Step 3: Citation searching	(1) Backward citation searching (hand-searching reference lists of included publications) and (2) forward citation searching (hand-searching studies citing included publications through Google Scholar) were repeated until no more relevant publications could be located
	Step 4: Contacting authors	1. Authors of conference abstracts meeting inclusion criteria contacted for full-text publications 2. Authors of included papers contacted where relevant data were missing from publications
Eligibility criteria	Inclusion criteria	1. Primary research studies 2. Full-text research articles 3. English language publications 4. Studies reporting the use of observer-rated measures 5. Studies conducted with adult (>18) palliative care patients 6. Scales assessing and/or monitoring depth of sedation/consciousness level
	Exclusion criteria	1. Non-primary studies, including systematic reviews 2. Opinion articles, editorials, book chapters 3. Case report studies and studies providing no information about sample size 4. Non-English language publications 5. Studies with non-adult (<18) palliative care patients 6. Studies reporting the use of patient/self-reported measures 7. Scales measuring drowsiness or somnolence 8. Studies reporting on the use of binary-response measures

CENTRAL: Cochrane Central Register of Controlled Trials; CINAHL: Cumulative Index to Nursing and Allied Health Literature; WoS: Web of Science.

of the level of consciousness scale with other instruments that are known to measure the same construct. Pearson's or Spearman's correlation coefficient of 0.6 or

above was considered acceptable in this review;<sup>25</sup> (3) structural validity: assessed through the degree of variance explained by factor analysis. There is no agreed

**Table 2.** Quality criteria for measure appraisal.

Domain	Property	Score	Description
Validity	Number of participants	2	$N \geq 100$ and the number of palliative care patients included was relative to the number of items/variables or $50 < N < 100$ and corrected for multiple testing
		1	$50 < N < 100$ and the number of palliative care patients included was relative to the number of items/variables or $N < 50$ and corrected for multiple testing
		0	$N < 50$ or number of palliative care patients included not relative to the number of items/variables or $N < 50$ and not corrected for multiple testing
	Content validity	2	A description of the construct that is being measured is provided and target population is involved in item selection
		1	A description of the construct that is being measured is provided or target population is involved in item selection
		0	The construct that is being measured is not described and limited/no involvement of target population in item selection
	Criterion validity	2	Correlates acceptable to high ( $r > 0.60$ ) according to the 'gold standard' or according to a 'silver standard'
		1	Correlates moderate-acceptable ( $0.40 < r < 0.60$ ) according to the 'gold standard' or according to a 'silver standard'
		0	Correlates low ( $r < 0.40$ )
	Structural validity	2	Appropriate method of factor analysis performed and factors account for $\geq 50\%$ of the total variance
		1	Factor analysis performed but another method would have been more appropriate
		0	Factors account for $< 50\%$ of the total variance
	Construct validity	2	Correlates with other level of consciousness measures acceptable to high ( $r > 0.60$ )
		1	Correlates with other level of consciousness measures are moderate ( $0.40 < r < 0.60$ )
		0	Correlates with other level of consciousness measures are low ( $r < 0.40$ )
Reliability	Homogeneity (internal consistency)	2	$0.70 < \alpha < 0.90$
		1	$\alpha > 0.90$ or $0.60 < \alpha < 0.70$
		0	$\alpha < 0.60$
	Inter-rater reliability	2	Reliability coefficient $> 0.80$
		1	$0.60 < \text{reliability coefficient} < 0.80$
		0	Reliability coefficient $< 0.60$
	Intra-rater and/or test-retest reliability	2	Reliability coefficient $> 0.80$
		1	$0.60 < \text{reliability coefficient} < 0.80$
		0	Reliability coefficient $< 0.60$
	Responsiveness	2	Appropriate method of detecting clinically meaningful change over time described and clinically meaningful change over time detected and 15% or less of respondents achieved the lowest or highest possible score, respectively
		1	Appropriate method of detecting clinically meaningful change over time described and clinically meaningful change over time detected or 15% or less of respondents achieved the lowest or highest possible score, respectively
		0	Appropriate method of detecting clinically meaningful change over time not followed or clinically meaningful change over time not detected or more than 15% of the respondents achieved the lowest or highest possible score, respectively
	Origin of items	2	Items specifically developed for use with palliative care patients
		1	Items were modified for use with palliative care patients
		0	Items originated from a scale developed for another population
Feasibility	2	Scale is short, manageable with instructions, scoring interpretation	
	1	Scale is manageable (one format)	
	0	Scale is more complex	

'gold standard' for measuring level of consciousness in palliative care, so we did not assess the fourth type of validity, (4) criterion validity: the extent to which a

proposed new measure correlates with another instrument generally accepted to accurately measure the construct of interest ('gold standard').<sup>26</sup>

Reliability refers to the overall consistency and reproducibility of a measure.<sup>26</sup> Four types of reliability estimates were included in our assessment criteria: (1) homogeneity (internal consistency), assessed through Cronbach's alpha coefficient; (2) inter-rater reliability; (3) intra-rater reliability; and (4) test-retest reliability. The common statistical methods for evaluating the latter three properties are intraclass correlation coefficient (ICC) for continuous measures and Cohen's kappa for nominal/ordinal measures.<sup>28</sup> We took values of less than 0.6, between 0.6 and 0.8, and greater than 0.8 as indicative of low, adequate and high reliability, respectively.

Responsiveness is the ability of an instrument to detect clinically meaningful changes over time in the construct measured. The most common approaches to assessing responsiveness are the correlations of change scores for an instrument over time with changes in other available variables, and the area under the receiver operator characteristic (ROC) curve (AUC).<sup>26,28</sup>

Feasibility is described as the user-friendliness of a measure in terms of administration and processing.<sup>26</sup> The burden on staff of collecting and processing data is an important parameter to consider when selecting a tool for use in clinical practice or for research purposes.<sup>26</sup>

Origin of items refers to whether the measure items were specifically developed for use with the target population, modified, or taken from a scale developed for another population.<sup>25</sup>

Evidence of psychometric performance was categorised according to the aforementioned criteria. For each property, measures were scored according to the following scheme: 2 if the property was evaluated and fully met criteria; 1 if criteria were partially met; and 0 when criteria were not met. If a property was not evaluated/not reported or the information provided was unclear, a rating was not given. Psychometric properties were independently evaluated by two raters (A.M.K. and E.M.), achieving a high initial agreement ( $\kappa = 0.91$ ). Raters conferred over discrepancies until full consensus on ratings was reached.

## Results

The database search yielded 13,827 results. After removing duplicates and initial screening of titles and abstracts, 491 potentially eligible articles remained, which were examined in full. Of these, 55 met criteria for inclusion. Further 10 eligible studies were identified through forward and backward citation searching, resulting in 65 included studies (see Figure 1). Only seven studies provided data on the psychometric performance of level of consciousness tools in the palliative population; 21 studies presented information on *ad hoc* measures (i.e. those developed specifically for the purposes of individual studies); and 37 reported using established scales, the

majority of which had been validated in non-palliative care settings. Table 3 presents a summary of study and measure characteristics.

## Description of included studies

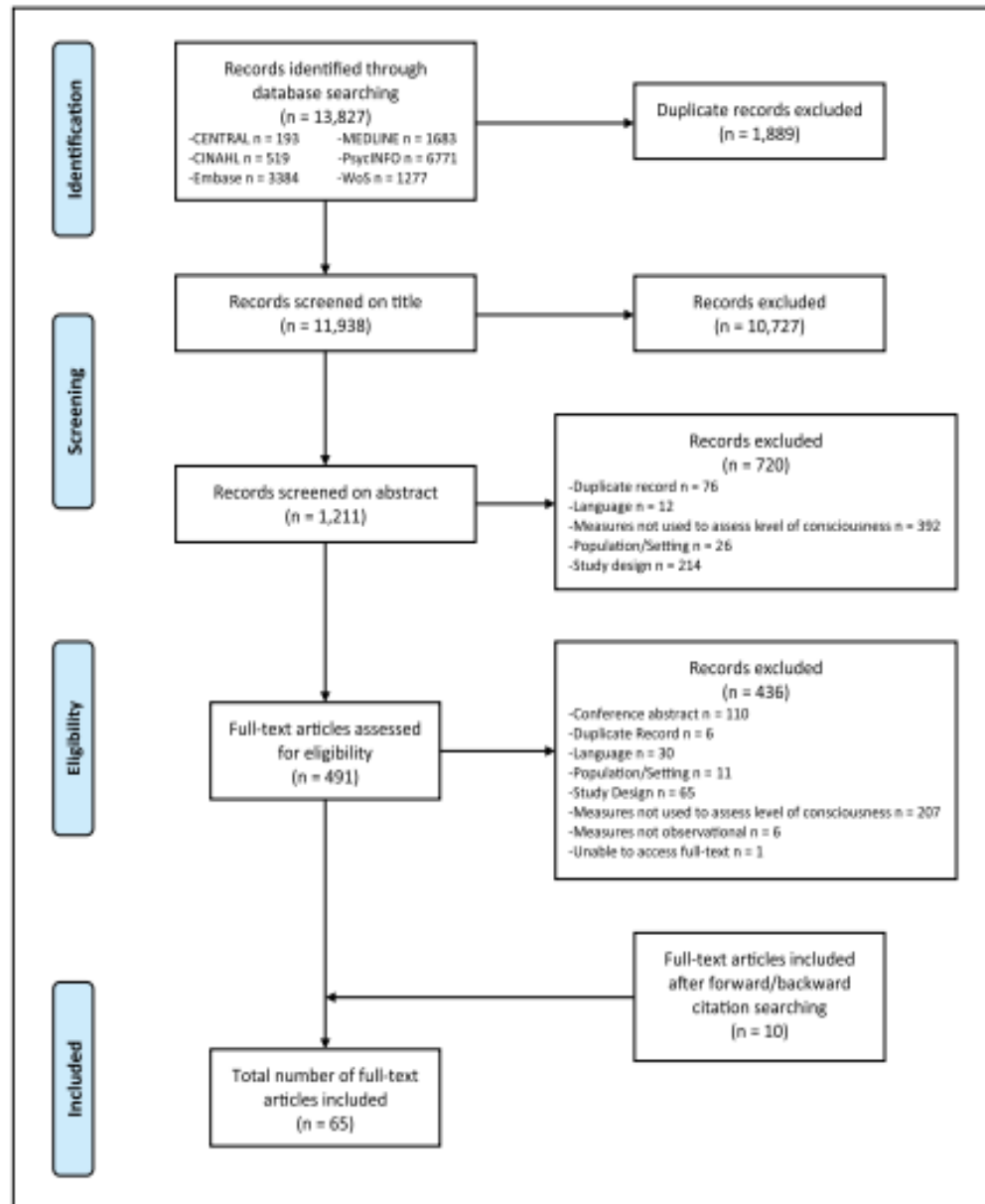
Morita et al.<sup>41,42</sup> published two articles in which separate analyses of data collected from a single study were performed. Similarly, Barbato et al.,<sup>53,54</sup> Campbell et al.,<sup>57,59</sup> Claessens et al.<sup>1,97,98</sup> and Van Deljck et al.<sup>48,49</sup> reported distinct findings from one study in two or more papers. Each of these papers described discrete study aims and outcomes, so we defined them as separate studies. A large number of studies reporting on level of consciousness measures have been published recently, with 26 of the 65 (40%) included studies published after 2013.

Most included studies were patient-based ( $n = 58$ ), with recruitment and data collection conducted prospectively ( $n = 49$ ). In eight studies some or all relevant data were obtained retrospectively from patients' medical records,<sup>4,35,38,41,42,55,79,90</sup> while in one study patients were recruited both prospectively (on admission) and retrospectively (after death).<sup>37</sup> Another study reported mixed methods for data collection, a prospective quantitative survey and semi-structured interviews with general practitioners involved in the practice of palliative sedation.<sup>10</sup> Six studies used questionnaires as a means of data collection.<sup>31,43,46-49</sup> In these, researchers asked clinicians (physicians ( $n = 4$ )<sup>43,47-49</sup> or nurses ( $n = 2$ )<sup>31,46</sup>), to provide information about patients under their care who had received sedative medication.

Studies were mainly conducted in a single setting ( $n = 36$ ); principally hospices, palliative care units or hospitals. Nine studies involved home care patients,<sup>4,10,31,56,62,67,81,84,90</sup> and an equal number included nursing home participants.<sup>31,37,44,46,48-50,92,93</sup> One study included patients recruited from a cancer centre.<sup>83</sup>

Sample size varied considerably (median: 132 participants, interquartile range (IQR): 44-266). The most prevalent diagnosis among study participants was cancer ( $n = 29$ ). Other reported diagnoses included dementia ( $n = 3$ )<sup>37,44,50</sup> and interstitial lung disease ( $n = 1$ ).<sup>79</sup> A total of 32 studies reported mixed diagnoses or did not provide this information. Patients in almost all studies were at an advanced or an end stage of disease.

Reflecting the wide diversity of study aims, level of consciousness tools in each study were employed to serve a number of distinct purposes. The most frequently reported were: to assess/monitor sedation depth after palliative sedation initiation ( $n = 29$ ), to assess effects or side effects of opioid use ( $n = 7$ ),<sup>29,34,45,54,56,81,91</sup> to evaluate signs/symptoms of impending death ( $n = 8$ )<sup>21-23,37,42,60,61,79</sup> and to examine associations between level of consciousness and discomfort or other symptoms ( $n = 6$ ).<sup>40,44,50,60,61,64</sup> It is noteworthy that only four studies sought to validate



**Figure 1.** PRISMA flow diagram of study selection process.<sup>24</sup>

CENTRAL: Cochrane Central Register of Controlled Trials; CINAHL: Cumulative Index to Nursing and Allied Health Literature; WoS: Web of Science.

level of consciousness instruments in the palliative care setting.<sup>18,73,87,93</sup> Of these, only one aimed to develop a new tool.<sup>18</sup>

#### Description of identified measures

A total of 35 different measures assessing level of consciousness were described in the articles included in this review. Only eight were measures for which evidence of psychometric quality in the palliative setting was available.

Fifteen were established instruments or single items taken from compound scales validated as a whole, and 17 were tools constructed for individual study purposes (*ad hoc* measures). Information on psychometric performance in palliative care was provided for five of the 15 established measures, therefore, there is an overlap between the first 2 described categories (see Figure 2). Across all categories, the tool most frequently employed was the original Richmond Agitation–Sedation Scale (RASS) or its modified versions ( $n = 17$ ).<sup>10,21,35,51,53–55,64,70,72,73,77,84,86,87,91,93</sup>

Table 3. Description of identified studies and measures.

