Improving Prescription in Palliative Sedation

Compliance With Dutch Guidelines

Jeroen G. J. Hasselaar, MSc; Rob P. B. Reuzel, PhD; Stans C. A. H. H. V. M. Verhagen, MD, PhD; Alexander de Graeff, MD, PhD; Kris C. P. Vissers, MD, PhD, FIPP; Ben J. P. Crul, MD, PhD

Background: Two guidelines addressing palliative sedation have been published in the Netherlands in 2002 and 2003. The objective of the present study is to determine adherence to the guidelines for palliative sedation with regard to prescription. The study is restricted to the practice of continuous deep palliative sedation.

Methods: A structured retrospective questionnaire was administered to 1464 physicians concerning their last case of deep sedation during the past 12 months. Physicians included Dutch hospital specialists, general practitioners, and nursing home physicians.

Results: The response rate was 36%. A total of 43% (95% confidence interval [CI], 37%-49%) of the responding physicians did not adhere to the guidelines. Sources of deviation were the use of basic medication other than a benzodiazepine (30%), which mostly involved morphine, and omissions in adjuvant medication (13%). Nonsignificant positive association was found for consultation of a palliative care expert (odds ratio [OR], 3.86; 95% CI, 0.92-8.87). Significant positive association was found for the physician being a palliative care expert himself or herself (OR, 4.42; 95% CI, 1.42-13.75) and the use of guidelines (OR, 1.74; 95% CI, 1.02-2.98). Treatment of pain symptoms (OR, 2.21; 95% CI, 1.28-3.82), anxiety (OR, 2.32; 95% CI, 1.33-4.06), vomiting (OR, 6.52; 95% CI, 1.08-39.50), and loss of dignity (OR, 3.93; 95% CI, 1.80-8.58) also correlated positively. Treatment of delirium correlated negatively with adherence to the guidelines (OR, 0.22; 95% CI,0.11-0.44).

Conclusions: The rate of 43% noncompliance to the guidelines was mostly owing to the omission of continued antipsychotic treatment for delirium and the use of morphine as the single therapy for the purpose of deep sedation. Future efforts, like better use and knowledge of the guidelines and a larger involvement of consultation teams, should increase adherence to the guidelines.

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Author Affiliations:
Departments of Anesthesiology, Pain, and Palliative Medicine (Mr Hasselaar and Drs Verhagen, Vissers, and Crul), Medical Technology Assessment (Dr Reuzel), and Oncology (Dr Verhagen), Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; and Department of Medical Oncology, University Medical Center Utrecht, Utrecht, the Netherlands (Dr de Graeff).

PALLIATIVE SEDATION HAS raised considerable controversy during the past years and has been compared with euthanasia.[1-3] The need for guidelines has been emphasized, and several proposals, which sometimes include drug schemes, have been published.[4-7] Although some studies have evaluated the moral and medical aspects of palliative sedation,[8,9] to our knowledge, adherence to guidelines for palliative sedation has not yet been investigated systematically. In the Netherlands, guidelines from 2 comprehensive cancer centers were published. Comprehensive cancer centers have been established by the Dutch Government to develop and support policy and knowledge about the treatment of cancer. The first set of guidelines, from the Comprehensive Cancer Center Middle Netherlands, was published in 2002,[10] followed by a more detailed set of guidelines from the Comprehensive Cancer Center East Netherlands in 2003.[11] It has been noted in the literature that the relevant terms used to refer to palliative sedation, and even the definition of *palliative sedation*—which is also called *terminal sedation* or *sedation during the last phase of life*—are often used in a disorderly manner, which makes guidelines difficult to compare.[12,13] *Palliative sedation* has been defined as the use of sedative medications to relieve intolerable and refractory distress by the reduction in patient consciousness.[12] This definition includes superficial and deep sedation as well as intermittent and continuous sedation. The objective of this study is to investigate compliance with the Dutch guidelines among physicians applying deep and continuous palliative sedation until death (hereinafter called *deep sedation*). Symptoms are considered refractory when alternatives to relieve the symptoms in a less drastic manner are not available in time or have unacceptable adverse effects.

