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Original Article

A Structured Intervention to Support Early Palliative Care Conversations for Oncology Patients – A Qualitative Feasibility Study

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Abstract

Aims: For patients with advanced cancer, early access to palliative care can have numerous psychosocial and disease management benefits. However, it can be difficult for clinicians to initiate these initial conversations about palliative care. The aim of the present study was to beta test an intervention to facilitate timely conversations about palliative care between patients and clinicians.

Materials and methods: The study reported forms one stage of a complex intervention development study following Medical Research Council guidance for developing complex interventions. Feasibility was explored from patient and clinician perspectives in an oncology outpatient setting.

Results: Sixteen patients and 18 clinicians participated. Three phases of the intervention were assessed through patient and clinician interviews. The analysis produced three themes in each phase: (i) Preparation (patient preparedness; healthcare professionals' perspectives on palliative care; administration, data and communication); (ii) STEP consultation (defining perspectives on palliative care; how palliative care fits with the current treatment plan; permission to explore future care); (iii) Outcomes (changes in perspective and approaches to coping; opening the door to future conversations; referrals and involvement of palliative services).

Conclusions: The STEP intervention generated important early conversations about end-of-life care that may otherwise not have occurred. No patients regretted having the STEP consultation, which resulted in palliative care referrals for some. Others felt better informed about the support services available and better able to have further conversations. Participating clinicians found the structured conversation guide useful, as it acted as a prompt for areas to cover, as well as providing an explicit way to open discussion about difficult topics.

Key words: Cancer; end-of-life care; palliative care; psychological care; quality of life; supportive care

Introduction

Palliative care aims to relieve suffering and improve quality of life for patients with advanced illnesses. For patients with advanced cancer, trials show early access to palliative care can improve quality of life, reduce acute hospital admissions, minimise aggressive treatments and enable patients to make choices about end-of-life care [1–3]. The accumulating evidence to support early referral is beginning to influence policy, with recommendations that 'palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden' [4]. The Royal College of Physicians recently recommended that 'conversations about the future can and should be initiated at any point' with patients with chronic/life-limiting illnesses [5] and are aiming to dispel the 'myth' that patients do not want to talk about death.

Despite increasing acknowledgement of the importance of timely palliative care conversations, in practice, referral often does not occur until a patient experiences an acute episode [6–8]. Healthcare professionals (HCPs) have identified barriers to timely referrals, including attempts to delay the termination of active treatment, believing they would be abandoning the patient, lack of expertise dealing with end-of-life issues and difficulty initiating conversations about palliative care [8,9]. Patients have described barriers including misconceptions regarding the solely end-of-life care role of hospices and Macmillan nurses [10], assumptions that palliative care is only for the very end of life

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and an incomplete awareness of the breadth of services provided [7,11].

There are evident misconceptions about palliative care from the patients' perspective and insufficient information provision and resources to support decision making [7,12,13]. Dedicating time to discussing a patient's perception of their health, treatment and prognosis has been shown as a key underlying factor in successful palliative care trials [14] and can enhance understanding and relevance of palliative services [15]. Furthermore, engaging patients in discussions and decision making in this area needs to be an active rather than a passive approach [16]. A recent structured intervention to introduce palliative care earlier in patient pathways showed patients experienced initial distress but found this approach beneficial overall. However, the authors also suggest that little is known about how patients experience these types of intervention [15].

The Serious Illness Care Programme [17] consists of clinical tools, training, support and systems innovations designed to improve the timing and quality of serious illness conversations between patients and clinicians. A randomised controlled trial in the USA showed the feasibility of having these conversations earlier and more frequently within serious illness care, resulting in reduced anxiety and depression, increased rapport with clinicians and better preparation for end of life. Clinicians reported increased conversation self-efficacy and satisfaction, and valued a structured conversation guide to help talk with patients about their goals, values and priorities.