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Studies reporting <i>ad hoc</i> measures							
Abermethy et al. <sup>20</sup> 2003 Australia	To determine the efficacy of oral morphine for the management of refractory dyspnoea	Palliative, general, respiratory, cardiac medicine clinics	48 outpatients with refractory dyspnoea	-	To measure sedation depth as a side effect of morphine use	S: - I: 1	4-level scale ('No', 'Mild', 'Moderate', 'Severe' sedation)
Aretha et al. <sup>20</sup> 2009 Greece	Evaluation of patient/family-controlled sedation with midazolam for intractable symptom control	Tertiary care university hospital	8 terminal cancer inpatients	-	Monitoring of patients after terminal sedation initiation	S: - I: 1	4-point scale (1='Awake', 2='Arousable with voice', 3='Arousable with light pain', 4='Unarousable')
Arevalo et al. <sup>21</sup> 2013 Netherlands	To describe nurses' experiences with the decision-making and performance of CPS	Home care organisations, palliative care units (based in nursing homes or inpatient hospices), hospitals	199 nurses reporting on their last patient receiving CPS	- (Scale included in the study questionnaire)	Monitoring of CPS	S: - I: 1	6-level scale ('Drowsiness', 'Eyes closed, reaction to verbal stimuli', 'Eyes closed, reaction to physical stimuli', 'Eyes closed, no reaction to physical stimuli', 'Other', 'I don't know')
Barbato <sup>22</sup> 2001 Australia	Exploration of the clinical application of BIS monitoring in palliative care	Hospice	12 unconscious palliative care inpatients	Consciousness Scale (modified GCS) <sup>23</sup>	Monitoring of consciousness level from the onset of unconsciousness and until death	S: 6 (breathing, movement, pulse volume, eyelash reflex, peripheries and response to name call) I: 1/subscale	4-point scale (1-4) for each subscale. Scores can be calculated per subscale and as a total score.
Baumann et al. <sup>24</sup> 1986 USA	Evaluation of the safety and efficacy of patient-controlled analgesia in patients with unsuccessfully treated chronic pain secondary to cancer	Not specified	8 terminally ill cancer patient	-	To evaluate sedation for the assessment of individual analgesic response	S: - I: 1	5-point scale (1='Wide awake', 2='Drowsy', 3='Dozing intermittently', 4='Mostly sleeping', 5='Only awakens when aroused')

(Continued)

Table 3. (Continued)

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Dean et al. <sup>35</sup> 2014 UK	Description of PS decision-making practices in a UK hospice over the course of five years	Hospice	234 patient charts	Sedation scale (modified RASS) <sup>19</sup>	Assessing level of sedation to guide PS clinical decision-making and documentation	S: - I: 1	6-point scale (+2 = 'Agitated/Distressed', +1 = 'Anxious/Restless', 0 = 'Alert, orientated, calm', -1 = 'Drowsy: Opening eyes and establishing eye contact for periods of 10 seconds or more, responds to commands', -2 = 'Moderate sedation: Rousable to voice or physical stimulation. Unable to communicate', -3 = 'Deep sedation: Unrousable')
Fainsinger et al. <sup>36</sup> 2000 South Africa, Israel, Spain	To provide a better understanding of the use of sedation for the management of uncontrolled symptoms in terminally ill patients	Hospices and hospital-based palliative care unit	387 palliative care patient	-	To assess level of consciousness after initiation of sedation for uncontrolled symptoms	S: - I: 1	3-level scale ('Alert', 'Drowsy', 'Unresponsive')
Hendriks et al. <sup>37</sup> 2014 Netherlands	To investigate symptoms, treatment and quality of life in patients with end-stage dementia	Nursing homes	330 end-stage dementia patients (213 recruited on admission, 117 retrospectively)	-	To assess the level of consciousness that most frequently occurred during the last week of life	S: - I: 1	6-level scale ('Awake and alert', 'Awake', 'Awake but drowsy looking', 'Falling asleep', 'Light sleep', 'Deep looking sleep')
Jaspers et al. <sup>38</sup> 2012 Germany	Description of the practice of PS in Germany	Palliative care units, inpatient hospices	1944 electronic patient records	- (Depth of PS item included in the standardised documentation system for palliative care patients)	To assess depth of PS	S: - I: 1	3-level scale ('Somnolence', 'Stupor', 'Coma')

(Continue d)

Table 3. (Continued)

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Morita et al. <sup>23</sup> 1998 Japan	To investigate the change in physical signs and medical interventions in the dying process	Palliative care unit	100 terminally ill cancer patient	Categorical scale (modified Riker Sedation-Agitation Scale <sup>39</sup> )	To examine changes in the level of consciousness in the last four weeks of life	S: - I: 1	4-level scale ('Awake; arousable, follows commands', 'Drowsy: difficult to arouse or unable to attend to conversation or commands', 'Very drowsy: awakens to noxious stimuli only', 'Coma: does not awaken to any stimuli')
Morita et al. <sup>40</sup> 2000 Japan	Identification of risk factors for the development and persistency of death rattle	Palliative care unit	245 terminally ill cancer patients (of whom 107 developed death rattle)	Categorical scale (modified Riker Sedation-Agitation Scale) <sup>39</sup>	To assess conscious level as a risk factor for the development/persistency of death rattle	Same as above	Same as above
Morita et al. <sup>41</sup> 2003 Japan	To investigate the effects of partial opioid substitution and hydration on the occurrence of agitated delirium in the final stage of cancer	Palliative care unit	284 terminally ill cancer inpatient charts	Fainsinger's consciousness scale (ad hoc scale described in Fainsinger et al. <sup>36</sup> )	Evaluation of consciousness level as part of the assessment of the degree of cognitive impairment	S: - I: 1	3-level scale ('Alert', 'Drowsy', 'Unresponsive')
Morita et al. <sup>42</sup> 2003 Japan	To establish the communication capacity level and identify factors contributing to communication capacity impairment and agitated delirium in cancer patients in their final week of life	Palliative care unit	284 terminally ill cancer inpatient charts	Fainsinger's consciousness scale (ad hoc scale described in Fainsinger et al. <sup>36</sup> )	Evaluation of consciousness level in the last week of life	Same as above	Same as above

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Table 3. (Continued)

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Papavasiliou et al. <sup>45</sup> 2014 Belgium	To compare physician-reported practices on CDSUD between general practitioner and medical specialists	Not specified	561 cases of CDSUD reported by physicians	– (Level of unconsciousness item included in questionnaire on end-of-life practices)	Level of unconsciousness (coma) used to assess the degree of patients' awareness during the practice of CDSUD	S: – I: 1	11-point scale (0= 'Symptom not present' to 10= 'Worst possible symptom')
Pasman et al. <sup>44</sup> 2005 Netherlands	To study the level and course of discomfort, and factors that are associated with discomfort in patients with dementia for whom artificial nutrition and hydration are forgone	Nursing homes	178 patients with severe dementia	–	To assess the level of consciousness as a determinant of discomfort	S: – I: 1	6-point scale (response options not described)
Portenoy et al. <sup>45</sup> 2006 USA	Exploration of the relationship between opioid use and survival at the end of life	Hospices	725 palliative care inpatients	–	Level of consciousness at the time of last opioid dose change assessed for its association with length of survival	S: – I: 1	4-level scale ('Full level of consciousness', 'Drowsy', 'Confused', 'Unable to respond')
Rys et al. <sup>46</sup> 2014 Belgium	Investigation of the practice of CSD in nursing homes	Nursing homes	249 nurse reports of their most recent patient treated with CSD	– (Depth of sedation scale included in the study questionnaire)	To assess depth of sedation reached after the administration of CSD	S: – I: 1	5-level scale (‘Drowsy’, ‘Eyes closed, response to voice’, ‘Eyes closed, response to painful stimuli’, ‘Eyes closed, no reaction to any stimulus’, 'Other')
Swart et al. <sup>47</sup> 2012 Netherlands	Description of the practice of CPS until death after the introduction of a national palliative guideline	Not specified	370 physicians providing information about their last patient who received CPS until death	– (Depth of continuous sedation item included in the study questionnaire)	To assess depth of continuous sedation reached after the administration of CPS until death	S: – I: 1	5-point scale ('Drowsy', 'Eyes closed, responding promptly to verbal command', 'Eyes closed, arousable only by physical stimuli', 'Eyes closed, not arousable by physical stimuli', 'Other')

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Table 3. (Continued)

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Van Deijck et al. <sup>48</sup> 2010 Netherlands	Investigation of the practice of CPS in elderly patients	Nursing homes	316 nursing home physicians reporting on their last case of CPS	– (Level of consciousness item included in the study questionnaire)	Evaluation of level of consciousness at adequate symptom relief after the administration of CPS	S: – I: 1	6-level scale (‘Alert and orientated’, ‘Drowsy’, ‘Eyes closed, following directives’, ‘Eyes closed, responding to physical stimuli’, ‘Eyes closed, not responding to physical stimuli’, ‘Disturbed brainstem function’)
Van Deijck et al. <sup>49</sup> 2015 Netherlands	To explore the characteristics of patients with existential suffering treated with CPS and the degree to which preconditions for administering CPS are fulfilled	Nursing homes	314 cases of patients who received CPS described by nursing home physicians	– (Level of consciousness item included in the study questionnaire)	Evaluation of level of consciousness at adequate symptom relief after the administration of CPS	Same as above	Same as above
Van Der Steen et al. <sup>50</sup> 2009 Netherlands	To compare discomfort in dementia patients dying from pneumonia with patients dying after intake problems, and to assess associations with treatment	Nursing homes	725 end-stage dementia patients	–	To explore the association between level of consciousness and discomfort	S: – I: 1	6-level scale (‘Awake and alert’, ‘Awake’, ‘Awake but drowsy looking’, ‘Falling asleep’, ‘Light sleep’, ‘Deep looking sleep’)
Studies reporting established measures							
Agar et al. <sup>34</sup> 2017 Australia	To determine the efficacy of risperidone or haloperidol relative to placebo for delirium symptoms among palliative care patients	Hospice and hospital palliative care inpatient services	247 palliative care inpatients with various diagnoses; predominantly cancer	RASS <sup>19</sup>	To measure sedation as an adverse effect of risperidone/ haloperidol use	S: – I: 1	10-point scale (+4= ‘Combative’, +3= ‘Very agitated’, +2= ‘Agitated’, +1= ‘Restless’, 0= ‘Alert and Calm’, –1= ‘Drowsy’, –2= ‘Light sedation’, –3= ‘Moderate sedation’, –4= ‘Deep sedation’, –5= ‘Unarousable’)

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Table 3. (Continued)

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Alonso-Babarro et al. <sup>4</sup> 2010 Spain	Assessment of the incidence and efficacy of PS for patients who died at home	Home	245 terminally ill cancer patient records	RS <sup>52</sup>	To monitor level of sedation after administration of PS	S: – I: 1	6-point scale (1 = 'Anxious and agitated or restless or both', 2 = 'Co-operative, orientated and tranquil', 3 = 'Responds to commands only', 4 = 'Briek response to a light glabellar tap or loud auditory stimulus, 5 = 'Sluggish response', 6 = 'No response')
Barbato et al. <sup>53</sup> 2017 Australia	To determine the validity of the BIS monitor and two observational scales	Palliative care unit	40 unresponsive palliative care inpatients	RASS <sup>10</sup>	To assess level of sedation for the exploration of the association with BIS values	Same as above	Same as above
Barbato et al. <sup>54</sup> 2018 Australia	To examine the effectiveness of breakthrough medication in unresponsive patients and the perception of patient comfort made by nurses and family	Palliative care unit	40 unresponsive palliative care inpatients	RASS <sup>10</sup>	To measure level of sedation for the assessment of the effect of breakthrough opioid/benzodiazepine use	Same as above	Same as above
Beritez-Rosario et al. <sup>55</sup> 2012 Spain	To assess the feasibility of a quality care project in PS	Hospital-based palliative care service	204 patient charts	RASS <sup>10</sup>	To assess the level of deep continuous sedation with the aim to reach a predetermined level (–5 RASS for patients with continuous dyspnoea at rest; –4 RASS for delirium or other reasons)	Same as above	Same as above
Boyd and Kelly <sup>56</sup> 1997 UK	Evaluation of the effectiveness of oral morphine for the symptomatic treatment of dyspnoea in patients with advanced cancer	Home, hospice	15 advanced cancer patients with dyspnoea	VAS	To measure sedation as a side effect of oral morphine	S: – I: 1	100 mm line anchored by two verbal descriptors; 0: 'Fully awake', 100: 'Asleep'

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Table 3. (Continued)

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Campbell et al. <sup>57</sup> 2009 USA	To investigate the self-reporting of dyspnoea at the very end of life	Palliative care unit	89 palliative care inpatients at the risk of experiencing dyspnoea	RLS85 <sup>58</sup>	To assess consciousness as patient characteristic for the exploration of the association with the ability to self-report dyspnoea symptoms	S: - I: 1	8-point scale (1 = 'Alert; No delay in response', 2 = 'Drowsy or confused; Responsive to light stimulation', 3 = 'Very drowsy or confused; Responsive to strong stimulation', 4 = 'Unconscious; Localizes but does not ward off pain', 5 = 'Unconscious; Withdrawing movement on pain stimulation', 6 = 'Unconscious; Stereotype flexion movements on pain stimulation', 7 = 'Unconscious; Stereotype extension movements on pain stimulation', 8 = 'Unconscious; No response to pain stimulation') Same as above
Campbell et al. <sup>59</sup> 2010 USA	To establish the reliability and construct validity of a revised RDOs	Palliative care unit	89 palliative care inpatients experiencing dyspnoea	RLS85 <sup>58</sup>	To assess consciousness for ascertaining the construct validity of RDOs	Same as above	Same as above
Campbell et al. <sup>60</sup> 2013 USA	To determine the effect of oxygen administration at the very end of life	Hospice, hospital-based palliative care service	32 hospice and hospital inpatients at the very end of life	RLS85 <sup>58</sup>	To measure consciousness for the correlation with respiratory distress and nearness to death	Same as above	Same as above
Campbell et al. <sup>61</sup> 2018 USA	Determination of the trajectory of dyspnoea and respiratory distress	Hospice	91 home-based palliative care patients	RLS85 <sup>58</sup>	To measure consciousness for the correlation with respiratory distress and nearness to death	Same as above	Same as above

(Continued)

Table 3. (Continued)

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Caraceni et al. <sup>62</sup> 2018 Italy	Comparison of PS practices in home care and hospice settings	Home-based palliative care services, hospices	531 terminal cancer patients receiving PS	MWSS <sup>60</sup>	Level of consciousness assessed as part of the PS monitoring process	S: – i: 1	5-point scale (1= 'Fully awake and oriented', 2= 'Drowsy but rousable', 3= 'Eyes closed but rousable to command', 4= 'Eyes closed but rousable to mild physical stimulation (earlobe tug)', 5= 'Eyes closed but unrousable to mild physical stimulation')
De la Cruz et al. <sup>64</sup> 2015 USA	To describe the prevalence and severity of delirium, in the final week of life and evaluate the usefulness of the Nursing Delirium Screening Scale	Hospice	78 terminally ill cancer patients	RASS <sup>19</sup>	To measure sedation or agitation as the predominant features of delirium	Same as above	Same as above
Franken et al. <sup>65</sup> 2018 Netherlands	To evaluate the variability in response to midazolam and to find clinically significant covariates that predict pharmacodynamic response	Palliative care centre	43 terminally ill inpatients receiving midazolam	RS <sup>52</sup>	To measure the effect of midazolam on patients' sedation level	Same as above	Same as above
Goncalves et al. <sup>66</sup> 2012 Portugal	Description of the sedation practice of Portuguese palliative care teams	Palliative care inpatient, home care, hospital support care services	181 palliative care patients for whom 27 received sedation)	CSPC <sup>18</sup>	To assess the deepest consciousness level reached after the administration of sedation	S: – i: 1	6-point scale (1= 'Awake', 2= 'Awakens when called by name and stays awake during discussion', 3= 'Awakens but falls asleep during discussion', 4= 'Reacts with movement/brief eye opening, but without eye contact, when called by name', 5= 'Reacts to trapezius muscle pinching', 6= 'Does not react')

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Table 3. (Continued)

