**Liverpool Care Pathway for patients with cancer in hospital: a cluster randomised trial**

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**Summary**

**Background** The quality of care provided to patients with cancer who are dying in hospital and their families is suboptimum. The UK Liverpool Care Pathway (LCP) for patients who are dying was developed with the aim of transferring the best practice of hospices to hospitals. We therefore assessed the effectiveness of LCP in the Italian context (LCP-I) in improving the quality of end-of-life care for patients with cancer in hospitals and for their family.

**Methods** In this pragmatic cluster randomised trial, 16 Italian general medicine hospital wards were randomly assigned to implement the LCP-I programme or standard health-care practice. For each ward, we identified all patients who died from cancer in the 3 months before randomisation (preintervention) and in the 6 months after the completion of the LCP-I training programme. The primary endpoint was the overall quality of care toolkit score. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT01081899.

**Findings** During the postintervention assessment, data were gathered for 308 patients who died from cancer (147 in LCP-I programme wards and 161 in control wards). 232 (75%) of 308 family members were interviewed, 119 (81%) of 147 with relatives cared for in the LCP-I wards (mean cluster size 14·9 [range eight to 22]) and 113 (70%) of 161 in the control wards (14·1 [eight to 22]). After implementation of the LCP-I programme, no significant difference was noted in the distribution of the overall quality of care toolkit scores between the wards in which the LCP-I programme was implemented and the control wards (score 70·5 of 100 vs 63·0 of 100; cluster-adjusted mean difference 7·6 [95% CI –3·6 to 18·7]; p=0·186).

**Interpretation** The effect of the LCP-I programme in our study is less than the effects noted in earlier phase 2 trials. However, if the programme is implemented well it has the potential to reduce the gap in quality of care between hospices and hospitals. Further research is needed to ascertain what components of the LCP-I programme might be effective and to develop and assess a wider range of approaches to quality improvement in hospital care for people at the end of their lives and for their families.

**Funding** Italian Ministry of Health and Maruzza Lefebvre D'Ovidio Foundation-Onlus.

**Introduction** In most high-income countries, between a third and two-thirds of patients with cancer die in hospitals.1–5 Deaths in institutions are estimated to increase substantially in the next decades.5,6 Best palliative care for dying patients with cancer and their families should be provided in all care settings.7 However, in hospitals, patients with cancer often have unrelieved and poorly treated physical, emotional, and spiritual distress.7 Family members often do not receive the desired support and effective communication before and after the patient’s death.8 Appropriate training in end-of-life care is often lacking for health-care professionals,9,10 although this care is crucial in medicine.11

Globally, an increasing concern is to improve the quality of end of life for patients.11 Several major initiatives and national strategies have been developed and implemented worldwide.12,13 These include complex educational interventions,11,14 and the introduction of advance planning15 and end-of-life care pathways.16,17

The Liverpool Care Pathway (LCP) programme for dying patients18 was developed during the late 1990s at the Royal Liverpool University Hospital with the Marie Curie Hospice Liverpool, Liverpool, UK. It aimed to transfer hospice practices of end-of-life care to hospitals. Results of qualitative studies19,20 and before-and-after non-controlled trials21,22 suggest that the LCP programme could improve the quality of end-of-life care for patients in hospitals. However, the conclusions drawn from the results of two systematic reviews23,24 were that without further evidence recommendations cannot be made for the use of end-of-life pathways for the care of dying patients.

In Italy, about a third of patients with cancer die in hospital.1 According to a national survey, patients dying with cancer had poorly treated or untreated symptoms. A third of family members expressed dissatisfaction with the quality of end-of-life care, and few received basic information about treatments and the process of care.25 This poor quality of care in Italian hospitals draws attention to the need for interventions to improve care. We translated and adapted the LCP programme to the Italian context (LCP-I), and piloted and assessed it in a phase 1/2 study.26,27,28 We designed a cluster randomised controlled study 23,24,29 involving 308 patients (147 in LCP-I programme wards and 161 in control wards). 232 (75%) of 308 family members were interviewed, 119 (81%) of 147 with relatives cared for in the LCP-I wards (mean cluster size 14·9 [range eight to 22]) and 113 (70%) of 161 in the control wards (14·1 [eight to 22]). After implementation of the LCP-I programme, no significant difference was noted in the distribution of the overall quality of care toolkit scores between the wards in which the LCP-I programme was implemented and the control wards (score 70·5 of 100 vs 63·0 of 100; cluster-adjusted mean difference 7·6 [95% CI –3·6 to 18·7]; p=0·186).

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trial to assess the effectiveness of the LCP-I programme in improving the quality of end-of-life care provided to patients with cancer dying in hospital wards. We tested the hypothesis that outcomes for patients and families could be improved through procedural changes by the introduction of the LCP-I programme.

Methods

Trial design and patients
In this cluster randomised trial, pairs of general medicine hospital wards were stratified by region, matched for assessment period, and randomly assigned to implement the LCP-I programme or to follow standard health-care practice.