Building on previous phases of intervention development [18,19] and findings of a preliminary qualitative study [7], this paper reports the initial implementation and beta testing of the STEP intervention. The intervention was designed to facilitate early and appropriate conversations about palliative care in an oncology outpatient setting and draws on resources available from the Serious Illness Care Program [17]. Following International Patient Decision Aids Standards guidelines [20], the STEP intervention described in this paper was piloted with patients and their clinicians, and assessed via patient and clinician questionnaires and interviews.

Materials and Methods

Design

Working with a pragmatic epistemology, the study design was informed by the acceptability testing phase of the Medical Research Council framework for developing complex interventions [21]. This paper reports the initial application of the STEP intervention in an oncology outpatient setting of a regional cancer centre. Feasibility and acceptability were assessed through qualitative data gathered using clinician immediate feedback forms and end-of-study interviews with patients and clinicians.

Sample

Participants were recruited from a gastrointestinal oncology clinic in the participating cancer centre over a 6-month period. Patients were eligible if they had an incurable cancer diagnosis, were not involved with palliative care services and were under the care of a participating clinician. Using these criteria, clinicians identified and approached eligible patients in outpatient clinics. Each clinician (Table 1) aimed to identify five patients during recruitment.

The STEP Intervention and Data Collection

The intervention (Figure 1) was a structured conversation guide (see Supplementary Material) designed to facilitate the initial discussion about palliative care and supporting materials for patients and clinicians (see Supplementary Material). The conversation guide was adapted from the Serious Illness Care Programme [17] in consultation with patient advisors and based on previous phases of STEP [7].

Previous findings from STEP [7] showed that patients can feel emotionally and practically unprepared when palliative care is first raised. Therefore we aimed to give patients time and information to prepare for this conversation (see Supplementary Material). Adapted from the Serious Illness Care Programme, clinicians had a handbook with advice about how to approach common difficulties arising from these conversations.

All data collection was conducted by the first author, who is an experienced qualitative researcher. During the week following the STEP consultation, face-to-face semi-structured interviews (see Supplementary Material) were conducted with participants in their own homes. A month later, a second interview was conducted via telephone. Face-to-face interviews were conducted with clinicians over video-conferencing software at the end of the study. All interviews were audio-recorded and transcribed verbatim for analysis.

Analysis

A directed content analysis [22] was used to explore patient and clinician reflections of three pre-defined phases: preparation, consultation and outcomes. The aim was to determine the perspectives of patients and health professionals on the content, process of delivery and engagement with the STEP intervention, and to reflect on any changes in perspective of palliative care, death and dying. Key concepts for each phase were defined by the first author through multiple careful readings of the transcripts and then further developed with the research team and patient

Table 1
Participant details

Patients		Clinicians - consented	
Total	16	Total	18
Gender		Gender	
Male	12	Male	10
Female	4	Female	8
Age group (years)		Role	
55–69	6	Oncologist	8
70–79	3	General practitioner	8
80+	5	Practice nurse	2
Cancer site			
Bowel	8		
Rectal	4		
Oesophageal	3		
Stomach	1		
Marital status			
Married	12		
Cohabiting	2		
Widowed	1		
Single	1		
Education			
Post-16	8		
Degree or equivalent	5		
Ethnicity			
White	16		
Employment status			
Working part-time	12		
Retired	2		
Not working – ill-health	2		