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Goncalves et al. <sup>67</sup> 2013 Portugal	To examine the activity of Portuguese palliative care teams	Inpatient, home care and hospital palliative care support services	164 palliative care patients	CSPC <sup>18</sup>	Evaluation of consciousness level as a patient characteristic	Same as above	Same as above
Ferraz Goncalves et al. <sup>68</sup> 2016 Portugal	Comparison of haloperidol alone and in combination with midazolam for the treatment of acute agitation in palliative care	Palliative care unit	79 palliative care inpatients	CSPC <sup>18</sup>	To assess level of consciousness when control of agitation is reached	Same as above	Same as above
Hsu et al. <sup>69</sup> 2013 Taiwan	To investigate the characteristics and outcomes of non-cancer palliative care patients in an acute general care setting	Acute general medicine ward	258 inpatients (of whom 193 did not meet criteria for cancer palliative care)	GCS <sup>33</sup>	To measure GCS score as a clinical characteristic for the comparison between cancer and non-cancer patients	S: 3 (motor response, verbal response, eye opening) I: 1/subscale	Eye opening: 4-point scale (1–4), Motor response: 6-point scale (1–6), Verbal response: 5-point scale (1–5)
Hui et al. <sup>21</sup> 2014 USA, Brazil	To examine the frequency and onset of bedside physical signs and their diagnostic performance for impending death	Acute palliative care units	357 advanced cancer inpatients	RASS <sup>19</sup>	Decreased level of consciousness (RASS ≤ -2) assessed as a clinical sign of impending death	Same as above	Same as above
Hui et al. <sup>70</sup> 2017 USA	To compare the effect of lorazepam versus placebo as an adjunct to haloperidol for persistent agitation	Acute palliative care unit	93 advanced cancer inpatients with agitated delirium	RASS <sup>19</sup>	To measure sedation and agitation for the evaluation of the effect of pharmacological interventions for the treatment of agitation	Same as above	Same as above

(Continued)

Table 3. (Continued)

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Hwang et al. <sup>22</sup> 2013 South Korea	To determine the events that herald the onset of dying process and evaluate their predictive value for death within 48 hours	Palliative care unit	181 terminal cancer inpatients	AVPU <sup>21</sup>	To measure conscious level as clinical sign of impending death	S: - I: 1	4-level scale (A = 'Eyes opened spontaneously, orientated speech, obeys commands, V = 'Any verbal, motor, or eye response to verbal stimulus', P = 'Any verbal, motor, or eye response to painful stimulus', U = 'Unresponsive to any stimulus')
Imai et al. <sup>72</sup> 2018 Japan	To investigate the effect of two types of PS therapy: proportional and deep sedation	Palliative care unit	50 cancer inpatients	Modified RASS <sup>73</sup>	To define deep sedation (RASS $\geq -4$ ) and the absence of agitation (RASS $\leq 0$ )	S: - I: 1	10-point scale (+4 = 'Combative' to -5 = 'Unarousable') Modifications to RASS: <sup>10</sup> Removal of reference to assisted ventilation from definition of agitation level Score '+1' can be present in patients who are not fully alert
Klepstad et al. <sup>74</sup> 2002 Norway	Investigation of the relationship between patient self-reports of CF and sedation with objective assessments of CF and sedation	Hospital-based palliative care unit	29 cancer inpatients	OAA/S <sup>75</sup>	To objectively assess sedation and compare scores with patient self-reports	S: 4 (responsiveness, speech, facial expression, eyes) I: 1/subscale	Responsiveness: 5-point scale (1-5), Speech: 4-point scale (2-5), Facial expression: 3-point scale (3-5), Eyes: 3-point scale (3-5)
Kohara et al. <sup>5</sup> 2005 Japan	Investigation of the influence of sedative drugs on consciousness	Hospital-based palliative care unit	124 terminally ill cancer inpatients (of whom 63 received sedation)	Communication Capacity Scale-Item 1 (Conscious level) <sup>76</sup>	To compare level of consciousness between sedated and unsedated patients	S: - I: 1 (for item 1)	6-point scale (0 = 'Awake with no drowsiness' to 5 = 'Cannot remain awake and cannot be awakened by physical stimuli')
Maltoni et al. <sup>77</sup> 2012 Italy	Evaluation of the practice of PS in two Italian hospices	Hospice	327 inpatients (of whom 72 received PS)	RASS <sup>10</sup>	RASS scores used for monitoring PS (negativisation of scores proxy indicator of the efficacy of PS)	Same as above	Same as above

(Continued)

Table 3. (Continued)

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Masman et al. <sup>76</sup> 2016 Netherlands	To determine the feasibility and validity of BIS monitoring in terminally ill patients	Palliative care centre	58 terminally ill inpatients	RS <sup>52</sup>	To assess level of sedation and evaluate the correlation between Ramsay scores and BIS values	Same as above	Same as above
Matsunuma et al. <sup>79</sup> 2016 Japan	Evaluation of the signs, symptoms and treatments of patients with ILLD before death	Community hospital	82 end-stage ILLD and lung cancer inpatient records	JCS <sup>80</sup>	To determine the frequency of loss of consciousness (defined as more than 1 point on JCS) before death and examine its causes	S: – I: 1	10-point scale (One level (0) for 'fully conscious', 3 levels (1–3) for the patient who is 'awake without any stimuli', 3 levels (10–30) for the patient who 'can be aroused after stimulation', 3 levels (100–300) for the patient who 'cannot be aroused with any forceful mechanical stimuli')
McMillan and Tittle <sup>81</sup> 1995 USA	To describe cancer and palliative care patients' pain, pain-related side effects and the nurses' assessment and responses to these	Cancer centre, hospice home care service	44 patients treated for pain	Sedation Item of the Pain Flow Sheet <sup>82</sup>	To evaluate level of sedation as a opioid-induced side effect	S: – I: 1 (for sedation item)	5-point scale (0= 'Fully alert', 1= 'Relaxed, awake', 2= 'Drowsy, dozing', 3= 'Arousable sleep', 4= 'Comatose')
Mercadante et al. <sup>83</sup> 2009 Italy	Assessment of the need and effectiveness of sedation for intractable symptoms, and the thoughts of relatives regarding sedation	Acute pain relief and palliative care unit	77 terminally ill cancer patient (of whom 42 received sedation)	Communication Capacity Scale—Item 1 (Conscious level) <sup>84</sup>	To assess patients' level of sedation after the initiation of PS	Same as above	Same as above

(Continued)



Table 3. (Continued)

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Mercadante et al. <sup>68</sup> 2017 Italy	To assess the attitudes of palliative care clinicians regarding PS at home	Home	150 physicians involved in end of life care decisions	RASS <sup>19</sup> RS <sup>52</sup> Rudkin Sedation Scale <sup>65</sup>	Monitoring of PS	RASS: <sup>19</sup> Same as above RS: <sup>52</sup> Same as above Rudkin Sedation Scale: <sup>65</sup> S: - I: 1	RASS: <sup>19</sup> Same as above RS: <sup>52</sup> Same as above Rudkin Sedation Scale: <sup>65</sup> 5-point scale (1= 'Fully awake', 2 = 'Drowsy', 3 = 'Eyes closed but rousable to command', 4 = 'Eyes closed but rousable to mild physical stimulation', 5 = 'Eyes closed and unrousable to mild physical stimulation') 10-point scale (-4= 'Combative' to -5 = 'Unrousable') Modifications to RASS: <sup>19</sup> Descriptors related to 'pulling tubes'/'fighting the ventilator' modified 'Any movement' refers to eye and body 'physical stimulation' changed to 'gentle physical stimulation' Clarification on how to score a patient with a mixed-type delirium
Mercadante et al. <sup>68</sup> 2018 Italy	To assess the efficacy of hyoscine butylbromide for the management of death rattle	Hospices	132 cancer inpatients with reduced level of consciousness	RASS-PA <sup>67</sup>	Identification of patients with reduced level of consciousness (RASS-PA <sub>1</sub> ≤ -3)	S: - I: 1	
Monreal-Carrillo et al. <sup>68</sup> 2017 Mexico	Characterisation of the level of consciousness of patients undergoing PS using BIS monitoring	Palliative care unit	20 advanced cancer inpatients receiving PS	RS <sup>52</sup>	Assessment of sedation level after initiation of PS	Same as above	Same as above
Morita et al. <sup>70</sup> 2001 Japan	Development and validation of the Communication Capacity Scale and the Agitation Distress scale	Palliative care unit based in a cancer institute	30 terminally ill cancer inpatients with delirium	Communication Capacity Scale-Item 1 (Conscious level) <sup>70</sup> Sedation Scale (modified Riker Sedation-Agitation Scale) <sup>70</sup>	To test the association between Communication Capacity scores and Sedation Scale scores	-Communication Capacity Scale-Item 1 (Conscious level): <sup>70</sup> Same as above Sedation Scale: 4-point scale (0= 'Calm and cooperative', 1 = 'Over-sedated', 2 = 'Very sedated', 3 = 'Unrousable') S: - I: 1	Communication Capacity Scale-Item 1 (Conscious level): <sup>70</sup> Same as above Sedation Scale: 4-point scale (0= 'Calm and cooperative', 1 = 'Over-sedated', 2 = 'Very sedated', 3 = 'Unrousable')

(Continue d)

Table 3. (Continued)

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Palacio et al. <sup>80</sup> 2018 Colombia	Description of the practice of PS	Specialised palliative care unit based in a cancer institute	66 advanced cancer inpatients undergoing PS	RS <sup>52</sup>	Assessment of sedation level after initiation of PS	Same as above	Same as above
Porzio et al. <sup>80</sup> 2010 Italy	Evaluation of the feasibility and efficacy of PS at home	Home care service	16 terminally ill cancer home patient charts	RS <sup>52</sup>	To monitor the level of sedation after the administration of PS with the aim to reach deep, continuous sedation (RSS $\geq$ 5)	Same as above	Same as above
Pype et al. <sup>10</sup> 2018 Belgium	To explore the practice of suboptimal PS in primary care	Home	Seven palliative care home teams and 7 general practitioners reporting on 27 cases of PS	RASS <sup>19</sup>	To measure depth of sedation throughout the procedure of PS	Same as above	Same as above
Schmitz et al. <sup>91</sup> 2016 Germany	To investigate the effectiveness of PCT in reducing breathlessness in patients with advanced malignant disease	Palliative care centre	18 patients with moderate or severe breathlessness	RASS <sup>19</sup>	To monitor changes in sedation and agitation levels after PCT onset	Same as above	Same as above
Van Deijck et al. <sup>92</sup> 2016 Netherlands	To explore which patient-related factors at admission are associated with receiving CPS in the terminal phase of life	Hospices, nursing home-based palliative care units	467 palliative care inpatients (of whom 130 received CPS)	GCS <sup>53</sup>	To evaluate the level of consciousness on admission as a patient-related characteristic and examine its association with CPS	Same as above	Same as above

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Table 3. (Continued)

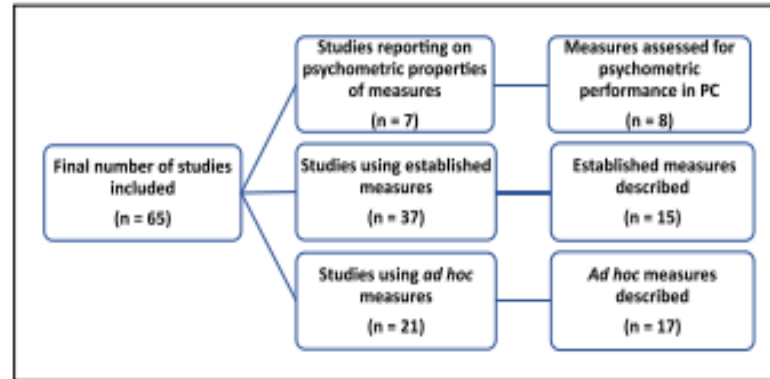
Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Studies reporting measure psychometric properties							
Arevalo et al. <sup>65</sup> 2012 Netherlands	To study the reliability and validity of observer-based sedation scales in PS	Hospices, nursing home	54 inpatients receiving PS	MSAT <sup>64</sup> (Dutch version) RASS <sup>19</sup> (Dutch version) VICSS <sup>65</sup> (Dutch version) KNMG <sup>66</sup>	To assess the level of consciousness before and during the course of PS	MSAT: <sup>64</sup> S: 3 (motor activity, arousal, quality of sedation therapy) I: 1/subscale RASS: <sup>19</sup> Same as above VICSS: <sup>65</sup> S: 2 (interaction, calmness) I: 5/subscale KNMG: <sup>66</sup> S: – I: 1	MSAT: <sup>64</sup> Motor activity: 4 levels (1–4), Arousal: 6 levels (1–6), Quality of sedation therapy: 3 levels ('Adequate', 'Oversedated', 'Undersedated') RASS: <sup>19</sup> Same as above VICSS: <sup>65</sup> Interaction: 6-point Likert-type scale per item (1 = 'Strongly disagree' to 6 = 'Strongly agree'; reverse scoring for last item) Calmness: 6-point Likert-type scale per item (1 = 'Strongly disagree' to 6 = 'Strongly agree'; reverse scoring for first item) KNMG: <sup>66</sup> 6-point scale (Level 1: (1) 'Awake and oriented', (2) 'Drowsy', (3) 'Eyes closed, responds promptly to verbal commands', (4) 'Eyes closed, arousable only by physical stimuli', Level 2: 'Eyes closed, not arousable by physical stimuli', Level 3: 'Basic brain functions affected') Same as above
Benitez-Rosario et al. <sup>73</sup> 2013 Spain	To test the appropriateness and reliability of the RASS in Spanish patients with advanced cancer	Palliative care unit	156 advanced cancer inpatients	Modified RASS <sup>73</sup>	To monitor sedation and agitation	Same as above	Same as above
Bush et al. <sup>87</sup> 2014 Canada	Exploration of the validity and feasibility of a version of the RASS modified for palliative care populations	Acute palliative care unit	10 inpatients with agitated delirium or receiving PS	RASS-PA <sup>87</sup>	To assess the level of sedation and agitation	Same as above	Same as above

(Continued)

Table 3. (Continued)

Author Year Country	Study aim	Study setting	Study population	Measure name/ acronym	Purpose of measure	Subscales/number of items	Response options
Claesens et al. <sup>97</sup> 2011 Belgium	Description of the characteristics of palliative care patients receiving sedation for the management of refractory symptoms	Palliative care units	266 terminally ill cancer inpatients (of whom 20 received PS)	GCS <sup>33</sup> (Dutch version)	Evaluation of level of consciousness at the start and during PS	S: 3 (motor response, verbal response, eye opening) I: 1/subscale	Eye opening: 4-point scale (1–4), Motor response: 6-point scale (1–6), Verbal response: 5-point scale (1–5)
Claesens et al. <sup>1</sup> 2012 Belgium	To examine the impact of PS on the level of consciousness of terminally ill patients	Palliative care units	266 terminally ill cancer inpatients (of whom 20 received PS)	GCS <sup>33</sup> (Dutch version)	Evaluation of level of consciousness with the aim to assess the effect of PS	Same as above	Same as above
Claesens et al. <sup>98</sup> 2014 Belgium	Description of the effect of PS on oral and/or artificial food and fluid intake in terminally ill patients	Palliative care units	266 terminally ill cancer inpatients (of whom 20 received PS)	GCS <sup>33</sup> (Dutch version)	To evaluate patients' level of consciousness at admission	Same as above	Same as above
Goncalves et al. <sup>18</sup> 2008 Portugal	Validation of a consciousness scale for palliative care	Palliative care unit	38 advanced cancer inpatients	CSPC <sup>18</sup>	To assess level of consciousness	S: – I: 1	6-point scale (1 = 'Awake', 2 = 'Awakens when called by name and stays awake during discussion', 3 = 'Awakens but falls asleep during discussion', 4 = 'Reacts with movement/brief eye opening, but without eye contact, when called by name', 5 = 'Reacts to trapezius muscle pinching', 6 = 'Does not react')

CPS: continuous palliative sedation; BIS: bispectral index; GCS: Glasgow Coma Scale; PS: palliative sedation; RAS: Richmond Agitation-Sedation Scale; CDSUD: continuous deep sedation until death; CSO: continuous sedation until death; RSS: Ramsay Sedation Scale; VAS: visual analogue scale; RLS88: Reaction Level Scale 88; RDOS: Respiratory Distress Observation Scale; MWSS: Modified Wilson Sedation Scale; CSPC: Consciousness Scale for Palliative Care; AVPU: Alert/Verbal/Painful/Unresponsive Scale; CF: cognitive function; OMA/S: Observer's Assessment of Alertness/Sedation; ILD: In-hospital lung disease; JCS: Japan Coma Scale; RASS-PAL: Richmond Agitation-Sedation Scale-Palliative version; PCT: patient-controlled therapy; MSAT: Minnesota Sedation Assessment Tool; WCS: Vancouver Interaction and Calmness Scale; KNMG: Sedation score proposed in the Guideline for Palliative Sedation of the Royal Dutch Medical Association.