In keeping with the relevant medical literature, the Dutch guidelines recommend the use of benzodiazepines and mid-

azolam in particular as the first choice for deep sedation with levomepromazine (methotrimeprazine) as a possible alternative for midazolam.[5] The guidelines reject the use of morphine as a single therapy to attain sedation owing to its unpredictable sedative effects. However, deep sedation in suppressing the experience of symptoms does not render specific treatment of symptoms unnecessary. For this reason, the Comprehensive Cancer Center East Netherlands recommends continued antipsychotic treatment when deep sedation is initiated in cases of refractory delirium. Administration of morphine, a common treatment for pain and dyspnea,[14] may be continued when symptoms become refractory and benzodiazepine administration is started for the purpose of deep sedation.[5] In both sets of guidelines, it is also recommended that a palliative care expert be consulted when the responsible physician doubts his or her own expertise. The guidelines have been published as part of a set of palliative care guidelines (Comprehensive Cancer Center Middle Netherlands),[10] by publication at the Web site of the Comprehensive Cancer Centers (Comprehensive Cancer Center East Netherlands guidelines),[11] and by education and training. However, there was no structured implementation strategy. In December 2005, after the closure of this study, the Royal Dutch Medical Association[15] launched a new set of national guidelines for palliative sedation.[16] The new guidelines originate directly from the guidelines that are the subject of the present study and reflect their recommendations for prescription.

Studies of adherence to guidelines are needed because it is uncertain whether the mere publication of a set of guidelines guarantees the necessary behavioral change on the part of the relevant health care professionals.[17,18] The aim of the present study is therefore to assess adherence to the Dutch guidelines for the practice of deep sedation and to identify those variables that appear to influence the compliance of health care professionals with the relevant recommendations. Given that the literature shows that physicians frequently encounter problems with the treatment of symptoms and the use of drugs in palliative care, the focus of the present article is on the guideline recommendations for the choice of drugs for sedation.[19] In sum, the following questions will be investigated within the confines of the present study: (1) Which drugs are used by physicians for deep sedation? (2) To what extent are the recommendations included in the guidelines adhered to in actual practice? (3) What variables appear to influence compliance with the guidelines? As factors possibly contributing to guideline compliance, the actual use of the guidelines by the physician, the consultation of a palliative expert, the expertise of the physician himself or herself, the type of physician, and the current symptoms indicating deep sedation will be considered.

METHODS

A structured, retrospective questionnaire concerning the most recent case of deep sedation during the past 12 months was sent to 1464 Dutch physicians. The questionnaire contained 61 questions and was mailed to the physicians most involved in palliative sedation in the Netherlands between 2003 and 2005. A response reminder was mailed when the physician had not responded within a period of 1 month. A pilot questionnaire was initially administered to 20 physicians, and nonresponse was recorded. The target group for this questionnaire included general practitioners (n=626), hospital specialists (n=727), and nursing home physicians (n=111). The sample included all of the respiratory and geriatric specialists registered in the Netherlands and all of the general practitioners, nursing home physicians, and internal medicine specialists (including medical oncologists) registered in the southeastern part of the Netherlands. To minimize any differences in the perception of sedation across the respondents, a definition of sedation was provided with the questionnaire. In this definition, sedation was explicitly restricted to continuous deep sedation that was expected to last until the patient's death.

The following situations were regarded as noncompliance with the guidelines: (1) not using a sedative (benzodiazepine or levomepromazine) for the purpose of deep sedation; (2) not using an antipsychotic agent combined with a sedative for deep sedation for refractory delirium; (3) using morphine combined with a sedative for symptoms other then pain or dyspnea. The data were analyzed using SPSS, version 12.0, software (SPSS Inc, Chicago, Ill). An α of .05 was used to test statistical significance; 95% confidence intervals (CIs) and χ^2 values were calculated, and a multivariate logistic regression analysis was performed to identify those variables that clearly correlated with adherence to the guidelines on the part of the physicians. Outcome of the multivariate analysis is reported in odds ratios (ORs).

The following variables were included in the regression model: physician employment as a palliative consultant (yes or no), physician consultation of a palliative expert prior to administration of deep sedation (yes or no), type of physician (medical specialist, general practitioner, or nursing home physician), and physician use of guidelines or protocol for deep sedation (yes, no, or sometimes). The latter variable did not address a specific set of guidelines or protocol and was transformed into a binary variable: yes (always or sometimes) or no. Finally, the possible indications for deep sedation were also included in the model (pain, dyspnea, anxiety, delirium, vomiting, nausea, exhaustion, loss of dignity, and/or existential suffering). The physicians were allowed to register more than 1 symptom.