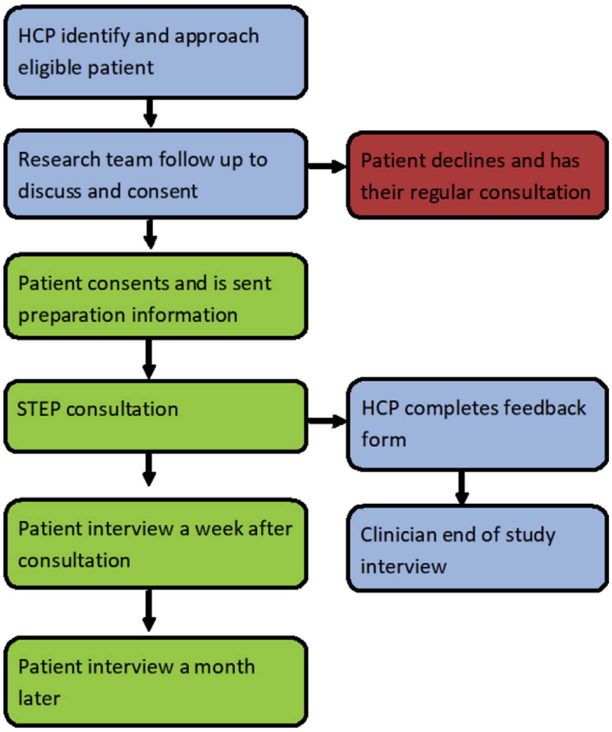

Fig 1. Flowchart of the STEP intervention, recruitment and data collection procedure.

advisors. Second coding of 25% of the transcripts was conducted by the final author. Interview data were managed in the NVIVO 10 software package.

Results

During the allotted 6-month period, 25 patients were approached to participate (Table 1). Sixteen entered the study, six declined and three became ineligible because of changes in their circumstances. Reasons for declining included: pressures on their time and hesitation over discussing palliative care. Eighteen clinical staff members consented to identify and approach potential participants in their clinics. However, 15 of the 16 patients in the final sample were recruited by the oncologists, with the other recruited by a general practitioner.

Three phases of the intervention were assessed through patient and clinician interviews. The analysis produced three themes in each phase.

Phase 1 – Preparation.

- Patient preparedness
- HCPs' perspectives on palliative care
- Administration, data and communication

Phase 2 – STEP consultation.

- Defining perspectives on palliative care
- How palliative care fits with the current treatment plan
- Permission to explore future care

Phase 3 – Outcomes.

- Changes in perspective and approaches to coping
- Opening the door to future conversations
- Referrals and involvement of palliative services

Preparation

Prior to the STEP consultation taking place, patients and HCPs each had pre-existing perspectives on discussing palliative care, which would influence how the consultation proceeded. There were additional administration, data and communication factors, which also complicated the preparation stage of the STEP process.

Patient Preparedness

On entering the study, participants broadly presented four different 'types' of active or passive approach to discussing palliative care and associated issues of death and dying: (i) proactively engaging in all aspects of the conversation, (ii) quickly and actively shutting down these conversations, (iii) taking the lead from those around them, (iv) passively preferring not to think about it.

> *Well they haven't really talked about palliative care much because as I say, I didn't really want to listen to it – Patient 01*

> *We know what we want to happen when we do die and that's it, we're not frightened of mentioning the word death which some people are, we realise that you've got to die at some stage, it's how you die that matters – Patient 09*

> *Well I just listen to what he has to say and I never really have that much to say – Patient 12*

The participant's particular orientation was influenced by how death and dying was discussed at home and their level of prior exposure to the hospice/palliative care experience through those around them. It was further impacted by their perception of their illness, treatment and of the HCPs caring for them. For some participants, their perception of the link between palliative care conversations and 'giving up' was a significant barrier to constructive conversations and planning.

All participants found the STEP preparation document (see Supplementary Material) appropriate and easy to understand, and were glad of forewarning about the conversation. Four participants actively prepared questions for the clinician or researched information about palliative care online. Others discussed the study and palliative care with family/friends, the researcher or other HCPs. Having timely information tailored to the next consultation seemed to help participants, who often mentioned being overwhelmed with information at the start of their treatment.

> *It's easy to take in, it's quick to read, it was understandable, so I found that useful – Patient 08*

Having time to prepare gave participants an opportunity to reflect on their priorities and any specific plans they wanted to discuss with their HCP. Several patients discussed wanting to plan for future care, coping with specific symptoms such as pain and maximising quality of life. Quality of life was often linked to specific events, such as attending a wedding, holiday or birthday.

