**BACKGROUND:** We studied the frequency of withdrawal of mechanical ventilation (MV) and/or vasoactive agents (VAs), the time until death, and dosages of opioids and sedatives in a Dutch academic intensive care unit (ICU), and compared these practices with international observations in this field.

**METHODS:** Retrospective data were collected from the electronic and paper files of all patients who died after withdrawal of treatment in a Dutch ICU between October 2006 and February 2007.

**RESULTS:** In this period, 471 patients were admitted to the ICU, of whom 88 died (18%). In 60 of these patients (68%), MV and/or VAs were withdrawn. This group represented 13% of the total ICU population. Of the 60 patients for whom MV and/or VAs were withdrawn, 54 (90%) died after withdrawal of MV (with or without VAs). Six (10%) died after withdrawal of VAs only, 33 (55%) after withdrawal of MV in combination with VAs, and 21 (35%) after withdrawal of MV only. Death occurred after withdrawal of MV in combination with VAs after a median of 30 minutes (interquartile range [IQR], 10–195 minutes). When only MV was discontinued, the median time until death was 50 minutes (IQR, 15–530 minutes). When only VAs were withdrawn, patients died after a median of 45 minutes (IQR, 20–715 minutes). Ten patients (17%) did not receive opioids or sedatives in their last hours. Fifty patients received opioids in their last hours. Fentanyl, with a median dosage at time of death of 100 μg/h, was the most frequently used opioid. Forty (80%) of the 50 patients mentioned above received some kind of sedative until death. In the MV withdrawal group, 34 of the 54 patients (63%) received sedatives in the last hours of their lives: 16 (27%) received midazolam (median, 10 mg/h), 12 (22%) propofol (median, 160 mg/h), and 6 (11%) lorazepam (2.0 mg/h). Sedatives were administered to all patients in whom only VAs were withdrawn.

**CONCLUSIONS:** Dutch patients who die in the ICU, or die after discharge from the ICU, die after MV and/or VAs are withdrawn. When treatments are withdrawn, death follows within 1 hour in most patients, which is a reflection of the severity of illnesses. At least 80% of patients receive opioids, and 67% receive sedatives until death. Fentanyl is the most used opioid, whereas midazolam is the most used sedative. Dosages of opioids and sedatives did not significantly exceed the ranges described as usual in the international literature. (Anesth Analg 2011;112:628–34)
Our primary objective was to study the frequency of MV and/or VA withdrawal in anticipation of death, the frequency of opioid and sedative usage, the dosages of opioids and sedatives, and the relation of these factors to time of death in our Dutch ICU. Second, we compared our results with the literature from other countries, because there have not been any comparative studies published on this much-debated Dutch situation.

METHODS

Sample
We collected data from all patients for whom life-sustaining treatment was withdrawn between October 2006 and February 2007 in the 27-bed ICU of the Erasmus MC University Hospital in Rotterdam, the Netherlands. Patients were from a mixed population of medical, general surgical, neurological, neurosurgical, and trauma cases.

Data Collection
Data were collected from both electronic and paper patient files. We gathered information on MV and/or VA withdrawal, time until death, and data concerning the administration of fentanyl, morphine, midazolam, propofol, and lorazepam to patients whose MV and VAs were withdrawn. In the studied patient group, no other kinds of sedatives, opioids, barbiturates, or muscle relaxants were used in this period. Additionally, we gathered data on background characteristics of the patient (i.e., gender, age, length of stay in the ICU, length of stay in the ward after discharge from the ICU, Acute Physiology and Chronic Health Evaluation [APACHE] II score, Sequential Organ Failure Assessment [SOFA] score, and primary admission diagnosis). For data collection from already deceased patients who were not part of an interventional study, no informed consent or additional approval was necessary, according to Dutch law.16 Treatment was withdrawn only after multidisciplinary consent, when patients failed to respond to therapy in the case of multiple organ failure, or when the inevitable poor prognosis of the acute disease became evident. Treatments were always withdrawn together and not separately or consecutively. During the study period, there was no distinct, uniform protocol for end-of-life care in use by the ICU specialists.