The objective of the LCP-I programme was to improve the quality of care for patients dying with cancer, but the targets of the intervention were the ward professionals. The effect of the LCP-I programme was measured on clusters of patients and their families in hospital wards.

The study protocol, published and registered on ClinicalTrials.gov, was approved by the ethics committees of the National Cancer Institute of Genoa, Genoa, Italy (Sept 14, 2009), and all participating hospitals.

The ethical issues of this research have been discussed in detail in the protocol. A bioethicist, and clinicians, among others provided advice about the ethical issues, which were monitored throughout the study. LCP is a quality improvement programme, which has been introduced in many hospitals internationally, with clinical and hospital management approval but not ethical approval—a standard practice for such programmes. However, ethical approval was sought because LCP-I was introduced with research and used to assess the effects of the research. Another important consideration is the assessment of the vulnerable and bereaved family members. Our research interviewers were professionals with experience in supporting bereaved family members, and were trained to listen to their concerns and views in a supportive manner. We established procedures for support provided by the interviewers of bereaved family members, including checking whether the family members wished to stop the interview, and provision of information about local services. These procedures are in accordance with the MORECare guidance.

Inclusion criteria for the wards were at least 25 cancer deaths per year, consent from the hospital management and the head of the ward, and a specialist palliative care team (PCT; from inside or outside the hospital) to implement the LCP-I programme in the ward. To prevent contamination, only one ward per hospital was identified for inclusion in the study.

For each ward, all patients who died in the 3 months before randomisation (preintervention assessment) and in the 6 months after the conclusion of the LCP-I programme were identified. Patients who died from cancer (International Classification of Diseases, Ninth Revision: 140-0 to 239-9) were eligible for inclusion in the assessment. Those who were relatives of a doctor or a nurse working in the hospital were excluded.

Information about the patient, closest family member during the last week of the patient’s life in hospital, and the general practitioner was obtained for all cancer deaths. 2 months after the patient’s death, the regional coordinator sent a letter to the identified family member to introduce the study. A subsequent telephone contact was made to ascertain agreement for participation.

15 general hospitals and one university hospital were identified. All PCTs were part of the inpatient units, with the remit of consultation in hospital wards (not necessarily the hospital they were matched to for the study). PCT physicians and nurses were formally trained in and dedicated to full-time palliative care. All the teams were trained to use LCP-I in the 6 months before the start of the trial although they had already introduced the pathway in their inpatient units.

Randomisation and masking

Between Nov 23, 2009, and Dec 28, 2010, eight pairs of general medicine hospital wards from five Italian regions were identified as being eligible and having a specialist PCT that agreed to participate in the study. Randomisation was centralised at the trial centre of the National Cancer Research Institute of Genoa, which verified the eligibility and recorded details of each pair of wards and matched PCTs, assigned a numerical code for identification, and recorded the allocation.

Due to the nature of the intervention, the hospital staff, PCTs, and interviewers could not be masked to the allocation status. Family members were informed about the general aim of the study but not of the group assignment.

Panel 1 shows the details of the LCP-I programme. The LCP clinical documentation (version 11 for hospitals) was translated into Italian in compliance with the original format. A manual for support of the procedures of implementation by a PCT was developed for the study. Two leaflets, addressed to relatives or family members, were provided after the patient’s death. One provided practical information about local services and the other provided information about common emotional reactions after bereavement and local contacts for support.

The LCP-I programme is articulated in ten steps, each with specific goals (panel 1). The implementation commenced with the PCTs providing an intensive 12 h training phase for all ward physicians and nurses, with focus on care of the dying individual and on the procedures for the LCP-I documentation (step 4). Afterwards, the ward staff, closely supported by the PCT, started using the LCP-I clinical documentation for all identified patients who were dying (steps 5–8). The PCT supported and supervised the implementation process through repeated coaching, telephone and direct guidance, and clinical audits with discussion of clinical cases.
Assessment
Outcomes and processes of care were assessed in the 6 months after the end of the implementation of the LCP-I programme. Outcomes were assessed during face-to-face interviews of family members 2–4 months after the patient’s death. A longer interval (up to 1 year) and a telephone interview were allowed only as a second choice. The random assignment of the interviewers to

Panel 1: LCP-I programme steps and goals

Development of the implementation project
Step 1: Establishment of the project and preparation of the environment
• Identify and describe the characteristics of the ward
• Identify and describe the characteristics of the PCT
• Obtain consent from hospital management and the head of the ward
• Present the general outlines of the LCP-I programme to the ward staff
• Outline the LCP-I programme on the ward
• Begin the approval procedure for the training programme
• Register the project at the national centre for LCP-I

Step 2: Development of the documentation
• Acquire educational materials for training
• Prepare the necessary documentation for the ward

Step 3: Base review—retrospective evaluation of variances
• Review the medical documentation of the patients who died in the ward
• Investigate the variances with the ward staff

Implementation of the LCP-I programme (6·0 months)
Step 4: Intensive education programme (≤1 month)
• Undertake three modules of 4 h (total 12 h), repeated twice to allow the participation of all clinical ward staff (doctors and nurses)