**Figure 2.** Number of identified studies and measures by instrument category.

Three of the *ad hoc* measures were modified versions of the existing tools: the Glasgow Coma Scale (GCS),<sup>32,33</sup> RASS<sup>19,35</sup> and Riker Sedation–Agitation Scale.<sup>23,30</sup> All other *ad hoc* measures comprised unique tools. None of the reported *ad hoc* measures had been formally validated before use.

The established measures most commonly used were the RASS<sup>19</sup> ( $n = 11$ )<sup>10,21,51,53–55,64,70,77,84,91</sup> and Ramsay Sedation Scale (RSS;<sup>52</sup>  $n = 7$ ).<sup>4,65,78,84,88–90</sup> Most established measures had been developed and validated for use in settings other than palliative care; mainly the intensive care unit. The studies with palliative care patients in which these measures were used provided no information on their validity or reliability.

Two of the existing measures used for the evaluation of level of consciousness consisted of items extracted from multi-item tools developed to assess constructs other than level of consciousness (i.e. the conscious level item of the Communication Capacity Scale (CCS)<sup>5,76,83</sup> and the sedation item of the Pain Flow Sheet<sup>81,82</sup>). These tools had been evaluated psychometrically in palliative care settings, but validity and reliability have only ever been established for each measure as a whole, not for the individual items measuring levels of consciousness.

Almost all of the described measures consisted of one item with a range of mutually exclusive scoring options ( $n = 27$ ), usually involving observation of spontaneous activities, such as eye opening, or responses to auditory and/or tactile stimuli performed in a logical progression. The majority of these tools ( $n = 23$ ) evaluated a single construct: consciousness in terms of arousal, while the remaining measures ( $n = 4$ ) incorporated the assessment of agitation into single scales for consciousness/sedation.

Evidence of psychometric performance was provided for: the Minnesota Sedation Assessment Tool (MSAT),<sup>93,94</sup> RASS,<sup>19,93</sup> Vancouver Interaction and Calmness Scale (VICS),<sup>93,95</sup> Sedation score proposed in the Guideline for Palliative Sedation of the Royal Dutch Medical Association (KNMG),<sup>93,96</sup> Modified RASS,<sup>19,73</sup>

Richmond Agitation–Sedation Scale–Palliative version (RASS-PAL),<sup>19,87</sup> GCS<sup>1,33,97,98</sup> and Consciousness Scale for Palliative Care (CSPC).<sup>18</sup>

Dutch versions of original English language measures were created by researchers for the MSAT,<sup>93,94</sup> RASS,<sup>19,93</sup> VICS<sup>93,95</sup> and GCS.<sup>1,33,97,98</sup> The RASS modified by Benitez-Rosario et al.<sup>73</sup> was translated and further adjusted for use with Spanish palliative care patients. Modifications to the original RASS<sup>19</sup> included the removal of descriptors relating to the mechanical ventilation of patients and a clarification to the scoring instructions addressing the possibility that restless behaviour may be present in patients who are not fully alert. Similarly, Bush et al.<sup>87</sup> reported performing minor changes to the RASS<sup>19</sup> when testing its psychometric performance in the palliative care setting. The CSPC was validated in its source language (Portuguese) and, subsequently, translated by its authors into English.<sup>18</sup>

### Appraisal of psychometric performance

Evidence regarding structural validity, test–retest and intra-rater reliability was not provided for any of the evaluated measures, so we do not present findings relating to these properties. The CSPC<sup>18</sup> and a modified version of the RASS<sup>73</sup> achieved the highest ratings in our quality appraisal, but our evaluation was based on evidence obtained from just one study for each measure. Table 4 provides a summary of the quality appraisal process for each instrument.

**Content validity.** All studies provided a clear description of the construct measured by the reported instruments. However, the involvement of the target population in selecting or modifying scale items was described only for three of the eight evaluated measures: the CSPC,<sup>18</sup> RASS-PAL<sup>87</sup> and Modified RASS.<sup>73</sup> One study<sup>18</sup> reported receiving feedback on the content of the CSPC from seven palliative care doctors and nurses at the construction stage on the scale. Likewise, the input of palliative care professionals guided the

Table 4. Appraisal of psychometric performance of observational level of consciousness measures.

Measure and studies	Number of participants	Content validity	Criterion validity	Structural validity	Construct validity	Homogeneity (internal consistency)	Intra-rater reliability	Intra-rater and/or test-retest reliability	Responsiveness	Origin of items	Feasibility
MSAT (Dutch version) Arevalo et al. <sup>31</sup>	N=54 No correction for multiple testing	Description of construct provided. No involvement of target population in item selection	Gold standard not available	NE/NR	Assessed per subscale MSATa: Spearman's correlation coefficient ranged from 0.48 to 0.83 (mostly above 0.60) MSATm: Spearman's correlation coefficient ranged from 0.42 to 0.61	NE/NR	Assessed per subscale MSATa: ICC ranged from 0.59 (95% CI: 0.45 to 0.70) to 0.64 (95% CI: 0.46 to 0.77) depending on time difference between paired assessments MSATm: ICC ranged from 0.08 (95% CI: -0.25 to 0.23) to 0.11 (95% CI: -0.09 to 0.29) depending on time difference between paired assessments MSATq: Cohen's kappa ranged from 0.436 to 0.545 depending on time difference between paired assessments	NE/NR	NE/NR	Items originated from a scale developed for another population	Evaluated as clear and easy to use (When compared with the Dutch versions of RMS5 and VCS)
Rating	1	1	-	-	MSATa: 2 MSATm: 1	-	MSATa: 1 MSATm: 0 MSATq: 0	-	-	0	2
VCS (Dutch version) Arevalo et al. <sup>31</sup>	N=54 No correction for multiple testing	Description of construct provided. No involvement of target population in item selection	Gold standard not available	NE/NR	Assessed per subscale VCS: Spearman's correlation coefficient ranged from 0.31 to 0.72 (mostly above 0.40) VCSq: Spearman's correlation coefficient ranged from 0.31 to 0.57 (mostly above 0.40)	NE/NR	Assessed per subscale VCS: ICC ranged from 0.77 (95% CI: 0.64 to 0.86) to 0.85 (95% CI: 0.73 to 0.92) depending on time difference between paired assessments VCSq: ICC ranged from 0.12 (95% CI: -0.38 to 0.40) to 0.34 (95% CI: 0.1 to 0.52) depending on time difference between paired assessments	NE/NR	NE/NR	Items originated from a scale developed for another population	Evaluated as the least clear and easy to use (When compared with the Dutch versions of RMS5 and MSAT)
Rating	1	1	-	-	VCS: 1 VCSq: 1	-	VCS: 2 VCSq: 0	-	-	0	1
RASS (Dutch version) Arevalo et al. <sup>31</sup>	N=54 No correction for multiple testing	Description of construct provided. No involvement of target population in item selection	Gold standard not available	NE/NR	Spearman's correlation coefficient ranged from 0.57 to 0.84	NE/NR	ICC ranged from 0.71 (95% CI: 0.60 to 0.79) to 0.73 (95% CI: 0.58 to 0.83) depending on time difference between paired assessments	NE/NR	NE/NR	Items originated from a scale developed for another population	Evaluated as the least time-consuming, clearest and easiest to use (When compared with Dutch MSAT and VCS)
Rating	1	1	-	-	2	-	1	-	-	0	2
KNMG Arevalo et al. <sup>31</sup>	N=54 No correction for multiple testing	Description of construct provided. No involvement of target population in item selection	Gold standard not available	NE/NR	Spearman's correlation coefficient ranged from 0.44 to 0.84	NE/NR	ICC ranged from 0.66 (95% CI: 0.54 to 0.78) to 0.71 (95% CI: 0.55 to 0.82) depending on time difference between paired assessments	NE/NR	NE/NR	Measure specifically developed for use with palliative care patients	NE/NR

(Continued)

Table 4. (Continued)

Measure and studies	Number of participants	Content validity	Criterion validity	Structural validity	Construct validity	Homogeneity (internal consistency)	Inter-rater reliability	Intra-rater and/or test-retest reliability	Responsiveness	Origin of items	Feasibility
Rating	1	1	-	-	2	1	-	-	-	2	-
Modified RASS Benzler-Rosario et al. <sup>31</sup>	N = 156	Description of construct provided. Target population involved in item modification	Gold standard not available	NE/NR	Spearman's correlation coefficient ranged from 0.81 to 0.89 (p < 0.001)	NE/NR	Weighted Cohen's kappa ranged from 0.85 (95% CI: 0.85 to 0.92) to 0.95 (95% CI: 0.91 to 0.98)	NE/NR	Not adequate information provided	Items modified for use with palliative care patients	Reported as a very useful, manageable tool that could facilitate fluid communication among the palliative care team
Rating	2	2	-	-	2	2	-	-	-	1	2
RASS-PAL Bush et al. <sup>67</sup>	N = 10 No correction for multiple testing	Description of construct provided. Target population involved in item modification	Gold standard not available	NE/NR	NE/NR	NE/NR	ICC ranged from 0.84 (95% CI: 0.56 to 0.93) to 0.98 (95% CI: 0.95 to 1.00)	NE/NR	NE/NR	Items modified for use with palliative care patients	Evaluated as easy to use, simple and brief
Rating	0	2	-	-	-	2	-	-	-	1	2
GCS (Dutch version) Clarens et al. <sup>32,33</sup>	N = 266	Description of construct provided. No involvement of target population in item selection	Gold standard not available	NE/NR	NE/NR	NE/NR	ICC = 0.807 (CI = 0.671-0.891; p = 0.000)	NE/NR	NE/NR	Items originated from a scale developed for another population	NE/NR
Rating	2	1	-	-	-	2	-	-	-	0	-
CSPC Goncalves et al. <sup>34</sup>	N = 38 No correction for multiple testing	Description of construct provided. Target population involved in item selection	Gold standard not available	NE/NR	Spearman's correlation coefficient ranged from 0.82 to 0.95 (p < 0.001)	Cronbach's $\alpha = 0.99$	ICC = 0.99 (p < 0.001)	NE/NR	NE/NR	Scale specifically developed for use with palliative care patients	Evaluated as easy to use and useful in clinical practice
Rating	0	2	-	-	2	2	-	-	-	2	2

MSAT: Minnesota Sedation Assessment Tool; NE: not evaluated; NR: not reported; MSATa: Minnesota Sedation Assessment Tool arousal subscale; ICC: intraclass correlation coefficient; CI: confidence interval; MSATm: Minnesota Sedation Assessment Tool motor activity subscale; MSATq: Minnesota Sedation Assessment Tool quality of sedation subscale; RASS: Richmond Agitation-Sedation Scale; VICS: Vancouver Interaction and Calmness Scale; VICSi: Vancouver Interaction and Calmness Scale interaction subscale; VICSs: Vancouver Interaction and Calmness Scale calmness subscale; RMMG: Sedation score proposed in the Guideline for Palliative Sedation of the Royal Dutch Medical Association; RASS-PAL: Richmond Agitation-Sedation Scale-Palliative version; GCS: Glasgow Coma Scale; CSPC: Consciousness Scale for Palliative Care.

modification of scale items for the RASS-PAL<sup>87</sup> and RASS modified by Benitez-Rosario et al.<sup>73</sup>

**Construct validity.** Information on construct validity was available for six of the eight included measures: the MSAT,<sup>93,94</sup> VICS,<sup>93,95</sup> RASS,<sup>19,93</sup> KNMG,<sup>93,96</sup> CSPC<sup>18</sup> and Modified RASS.<sup>73</sup> For these, construct validity was evaluated through the correlation of the tested instrument with others that were assumed to measure the same construct (convergent validity). Discriminant validity was not assessed for any tool.

Correlations were reported per subscale for the MSAT and VICS.<sup>93–95</sup> The MSAT arousal subscale performed better than the motor activity subscale with Spearman's correlation coefficient ranging from 0.48 to 0.83, depending on the measure with which it was correlated (RASS, KNMG and VICS). Low to moderate correlations were reported for the motor activity subscale of the MSAT ( $\rho=0.42–0.61$ ). Mostly moderate correlations were found between both subscales of the VICS with other tools measuring level of consciousness (interaction subscale:  $\rho=0.31–0.72$ , calmness subscale:  $\rho=0.31–0.57$ ).<sup>93–95</sup>

Construct validity of the RASS and KNMG was supported by moderate-strong associations when compared with corresponding instruments.<sup>19,93,96</sup> Strong correlations with other tools measuring level of consciousness were reported for the Modified RASS and CSPC.<sup>18,73</sup> Spearman's correlation coefficient for the Modified RASS to the GCS<sup>33</sup> ranged from 0.81 to 0.85 and 0.82–0.89 when compared with the RASS,<sup>52</sup> depending on the group of professionals scoring the scales (palliative care physicians or medical residents).<sup>73</sup> Likewise, the CSPC correlated highly with a 100 mm visual analogue scale (VAS) anchored in the terms 'awake' and 'unarousable' ( $\rho=0.94–0.95$ ) and with the GCS ( $\rho=0.82–0.85$ ).<sup>18,33</sup>

**Homogeneity (internal consistency).** As the aim of some of the studies was not to address unique measure characteristics, homogeneity was evaluated for only one of the appraised measures, the CSPC.<sup>18</sup> For this instrument, the reported Cronbach's alpha coefficient was very high ( $\alpha=0.99$ ).<sup>18</sup>

**Inter-rater reliability.** ICC or weighted Cohen's kappa was used for the assessment of inter-rated reliability in all of the included studies. From the tested measures, inter-rater reliability was found to be high for the CSPC (ICC=0.99),<sup>18</sup> GCS (ICC=0.807),<sup>1,33,97,98</sup> RASS-PAL (ICC=0.84–0.98)<sup>87</sup> and Modified RASS ( $\kappa=0.85–0.95$ ).<sup>73</sup> Moderate correlations within paired observational assessments were reported for the RASS (ICC=0.71–0.73)<sup>19,93</sup> and KNMG (ICC=0.66–0.71).<sup>93,96</sup> Of the MSAT and VICS subscales, the VICS interaction scale performed best with ICC ranging from 0.77 to 0.85, followed by the MSAT arousal scale (ICC=0.59–0.64).<sup>93–95</sup> Depending on the time interval between paired assessments, Cohen's kappa

coefficient ranged from 0.44 to 0.54 for the MSAT overall quality of sedation subscale, suggesting low agreement between scale assessors. No correlations were found for the MSAT motor activity and VICS calmness subscales.<sup>93–95</sup>

**Responsiveness.** Change scores indicating clinically meaningful change over time in consciousness/sedation levels were not described for any of the appraised measures. Bush et al.<sup>87</sup> provided some information on the floor and ceiling effects for the RASS-PAL but it is not adequate for the assessment of responsiveness.