> *Next March it's our diamond wedding so I want to be reasonably well for that – Patient 09*

Several participants described having increasing numbers of professionals and services involved in their care, and they wanted clarity about who to contact for information or if they experienced specific problems. Others had practical concerns such as finances, funeral plans or home adaptations

> *If I feel bad, but not quite bad enough for an emergency, but think I ought to tell somebody, I'm hoping they may be that point of contact – Patient 08*

HCPs' Perspectives on Palliative Care

To identify which patients to have the STEP consultation with and when might be the best time, HCPs seemed to rely on their individual judgement or a triggering clinical issue, such as increasing pain. The nature of an individual HCP's perspective on palliative care was important because decisions to raise these conversations were often taken unilaterally in the process of outpatient appointments and not as part of a wider team discussion. This could result in patients having variable opportunities to have early discussions about palliative care depending on their individual HCP.

> *Quite often you don't start out a consultation thinking 'oh I'll refer this person to palliative care', but then actually in the process of the assessment, if actually they're more symptomatic than you thought or if they're really struggling or if a member of their family are really struggling ... then you would change your mind so I think [for STEP] it was quite difficult because we had to identify people ahead of seeing them – Clinician 15*

The preparation aspect of the study required HCPs to raise the possibility of discussing palliative care at the patient's next appointment, without elaborating on it at the time. This was essential to facilitate the preparation time, but thought to be more complicated moving forward as part of routine practice.

> *Once you've started it, you then have to elaborate on it ... I don't know, it just seemed a natural thing that you would just carry on with trying to explain a bit more – Clinician 08*

All HCPs in this study endorsed the benefit of early discussions of palliative care, but could still be hesitant to broach the subject with patients until there was an immediate need. HCPs sometimes perceived community palliative services to be under resourced, which could also delay initiating early conversations with patients. The perception of their patient could also affect the timing and approach to raising and discussing palliative care. The STEP study produced examples of HCPs who were surprised by the positive reactions patients had to the consultation.

> *Having a more structured way of at least allowing us to approach the patient and the patient to approach us, is what I wish I had more of an opportunity to do in some respect, because one case I did I was pleasantly surprised at the patient's reaction and how positive that was – Clinician 11*

At the outset of the project, two of the HCPs reported referring to the STEP handbook to consider issues that might be raised and strategies to respond. HCPs knew the patient would be expecting to discuss palliative care issues in the STEP consultation, so some gathered relevant information to have available and/or reviewed this information themselves.

> *It seemed to be a resource that you could dip into and maybe glean some more helpful phrasings to address different issues. But it seemed to be something that you'd have a difficult consultation and then you go away and maybe read that and think oh actually this consultation fits into this part of the booklet – Clinician 12*

Administration, Data and Communication

When discussing the STEP consultation process, all clinicians reflected that they do not have a 'prompt' for considering whether a patient would benefit from an early conversation about palliative care in amongst conversations about treatment and cancer progression. They also discussed having very limited time to prepare clinics in advance, which resulted in decisions to discuss palliative care being made by individual clinicians during busy clinics.

> *The problem is that I don't prep my clinic properly and even when I do it's the day before. I mean if you see somebody coming you quite often don't know their scan result until the day – Clinician 14*

The STEP project highlighted the limited documentation of palliative care conversations in medical records and a disconnection between oncology and primary care. Primary care was unclear from letters and patient notes whether patients had discussed palliative care and what the intention of their treatment was. Conversely, oncologists did not know whether a patient was registered on the Gold Standards Framework (a general practitioner practice register of patients within the practice who have been identified as having palliative care needs) or have a clear understanding of how palliative care services were being delivered in primary care. This disconnection made it possible for patients to miss having relevant conversations and services.