Step 5: Clinical implementation of the LCP-I documentation
Intensive support to the ward staff (1·5 months)
• The ward staff, closely supported by the PCT team, oversee the implementation process, and start using the LCP-I documentation for patients who are dying

Step 6: Semi-intensive support to the ward staff (1·5 months)
• Ward staff, accompanied by the PCT team overseeing the implementation process, learn to use the LCP-I documentation as a standard procedure for patients who are dying; clinical audits are planned for difficult cases

Step 7: Assessment and further training (at the end of the fourth month)
• PCT team assesses the outcome of the preliminary steps with the aim of developing an appropriate training strategy for the ward staff during the subsequent stages of the implementation process

Step 8: Consolidation phase (2·0 months)
• LCP-I documentation is established in the ward as an indicator of the quality of end-of-life care for all patients who are dying; the PCT team support the ward staff using the most suitable means for consolidation of the changes introduced by the LCP-I programme

Sustainability of high standards of quality of end-of-life care
Step 9: Initiation of a strategy for sustainability
• The LCP-I programme is established as a routine procedure on the ward and in the hospital
• Develop an end-of-life care strategy for the ward

Step 10: Regional and national strategy
• Use the outcome of the trial study to stimulate discussions at regional and national levels about issues linked to the quality of end-of-life care

LCP-I=Italian version of Liverpool Care Pathway. PCT=palliative care team.

Figure 1: Flow chart of preintervention phase
Cluster sizes are provided as mean (range).

16 eligible hospital wards identified

608 patients died during the 3 months before randomisation

460 not cancer deaths
3 relatives of health-care professionals

145 died from cancer (9.1 per cluster [3–23])

111 family members interviewed
(6.9 per cluster [2–18])
23 refusals
9 not found
2 others

129 general practitioners interviewed
(8.1 per cluster [2–22])
14 not found
2 others

143 procedure (medication) information obtained
(8.9 per cluster [3–22])
2 procedure (medication) information not obtained
the family members for each pair of wards was successful for six hospitals in the preintervention assessment and for 12 in the postintervention assessment.

The interview included questions from the toolkit after-death bereaved family member interview,13,14 and the Italian version of the view of informal carers-evaluation of services.15 At the end of the interview, the interviewer assessed the quality of the information (three items) and the emotional effect of the interview on the family member (one item) by responding to four questions that were answered on a five-point Likert scale.

The toolkit was developed and validated to measure the quality of care at the end-of-life from the perspective of family members.13 The interview contains 33 open-ended questions (and one filter question) focused on the patient’s last week of life in the ward or, for shorter duration, the time spent in the ward. According to the original manual,38 toolkit items can be grouped into seven scales: informing and making decisions (eight items); advance care planning (three items after a filter question); respect, dignity, and kindness (six items); family emotional support (three items); coordination of care (three items); family self-efficacy (three items); and the overall rating of patient-focused, family-centred care (six items). The scores of each scale were calculated on a range of 0 (worst) to 100 (best end-of-life care).

The view of informal carers-evaluation of services consists of questions about pain, breathlessness, and nausea or vomiting. For each symptom, the interview allows the estimation of the proportion of patients with an overall control of that symptom.

The general practitioners were interviewed by telephone after the patient’s death about the information they received (or not) from hospital staff about the dying phase of the patient (first question) and his or her death (second question).

For each eligible patient, information about the care procedures and medications administered during the patient’s last 2 days of life in the ward was gathered with an assessment questionnaire previously used in the phase 2 study.17 Medications were judged as being potentially appropriate (information aggregated in six classes) and potentially inappropriate (ten classes) according to the results of the phase 2 study.17 Other indicators were the mean number of drugs administered per day and the percentage of drugs only given subcutaneously during the last 2 days of life.

**Statistical analysis**

The primary endpoint was the mean score on the toolkit scale overall rating of patient-focused, family-centred care.38 Secondary endpoints were informing and making decisions; advance care planning; respect, dignity, and kindness; family emotional support; coordination of care; family self-efficacy; overall control of pain; overall control of breathlessness; overall control of nausea or vomiting; and indicators related to the processes of care: potentially appropriate medications, potentially inappropriate medications, mean number of drugs administered per day, and the percentage of drugs only given subcutaneously. Analyses were by intention to treat.

The sample size was estimated to quantify the effectiveness of the LCP-I programme, with a 0.05 and power 80%, assuming an intraclass correlation coefficient of the primary endpoint ranging from 0.01 to 0.1 and a mean cluster size of about 20. We estimated that 20 hospital wards (400 patients) would be sufficient to detect an absolute increase of at least 10 points on the global scale of the toolkit.

In accordance with the predefined statistical analysis plan,27 primary and secondary endpoints were analysed with a generalised hierarchical linear model that accounted for the cluster study design (ie, patients nested within hospitals),28 adjusted for regions and the mean of the endpoints at the preintervention assessment.
An additional per-protocol analysis was done by exclusion of the only centre that partly implemented the intervention.