**Origin of items.** Items for half of the measures for which evidence of psychometric performance was available originated from scales developed for non-palliative care patients. Specifically, aspects of the measurement properties of the Dutch versions of the MSAT,<sup>93,94</sup> VICS,<sup>93,95</sup> RASS<sup>19,93</sup> and GCS<sup>1,33,97,98</sup> were appraised by study authors adopting the original items of these scales without assessing their appropriateness for the palliative care setting.

For the other half of the scales, items were either modified (RASS-PAL<sup>87</sup> and Modified RASS<sup>73</sup>) or particularly developed (KNMG<sup>96</sup> and CSPC<sup>18</sup>) for monitoring palliative care patients' level of consciousness.

**Feasibility.** In a comparison for user-friendliness between the Dutch versions of the RASS,<sup>19</sup> MSAT<sup>94</sup> and VICS,<sup>95</sup> Arevalo et al.<sup>93</sup> reported that most palliative care professionals found RASS the least time-consuming, clearest and easiest to use. Acceptable ratings were achieved for the MSAT, while the VICS was evaluated as the least clear and easy to use among the three tools. The RASS-PAL,<sup>87</sup> CSPC<sup>18</sup> and Modified RASS<sup>73</sup> were also regarded as feasible and useful tools by healthcare professionals.

## Discussion

### Main findings

This systematic review aimed to identify, describe and appraise the psychometric performance of observational level of consciousness measures used in palliative care. We found 35 different levels of consciousness tools used in 65 studies. Evidence of psychometric performance, however, was available for only eight of these instruments. Two of these eight tools were specifically developed for palliative care populations (CSPC<sup>18</sup> and KNMG<sup>96</sup>), two were versions of an existing tool (i.e. the RASS<sup>19</sup>) modified for use in palliative care (Modified RASS<sup>73</sup> and RASS-PAL<sup>87</sup>) and four were measures developed for different populations, tested for aspects of validity and/or reliability in the palliative setting (GCS,<sup>1,33,97,98</sup> MSAT,<sup>93,94</sup> RASS<sup>19,93</sup> and VICS<sup>93,95</sup>). None of these tools had been evaluated across all relevant psychometric properties; hence no measures appraised had been fully validated.



The majority of measures identified were either *ad hoc* tools for which no formal validation had been undertaken ( $n=17$ ) or tools developed and validated mainly in non-palliative care settings ( $n=15$ ). This widespread use of non-validated measures raises questions regarding the methodological robustness of studies and the quality of reported evidence,<sup>99</sup> not least because, although tools' psychometric performance may have been investigated in specific contexts, this does not transfer to other settings.<sup>100</sup> It is therefore essential, as with any measures to be used in palliative care, that tools assessing level of consciousness should be thoroughly validated with palliative care patients in order to be certain that they are reliable for this population.

Most measures identified sought to measure consciousness in terms of wakefulness and, therefore, mostly ( $n=23$ ) comprised one item with a range of levels describing patients' responses to verbal and/or physical stimulation. Apart from consciousness, a small number of tools ( $n=4$ ) included the assessment of agitation, as a domain related to sedative and analgesic use, in a single scale. These tools have been criticised for various reasons, including the lack of clarity in the definition of different consciousness levels, and the poor standardisation of employed stimuli.<sup>16,18</sup> Moreover, the assessment of patients presenting decreased consciousness and restlessness at the same time may be compromised when both conditions are evaluated on the same scale.<sup>14,16</sup> Nevertheless, the most commonly employed measure was the RASS<sup>19</sup> (a tool assessing sedation and agitation on a single-item scale) or modified versions of it ( $n=17$ ). An explanation for this may be that the RASS requires minimal training and can be quickly and easily administered at the bedside.<sup>19</sup> These are particularly desirable features for a scale intending to measure level of consciousness, an often unstable characteristic, in clinical environments where patients are cared for by professionals of different backgrounds, as in palliative care.<sup>18</sup>

Limited information was available on the measurement properties of tools, thus making it difficult to draw definitive conclusions about their psychometric performance. Our evaluation was based on evidence obtained from a single study, rather than a group of studies, for each measure. Some studies did not aim to specifically develop and/or validate level of consciousness measures.<sup>1,91,97,98</sup> As a result, these studies assessed only certain psychometric properties on each occasion, and no tools were tested across all measurement properties. Our quality assessment outcomes should be treated with caution, therefore, until further evidence on the psychometric performance of the appraised measures becomes available.

Information on inter-rater reliability and internal consistency was provided by all studies, with most tools performing adequately on both properties. Due to the lack of a 'gold standard' level of consciousness measure in palliative care, criterion validity could not be assessed. Instead,

in three studies the tested tools were compared with other instruments known to measure level of consciousness.<sup>18,73,93</sup> However, although the reported correlations between the assessed measures and other comparable tools were acceptable to high, the reference measures were not themselves tested for their psychometric performance in a palliative care context.

No publications provided any information regarding test-retest or intra-rater reliability, although all studies described collecting data at more than one time point. This might be explained by the lack of stability of the construct measured, that is, palliative care patients' fluctuating level of consciousness. Thus, the assessment of these psychometric properties may not be feasible for level of consciousness measures in this population.

The measures with the highest ratings in our appraisal were the CSPC,<sup>18</sup> a tool specifically developed to measure level of consciousness in palliative care, and a version of the RASS modified for use with palliative care patients.<sup>73</sup> However, the only information available about the psychometric performance of either was restricted to that of initial validation studies and insufficient for assessing all appraised measurement properties. Palliative care clinicians and researchers should be mindful of these restrictions when using level of consciousness measures, therefore.

Our findings agree with those of previously published reviews. In their review of level of sedation instruments, De Jonghe et al.<sup>14</sup> reported that responsiveness had not been tested for any of the scales identified. They commented that responsiveness is an important measurement property because it can inform the titration, initiation and withdrawal of sedative drugs.<sup>14</sup> Apart from these benefits, a measure that can reliably detect changes in patients' level of consciousness over time may enable the longitudinal evaluation of patients and provide a useful outcome measure for palliative care research. Nevertheless, like De Jonghe et al.,<sup>14</sup> we did not find adequate evidence to appraise responsiveness in our review. When seeking to determine clinically important changes in patients' status or evaluate the effects of medical interventions it may be problematic to use measures that do not demonstrate satisfactory responsiveness, since changes in scores may result from measurement error rather than true changes in patients' consciousness levels. Thus, it is important that clinicians and researchers are aware of the limited evidence regarding responsiveness when choosing measures to evaluate treatment/intervention outcomes or interpreting level of consciousness scale scores. In order to enable clinical assessment and decision-making, and support the testing of new interventions, future studies that seek to develop new level of consciousness tools or validate existing ones should aim to provide strong evidence on the responsiveness of these measures.

Brinkkemper et al.<sup>101</sup> identified seven scales measuring level of awareness reported in primary studies. Of these, similar to our findings, a significant proportion were *ad hoc*

measures, while the RASS<sup>29</sup> was the most commonly used of the established scales. Brinkkemper et al.<sup>101</sup> found only one tool, the CCS,<sup>76</sup> for which information on psychometric performance was available. Although the authors presented this information, they did not formally evaluate the psychometric quality of the CCS<sup>76</sup> because this was outside the scope of their review. Our search identified the CCS,<sup>5,76,83</sup> but it was excluded from our quality appraisal because the scale used for the assessment of consciousness level constitutes an individual item extracted from a compound measure for assessing the ability of terminally ill patients to communicate that was developed and tested as a whole. Hence, the psychometric evidence provided pertains to the CCS<sup>76</sup> measure as a whole, not its individual items.

Brinkkemper et al. identified a substantially smaller number of tools than we did, because their review focused specifically on the effects of palliative sedation. Our inclusion criteria were broader, allowing the inclusion of studies reporting the use of observational measures regardless of the purpose for which these were employed. Moreover, an increasing number of studies using level of consciousness tools have been published since the publication of their review in 2013. Of the 65 included studies in our review, 26 (40%) have been published since 2013. A possible explanation for this upwards trend may be the recent publication of high impact guidelines recommending the use of observational scales for the monitoring of level of consciousness of palliative care patients receiving sedative medication.<sup>2,102</sup>

### Strengths and limitations

A strength of this systematic review is the comprehensive yet broad search strategy followed, including six databases without applying date restrictions. We also performed a thorough backward and forward citation search for all included articles and contacted abstract authors in order to ensure that all relevant publications were identified. A limitation is that we included only English language publications. It is possible that studies providing evidence on measurement properties of translated versions of tools were missed. We are aware of at least one validation study, which was excluded from this review due to language restrictions.<sup>103</sup>

Two reviewers (A.M.K. and E.M.) independently performed the appraisal of the psychometric performance of the identified measures against well-defined quality criteria. Nevertheless, comparability of evidence was hindered by the heterogeneity of studies reporting data on psychometric properties in terms of setting, sample size, participant population, study design and objectives, and of the purposes for which tools were employed on each occasion. Our evaluation, therefore, was based on the limited published evidence from individual studies for each appraised measure.

### Conclusion

This systematic review demonstrates that although an increasing number of studies are using observational level of consciousness measures, only a few of these tools have been tested for their psychometric performance in the palliative care setting, and none across all relevant measurement properties. The CSPC and a modified version of the RASS achieved the highest ratings in our appraisal, but further evidence on their measurement properties is needed before either can be recommended as valid and reliable measures for use in palliative care practice and research. Future research in this area should use, and seek to further validate and refine existing level of consciousness measures, rather than developing new tools or using *ad hoc* instruments.

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## Appendix 2 Research materials for qualitative study exploring key stakeholders' perceptions about the potential use of BIS (Chapters 3–4)

### Appendix 2.1 Information sheet (adapted for use with each participant group)

University College London Hospitals   
NHS Foundation Trust



#### **Acceptability of sedation monitoring in palliative care. IRAS ref: 199211**

*We would like to invite you to take part in our research study, which will involve participating in either an individual interview or a group discussion. Before you decide on whether or not you would be happy to take part in this research, we would like you to understand why the research is being done and what it would involve for you. One of our team will go through this information sheet with you and answer any questions you have. This should take about 10 minutes. You are also free to talk to other people about the study if you would like to. Please ask if anything is not clear, or if you would like more information. It is up to you to decide whether to take part or not. Deciding not to take part will not cause a problem for you in any way. If you do decide to take part you are still free to stop at any time, and without giving a reason.*

#### **Why is the study being done?**

We are trying to improve care and support for people who are receiving palliative care, particularly people who become agitated and distressed towards the ends of their lives. People in this situation may be given sedative medication to make them calm and drowsy. However, at present, the level of sedation is not always routinely monitored, so it is not easy to know whether people are receiving precisely the right amount of sedative medication. If staff were able to systematically assess and monitor the depth of a person's sedation, this might help determine the best amount of sedative medication to give that person.

We are therefore doing this study to help us understand what patients, relatives, and health care professionals think about possible ways in which health care staff might assess and monitor the depth of sedation of people receiving sedative medication. We want to interview 15-20 patients to find out their views about how this might be done, in general, and also with regard to some specific ways of doing it.

#### **Why have I been chosen?**

You are a patient, and a member of the clinical team thought you might be interested in taking part in this study.

#### **Taking part in the study**

If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. Even if you do decide to take part you are free to withdraw from the study at any time and without giving a reason. If you do withdraw from the study, your care will not be affected in any way.

#### **What do I have to do?**

If you agree to participate in the study, you will be invited to take part either in a group discussion

with 3-5 people, or, if you prefer, to take part in a joint interview with a relative of your choice, or in a one-to-one interview with a member of the research team.

We expect the group discussion will take 40-50 minutes, and the interview 30-40 minutes. The group discussion will be led by one researcher, with another researcher present as an observer. The interviews and discussions will all be voice-recorded, and we will also take some notes by hand, to help us check that we have recorded everything that has been said.

We will ask you whether you personally have any knowledge or experience of sedation medication being used for yourself or someone else. We will show you some paper documents and some technical tools which may be used for checking or monitoring the level of sedation of a patient receiving sedative medication. We will ask you for your thoughts and feelings around these possible options, and your views on which documents or tools, if any, you think would be best for use in actual practice.

**What will happen to the information that I give?**

We will put the information gathered from the interviews and group discussions with patients and their relatives together with information from interviews and group discussions with health care professionals. We will look at all of this information and decide whether it would be helpful to run a further study, exploring how documents and tools might be used to monitor sedation for patients in hospital or hospice.

**How long will I be in the study?**

You will be asked to participate in one group discussion of 40-50 minutes, or one interview of 30-40 minutes.

**Benefits of taking part**

There will be no direct benefit to you for taking part in this study. However, by taking part you may be helping people who receive palliative care in the future. The information you give will help to improve understanding of the issues for some people receiving palliative care, and we hope that this will then highlight potential ways for care and support to be improved. If anything comes up in your interview or in the group discussion where you would like more information, advice or support, we will direct you to people who may be able to help you further.

**Harm of taking part**

We do not anticipate any risks or harm to you as a result of taking part in this study, though it is possible that these discussions may touch on some difficult issues. We will ensure that if this is the case, an experienced health care professional will be available for you to speak with if you wish. If you have any questions about sedation in general, or about your care, a member of the clinical team will also be available to speak with you.

**What if there is a problem?**

If you are concerned about any aspect of this study, please speak to the researchers who will do their best to answer your questions. Please contact: Dr Bella Vivat ( ). If you remain unhappy, you can make a formal complaint through the National Health Service (NHS) complaints procedure. Details can be obtained through the University College

London Hospitals (UCLH) Patient Advice and Liaison Service (PALS) on 0207 3447 3041, email: [PALS@uclh.nhs.uk](mailto:PALS@uclh.nhs.uk), address: PALS, Ground Floor Atrium, University College Hospital, 235 Euston Road, London, NW1 2BU. University College London (UCL) holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

### **Confidentiality**

All information that is collected about you during the course of the research will be kept strictly confidential, except if we discover or you disclose any information that is criminal in nature, or any other information that we are required to report by law then we may need to break confidentiality and inform the relevant authorities.

Any personal information will have your name and address removed so that you cannot be identified from it. Only the research team will have access to the notes from the meetings. An additional external transcriber may listen to the voice recordings and type these up as written scripts, but this person will have signed a confidentiality agreement with UCL. All data will be handled, processed, stored and destroyed in accordance with the Data Protection Act (1998). Voice recordings will be downloaded from the portable recorder onto a secure computer server, and the original recording deleted.

### **Results of the research study**

We will present the results of the study to expert and support groups for service users, to people working in palliative care, to academic colleagues, and to Marie Curie. We will also seek to publish papers in scientific journals. All information collected during the study will be combined to form the results, so no individual will be identified in any report or publication. If you take part in the study you will be asked if you wish to receive a written summary of the results.

### **Funding and review of the research study**

This research has been reviewed and funded by Marie Curie, and is being conducted by researchers in the Marie Curie Palliative Care Research Department at UCL. It has been reviewed by an NHS national research ethics committee, ref: 16/LO/0686. Ethical approval was given on 3 June 2016.