> *I can't remember ever seeing a letter coming out explaining what's being said in these conversations with patients – Clinician 08*

Scheduling suitable appointments with enough forewarning and time for these conversations was an important administration factor. Knowing in advance that a palliative care conversation was scheduled meant longer appointment slots could be booked (the mean STEP appointment time was 47 min). Having longer appointment times allowed patients and clinicians to focus on the conversation, rather than fitting it around other issues. One HCP in particular thought longer dedicated appointments now would save time in the long run.

> *I think down the line it will probably save as much time as it took – Clinician 12*

Patients were also aware of time pressures and covering pressing treatment issues during routine appointments, so a dedicated appointment during STEP appeared to reduce this anxiety. Other HCPs did not think much additional time was needed, especially if a clinical nurse specialist was available in the clinic to have follow-up conversations. Some participants preferred having the full conversation with their doctor, especially if they had a good relationship, but one participant thought palliative care conversations should be someone else's role.

> *I would feel a little bit uneasy about taking an inordinate length of his time talking about something that I don't see as ... his job ... I see the palliative care side of it as someone else's job – Patient 15*

STEP Consultation

The STEP consultation provided an opportunity for patients and HCPs to discuss the nature of palliative care services, how those services could fit with the current treatment plan and what might be needed in the future.

Defining Perspectives on Palliative Care

All participants initially thought palliative care was solely concerned with hospices, dying and end-of-life support. The STEP consultation allowed HCPs to help participants reconceptualise palliative care and comprehend the variety of services and support available. Overall, this was well received by participants and was often reassuring.

> *Well I thought it was sort of just an end-of-life thing until Dr [NAME] explained it wasn't. That made me feel a bit easier – Patient 14*

However, despite now conceptually understanding the variety of services offered by palliative care, not all participants thought it was applicable to their own situation. This seemed to be because it challenged existing coping strategies, such as hope of a cure.

> *I understand that somebody can be receiving palliative care for a lot of years so it didn't frighten me in that respect but it's still quite a big thing to hear ... I think it just hammers home about having a condition that's not going to get better – Patient 21*

How Palliative Care Fits with the Current Treatment Plan

The STEP study highlighted to some HCPs that their patients do not always have a clear understanding of the intention of their treatment. Even if the HCP believed they had explained the non-curative intent, participants often equated having treatment with hope of a cure. This misperception appeared to be an active barrier to involvement of palliative care for some participants.

> *He says we're always doing something. That's more or less what he said, there's always something else we can try – Patient 11*

Patients could also find integrated care confusing and to some it seemed 'bizarre to have a foot in both camps'. Several participants expressed wanting their oncology and palliative care to be clearly separate. How integrated care would work in practice was not always clear for HCPs either.

> *The Dr was very clear that he doesn't give chemotherapy to just make you feel a bit better, it's an active treatment so it's hard to be in that situation where even though you know the chemotherapy's not going to cure you, if you're going somewhere every week or every 2 weeks of having these horrible chemicals put in you, that's treatment, it's not a symptomatic relief, it's not some pain relief, it's not that, so it's difficult to see yourself in both camps – Patient 21*

At the conclusion of the STEP consultation, HCPs were prompted to define clear next steps for participants. During follow-up interviews, all participants seemed clear about the next steps for them. Those who had been referred to palliative care knew whether they were expecting telephone calls, letters or visits from representatives of those services. Those who had not been referred appeared clear about what was available and that it was something that could become relevant for them in the future.

Permission to Explore Future Care

Although all participating HCPs had significant prior experience of sensitive conversations with patients, they still found the structured conversation guide useful. It acted as a prompt for areas to cover with the participants, but perhaps more importantly it gave them an explicit and easy way to open potentially difficult topics.

> *It almost provided a bit of a safety blanket to cover some of these issues – Clinician 11*

Some participants also seemed to benefit from having permission and dedicated time to explore future care options and discuss timescales. Although some viewed it as something in the distance, others were pleased to have the opportunity to discuss specific topics, such as prognosis, symptom control, hearing what services were available to them and their families, end-of-life wishes and funeral plans.