Results were expressed as estimated means, proportions, or incidences for hierarchical linear, logistic, and Poisson models, respectively. Comparisons were reported in terms of mean differences, odds ratios (ORs), and incidence rate ratios with their 95% CIs. Survival was estimated from the first day in the ward until the day of death.

The probability of the carers refusing to be interviewed was estimated with a multivariable logistic regression analysis fitted to the data of the postintervention sample. Regions, all the characteristics of the patients and the family members, and the medications administered during the last 2 days of life were included as independent variables and removed in the final model with a step-down procedure (for p<0·10).

All the cluster-adjusted analyses were done with the SAS (version 9.1).

To interpret the magnitude of the effects, we estimated effect size indices for the seven toolkit scales using the cluster-adjusted mean differences. This study is registered with ClinicalTrials.gov, as NCT01081899.

Role of the funding source

The sponsors of the study had no role in the design, data gathering, analysis, and interpretation, and writing of the report. The corresponding author had full access to all data in the study and had final responsibility to submit the report for publication.

Results

16 hospital wards, different from those in the phase 2 study,27 met the inclusion criteria for the current study. At the time of randomisation, in seven wards (four intervention and three control), a PCT from outside the hospital provided consultations. In one intervention ward, consultations were provided by a PCT from inside the hospital. 145 (24%) patients who died from cancer (total 608 deaths from all causes) were identified in the preintervention period, and 111 (77%) family members were interviewed (figure 1). The mean number of patients assessed in the cluster was 6·9 (figure 1).

The implementation of the LCP-I programme started after randomisation (median 3 months, range 1–5) when the PCTs completed the required preliminary procedures (steps 1–3; panel 1). All PCTs had the training programme in the eight intervention hospital wards (step 4; panel 1). All PCTs had the training programme in the eight intervention hospital wards (step 4; panel 1). All PCTs had the training programme in the eight intervention hospital wards (step 4; panel 1). All PCTs had the training programme in the eight intervention hospital wards (step 4; panel 1). All PCTs had the training programme in the eight intervention hospital wards (step 4; panel 1). All PCTs had the training programme in the eight intervention hospital wards (step 4; panel 1). All PCTs had the training programme in the eight intervention hospital wards (step 4; panel 1).

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Table 1: Characteristics of patients and their family members

<table>
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<tr>
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<th>All patients (n=161)</th>
<th>Control wards (n=113)</th>
<th>Patients assessed with interview of family members (n=119)</th>
<th>LCP-I wards (n=147)</th>
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<td>≤5</td>
<td>64·118 (54%)</td>
<td>69·118 (58%)</td>
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<td>6–8</td>
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<td>&gt;8</td>
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<tr>
<td>Education (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>15·119 (13%)</td>
<td>11·112 (10%)</td>
<td>15·118 (13%)</td>
<td>11·112 (10%)</td>
<td></td>
</tr>
<tr>
<td>6–8</td>
<td>36·119 (30%)</td>
<td>40·112 (36%)</td>
<td>35·118 (30%)</td>
<td>40·112 (36%)</td>
<td></td>
</tr>
<tr>
<td>&gt;8</td>
<td>68·119 (57%)</td>
<td>61·112 (54%)</td>
<td>68·118 (58%)</td>
<td>61·112 (54%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>28</td>
<td>49</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Data are n/N (%), median (range), or mean (SD). LCP-I=Italian version of Liverpool Care Pathway.
In the 6 months postintervention assessment, 147 (27% of 536 deaths from all causes) patients who died from cancer were identified in the intervention wards and 161 (22% of 721 deaths from all causes) in the control wards (figure 2). The characteristics of patients and family members were similar in both groups (table 1).

232 (75%) of 308 family members were interviewed (figure 2) at a median of 107 days (range 29–231) after death. A smaller proportion of family members responded in the control wards than in the intervention wards (70% vs 81%), and a higher proportion refused to be interviewed in the control wards than in the intervention wards (25% vs 16%; p=0.090; table 2). Similarly, a lower proportion of face-to-face interviews were done in the control wards than in the intervention wards (69% vs 78%; p=0.115; table 2). The mean cluster size assessed in the two groups was similar (14±9 patients [8–22] in the intervention ward and 14±1 [8–22] in the control ward).

In the multivariable logistic regression analysis, the probability of interview refusals was associated with the administration of morphine (32 of 119 patients in the subgroup that did not receive the drug vs 31 of 173 in the subgroup that did; p=0.002) and midazolam (55 of 270 patients in the subgroup that did not receive the drug vs eight of 22 in the subgroup that did; p=0.016). We noted a higher probability of refusals when the interviewee was the patient’s relative (p=0.020). Heterogeneity between the five regions was significant (p=0.015).

Other characteristics of the interviews (time from death, setting, and duration) were similar for the intervention and control wards (table 2). The interview did not distress, or only slightly distressed, 206 (90%) of 230 family members, with similar distribution in both groups (table 2). Overall, 260 (84%) of 308 general practitioners were interviewed, with similar proportions in both groups (table 2). Information about the procedures of care were obtained for 304 (99%) of 308 patients in both groups (table 2).