### **Contact for further information**

For further information please contact Dr Bella Vivat via email:

or telephone:

*Thank you for taking the time to read this information sheet.  
Your help makes our research possible.*





## Appendix 2.3 Interview/focus group topic guide (adapted for use with each participant group)



### ***Topic guide for acceptability of sedation monitoring (patients)***

- Preamble
- Explanation of sedation
- Presentation of BIS

#### *Questions (plus prompts, if needed)*

1. Do you have any prior knowledge or experience of the use of sedative medicines?
  - a. Have you ever discussed the use of sedatives with anyone before today?
  - b. Do you have any prior knowledge or experience of how levels of sedation are monitored?
2. Do you have any thoughts about how the technology we have shown you might be used in palliative care?
  - a. What might be the benefits/advantages of using something like this in palliative care?
  - b. What might be the disadvantages?
  - c. If you personally needed to be sedated, how would you feel about your level of sedation being monitored using a device like the one we have shown you?
  - d. How would you feel if a relative needed to be sedated and their level of sedation was monitored using a device like this one?
  - e. Do you think this kind of device should be used in the same ways, or in different ways, for people in hospital, in a hospice, or at home?

3. If a person receiving palliative care is given sedative medicine, would it be acceptable to use this kind of device to monitor that person for the whole time they are sedated?
- a. How long do you feel it would be ok to monitor you or a relative using a technical device like this?
  - b. For minutes; for hours; for days?
  - c. As long as necessary?
  - d. For as short a time as possible/just long enough to assess how deeply sedated the person is?

## Appendix 3 Research materials for exploratory study (Chapters 5–6)

### Appendix 3.1 Brief information sheet



#### Brief Participant Information Sheet for Patients

**Study Title:** Feasibility of monitoring sedative use in palliative care  
**Protocol Reference Number:** 17/0179

*We would like to invite you to take part in our research study. Your doctor or nurse has given you this information leaflet which briefly explains why this study is being done and what it would involve for you. If, after reading this leaflet, you might be interested in receiving some more information about this study and you would like to speak to a member of the research team, please let your doctor or nurse know and they will arrange for a researcher to meet with you. Before you decide whether you would like to take part in the study, a researcher will go through a more detailed information sheet with you and answer any questions that you may have.*

#### **Why is the study being done?**

We are trying to improve care and support for people who are receiving palliative care, particularly people who may require medicines that can have a sedating effect. At present, the level of sedation caused by medication is not always routinely measured. Systematic monitoring of the depth of a person's sedation might help determine the right amount of sedative medication to give that person. However, at the moment we do not know the best way to undertake this monitoring.

We are doing this study to help us understand whether a technical device, or regular observations by a member of staff with a checklist could provide useful information about the alertness of people receiving palliative care. The Bispectral Index (BIS) monitor is non-invasive, and measures the electrical activity of the brain by means of a 12cm strip sensor that is applied to the forehead (*please see picture of the BIS monitor and strip sensor*). The observational checklist is a simple questionnaire that clinical staff complete, based on their impressions about how awake and alert patients are.



We would like to monitor 100 patients to find out if these different approaches provide useful measures of patients' alertness. We would also like to explore patients' experiences and opinions about the measures.

**What do I have to do?**

If you consent to take part in the study, you will be asked to use the BIS monitor for 4 hours. A member of the research team will apply the strip sensor on your forehead which will then be attached to the monitoring screen. The strip uses sticky pads and it will be applied from the middle of your forehead to one of your temples. During the time that you are monitored with the BIS, you will be asked to score your pain and how alert you feel on a scale of 0 - 10. You will be asked to mark the value that best describes how you feel, in terms of pain and alertness, at the time that you are completing the scales. A researcher will ask you to rate these symptoms at the beginning of the monitoring and every hour while you are using the device. Completing the scales will take 1-2 minutes on each occasion.

At the end of the monitoring period with the BIS, you will be given a brief questionnaire to fill out (5-10 minutes). This will contain eight questions on your experience of using the monitor which you will be able to answer by choosing between different options.

**Do I have to take part?**

It is up to you to decide to join the study. If you are interested in taking part in this study, a member of the research team will discuss with you the aim and purposes of the study and what taking part would involve for you. They will also give you a detailed information sheet to keep. If you are willing to participate, you will be asked to sign a consent form. Even if you do decide to take part you are free to withdraw from the study at any time and without giving a reason. If you do withdraw from the study, your care will not be affected in any way.

*Thank you for taking the time to read this information sheet.*



## Participant Information Sheet for Patients

**Study Title: Feasibility of monitoring sedative use in palliative care**  
**Protocol Reference Number: 17/0179**

*We would like to invite you to take part in our research study. Before you decide on whether or not you would like to take part in this research, we want you to understand why the research is being done and what it would involve for you. You have previously received a brief version of this information sheet by one of your doctors or nurses and expressed that you would like the researchers to provide some additional information about this study. One of our team will go through this more detailed information sheet with you and answer any questions you may have. This should take about 10 minutes. You are also free to talk to other people about the study if you would like to. Please ask if anything is not clear, or if you would like more information. It is up to you to decide whether to take part or not. Deciding not to take part will not affect your care in any way. If you do decide to take part you are still free to stop at any time, and without giving a reason.*

### **Why is the study being done?**

We are trying to improve care and support for people who are receiving palliative care, particularly people who may require medicines that can cause sedation. At present, the level of sedation caused by medication is not always routinely measured. Systematic monitoring of the depth of a person's sedation might help determine the right amount of sedative medication to give that person. However, at the moment we do not know the best way to undertake this monitoring.

We are doing this study to help us understand whether a technical device, or regular observations by a member of staff with a checklist could provide useful information about the alertness of people receiving palliative care. The Bispectral Index (BIS) monitor is non-invasive, and measures the electrical activity of the brain by means of a 12cm strip sensor that is applied to the forehead (*please see picture of the BIS monitor and strip sensor*).

The observational checklist is a simple questionnaire that clinical staff complete, based on their impressions about how awake and alert patients are.



We would like to monitor 100 patients to find out if these different approaches provide useful measures of patients' alertness. We would also like to explore patients' experiences and opinions about the measures.

**Why have I been chosen?**

You have been chosen because you are a patient in the hospice and a member of the clinical team thought that you might be interested in taking part in this study.

**Do I have to take part?**

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. Even if you do decide to take part you are free to withdraw from the study at any time and without giving a reason. If you do withdraw from the study, your care will not be affected in any way.

**What will happen to me if I take part?**

If you agree to participate in the study, you will be monitored with the BIS technology for 4 hours. After this period, you will be given a short questionnaire to complete (5-10 minutes). During the monitoring period, the researchers will collect data on your pain and alertness levels. The researchers will also collect some information from your medical record. After the 4 hours of monitoring you may be invited to participate in one or two other related studies, but are under no obligation to do so.

**What do I have to do?**

If you consent to take part in the study, you will be asked to use the BIS monitor for 4 hours. A member of the research team will apply the strip sensor on your forehead which will then be attached to the monitoring screen. The strip uses sticky pads and it will be applied from the middle of your forehead to one of your temples. During the time that you are monitored with the BIS, you will be asked to score your pain and how alert you feel on a scale of 0 - 10. You will be asked to mark the value that best describes how you feel, in terms of pain and alertness, at the time that you are completing the scales. A researcher will ask you to rate these symptoms at the beginning of the monitoring and every hour while you are using the device. Completing the scales will take 1-2 minutes on each occasion.

At the end of the monitoring period with the BIS, you will be given a brief questionnaire to fill out. This will contain eight questions on your experience of using the monitor which you will be able to answer by choosing between different options.

**Optional involvement in additional studies**

If you consent to take part in the study, you will be monitored with the BIS technology for four hours. At the end of the 4-hour period of monitoring, we will ask you whether you would be willing to participate in one or two additional studies related to this project.

One of these studies is a short interview with a researcher which will last approximately 20-30 minutes. The interview will be about your experience of using the monitor. The other study will involve a further 4-hour period of monitoring later in your admission at the hospice.

*At this time, we are only asking for your permission to be involved in the first four-hour period of monitoring.*

If after the end of the four-hour monitoring period, you want to know more about these additional studies, we will provide you with further information sheets which describe them in more detail and you will be given at least 24 hours to consider whether you would like to participate in any of these.

Please note that agreeing to participate in the first stage of the research does **not** put you under any obligation to volunteer to participate in the additional studies.

**What are the possible benefits of taking part?**

There will be no direct benefit to you for taking part in this study. However, by taking part you may be helping people who receive palliative care in the future.

**What are the possible disadvantages and risks of taking part?**

We do not anticipate any major risks or harm to you as a result of taking part in this study, though it is possible that the use of the strip sensor may cause some discomfort and/or irritate your skin. We will ensure that, if this is the case, an experienced health care professional is aware of the situation and attends to you as necessary.

**What will happen to the information that I give?**

We will put all the data and information gathered during the monitoring period(s) from all patients together. We will analyse this information and decide whether it would be helpful to run a further, bigger study where the effectiveness of monitoring will be evaluated.

**What will happen if I don't want to carry on with the study?**

If you withdraw from the study, the monitoring with the BIS technology will stop and we will not collect any further data, but we will need to use the data collected up to your withdrawal.

**What if there is a problem?**

If you are concerned about any aspect of this study, please speak to the researchers who will do their best to answer your questions. Please contact: Anna-Maria Kroupa (telephone: [redacted] email: [redacted]). If you remain unhappy, you can make a formal complaint through the Marie Curie complaints procedure. Details can be obtained through the Marie Curie support line: 0800 090 2309 or via a letter to the Marie Curie Patient and Carer Experience Team; Marie Curie, 89 Albert Embankment, London SE1 7TP. University College London (UCL) holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospice, the hospice continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospice's duty of care, or any negligence on the part of hospice employees. This applies whether the hospice is an NHS Trust or otherwise.

**Will my taking part in this study be kept confidential?**

All information that is collected about you during the course of the research will be kept strictly confidential, except if we discover or you disclose any information that is criminal in nature, or any other information that we are required to report by law then we may need to break confidentiality and inform the relevant authorities.



Any personal information that will have your name and address will be removed so that you cannot be identified from it. Only the research team will have access to this information. For the interviews, an additional external transcriber may listen to the voice recordings and type these up as written scripts, but this person will have signed a confidentiality agreement with UCL.

All data will be handled, processed, stored and destroyed in accordance with the Data Protection Act (1998). Voice recordings will be downloaded from the portable recorder onto a secure computer server, and the original recording deleted.

**What will happen to the results of the research study?**

We will present the results of the study to expert and support groups for service users, to people working in palliative care, to academic colleagues, and to Marie Curie. We will also seek to publish papers in scientific journals. All information collected during the study will be combined to form the results, so no individual will be identified in any report or publication.

**Who is organising and funding the research?**

This research has been reviewed and funded by Marie Curie, and is being conducted by researchers in the Marie Curie Palliative Care Research Department at UCL.

**Who has reviewed the study?**

All research in the NHS, and organisations working in partnership with the NHS, is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by Camden and King's Cross Research Ethics Committee.

**Contact for further information**

For further information please contact Anna-Maria Krooupa via telephone: \_\_\_\_\_ or  
email: \_\_\_\_\_

*Thank you for taking the time to read this information sheet.  
Your help makes our research possible.*

## Appendix 3.3 Consent form

### Participant Consent Form



Please complete this form after you have read the Information Sheet and/or listened to an explanation of the research.

**Study Title:** Feasibility of monitoring sedative use in palliative care

**Name of Researcher:** Anna-Maria Krooupa **Protocol Reference Number:** 17/0179

Thank you for your interest in taking part in this research. Before you agree to take part, the people running the research project must explain it to you.

If you have any questions arising from the Information Sheet or explanation given to you, please ask the researcher before you decide whether or not to take part. You will be given a copy of this Consent Form to keep and refer to at any time.

**Please INITIAL box**

1. I confirm that I have read and understand the information sheet v 2, dated 02/10/17, for the above study and that I have had the opportunity to ask questions.	
2. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason and without either my legal rights or my care being affected.	
3. I understand that any relevant personal information, which may be collected during the study, will be made anonymous and added to that of others to form the results, which may be used in reports, publications or presentations. I understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998, except if confidentiality needs to be broken to safeguard patients and/or staff.	
4. I understand that I will not gain financially or otherwise from participation in this study.	
5. I agree that the research project named above has been explained to me and I agree to take part in the above-named study.	
6. <b>OPTIONAL:</b> I agree to be approached by a researcher to discuss my willingness to participate in the second stage of the study (additional 4 hours of monitoring).	
7. <b>OPTIONAL:</b> I agree to be approached by a researcher to discuss my willingness to participate in a one-to-one interview (approximately 20-30 minutes).	

.....  
Name of participant

.....  
Date

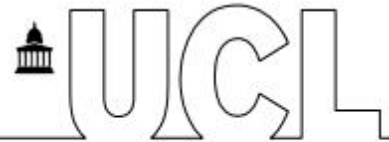
.....  
Signature

.....  
Researcher

.....  
Date

.....  
Signature

*When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.*



## Participant Information Sheet for Patients

**Study Title:** Feasibility of monitoring sedative use in palliative care  
**Protocol Reference Number:** 17/0179

*We would like to invite you to take part in our research study. Before you decide on whether or not you would like to take part in this research, we want you to understand why the research is being done and what it would involve for you. One of our team will go through this information sheet with you and answer any questions you may have. This should take about 10 minutes.*

*You are also free to talk to other people about the study if you would like to. Please ask if anything is not clear, or if you would like more information. It is up to you to decide whether to take part or not. Deciding not to take part will not affect your care in any way. If you do decide to take part you are still free to stop at any time, and without giving a reason.*

### **Why is the study being done?**

We are trying to improve care and support for people who are receiving palliative care, particularly people who may require medicines that can cause sedation. At present, the level of sedation caused by medication is not always routinely measured. Systematic monitoring of the depth of a person's sedation might help determine the right amount of sedative medication to give that person. However, at the moment we do not know the best way to undertake this monitoring.

We are doing this study to help us understand whether a technical device, or regular observations by a member of staff with a checklist could provide useful information about the alertness of people receiving palliative care. The Bispectral Index (BIS) monitor is non-invasive, and measures the electrical activity of the brain by means of a 12cm strip sensor that is applied to the forehead (*please see picture of the BIS monitor and strip sensor*).

The observational checklist is a simple questionnaire that clinical staff complete, based on their impressions about how awake and alert patients are.



We would like to monitor 100 patients to find out if these different approaches provide useful measures of patients' alertness. We would also like to explore patients' experiences and opinions about the measures.

**Why have I been chosen?**

You have been chosen because you are a patient in the hospice, you have used the BIS monitor for the first four hours of monitoring, and you have indicated that you are willing to take part in the second four-hour period of monitoring.

**Do I have to take part?**

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. Even if you do decide to take part you are free to withdraw from the study at any time and without giving a reason. If you do withdraw from the study, your care will not be affected in any way.

**What will happen to me if I take part?**

If you agree to participate in the study, the same procedures used in the first stage of the study will be repeated. However, on this occasion, if you are too sleepy or are feeling less well, then you will not need to complete any of the questionnaires that you previously used. As during the previous monitoring phase, researchers will collect data on your pain and alertness levels. The researchers will also collect some information from your medical record.