RESULTS

Of the 1464 physicians invited to respond, a total of 525 (36%) returned the questionnaire. The response rate varied across specialties (medical specialists, 27% [n=192]; general practitioners, 37% [n=234]; nursing home physicians, 59% [n=66]). The other 33 respondents did not fit into any of these 3 categories of physician. A case of deep sedation within the past 12 months was reported on the questionnaires of 312 physicians. Eight of these questionnaires had to be excluded because they were not completed by a hospital specialist, general practitioner, or nursing home physician. On 7 of the other questionnaires, no data on drug administration were reported. Finally, 297 reported cases of deep sedation were included in the study (123 medical specialists, 128 general practitioners, and 46 nursing home physicians) (**Table 1**). Most of the respondents (67%) were men, and the average age was 46 years.

The physicians in the present sample reported the following with regard to the use of a set of guidelines or protocol for deep sedation: always (23%), sometimes (24%),

Table 1. Characteristics of Physicians Responding to Deep Sedation Questionnaire

Characteristic	Physicians, No. (%) (n = 297)
Ever followed a course in palliative care	116 (40)*
Was involved in the dying process of a patient >5 times in the last 12 months	169 (58)†
Decided to use palliative sedation >5 times in last 12 months with the expectation that the patient would die while under sedation	58 (20)‡
Has ever discontinued sedation before the death of the patient	30 (11)§

*Data missing for 8 physicians.
†Data missing for 3 physicians.
‡Data missing for 2 physicians.
§Data missing for 4 physicians.

Table 2. Patient Characteristics for Last Cases of Deep Sedation

Characteristic	Patients, No. (%) (n = 297)
Age, y*	
≤40	12 (4)
41-60	48 (16)
61-80	152 (52)
>80	83 (28)
Sex†	
Male	147 (51)
Female	143 (49)
Symptoms indicating deep sedation‡	
Pain	171 (58)
Dyspnea	154 (52)
Anxiety	126 (42)
Exhaustion	100 (34)
Delirium	59 (20)
Loss of dignity	53 (18)
Existential suffering	51 (17)
Vomiting	20 (7)
Nausea	20 (7)
Other	33 (11)

*Data missing for 2 patients.
†Data missing for 7 patients.
‡ More than 1 symptom could be reported.

or never (53%). Of the physicians in our survey, 81% stated that a palliative care consultant was available locally, while 25 physicians actually used this service during their last case of sedation. Overall, 20% of physicians (Table 1) administered palliative sedation more than 5 times in the last 12 months. Deep and continuous sedation, although intended to be administered until death, was discontinued in 11% of the patients. Of the patients in our sample, 51% were men (n=147), and 28% were older than 80 years (n=83) (**Table 2**). Pain was the symptom most often reported as an indication for deep sedation (58%), followed by dyspnea (52%), anxiety (42%), exhaustion (34%), delirium (20%), loss of dignity (18%), existential suffering (17%), nausea (7%), and vomiting (7%). Pain was the sole indication for sedation in 3% of the patients (n=10), and was often accompanied by dyspnea (47% [n=81]), exhaustion (35% [n=59]), or anxiety (40% [n=69]). Anxiety, loss of dignity, existential suffering, and exhaustion, without comorbidity from refractory physical symptoms, were the indication for sedation in 25 patients (8%).

Midazolam (n=149) and diazepam (n=57) were the benzodiazepines most often used for deep sedation and mostly in combination with morphine (**Table 3**). Levomepromazine was used in 14 patients. Haloperidol was frequently used for deep sedation, usually in combination with a sedative (41 [67%] of 61). Morphine was used in 224 (75%) of the 297 patients. Of all the patients, 22% (95% CI, 17%-27%) received a sedative without morphine; 48% (95% CI, 42%-53%) received a combination of a sedative and morphine; and 28% (95% CI, 23%-33%) received morphine without a sedative (Table 3).

Of all physicians, 57% (95% CI, 51%-63%) adhered to the guideline recommendations for the prescription of medication for deep sedation, while 43% did not (**Table 4**). Of the noncompliant physicians, 30% (n=89) used primary medication other than a sedative; 7% (n=22) did not administer an antipsychotic agent for refractory delirium; and 6% (n=17) administered morphine in combination with a sedative for symptoms other than pain or dyspnea. Further analysis showed that medical specialists prescribed a sedative less often overall than did other physicians ($P=.01$), and prescribed a combination of sedative and morphine for symptoms other than pain and/or dyspnea less often than other physicians ($P=.01$). Differences between general practitioners and nursing home physicians were not significant, nor were differences between physicians with regard to administration of additional antipsychotic agents for refractory delirium. The results of other analyses showed that physicians did not administer morphine at all in 39 (24%) of 163 cases of sedated patients with refractory pain or dyspnea, with significant differences seen among medical specialists (11%), general practitioners (38%), and nursing home physicians (20%) ($P=.001$).