We did not note any difference in the primary outcome overall rating of patient focused, family-centred care...
toolkit scale between groups, with or without the pre-
diagnosis treatment adjustment (table 3). The results of the per-
protocol analysis, excluding the centre that only partly
implemented the LCP-I programme, also showed no significant effect with wide 95% CIs (mean difference
8·0; 95% CI –4·2 to 20·2; p=0·201).

A difference was noted for the secondary outcome
respect, dignity, and kindness scale between the inter-
vention and control wards (table 3). Only 48 (21%) of
227 family members (23 [20%] of 117 in the LCP-I wards
and 25 [23%] of 110 in the control wards, p=0·781) reported that the patients had wishes or plans about the preferred types of medical treatment at the end of their
life, making the estimation of the advance care planning

Table 4: Cluster-adjusted view of informal carers-evaluation of services symptom scales in the postintervention assessment

<table>
<thead>
<tr>
<th></th>
<th>LCP-I wards (n=159)</th>
<th>Control wards (n=113)</th>
<th>Comparison (preintervention adjusted)</th>
<th>Comparison (not preintervention adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Odds ratio (95% CI)</td>
<td>p value ICC</td>
</tr>
<tr>
<td>Overall control of pain</td>
<td>100 (70·7%)</td>
<td>89 (65·0%)</td>
<td>1·3 (0·7–2·6)</td>
<td>0·461 &lt;0·01</td>
</tr>
<tr>
<td>Overall control of breathlessness</td>
<td>108 (54·4%)</td>
<td>97 (86·9%)</td>
<td>2·0 (1·1–3·8)</td>
<td>0·026 &lt;0·01</td>
</tr>
<tr>
<td>Overall control of nausea or vomiting</td>
<td>102 (83·9%)</td>
<td>91 (77·2%)</td>
<td>1·5 (0·7–3·2)</td>
<td>0·252 &lt;0·01</td>
</tr>
</tbody>
</table>

LCP-I=Italian version of Liverpool Care Pathway. ICC=intraclass correlation coefficient. All estimates (percentages and odds ratios [95% CI]) are cluster adjusted.

Table 5: Cluster-adjusted estimates of medications administered in the last 2 days of life of the patient in the postintervention assessment

<table>
<thead>
<tr>
<th></th>
<th>LCP-I wards (n=145)</th>
<th>Control wards (n=159)</th>
<th>Comparison (preintervention adjusted)</th>
<th>Comparison (not preintervention adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Odds ratio (95% CI)</td>
<td>p value ICC</td>
</tr>
</tbody>
</table>
| Potentially appropriate medications

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>0·82%</td>
<td>65·5%</td>
<td>2·5 (1·0–6·3)</td>
</tr>
<tr>
<td>Morphine</td>
<td>0·73%</td>
<td>49·8%</td>
<td>2·9 (0·9–8·8)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>1·3%</td>
<td>1·0%</td>
<td>1·1 (0·4–2·8)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>19·0%</td>
<td>8·5%</td>
<td>2·5 (0·6–11·9)</td>
</tr>
<tr>
<td>For pulmonary secretions</td>
<td>26·0%</td>
<td>2·5%</td>
<td>1·3 (1·3–51·4)</td>
</tr>
<tr>
<td>For nausea or vomiting</td>
<td>21·4%</td>
<td>15·4%</td>
<td>1·5 (0·6–3·6)</td>
</tr>
</tbody>
</table>

Data are percentages or means per day (SE), unless otherwise indicated. All estimates (percentages and odds ratios [95% CI]) are cluster adjusted. LCP-I=Italian version of Liverpool Care Pathway. ICC=intraclass correlation coefficient. *Percentage of last 2 days of life the patient was given drugs subcutaneously only.
time in the intervention wards than in the control wards (table 5).

There were no differences in the proportion of patients for whom general practitioners reported they were informed about by ward professionals of the patient’s terminal illness (OR 2.67, 95% CI 0.34–21.1; p=0.353) or death (1.95, 0.33–11.7; p=0.463).

Table 1 shows that the survival time for patients in wards in which the LCP-I programme was implemented (median 8 days) was not different from that for patients in the control wards (7 days; p=0.429; table 1).

Discussion
The results of this pragmatic cluster trial do not show a significant difference in the overall quality of care toolkit scores (the primary endpoint) between the wards in which the LCP-I programme was implemented and the control wards. Of the nine secondary outcomes reported by family members, two showed improvements—respect, dignity and kindness, and control of breathlessness. We noted few differences in the medications that were prescribed and no differences in the period of survival after admission. The study was underpowered; we enrolled 80% of the planned hospitals and slightly overestimated the expected number of cancer deaths.