**What do I have to do?**

If you consent to take part in the study, you will be asked to use the BIS monitor for a further period of 4 hours. This period of monitoring will coincide with an occasion when you happen to be receiving medication with sedative side-effects. You will **not** be given any medication as part of the study, but if you are due to be given medication with sedative side-effects as part of your routine clinical care, then you will be asked to verbally reconfirm your consent to having the BIS attached for a second period of 4 hours (see below).

After the end of the monitoring period, you will be given a short questionnaire to complete (5-10 minutes), if appropriate.

**Reconfirmation of consent**

If you agree to take part in the second four hours of monitoring, the researcher will first ask you to sign a written consent form. This will let us know that you agree to take part in the study "in principle".

It is possible that you may never actually receive any drugs with sedative side-effects during the rest of your stay in the hospice in that case you will not need to be involved in the study again, and we thank you for your willingness to be involved.

It is also possible that, after signing the initial consent form indicating your willingness to participate in the research "in principle", you will not actually receive any drugs with sedative side-effects until several days or weeks later. For that reason, we will always seek your verbal agreement to take part in the study just before you are about to be monitored with the BIS technology for the second time. If you are unable to verbally reconfirm your consent (for instance because you are too drowsy or unwell), the research team will seek the advice of a relative, friend or carer (or a member of staff unconnected to the research if no-one else is available) regarding your continuation in the study. This person will advise the research team about whether or not your previously expressed willingness to participate in the study should be accepted, or whether there is any reason to believe that you may have changed your mind.

You will be asked to nominate which person you would like us to contact to seek advice if you are no longer able to reconfirm your willingness to participate in this study. In the event that you cannot identify a person to undertake this role, the research team will nominate a clinician who is not involved in the research project provide to advise whether or not you should remain in the study.

**What are the possible benefits of taking part?**

There will be no direct benefit to you for taking part in this study. However, by taking part you may be helping people who receive palliative care in the future.

**What are the possible disadvantages and risks of taking part?**

We do not anticipate any major risks or harm to you as a result of taking part in this study, though it is possible that the use of the strip sensor may cause some discomfort and/or irritate your skin. We will ensure that, if this is the case, an experienced health care professional is aware of the situation and attends to you as necessary.

**What will happen to the information that I give?**

We will put all the data and information gathered during the monitoring period(s) from all patients together. We will analyse this information and decide whether it would be helpful to run a further, bigger study where the effectiveness of monitoring will be evaluated.

**What will happen if I don't want to carry on with the study?**

If you withdraw from the study, the monitoring with the BIS technology will stop and we will not collect any further data, but we will need to use the data collected up to your withdrawal.

**What if there is a problem?**

If you are concerned about any aspect of this study, please speak to the researchers who will do their best to answer your questions. Please contact: Anna-Maria Krooupa (telephone: \_\_\_\_\_, email: \_\_\_\_\_). If you remain unhappy, you can make a formal complaint through the Marie Curie complaints procedure. Details can be obtained through the Marie Curie support line: 0800 090 2309 or via a letter to the Marie Curie Patient and Carer Experience Team; Marie Curie, 89 Albert Embankment, London SE1 7TP. University College London (UCL) holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospice, the hospice continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospice's duty of care, or any negligence on the part of hospice employees. This applies whether the hospice is an NHS Trust or otherwise.

**Will my taking part in this study be kept confidential?**

All information that is collected about you during the course of the research will be kept strictly confidential, except if we discover or you disclose any information that is criminal in nature, or any other information that we are required to report by law then we may need to break confidentiality and inform the relevant authorities.

Any personal information that will have your name and address will be removed so that you cannot be identified from it. Only the research team will have access to this information. For the

interviews, an additional external transcriber may listen to the voice recordings and type these up as written scripts, but this person will have signed a confidentiality agreement with UCL. All data will be handled, processed, stored and destroyed in accordance with the Data Protection Act (1998). Voice recordings will be downloaded from the portable recorder onto a secure computer server, and the original recording deleted.

**What will happen to the results of the research study?**

We will present the results of the study to expert and support groups for service users, to people working in palliative care, to academic colleagues, and to Marie Curie. We will also seek to publish papers in scientific journals. All information collected during the study will be combined to form the results, so no individual will be identified in any report or publication.

**Who is organising and funding the research?**

This research has been reviewed and funded by Marie Curie, and is being conducted by researchers in the Marie Curie Palliative Care Research Department at UCL.

**Who has reviewed the study?**

All research in the NHS, and organisations working in partnership with the NHS, is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by Camden and King's Cross Research Ethics Committee.

**Contact for further information**

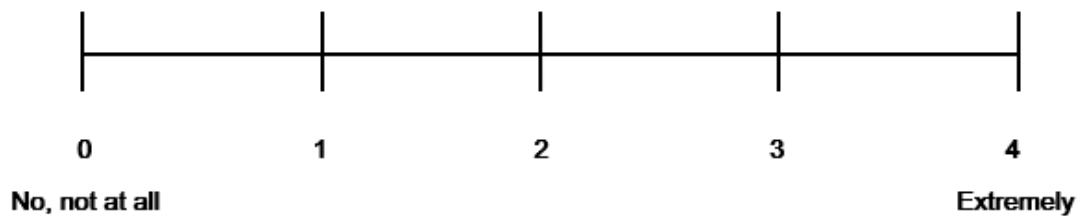
For further information please contact Anna-Maria Krooupa via telephone: \_\_\_\_\_ or  
email: \_\_\_\_\_

*Thank you for taking the time to read this information sheet.  
Your help makes our research possible.*

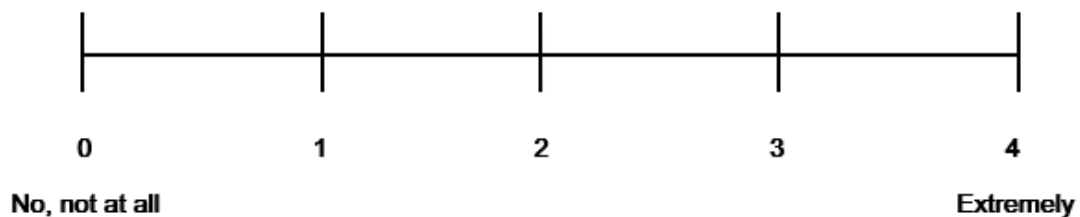
### Appendix 3.5 Participant experience questionnaire (Phase 1)

Please read each of the following questions and **circle** the number that best describes your experience

- 1) During the time that you were monitored with the BIS technology, did the strip sensor feel uncomfortable on your forehead/skin?



- 2) During the time that you were monitored with the BIS technology, did using the monitor affect your movement/activity inside or outside your room?  
(If you answer **1-4**, please go to question 3. If you answer **0**, please go to question 4)



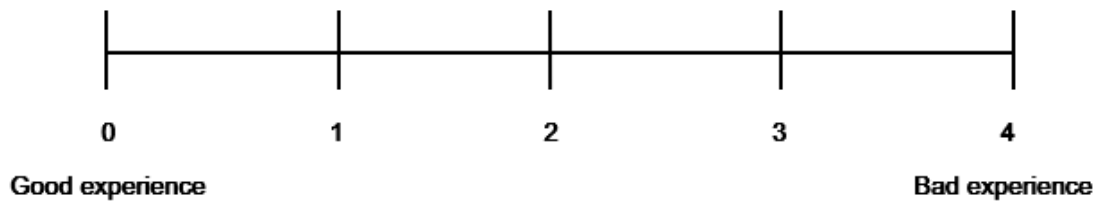
- 3) How did using the monitor affect your movement/activity? (circle **all** that apply)

1. Difficulty turning/moving in bed
2. Difficulty performing daily activities, i.e. eating, personal hygiene activities
3. Difficulty moving inside the room, i.e. accessing the toilet, sitting in armchair
4. Difficulty moving outside the room
5. Other (please state in the space below)

- 4) Did you have any concerns/issues about wearing the strip sensor?
1. Yes (please go to question 5)
  2. No (please go to question 6)

- 5) If Yes, please indicate below (circle **all** that apply)
1. Appearance of the strip sensor
  2. Amount of time spent being monitored
  3. Skin irritation caused by the strip sensor
  4. Other (please state in the space below)

- 6) Overall, how would you describe your experience of using the BIS monitor for the purposes of this study?

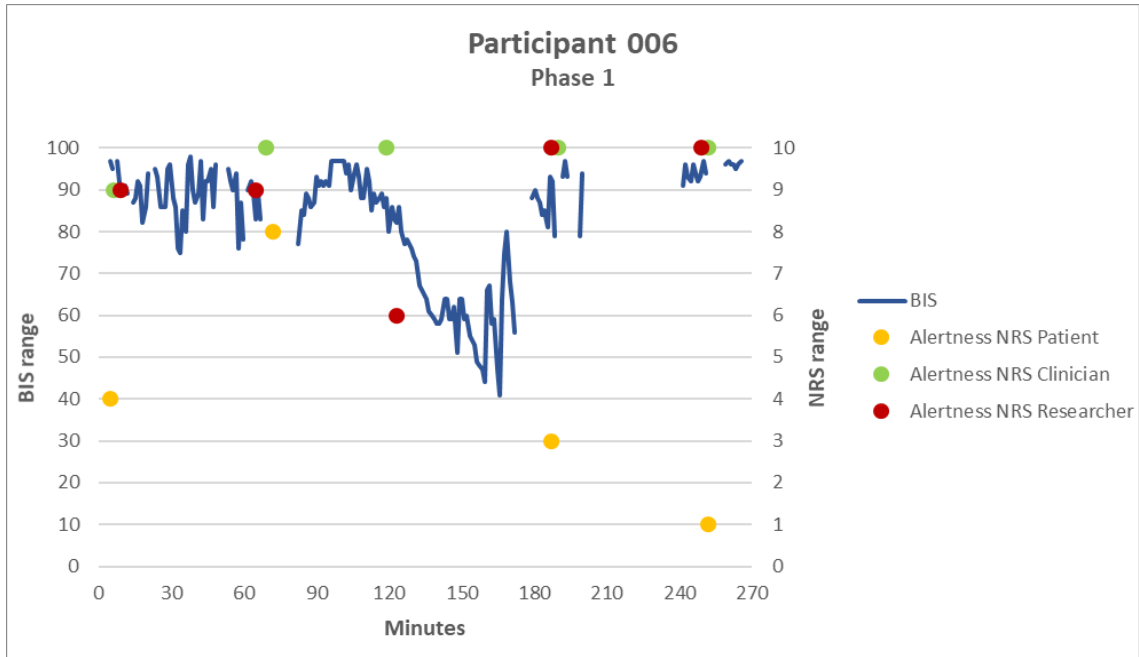


- 7) Would you be willing to be monitored with the BIS for a further 4-hour period on another occasion during your stay at the hospice?
1. Yes
  2. No
  3. I need more time/to discuss with others to decide
  4. I prefer not to say/ I am not sure

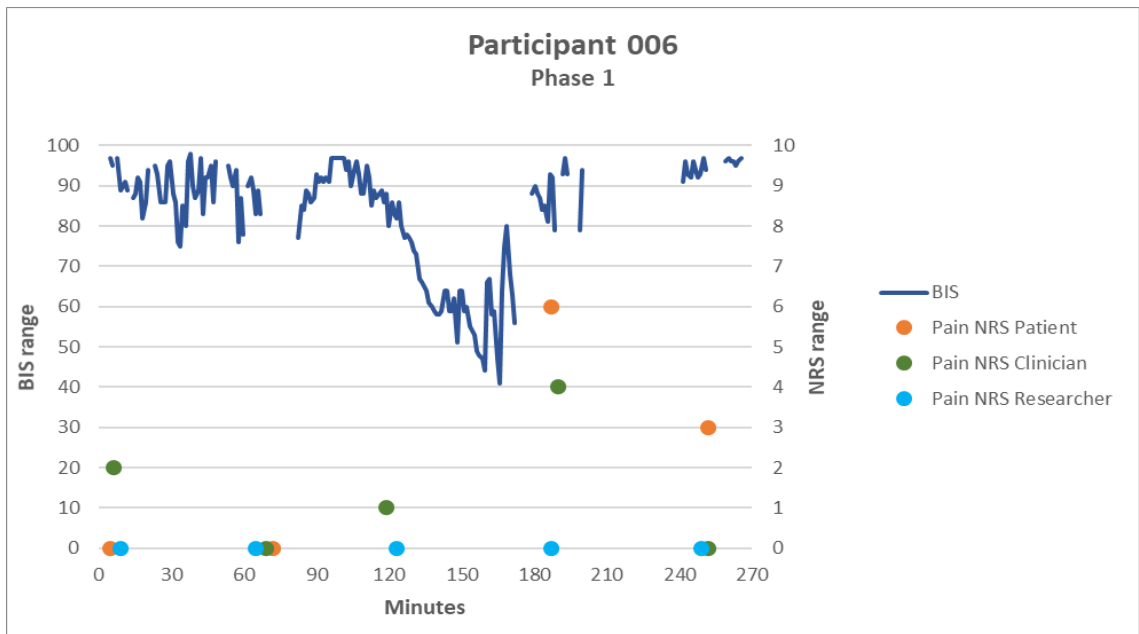
- 8) How did you complete this questionnaire?
1. On my own
  2. With the help of a friend or relative
  3. With help from a member of the clinical team



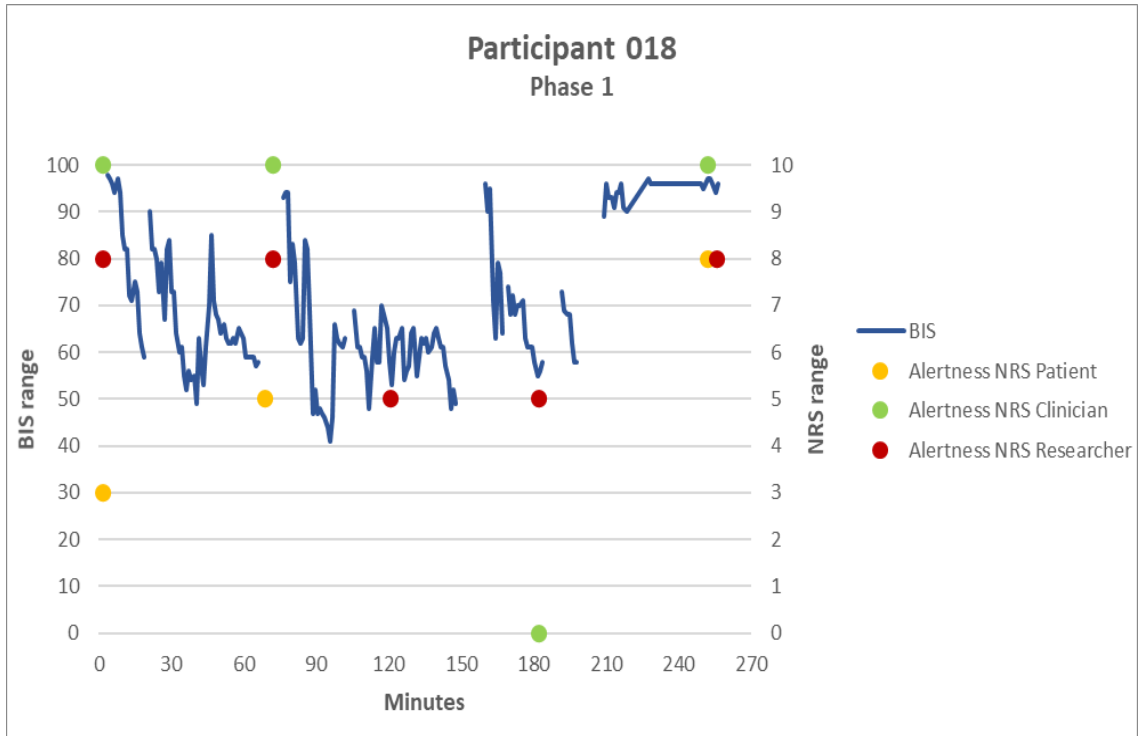
**Appendix 4 Plotted BIS and alertness NRS data, and BIS and pain NRS data for selected individual participant cases**