The multivariate logistic regression analysis (**Table 5**) showed the following 2 physician characteristics to positively predict compliance with the guidelines for sedation: palliative expertise (OR, 4.42; 95% CI, 1.42-13.75) ($P=.01$) and following a set of guidelines or protocol for deep sedation (OR, 1.74; 95% CI, 1.02-2.98) ($P=.04$). The predictive value of consulting a palliative care expert was considerable although not significant (OR, 3.86; 95% CI, 0.92-8.87) ($P=.07$). The results of the logistic regression analyses further showed positive correlations between guideline adherence and treatment of pain (OR, 2.21; 95% CI, 1.28-3.82) ($P=.004$), anxiety (OR, 2.32; 95% CI, 1.33-4.06) ($P=.003$), vomiting (OR, 6.52; 95% CI, 1.08-39.50) ($P=.04$), and loss of dignity (OR, 3.93; 95% CI, 1.80-8.58) ($P=.001$), while a negative correlation was detected for treatment of delirium in connection with deep sedation (OR, 0.22; 95% CI, 0.11-0.44) ($P<.001$). Treatment of dyspnea, nausea, exhaustion, and existential suffering as well as type of physician did not correlate significantly with guide-

Table 3. Use of Sedatives and Other Drugs for the Purpose of Deep Sedation*

Drug Type	Sedatives Without Morphine†	Sedatives With Morphine‡	Morphine Without a Sedative§	No Sedative and No Morphine	Total (n = 297)
Sedative					
Midazolam	47	102	0	0	**149**
Diazepam	17	40	0	0	**57**
Clonazepam	1	1	0	0	**2**
Levomepromazine	5	9	0	0	**14**
Subtotal of cases	66	142	0	0	**208**
Other drug					
Morphine	0	142	82	0	**224**
Haloperidol	11	30	13	7	**61**
Chlorpromazine	2	0	0	0	**2**
Promethazine	3	3	1	2	**9**
Ketamine	0	1	0	1	**2**
Subtotal of cases	16	142	82	7	**247**
Total cases, No. (%)	66 (22)	142 (48)	82 (28)	7 (2)	**297 (100)**

*Unless otherwise indicated, data are reported as number of patients. More than 1 drug might have been used in 1 patient
†Morphine was explicitly excluded here; other medication might have been administered.
‡Morphine and sedatives were with explicitly included here; other medication might have been administered.
§Sedatives were explicitly excluded here; other medication might have been administered.
‖More than 1 drug might have been used in 1 patient.

line adherence. A significant interaction variable involving vomiting and anxiety was found.

COMMENT

To our knowledge, the present study is the first to systematically investigate the factors predictive of deep sedation guideline compliance . The results show that 57% of the physicians in our sample complied with the deep sedation prescription guidelines (Table 4). The logistic regression results show better compliance with the guidelines when the physicians themselves were palliative care experts, explicitly reported the use of a set of guidelines or protocol for deep sedation, or consulted with palliative care experts. In contrast to our findings with regard to deep sedation for pain, anxiety, vomiting, and loss of dignity, we found a very high level of noncompliance for deep sedation in cases involving delirium.

Guideline noncompliance manifested on several fronts. First, the use of drugs other than a benzodiazepine or levomepromazine was responsible for the largest amount of deviation from the guidelines (30%). This was mostly owing to the use of morphine as the single therapy for the purpose of deep sedation. In such cases, the sedation might actually have been the result of a dose in excess of that required for the relief of pain or dyspnea, which increases the risk of adverse effects like delirium and restlessness.[20] Moreover, these adverse effects might be mistaken for refractory symptoms of the terminal patient.