To the best of our knowledge, this study is the first randomised trial to test the effectiveness of the LCP programme for the improvement of the quality of care for patients with cancer who are dying in hospital (panel 2). With the exception of our phase 2 trial, the effect of LCP implementation in hospital with the views of bereaved relatives was only assessed in a before-and-after Dutch study. In our phase 2 study, we noted a significant improvement in four toolkit scales—respect, dignity and kindness, family emotional support, family self-efficacy, and coordination of care—with effect sizes ranging from 0.35 to 0.77. In this randomised trial, we noted smaller effects and no significant differences in the scales for the support provided to the family. A significant reduction was reported in symptom burden after LCP implementation in the Dutch study, but no significant difference was noted in the quality of communication with family members.

In this trial, a significant improvement in the intervention wards was noted with the scale for assessment of whether the dying person was treated with respect, dignity, and kindness, which explores a dimension of care largely provided by the nurses. The result is for a secondary outcome, and so should be treated cautiously. However, it is in agreement with the qualitative reports of the effect of the end-of-life care pathways.

Control of breathlessness (secondary outcome) was better in the intervention wards. Breathlessness is a particularly difficult symptom to alleviate. A higher proportion of patients received drugs for pulmonary secretions in the LCP-I wards than in the control wards. It is possible that some family members noted a difference in symptoms due to pulmonary secretions, which can present as breathlessness. Conversely, there was no significant improvement in the control of pain and nausea or vomiting.

Although the results of this trial should be interpreted with caution, consideration of the gap between the quality of inpatient hospice and hospital care might be important for the interpretation of the results. According to the results of a national survey of 18000 bereaved relatives in the UK in 2011, a higher proportion of inpatient hospices were reported as outstanding or excellent than were hospitals (59% vs 32%). Data from an Italian study showed that bereaved relatives rated hospices with a mean score of 90 of 100 for quality of care with Teno and.
colleagues’ scales (table 6).

These hospice data cannot be thought of as normative and our findings should be considered cautiously, although they were gathered by the same research team in a sample of Italian hospices using the same procedures of assessment. According to these data, the LCP-I programme seems to reduce the gap in the overall quality of care between hospices (rated as 90 of 100) and hospitals (rated as 63 of 100) by up to 27·5% (table 6). The gap might be reduced by between 22% and 40% for most toolkit scales. The improvement might be important, taking into account the concerns about the quality of care received by patients with cancer in hospital and the increasing demand for a positive change.3,4 However, the magnitude of the change is far from bridging the gap. The process of change is difficult to manage and hospital staff, even trained in and supported by LCP-I, are unlikely to achieve the excellence of specialised PCT in hospices. Our findings suggest an important continuing role for inpatient hospices and specialist palliative care units, in which the total culture of care (environment, staffing, procedures, and philosophy) differs from that in hospitals. The independent review of LCP recognised the role of PCTs and recommended an extension of their availability in hospitals at any time, 7 days a week, and drew attention to good-practice hospice wards within hospitals.44

Any end-of-life care pathway is a complex intervention and as such includes many components that can enhance or reduce its potential effects.43 By contrast with the UK version, the Italian version of the LCP did not use dedicated facilitators to introduce the pathway. Instead, the process of LCP-I implementation was led by a specialist PCT trained in the use of the programme. Moreover, we required 12 h of training for all nurses and physicians in the ward from the PCT before starting the clinical documentation of the use of the LCP-I programme. Although this process was complex and time consuming, it was developed to ensure the correct interpretation of the LCP-I programme.

We noticed wide variability in the implementation process between the eight hospitals. All complex interventions are prone to variability while they are introduced into complex systems. The low reliability of the programme implementation should be analysed in detail. Reasons for the low adherence by physicians need investigation. Palliative care in Italy is not part of the undergraduate medical training. Perhaps physicians do not perceive providing appropriate care to the dying patients as a professional duty. McConnell and colleagues46 reported that the ten recommended steps in the implementation process are not sufficient to ensure successful implementation and sustainability of the LCP-I programme. The new MORECare statement,49 providing guidance for the assessment of complex interventions in end-of-life care could help future research.49

Patients were cared for with the LCP-I programme for a median of 31·5 h, similar to the 27 h in the National Care of Dying Audit—Hospitals in the UK in 2011.46 This period is too short to control symptoms, ensure good communication, and support families. To achieve the best in communication and symptom control, earlier palliative care might be needed.

There are at least seven methodological and logistic limitations that should be considered when interpreting the results of our study. First, as for most quality improvement interventions, the LCP programme could not be masked to ward professionals. Masking the interviewers to group assignment was possible in theory,50 but, in this trial, was workable in practice.

Second, a major bias might result from the different response rates and types of outcome assessment between LCP-I and control wards. There was a higher proportion of refusals by family members and, to a lesser extent, telephone interviews in the control wards. We cannot exclude the possibility that families who witnessed more distressing deaths were more likely to refuse participation in interviews, resulting in an underestimation of the true effect of LCP-I in our study, but we do not have data to support this hypothesis. The inability to make reasonable assumptions about non-interviewed individuals made any sensitivity analyses challenging, and precluded full intention-to-treat analyses of the data.