Analysis
The median duration of time until death after withdrawal of MV and VAs was calculated. Retrospectively, 3 groups could be distinguished:

1. Patients in whom MV in combination with VAs was withdrawn.
2. Patients in whom only MV was withdrawn, and no VAs were present.
3. Patients in whom only VAs were withdrawn, and no MV was present.

The median quantities and ranges of opioids and sedatives administered per IV syringe pump infusion per hour and by bolus injection were registered. Analyses were conducted using SPSS 12.1 (SPSS, Inc., Chicago, IL).

RESULTS

During the study period, 471 patients were admitted to the ICU, 88 of whom died. Thirty-six of these 88 patients died after withdrawal of treatment, as shown in Figure 1. Twenty-eight patients died spontaneously during the study period without withdrawal of VAs and/or MV; these patients died as a result of withholding therapy, unsuccessful cardiopulmonary resuscitation, cerebral herniation, fulminant therapy-resistant septic shock, or massive unstoppable bleeding after trauma.

The general characteristics of the 60 patients who died after withdrawal of MV, VAs, or a combination of both are shown in Table 1.

MV and/or VA Withdrawal

MV and/or VAs were withdrawn for 60 patients, representing 13% of all ICU admissions. Because 88 patients died, 68% (n = 60) of this subset of patients died as a result of withdrawal of MV and/or VAs.

MV was withdrawn in 11% (54) of all (471) ICU admissions, representing 61% of all patients who died. Of all patients admitted to the ICU, only 1% had only VAs withdrawn, which represents 7% of all the patients who died in the ICU.

In 42 of the 60 patients, not only was MV terminated, but the endotracheal tube was also removed. One patient had a tracheostomy, which was not removed. Only 4 patients remained on the ventilator until death. Nine patients in whom MV was withdrawn were discharged to a special-care ward almost directly after cessation of MV therapy. After tracheal extubation, oxygen was not administered systematically.

Twenty-one (35%) of the 60 patients died after withdrawal of MV in combination with VAs, 33 (55%) died after withdrawal of MV alone, and 6 (10%) died after withdrawal of VAs only. Fifty patients died in the ICU, and 10 died after discharge from the ICU to a general ward.

SOFA scores were higher in patients for whom MV and VA support were withdrawn than in patients for whom only MV was withdrawn (24 hours after admission: median 11 vs 8, P = 0.03; 24 hours before death: 11 vs 7, P < 0.01).

Time Until Death After Withdrawal of Life-Sustaining Treatment

Death occurred a median of 30 minutes (interquartile range [IQR], 10–195 minutes) after withdrawal of MV in combination with VAs, as shown in Table 2. When only MV was discontinued, the median time until death was 50 minutes (IQR, 15–530 minutes). In our small series in which only VAs were withdrawn, patients died after a median of 45 minutes (IQR, 20–715 minutes). The differences in time until death among these 3 withdrawal categories were not statistically significant.

Patients who were transferred to the ward after the withdrawal of MV died after a median of 63 hours (IQR, 13–192 hours). The one patient who was transferred to the ward after withdrawal of both VAs and MV died 35 minutes after cessation of both therapies.

Sedatives and Opioids

Table 3 displays the cumulative quantities and dosage distribution of sedatives and opioids in all patients (n = 60) who died after withdrawal of MV and/or VAs for all 3 withdrawal categories and 3 different time periods.
Opioids
Fifty of the 60 patients (83%) who died after withdrawal of therapy received some kind of opioid. Thirty-five patients received fentanyl and 15 patients received morphine. Fentanyl was discontinued in 2 patients 4 hours before death. As a result, 33 patients received fentanyl until death. The median overall dosage for fentanyl was 88 μg/h, and the maximum dosage at any time was 500 μg/h.

Morphine was discontinued during withdrawal in 4 patients; therefore, 11 patients eventually received morphine until death. Six of the patients receiving morphine died on the ward. The median overall morphine dosage was 6 mg/h, and the maximum dosage given at any time was 30 mg/h. The dosages of opioids did not differ statistically among the 3 withdrawal groups at any time point. Furthermore, only 8 patients received a bolus injection of opioids after therapy was withdrawn, as indicated in Table 4.