> *If I get to a certain stage they won't be able to look after me anyway, I need specialist help and so that's another reason for looking at palliative care very carefully because at some stage, if this goes the wrong way as far as I'm concerned and I can't get rid of it then they're going to come into play a lot more – Patient 13*

Outcomes

Following the consultation, participants discussed a variety of outcomes, including changes in perspective and approaches to coping, facilitation of subsequent conversations and direct referrals to and involvement of new services.

Changes in Perspective and Approaches to Coping

As a result of the STEP consultation, some participants began to change their perspective on palliative care and associated issues of end of life. Others were already having these kinds of conversation and found the STEP consultation an extension of that process.

> *I wasn't over eager to start talking to those people but since I've thought about it you know if there is something there that they could or should be doing for me or that could help – Patient 15*

Importantly, no participants regretted having the STEP consultation. However, some still found the idea of palliative care in conflict with their coping strategies and linked with giving up hope and pessimistic ways of thinking. This was exemplified by the language and metaphors some participants used to describe thinking about death and dying, such as 'giving in' or 'morbid', compared with others who used terms like 'preparing' or 'accepting'.

However, even when some participants, such as Patient 14 below, understood they had an incurable cancer diagnosis, and also understood the full variety of services offered by palliative care, there was still sometimes a barrier to accepting these things applied to them as an individual.

> *But I know I'm not bad where I need palliative care so that's comes eventually, if that comes one day it does we'll just sort it out when it comes. But hopefully I'm going to get better. Get another 20 odd years out of me – Patient 14*

Another participant said contacting palliative care 'never even crossed my mind', despite a period of being very seriously ill in hospital and having been through the entire STEP study.

Opening the Door to Future Conversations

Some participants, who were not directly referred to palliative services, discussed how the STEP consultation had facilitated subsequent conversations with partners, family members, friends and HCPs. Many participants said they felt more confident raising the subject with family and friends following the STEP consultation.

> *Thinking oh we've had the conversation and they just say oh don't talk like that you know and I said no it's got to be spoken about – Patient 06*

Many participants said they had taken time to reflect on what they had discussed with the clinician and how this might impact their current and future care. Having had time to further develop their own perspective on the situation, they were then able to approach subsequent conversations with a clearer idea of what was on offer and how it might be relevant to them.

> *He had not been in an acceptance part of his disease and actually we had a really good conversation today where he has taken on board what I said previously at the STEP appointment – Clinician 14*

Referrals and Involvement of Palliative Services

Six participants were referred to palliative care services as a result of the STEP consultation. Some had initial contact with the service for information and were given contact details to be used in the future. Others engaged with complimentary, psychosocial or financial services, and drug prescriptions. Two participants required direct medical care from these services during the study.

> *As far as I'm concerned I want to go there with an open mind and see what these people can offer me – Patient 13*

Despite accepting referrals to palliative care, some patients continued to have difficulty with the concept of integrated care. Palliative care was still seen by some as something to call upon only in an end-of-life capacity.

> *I'd have to really, really deteriorate, to get in touch, to mention it to him, or mention it to Macmillan or whoever, it would have to really get bad – Patient 14*

There were also examples of participants still relying on and waiting for oncology appointments to discuss symptoms, where they could have contacted palliative services who were now involved in their care.

> *Disappointingly he came to see me about 4 weeks ago and he was very symptomatic from his cancer and I suppose what was quite disappointing was he hadn't contacted the community palliative care team ... My heart sank thinking he'd been sitting like this for 3 weeks with this really bad*

pain and because he knew he was seeing me he didn't ... .I think he was scared – Clinician 14

Discussion

This study tested the feasibility of an intervention to facilitate early and appropriate conversations about palliative care. In keeping with previous research, the STEP intervention showed there is value in having discussions about palliative care services at an early stage of a patient's cancer journey [1–3,23], and that although these conversations are often sensitive, they are rarely regretted by patients and can be surprising for clinicians. For patients, an important outcome of the STEP consultation was the facilitative effect on their ability to have subsequent conversations of this nature with family, friends and HCPs. This provides more support for the potential benefit of earlier conversations and that these do not have to result in a direct referral to be worthwhile.