Third, the LCP-I programme was assessed in an unselected series of patients. Sudden deaths occur in a small proportion of patients with cancer admitted to hospital wards, and the dying phase should be more easily recognised when the patient has a progressive deterioration in physical functioning as a result of the cancer.51 Limitation of the eligibility for assessment to the subgroup of patients with a recognised dying phase was not feasible and the only choice was to analyse all cancer deaths.

Fourth, the specificity of the Italian LCP reduces the external validity of the results. In Italy, the practice of appropriate communication at the end of life with the

<table>
<thead>
<tr>
<th>Hospital control wards (n=8)*</th>
<th>Hospital LCP-I wards (n=8)*</th>
<th>Hospice†</th>
<th>Hospital-hospice differences bridged by the LCP-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall quality of care</td>
<td>63·0 (4·1)</td>
<td>70·5 (3·9)</td>
<td>90·3 (1·6)</td>
</tr>
<tr>
<td>Informing and making decisions</td>
<td>64·3 (3·8)</td>
<td>73·5 (3·0)</td>
<td>87·4 (2·0)</td>
</tr>
<tr>
<td>Advance care planning</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Respect, dignity, and kindness</td>
<td>70·4 (2·2)</td>
<td>78·8 (2·9)</td>
<td>95·8 (1·2)</td>
</tr>
<tr>
<td>Family emotional support</td>
<td>38·6 (4·7)</td>
<td>46·6 (4·3)</td>
<td>75·7 (5·9)</td>
</tr>
<tr>
<td>Coordination of care</td>
<td>76·8 (3·3)</td>
<td>81·4 (3·0)</td>
<td>90·3 (1·7)</td>
</tr>
<tr>
<td>Family self-efficacy</td>
<td>44·4 (3·9)</td>
<td>48·9 (2·9)</td>
<td>56·2 (3·6)</td>
</tr>
</tbody>
</table>

Data are cluster-adjusted mean (SE), unless otherwise indicated. LCP-I=Italian version of the Liverpool Care Pathway. NE=not estimable. *Data adjusted for cluster and preintervention. †Data estimated from the preintervention samples of a before-and-after phase 2 cluster trial for the assessment of the effect of the LCP-I programme in five hospices in Liguria, Italy; the assessment was done with the same eligibility criteria and the same procedures used in this cluster trial. Between January and April, 2011, 127 cancer deaths were identified in the five hospices during the 2 months before the implementation of the LCP-I programme, and 95 (75%) family members were interviewed with the toolkit.

Table 6: Estimated differences in toolkit scales between hospital and hospice bridged by the LCP-I implementation in hospital wards
patients and the family members has been reported to be poor.\textsuperscript{23,24} It is possible that in this context the programme could have worked less well than in other countries. However, perhaps greater effects were noted because greater improvement is needed.

Fifth, the study was underpowered and therefore might be prone to a type 2 error. This problem is common in assessments of quality improvement in hospitals. In a recent review, only one randomised controlled trial of quality improvement in health care was identified.\textsuperscript{25}

Sixth, theoretically, knowledge and use of the pathway—either through existing knowledge and practice, or through the more usual contamination problem of picking this up during the study could have reduced the estimated treatment effects. However, such contamination is unlikely, because we allowed only one ward per hospital and the LCP-I was not introduced in any Italian hospital before the initiation of the study.

Last, these results are for patients with cancer. LCP-I is often used for other patients who are dying from other diseases. The strategy of assessment of the LCP-I programme in Italy was specific for disease and setting. Trials are needed to test ways to improve care for patients without cancer.

In conclusion, the results of our trial show that the effects of the LCP-I programme were smaller than those of the earlier phase 2 studies.\textsuperscript{26,27} We did not note any negative effects. The LCP-I programme seemed not as good as that provided by specialised PCTs.

In the UK, there have been concerns about the use of the LCP programme, especially for patients with illnesses other than cancer. As a result the UK Government established an independent review.\textsuperscript{28} The conclusion of this review was that when operated with well trained and resourced clinical teams the LCP programme works well. However, repeated instances of poor practice were also reported, with the LCP programme used as a box-tick exercise with a lack of discussion about appropriate treatment and respect for patients and families. The review recommends phasing out LCP, raises concerns about the term pathway, and proposes an increase in individual end-of-life-care plans. Any future strategy for improvement should take into account what we have learned about the LCP programme, from the results of this and other studies. We still need to know what components of quality improvement programmes work best, for whom and in what circumstances, and how to sustain improved practice and ensure consistency. The poor quality of care in hospitals remains a concern and shows that there is an urgent need to develop and assess the outcomes of a wide range of interventions to improve palliative and end-of-life care, taking into account the role of education, cultural change of the environment, professional attitudes, and support and leadership from palliative-care specialists and senior medical and nursing staff.