Sedatives
Forty of the 50 patients (80%) mentioned above received some kind of sedative until death. Nineteen patients received midazolam; it was stopped 4 hours before death in 1 patient. Overall, patients received a median dosage of 6 mg/h. The highest median dosage (8.5 mg/h) was observed in the MV withdrawal group in the last hour before death. The dosages of midazolam did not differ significantly among the 3 withdrawal groups.

Fifteen patients received propofol, and none of these patients was transferred to the ward. In patients receiving propofol, 7 had both MV and VAs withdrawn, 5 had only MV withdrawn, and in the remaining 3 patients, only VAs were withdrawn. Overall, the patients received a median dosage of 90 mg/h; 4 hours before death, they

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**Table 1. Characteristics of 60 Patients Who Died After Withdrawal of Mechanical Ventilation and/or Vasoactive Agents**

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>36 (60%)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>64 (52–73)</td>
<td></td>
</tr>
<tr>
<td>Length of stay in ICU (d)</td>
<td>4 (1–10)</td>
<td></td>
</tr>
<tr>
<td>APACHE II score</td>
<td>30 (25–34)</td>
<td></td>
</tr>
<tr>
<td>SOFA score day 1 ICU</td>
<td>8 (7–11)</td>
<td></td>
</tr>
<tr>
<td>SOFA score day before withdrawal</td>
<td>8 (7–12)</td>
<td></td>
</tr>
<tr>
<td>Primary admission diagnosis ICU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>27 (45%)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>10 (17%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>11 (18%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal/hepatic</td>
<td>9 (15%)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>MV withdrawn</td>
<td>54 (90%)</td>
<td></td>
</tr>
<tr>
<td>Only MV withdrawn</td>
<td>33/54 (61%)</td>
<td></td>
</tr>
<tr>
<td>MV and vasoactive agents withdrawn</td>
<td>21/54 (39%)</td>
<td></td>
</tr>
<tr>
<td>Vasoactive agents withdrawn (no MV)</td>
<td>6 (10%)</td>
<td></td>
</tr>
<tr>
<td>Received opioids until death</td>
<td>50 (83%)</td>
<td></td>
</tr>
<tr>
<td>Received sedatives until death</td>
<td>40 (67%)</td>
<td></td>
</tr>
<tr>
<td>Received neither opioids nor sedatives until death</td>
<td>10 (17%)</td>
<td></td>
</tr>
<tr>
<td>Died in ICU</td>
<td>50 (83%)</td>
<td></td>
</tr>
<tr>
<td>Died on ward</td>
<td>10 (17%)</td>
<td></td>
</tr>
</tbody>
</table>

IQR = interquartile range; MV = mechanical ventilation; APACHE = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment; ICU = intensive care unit.

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**Opioids**
Fifty of the 60 patients (83%) who died after withdrawal of therapy received some kind of opioid. Thirty-five patients received fentanyl and 15 patients received morphine. Fentanyl was discontinued in 2 patients 4 hours before death. As a result, 33 patients received fentanyl until death. The median overall dosage for fentanyl was 88 μg/h, and the maximum dosage at any time was 500 μg/h.

Morphine was discontinued during withdrawal in 4 patients; therefore, 11 patients eventually received morphine until death. Six of the patients receiving morphine died on the ward. The median overall morphine dosage was 6 mg/h, and the maximum dosage given at any time was 30 mg/h. The dosages of opioids did not differ statistically among the 3 withdrawal groups at any time point. Furthermore, only 8 patients received a bolus injection of opioids after therapy was withdrawn, as indicated in Table 4.

**Sedatives**
Forty of the 50 patients (80%) mentioned above received some kind of sedative until death. Nineteen patients received midazolam; it was stopped 4 hours before death in 1 patient. Overall, patients received a median dosage of 6 mg/h. The highest median dosage (8.5 mg/h) was observed in the MV withdrawal group in the last hour before death. The dosages of midazolam did not differ significantly among the 3 withdrawal groups.