Second, 7% of the cases of deep sedation were not performed in accordance with the guidelines because administration of antipsychotic drugs was not continued for the treatment of refractory delirium after initiating deep sedation (Table 4). Delirium, although often present at the end of life, is difficult to identify and to treat, which might explain the large omission of treatment with antipsychotic drugs during sedation. But sole therapy with benzodiazepine is regarded as suboptimal treatment and might even increase agitation due to medication effects.[21]

Table 4. Physician Compliance and Noncompliance With Dutch Guidelines for Deep Sedation

Compliance/Noncompliance Characteristic	Physicians, No. (%) (95% Confidence Interval)
Full compliance with guidelines*	169 (57) (51-63)
Noncompliance with guidelines	128 (43) (37-49)
Deep sedation without a sedative†	89 (30) (25-35)
Morphine‡	82 (28) (23-33)
Other medications§	7 (2) (1-4)
Treatment of delirium with a sedative but without antipsychotic agent‖	22 (7) (4-10)
Using a combination of morphine and a sedative for symptoms other than pain or dyspnea	17 (6) (3-8)

*Compliance was calculated as total population of physicians (n = 297) minus the number of noncompliant physicians (n = 128).
†Sedatives included midazolam, diazepam, clonazepam, and levomepromazine.
‡In 13 of these cases, a combination of haloperidol and morphine was administered.
§In all cases, haloperidol was administered; in 2 cases in combination with promethazine.
‖This category also includes 1 case in which no antipsychotic agent was administered for delirium; pain and dyspnea were absent; and morphine was administered. Antipsychotic agents include haloperidol, chlorpromazine, and promethazine; levomepromazine is regarded as both a sedative and an antipsychotic agent.

Third, the physicians reported using a combination of a sedative and morphine for indications other than pain or dyspnea in 6% of all the cases. In the absence of pain and dyspnea, however, the reason for morphine administration for refractory symptoms is unclear.[22] Moreover, the use of morphine might increase the risk for morphine-induced delirium. The considerable practice (24%) of not administering morphine at all in deep

Table 5. Multivariate Logistic Regression Results for Compliance With the Guidelines for Physicians Administering Deep Sedation*

Independent Variable†	Direction	Compliance Rate, % (Physicians, No.)	Odds Ratio (95% Confidence Interval)	*P* Value
Physician is palliative care expert	Present	79 (19)	4.42 (1.42-13.75)	.01
	Not present	55 (148)	1 [Reference]	
Physician consulted a palliative care expert	Present	76 (19)	3.86 (0.92-8.87)	.07
	Not present	55 (150)	1 [Reference]	
Physician always/sometimes uses protocol/guideline	Present	65 (89)	1.74 (1.02-2.98)	.04
	Not present	51 (77)	1 [Reference]	
Pain	Present	64 (110)	2.21 (1.28-3.82)	.004
	Not present	47 (59)	1 [Reference]	
Anxiety	Present	65 (82)	2.32 (1.33-4.06)	.003
	Not present	51 (87)	1 [Reference]	
Delirium	Present	34 (20)	0.22 (0.11-0.44)	<.001
	Not present	63 (149)	1 [Reference]	
Vomiting	Present	75 (15)	6.52 (1.08-39.50)	.04
	Not present	57 (154)	1 [Reference]	
Loss of dignity	Present	76 (40)	3.93 (1.80-8.58)	.001
	Not present	53 (129)	1 [Reference]	

*Estimated model, $\chi^2 = 63.63$; $R^2 = 0.27$ ($P<.001$).
†One interaction variable involving vomiting and anxiety was detected and corrected for ($P = .01$).

sedation for pain and/or dyspnea raises serious doubts whether these symptoms should actually be considered refractory. Therefore, this study suggests that physicians have considerable problems identifying truly refractory symptoms and adequately coping with delirium in terminally ill patients.

Although only half of the physicians reported the use of a set of guidelines or protocol for deep sedation, this group showed significantly better compliance than physicians who reported otherwise. This finding shows that guidelines and protocols foster correct drug use once they are put into use. But this finding also shows that the guidelines and concomitant protocols were poorly implemented at the time of this study. A well-structured implementation and dissemination strategy for the new guidelines is therefore of major importance.

Guideline compliance was similarly found to strongly correlate with the consultation of palliative care experts. Although palliative care expertise was locally available to most of the physicians in the present study, only a very few physicians actually made use of it, which might explain why the considerable effect size was not statistically significant. Literature about quality of care supports the view that outreach visits such as expert consultation, preferably combined with other efforts for quality improvement, stimulate appropriate drug prescription by physicians.[23] The involvement of consultation teams in palliative sedation should therefore be encouraged.