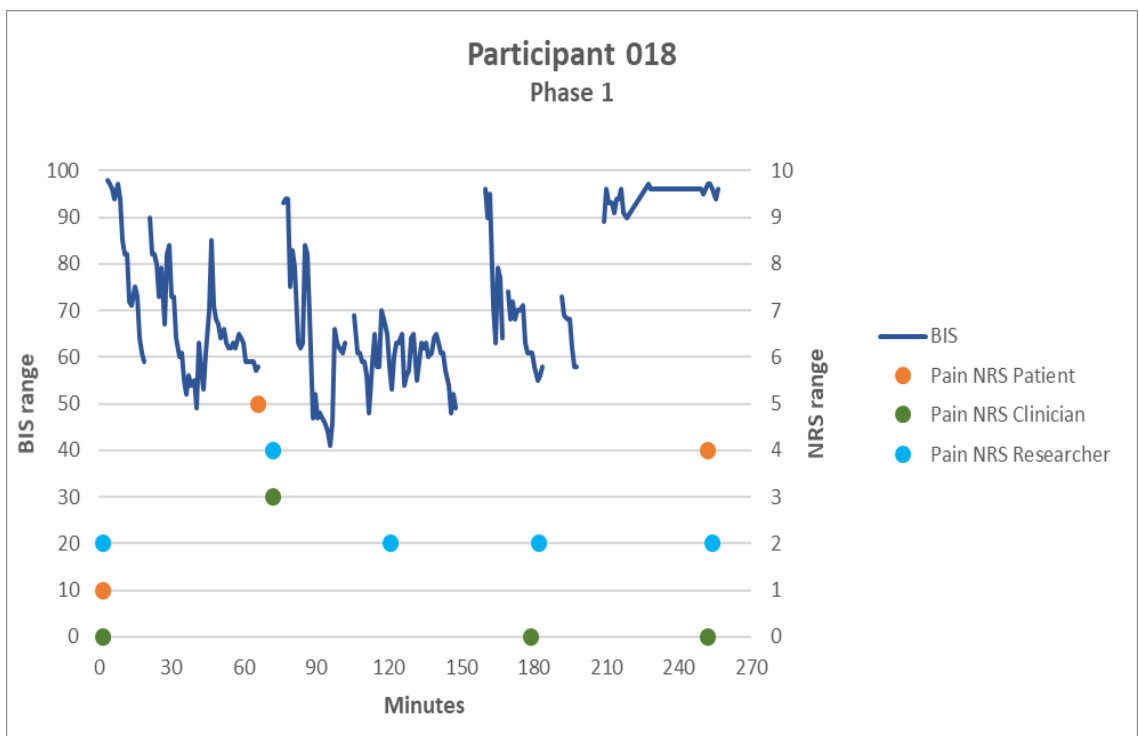
**Figure A.1:** BIS and alertness NRS data collected for participant 006 in Phase 1



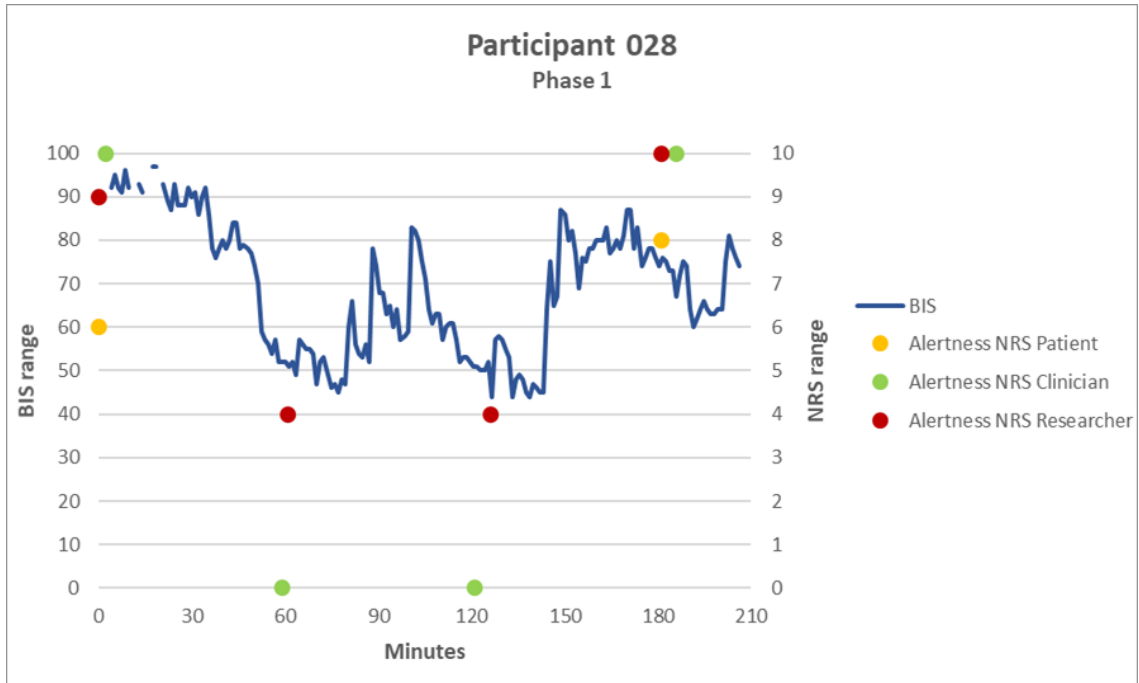
**Figure A.2:** BIS and pain NRS data collected for participant 006 in Phase 1



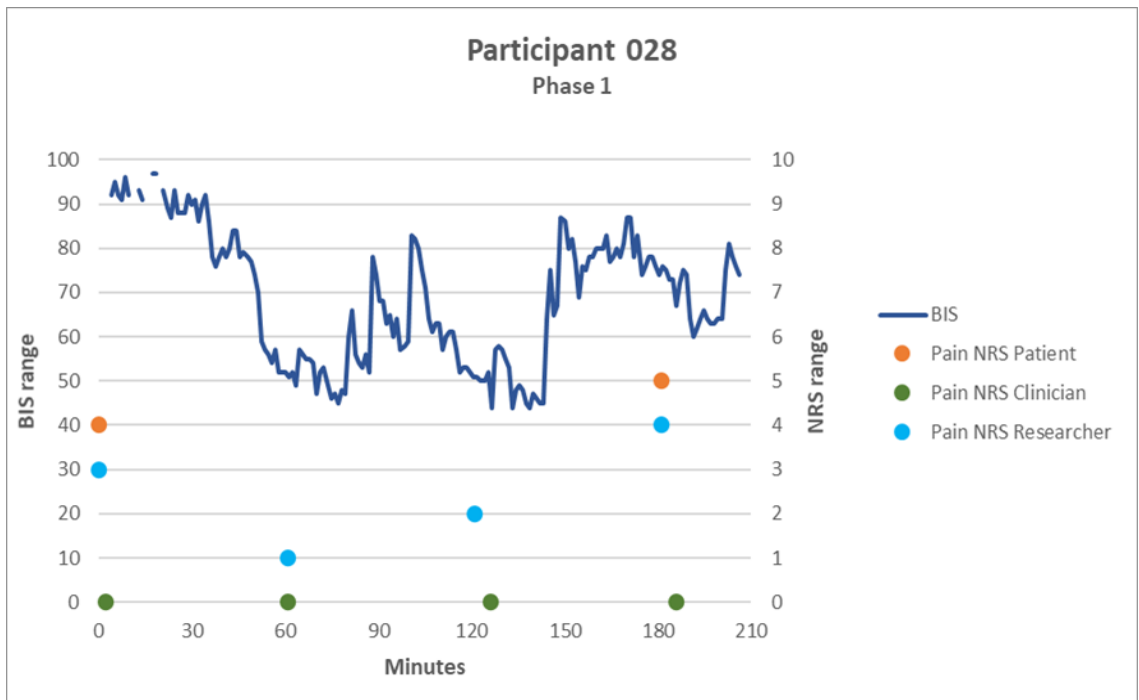
**Figure A.3:** BIS and alertness NRS data collected for participant 018 in Phase 1



**Figure A.4:** BIS and pain NRS data collected for participant 018 in Phase 1



**Figure A.5:** BIS and alertness NRS data collected for participant 028 in Phase 1



**Figure A.6:** BIS and pain NRS data collected for participant 028 in Phase 1

## Appendix 5 Research materials for qualitative study exploring key stakeholders' direct experiences of BIS monitoring (Chapters 7–8)

### Appendix 5.1 Information sheet (adapted for use with each participant group)



#### Participant Information Sheet for Patients

**Study Title: Feasibility of monitoring sedative use in palliative care**  
**Protocol Reference Number: 17/0179**

*We would like to invite you to take part in an individual interview, as a part of our research study. Before you decide on whether or not you would like to take part in this research, we would like to remind you why the research is being done and what it would involve for you. One of our team will go through this information sheet with you and answer any questions you may have. This should take about 10 minutes. You are also free to talk to other people about the study if you would like to. Please ask if anything is not clear, or if you would like more information. It is up to you to decide whether to take part or not. Deciding not to take part will not affect your care in any way. If you do decide to take part you are still free to stop at any time, and without giving a reason.*

#### **Why is the study being done?**

We are trying to improve care and support for people who are receiving palliative care, particularly people who may require medicines that can cause sedation. At present, the level of sedation caused by medication is not always routinely measured. Systematic monitoring of the depth of a person's sedation might help determine the right amount of sedative medication to give that person. However, at the moment we do not know the best way to undertake this monitoring.

We are doing this study to help us understand whether a technical device, or regular observations by a member of staff with a checklist could provide useful information about the alertness of people receiving palliative care. The Bispectral Index (BIS) monitor is non-invasive, and measures the electrical activity of the brain by means of a 12cm strip sensor that is applied to the forehead (*please see picture of the BIS monitor and strip sensor*). The observational checklist is a simple questionnaire that clinical staff complete, based on their impressions about how awake and alert patients are.



We would like to explore the opinions and thoughts of 18-20 patients who have had the experience of using the BIS monitor about their views of this technology.

**Why have I been chosen?**

You have been chosen because you are a patient in the hospice, you have recently used the BIS monitor, and you have indicated that you may be willing to take part in an individual interview.

**Do I have to take part?**

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. Even if you do decide to take part you are free to withdraw from the study at any time and without giving a reason. If you do withdraw from the study, your care will not be affected in any way.

**What do I have to do?**

If you agree to participate in the study, you will have an interview with a member of the research team. We expect the interview to take 20-30 minutes. The interview will be audio-recorded, and some notes will also be taken by hand, to help us check that we have recorded everything that has been said. We will ask you about your thoughts and opinions regarding the use of monitoring in hospice patients. Having had the experience of using the BIS monitoring device, we will ask you about your views of this technology.

**How long will I be in the study?**

You will be asked to participate in one interview of 20-30 minutes.

**What are the possible benefits of taking part?**

There will be no direct benefit to you for taking part in this study. However, by taking part you may be helping people who receive palliative care in the future.

**What are the possible disadvantages and risks of taking part?**

We do not anticipate any risks or harm to you as a result of taking part in this study, though it is possible that these discussions may touch on some difficult issues. We will ensure that if this is the case, an experienced health care professional will be available for you to speak with if you wish.

**What will happen to the information that I give?**

We will put the information gathered from the interviews with patients, their relatives and health care professionals together with information gathered during the monitoring of study participants. We will analyse this information and decide whether it would be helpful to run a further, bigger study where the effectiveness of monitoring will be evaluated.

**What will happen if I don't want to carry on with the study?**

If you withdraw from the study, the interview data will be destroyed and will not be included in the analysis.

**What if there is a problem?**

If you are concerned about any aspect of this study, please speak to the researchers who will do their best to answer your questions. Please contact: Anna-Maria Krooupa (telephone: ( ), email: ( )). If you remain unhappy, you can make a formal complaint through the Marie Curie complaints procedure. Details can be obtained through the Marie Curie support line: 0800 090 2309 or via a letter to the Marie Curie Patient and Carer Experience Team; Marie Curie, 89 Albert Embankment, London SE1 7TP. University

College London (UCL) holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospice, the hospice continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospice's duty of care, or any negligence on the part of hospice employees. This applies whether the hospice is an NHS Trust or otherwise.

**Will my taking part in this study be kept confidential?**

All information that is collected about you during the course of the research will be kept strictly confidential, except if we discover or you disclose any information that is criminal in nature, or any other information that we are required to report by law, then we may need to break confidentiality and inform the relevant authorities.

Any personal information will have your name and address will be removed so that you cannot be identified from it. Only the research team will have access to this information. An additional external transcriber may listen to the voice recordings and type these up as written scripts, but this person will have signed a confidentiality agreement with UCL. All data will be handled, processed, stored and destroyed in accordance with the Data Protection Act (1998). Voice recordings will be downloaded from the portable recorder onto a secure computer server, and the original recording deleted.

**What will happen to the results of the research study?**

We will present the results of the study to expert and support groups for service users, to people working in palliative care, to academic colleagues, and to Marie Curie. We will also seek to publish papers in scientific journals. All information collected during the study will be combined to form the results, so no individual will be identified in any report or publication.

**Who is organising and funding the research?**

This research has been reviewed and funded by Marie Curie, and is being conducted by researchers in the Marie Curie Palliative Care Research Department at UCL.

**Who has reviewed the study?**

All research in the NHS, and organisations working in partnership with the NHS, is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by Camden and King's Cross Research Ethics Committee.

**Contact for further information**

For further information please contact Anna-Maria Krooupa via telephone: \_\_\_\_\_ or  
email: \_\_\_\_\_

*Thank you for taking the time to read this information sheet.  
Your help makes our research possible.*

## Appendix 5.2 Interview topic guide (adapted for use with each participant group)



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### Topic guide for individual interviews (Patients)

#### Questions (plus prompts, if needed)

1. How did you find using the BIS monitor as a part of this research project?
  - a. How did you feel / what were your thoughts when being monitored with the BIS?
  - b. How did you find having the strip sensor applied to your forehead? How did you feel after it was taken off?
  - c. How did you find having the monitor attached in terms of moving inside/outside the room and / or sitting up / changing sides in your bed?
  
2. After having the experience of being monitored with the BIS, do you have any thoughts about using this technology in palliative care?
  - a. Would you be willing to be monitored with the BIS again if it was suggested by your doctor as part of routine clinical care?
  - b. How long would you be willing to be monitored for? For minutes; hours; days? For as long as necessary? For as short a time as possible?
  - c. What do you think about having the monitor attached if you were less conscious / unconscious?
  
3. During your participation in this study you have used the BIS monitor, recorded your pain and alertness levels on two scales that were given to you at different time points and completed a questionnaire. How did you find the overall experience of taking part in this research project?
  - a. Do you have any thoughts about particular aspects of this study that may have affected your experience of participation?
  - b. Was there something particularly positive / negative? Something that you would change?
  
4. Would you be willing to participate in a future study if it involved some patients having regular monitoring with BIS and some patients being monitored by being observed by clinical staff (if the decision about which form of monitoring was decided randomly by a computer)?
  - a. Do you have any thoughts about taking part in such a study?