Fifteen patients received propofol, and none of these patients was transferred to the ward. In patients receiving propofol, 7 had both MV and VAs withdrawn, 5 had only MV withdrawn, and in the remaining 3 patients, only VAs were withdrawn. Overall, the patients received a median dosage of 90 mg/h; 4 hours before death, they
received 134 mg/h, and 1 hour before death, they received 160 mg/h. Patients in whom only MV was withdrawn received significantly more propofol 4 hours before death and 1 hour before death than the other 2 groups (323 mg/h vs 100 and 71 mg/h, \(P = 0.03\); and 495 mg/h vs 160 and 71 mg/h, \(P = 0.04\), respectively).
In the MV withdrawal group, 34 of 54 patients (63%) received sedatives in the last hours of their lives: 16 (27%) received midazolam (median, 10 mg/h), 12 (22%) propofol (median, 160 mg/h), and 6 (11%) lorazepam (2.0 mg/h). Sedatives were also administered to all patients in whom only VAs were withdrawn; 3 received midazolam, whereas 3 received propofol.

Only 6 patients received lorazepam, and none of these patients was transferred to the ward. The median overall dosage of lorazepam was 1 mg/h, and the maximum median dosage was 1.7 mg/h 1 hour before death. Most patients were sedated by continuous IV syringe pump infusion. After withdrawal of treatment, only 3 patients received bolus injections of a sedative (midazolam was used 3 times, with a median of 5 mg/bolus).

Twenty (33%) of the patients who died after withdrawal of therapy did not receive any sedative.

**DISCUSSION**

In our series, life-sustaining therapy was withdrawn in 13% of all ICU admissions. This is higher than reported in studies from other countries, in which withdrawal of therapy accounts for only 1% to 8% of all ICU admissions.17–20 However, our study results are closer to findings from the Ethicus study7 (9.8%), the report of Vincent et al.21 from Belgium (9%), and the results from the cohort survey in the United Kingdom (UK),9 where a maximum withdrawal percentage of 9.9% was reported. Notably, the UK survey showed a remarkably high level of interhospital difference in the incidence of death as a result of withdrawal of treatment, which varied from 1.7% to 96%.5 Therefore, our results will probably not be representative of Dutch ICUs in general.

The incidence of MV withdrawal with or without VAs in our study was also higher than in other studies, which report that MV withdrawals occur in 4% to 39% of all ICU deaths.17,19,20,22 In our study, only 7% of patients died after withdrawal of only VAs, which is lower than reported in other studies, in which 9% to 59% of patients died after withdrawal of VAs.17–19,22,23 These differences may be explained by the fact that, in contrast to what is reported by Keenan et al.,24 we did not use a fixed order for withdrawing the different elements of supportive therapy. As can be derived from Table 2, VAs and MV are often withdrawn together. In addition to this, there is generally only a small group of incurably ill patients in the ICU who are VA dependent but not MV dependent. These facts together explain our low incidence of VA withdrawal alone.

Some readers will conclude that our high percentage of withdrawal is not attributable to the severity of disease but rather that withdrawing life-sustaining therapy might be more accepted in the Netherlands than in the UK and some other Northern European countries.7 Another, more likely explanation for these data is the high percentage of acute catastrophic neurological diseases in our series. We hypothesize that ICUs that do not admit patients with severe neurological diseases will probably have lower rates of treatment withdrawal. Only one study has reported a comparably high number of acute neurological patients (51%), resulting in a death percentage due to withdrawal of treatment comparable to that in our study (11%), thus supporting our hypothesis.17 Furthermore, our patients seemed to be more severely ill compared with patients from other studies. In our study, the median APACHE II score was 30, versus 24 or 25 reported by other studies.19,24 It is reasonable to assume that patients with high APACHE scores would be less likely to respond to therapy; as a logical result, treatment was withdrawn more often in our group.