Compliance with guidelines further depends on the symptoms of the patient. Compliance was relatively better in cases involving pain, anxiety, vomiting, and loss of dignity but relatively worse in cases involving delirium. For the latter, education about adverse effects of opioids and sedatives, particularly the increased risk for agitation and delirium, will improve quality of care.[21] Although general compliance did not differ between types of physicians, there is evidence for significant differences between physicians with regard to the separate recommendations of the guidelines: medical specialists administer sedatives as a primary drug for sedation less often, and general practitioners and nursing home physicians use morphine for reasons other than pain or dyspnea more frequently. A strategy for dissemination of the guidelines should be sensitive to these differences.

When compared with the results of a nationwide study in the Netherlands performed in 2001 and published in 2004,[24] the results of the present study suggest a decreased use of morphine without sedatives (36% in the nationwide study vs 28% in this study) and an increased use of a sedative plus morphine combination (35% in the nationwide study vs 48% in this study). The publication of the guidelines in 2002 and 2003 may have contributed to this shift. It should be noted that the categorization of the nationwide study differed slightly from the present study. The interpretation of the mean compliance rate found in this study is rather difficult. Literature on this topic shows several Dutch guidelines to have a mean compliance rate of 61%.[25] In this regard, the compliance rate found in the present study can be considered as encouraging but not yet high enough. On the one hand, one might have expected greater compliance in light of the amount of attention being paid to palliative sedation during the past few years. On the other hand, this media attention may also have increased patient demand for palliative sedation, with physicians starting to administer sedation without knowing exactly what it is about.

In the present study, a retrospective design with a questionnaire concerning the last case of deep sedation during the past year was used. The response rate might have been lowered by the controversy surrounding palliative sedation. An advantage of the present study was the ability to reach a wide variety of physicians, which would otherwise be very difficult. A disadvantage of this approach is that a recall bias may occur on the part of the respondents. An investigation of the nonrespondents

(n=20) showed them to have not responded owing to time constraints (ie, the amount of time needed to complete the questionnaire) or insufficient experience with deep sedation. This might have caused a selection bias toward more experienced physicians. Presuming that less-experienced physicians comply with the guidelines less often, the compliance rate in this study might therefore be overestimated. Another possible reason for the overestimation of the compliance rate is the use of proportional titration, which should accompany the appropriate choice of drugs. Because only the latter was addressed in the present study, the measured compliance rate might be an overestimation of real compliance. Therefore, generalizability of the results should be carefully considered.

Future research should concentrate on the feasibility of, and strategies for, the implementation and dissemination of guidelines for palliative sedation, including the use of expert consultation and appropriate symptom management. Furthermore, it should be explored why physicians largely differ in their use of morphine in palliative sedation. Also, prospective research should be undertaken to investigate the titration of various drugs for the purpose of palliative sedation.

In conclusion, 57% of the physicians in the present study reported adherence to the guidelines for deep sedation concerning prescription. Noncompliance was caused by the use of primary medication other than benzodiazepines or levomepromazine, by the use of morphine with patients without a clear indication, and by a failure to use antipsychotic drugs to treat delirium during sedation. The present study shows that current practice is vulnerable with regard to prescription and the identification of truly refractory symptoms. This study demonstrates that encouraging the knowledge and use of the guidelines, the larger involvement of palliative care experts, and the better identification and treatment of difficult symptoms (delirium in particular), all contribute to a better compliance with guidelines for palliative sedation. The quest for improving the practice of deep sedation therefore continues.

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Correspondence: Jeroen G. J. Hasselaar, MSc, Department of Anesthesiology, Pain, and Palliative Medicine, Radboud University Nijmegen Medical Center, PO Box 9101, 6500 HB Nijmegen, the Netherlands, Internal Postal Number 550 (j.hasselaar@anes.umcn.nl).
Author Contributions: Mr Hasselaar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Hasselaar, Reuzel, Verhagen, and Crul. *Acquisition of data:* Hasselaar and Reuzel. *Analysis and interpretation of data:* Hasselaar, Reuzel, Verhagen, de Graeff, Vissers, and Crul. *Drafting of the manuscript:* Hasselaar, Reuzel, and Vissers. *Critical revision of the manuscript for important intellectual content:* Hasselaar, Reuzel, Verhagen, de Graeff, Vissers, and Crul. *Statistical analysis:* Hasselaar. *Administrative, technical, and material support:* Hasselaar. *Study supervision:* Reuzel, Vissers, and Crul.
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