As with most research findings in this area [7,10,12,13], participants had misconceptions about the nature of palliative care, but in some cases also about their own treatment or diagnosis. Although these misconceptions could be addressed and reshaped through the STEP consultation, it became apparent that reconceptualising a patient's knowledge and understanding was not always sufficient for them to appreciate the applicability of palliative care to their own situation. It may be that the orientations that people have towards discussing issues of death and dying have an influence on their readiness to accept the relevance of palliative care to their own situations. Palliative care interventions are often targeted based on clinical or demographic variables, but for future interventions and care to work effectively for all patients it may be beneficial to further understand and develop typologies [24] in this area related to the psychological preparedness of patients. Building on the four active and passive 'types' highlighted in this paper may provide a starting point to tailor and target interventions based on an individual's existing orientation to discussing sensitive end-of-life issues.

This study has shown that in a small cohort of patients and HCPs the STEP intervention was acceptable and feasible. Several issues have been identified that will enable further refinement, both of the intervention and its mode of delivery, prior to testing its efficacy in a trial.

- Patients should be routinely and systematically identified early in their treatment pathways for initial discussions about palliative care
- Patients and HCPs need time and support to prepare for conversations about palliative care
- Identifying how a patient currently views sensitive conversations in this area will help to tailor the intervention to their specific needs and approach
- Integrated care needs to be clearly explained to patients, both in terms of what it is, but also how it works in practice
- HCPs need to check and recheck a patient's understanding of the intent of their treatment
- Attaching palliative services to particular issues and priorities raised by patients, especially as a first step, can facilitate conversations and referrals
- Patients should be encouraged to have follow-up conversations with family, friends and other HCPs
- The STEP consultation can be revisited multiple times during the patient journey.

Conclusion

The STEP intervention generated valuable conversations about end-of-life care that otherwise may not have occurred at this stage of patient pathways. For some patients, the conversations resulted in a palliative care referral; for others, it resulted in feeling better informed about the support services available. No patients regretted having the STEP consultation and it often opened a dialogue that then continued with family and friends and clinicians. Participating clinicians found the structured conversation guide acted as a useful prompt for areas to cover with the patient and gave them an explicit and easy way to open potentially difficult topics. Despite the extra time needed for these, some thought that the additional time given at this early stage could save time later in the patient journey.

Limitations

The relatively small sample size of this study means that our conclusions require detailed exploration in future research. In addition, we were not able to recruit participants from non-White British demographic groups, so were not able to explore potential cultural differences or nuances in this study. Explaining the study for informed consent often resulted in initial conversations about palliative care with the researcher, which could have influenced the STEP consultation.

Ethics

Ethical approval was granted by North West, Greater Manchester East Research Ethics Committee 30/04/2019. All participants provided informed consent to take part in the study and for their anonymised data to be used within this paper.

Conflicts of interest

The authors declare no conflict of interest.

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Author contributions

SP was responsible for designing, organising and delivering the intervention, alongside conducting the data collection and leading the analysis. SP was the primary author for the manuscript. HB contributed valuable input into the origins of the STEP study, the direction and content of the intervention and into shaping the manuscript. MB was the head of the Academic Unit of Palliative Care during the STEP study and provided steering across all of aspects of STEP, including the direction of the manuscript. LZ was the lead researcher responsible for the inception and funding of the STEP research. LZ worked closely with SP in designing the intervention and planning the application within oncology. LZ also contributed to the analysis and had significant input into the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2022.05.012.

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