The decision to withdraw treatment in our ICU is always made by the medical staff and is based on multidisciplinary team discussions. It is not a joint decision by staff and the relatives of the patients, as is mentioned and suggested in other publications.25,26 This approach is supported by Dutch law, which generally places medical professionalism above the rights and wishes of patients or proxies.

No special selection is made for what therapy to withdraw or in which order. We prefer to withdraw all life-sustaining treatment at the same time to demonstrate to the family that the decision is final.

Although the relatives of the patient do not actively participate in the decision-making process itself, they are adequately informed in a timely and comprehensive manner, and special wishes are always taken into consideration. In addition, when desired or necessary, one of our religious advisers is always consulted. The exclusion of the family from the decision-making process is deliberate, to prevent the development of unnecessary guilt, stress, or even posttraumatic stress disorder, as described by Azoulay et al.27 Their study shows that active participation in the decision-making process results in a higher level of guilt and stress, and that the stress level becomes even higher when the family believes that they are not adequately informed. Therefore, we focus on providing adequate information to the family and not on engaging them in the decision-making process.

The short survival time in our study is comparable to the results described by Keenan et al.24 and Chan et al.12 They

### Table 4. Administration of Opioids and Sedatives, by Bolus Injection, in Patients Before and After Withdrawal of Mechanical Ventilation

<table>
<thead>
<tr>
<th>Opioid or Sedative</th>
<th>Median Dose</th>
<th>IQR</th>
<th>Median Dose</th>
<th>IQR</th>
<th>Median Dose</th>
<th>IQR</th>
<th>Median Dose</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fentanyl (µg/h)</strong></td>
<td>100</td>
<td>63–213</td>
<td>100</td>
<td>63–123</td>
<td>175</td>
<td>100–250</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td><strong>Morphine (mg/h)</strong></td>
<td>7.5</td>
<td>5–10</td>
<td>8</td>
<td>5–25</td>
<td>10</td>
<td>5–30</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Midazolam (mg/h)</strong></td>
<td>4</td>
<td>1–9</td>
<td>5</td>
<td>1–10</td>
<td>8</td>
<td>5–10</td>
<td>5–10</td>
<td></td>
</tr>
<tr>
<td><strong>Propofol (mg/h)</strong></td>
<td>80</td>
<td>—</td>
<td>80</td>
<td>—</td>
<td>50</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>Lorazepam (mg/h)</strong></td>
<td>0.3</td>
<td>—</td>
<td>0.3</td>
<td>—</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

IQR = interquartile range; MV = mechanical ventilation.
show, as did our own findings, that most patients who are dependent on any kind of support die within 1 hour of withdrawal of therapy. This indicates that these patients, because of the severity of their diseases, as reflected by high APACHE scores, were highly dependent on these therapies.

Because family satisfaction with the process of withdrawing MV seems to be higher when the patient is tracheally extubated, the endotracheal tube is removed in almost all patients when MV is withdrawn in our ICU, even if this may be associated with shorter survival. Our procedure is different from other studies showing that extubation is the least used procedure in the withdrawal of life-sustaining treatment. It may be the fear of unwanted symptoms, such as acute stridor and death rattle, which keeps many intensive care specialists from implementing this procedure.

Most ICU specialists and fellows in our ICU are aware that opioids are not to be used as a sedative and that the administration of (increasing doses of) opioids does not necessarily hasten death. Fentanyl is avoided for the treatment of breathlessness in cachectic patients or in patients with muscle weakness (e.g., patients with amyotrophic lateral sclerosis). Specific doses of opioids and sedatives are less important than titration to achieve the desired effect. Therefore, no fixed limits are applied to dosages in our ICU. However, doses are preferably not increased without titration or in the absence of demonstrable signs of discomfort or distress. Although the majority of patients did receive opioids until the time of death, the dosages used were lower than those reported by other authors and are, therefore, not outside the boundaries of the clinical practice described by others. However, the differences in the dosages could be explained by multiple other factors, many of which are not addressed in the different studies to which we are referring. For example, the level of pain the patient is expected to experience and the duration of morphine treatment before the decision is made for withdrawal may have influenced the amount of medication needed.