Contributors
MC, SDL, MB, and FP contributed to the study design. All authors discussed, critically revised, and approved the final study protocol. MC, VR, SDL, MB, and LB were responsible for organisation and conduct of the trial at the central level and VR, LB, PP, GM, DV, CP, FB, CF, SG, CB, and CM in the five regions of Italy. MC and VR undertook data management. FP, MC, VR, and IJH were responsible for the analyses. All authors discussed and approved the final strategy for analysis. MC, VR, FP, and IJH drafted the first version of the report. All authors discussed, critically revised, and approved the final version of the report for publication.

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Conflicts of interest
We declare that we have no conflicts of interest.

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Lessons from the Liverpool Care Pathway—evidence is key

Across health care there is a need to improve care for people who are dying, which has led to widespread uptake of the Liverpool Care Pathway (LCP) before adequate assessment. The effect of poor assessment was worsened when LCP was taken up by bureaucrats who did not understand the implications of widespread implementation of an initiative for which the net effects were poorly defined.1 2

LCP was taken up in emergency rooms,3 nursing homes,4 and inpatient units, including intensive care.5 Not every patient whose care was guided by LCP had necessarily been reviewed by a senior clinician to establish whether their illness was terminal. Implementation of LCP became a matter of pattern recognition, and could be applied in clinical scenarios where such patterns had differential diagnoses ranging from reversible to irreversible causes; at times, junior staff were asked to make these assessments.1

In The Lancet, Massimo Costantini and colleagues describe a rigorous assessment of the effects of LCP on patients and are to be commended for doing such an important study.6 In a multicentre cluster randomised trial comprising 308 patients with cancer and their families, carried out in Italian hospitals, there was no significant difference noted between patients who died in wards in which LCP had been implemented as compared with those in which it had not, as judged by the trial’s primary endpoint, the overall quality of care toolkit scores (70·5 vs 63·0 on a scale of 100, cluster-adjusted mean difference 7·6, 95% CI –3·6 to 18·7). Such studies are feasible, ethically necessary, and a crucial step in bridging clinical guidelines and widely implemented health-care policy. Guidance from the UK’s Medical Research Council for the assessment of complex interventions provides a clear framework for such research.7 This work is hard to do and data are often missing, but that does not reduce its importance or the necessity to deal with such limitations.

The results of Costantini and colleagues’ study did not show the benefits anticipated based on the results of less rigorous reports.8 There are a myriad potential explanations, including poorly chosen endpoints, and substantial differences between the Italian health system and that in the UK, where LCP was developed; it might be that the quality of care for people who are dying in Italy is much better than in other countries, reducing the opportunity to show benefit. A more likely conclusion is that the benefits generated by the systematic implementation of the pathway are, at best, slight. In view of the little or no clinical benefit compared with standard care, any harms to individuals exposed to LCP, including premature death, are unacceptable.

The study by Costantini and colleagues was done properly, with careful training of participating clinicians. It was not done in the emergency department but rather in hospital wards, where people had been adequately assessed both in the emergency department and during their subsequent clinical care. These features might also explain why the perceived harms reported in other places where LCP has been implemented2 were not reported in this study.

Every new intervention needs to be critically assessed for its benefits and harms. Often, as clinicians and policy makers, we focus on the perceived benefits without remembering to measure the harms to define the net effect. There is a special need to focus on any perverse incentives that might result from policy change, as has been suggested in the popular press and peer-reviewed literature.9 10 In much of the literature in which the evidence is addressed for the purpose of informing policy, the assumption is that good evidence is not being translated into policy.11 By contrast, when there is an absolute lack of evidence, policy makers have widely introduced a new method without adequate assessment.

There are important lessons to be learned from this process. Increasingly, clinicians are asked to justify their
practice against the best available evidence. By contrast, generally, policy makers are not. Any intervention is going to have drawbacks—not if, but when, how many, and of what magnitude, no matter how appealing the intervention. In health policy, a particular risk is that a perverse incentive for a suboptimum outcome is introduced through regulations and reimbursement.

As demonstrated by the results of Costantini and colleagues’ study, a government, when introducing such initiatives, should properly assess them in rigorous trials of health services, preferably randomised; if this cannot be achieved then a formal prospective assessment of new interventions as they are implemented must be the minimum standard. Either assessment should be done in a health-care environment where new interventions are thoughtfully introduced, corresponding data are routinely gathered for the interventions, and analyses inform understanding of the net benefit and opportunities for iterative enhancement—namely, a learning health system framework, as described by the US Institute of Medicine. Such a process could have avoided some of the pitfalls attributed to LCP. Not to put prospective assessment in place has long-term consequences that otherwise could be avoided. Such studies are not only feasible, as shown by Costantini and colleagues, but can be designed, undertaken, and analysed to change practice and policy.

The goal of any national policy initiative is to improve health outcomes. A decade after widespread uptake, which part of government should take responsibility for the widespread policy imperatives informed by the results from studies of LCP: politicians, bureaucrats, clinician advisers, or all three groups? The results of the only adequately powered study of LCP so far have not shown clinically meaningful differences for patients—the ultimate measure of useful health policy. Looking to the future, there is a need for government and other funders to be far more willing to fund research into health services that can inform policy and for many more senior clinicians to contribute to shaping national clinical policies.

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