The fact that morphine and fentanyl were discontinued in some cases in our study suggests that our opioid dosages were not increased in the absence of demonstrable signs of discomfort or distress, but were used for comfort care only and certainly not with the intention to hasten death. Although this seems to be a legitimate and logical conclusion, we are, nevertheless, aware of the thin line between initial intention and final result in the process of withdrawing treatment and the treatment of unwanted symptoms, as described by Sprung et al. The observation that some patients in our study who died after withdrawal of therapy did not receive opioids is explained by the high percentage of patients with primary catastrophic cerebral damage, who were deeply comatose and showed no signs of suffering during the process of dying.

Sedatives are used for end-of-life care in our ICU to prevent and treat terminal restlessness and delirium, as well as to increase the overall comfort of the patient during dying. The most often used medications are midazolam and propofol. Lorazepam is a known independent risk factor for delirium; thus, the use of this drug is avoided as much as possible in end-of-life care, or only low doses are used. This is reflected in the small percentage of patients who received lorazepam in our study.

In the ICU setting, propofol is increased before death to quantities appropriate for palliative purposes, when necessary. The sedative doses in this study were not increased outside the boundaries of intentional palliative practice and are lower than those reported by others. The fact that one-third of the patients did not receive any sedative can again be explained by the high percentage of deeply comatose patients with primary catastrophic cerebral damage. Indeed, 16 of the 27 patients who were admitted for acute neurological diseases did not receive continuous sedation.

### Study Limitations

This study has certain limitations that should be considered when interpreting the data. In other international studies, in contrast to this study, no clear distinction is made in the different life-sustaining treatments that are withdrawn. In these series, all life-sustaining treatment was withdrawn in 2.8%, 9.9%, and 10.4% of all ICU admissions, without making any subclassification as to the type of life-sustaining treatment used and withdrawn.

For this study, we used different sources of information. In the ICU, we used electronic patient files. Regrettably, time registration is not always accurate in these files, because the registration of vital signs is sometimes turned off to prevent unwanted alerts, for the sake of respect, when a patient is dying. Therefore, the exact time of death cannot always be found in the electronic medical record. For this reason, some of the recorded times might not have been fully accurate; thus, corrections were made with the help of the paper files. In our study, we only studied patients in one closed-format academic ICU. As a result, our findings may not be applicable to other Dutch (academic) ICUs or ICUs in other countries.

In addition, according to the reports in the patient files, most families seemed satisfied with the quality of communication and the implementation of the procedures, and there was a low incidence of conflicts regarding withdrawal of treatment issues. However, there was unfortunately no standardized and validated method, such as the Family Satisfaction-ICU, available in the Netherlands to measure family and/or nurse/doctor satisfaction in the ICU during the study period. In this study, we did not focus on the possible relationship between individual dosages of opioids and sedatives and the time until death.

Finally, seasonal influences (e.g., the high percentage of severe brain injury due to traffic incidents in the winter) cannot be excluded, because we only gathered information for the period between October and February.

### CONCLUSIONS

MV and/or VAs are withdrawn in the majority of patients who die in the ICU or who die shortly after discharge from the ICU. When these treatments are withdrawn, most patients die within 1 hour, reflecting the severity of the underlying illness, as expressed by the high SOFA and APACHE scores. Eighty percent of patients who died in the ICU after withdrawal of life-sustaining treatment received...
Withdrawing Therapy in a Dutch ICU

opioids, and 67% received sedatives until they died. Fentanyl was the most frequently used opioid, and midazolam was the most frequently used sedative. Opioids and sedatives were used in normal doses up to the optimal titration for relief of symptoms. This study suggests that in our ICU, after withdrawal of MV and VAs, opioids and sedatives are used in generally accepted dosages, which are comparable to the dosages reported in other studies. This is in contrast with what is often suggested about Dutch ICU end-of-life practices. Further qualitative and quantitative research is needed to better describe end-of-life care in Dutch ICUs, thereby facilitating improvements in quality of care in the near future.

ACKNOWLEDGMENTS

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