Healthcare professionals’ views of the use of oral morphine and transmucosal diamorphine in the management of paediatric breakthrough pain and the feasibility of a randomised controlled trial: A focus group study (DIPPER)

Liz Jamieson1,2, Emily Harrop3,4, Margaret Johnson5, Christina Liossi6,7, Christine Mott8,9, Kate Oulton7, Simon S. Skene10, Ian CK Wong1,2,11 and Richard F Howard7

Abstract
Background: Oral morphine is frequently used for breakthrough pain but the oral route is not always available and absorption is slow. Transmucosal diamorphine is administered by buccal, sublingual or intranasal routes, and rapidly absorbed.
Aim: To explore the perspectives of healthcare professionals in the UK caring for children with life-limiting conditions concerning the assessment and management of breakthrough pain; prescribing and administration of transmucosal diamorphine compared with oral morphine; and the feasibility of a comparative clinical trial.
Design/ participants: Three focus groups, analysed using a Framework approach. Doctors, nurses and pharmacists (n = 28), caring for children with life-limiting illnesses receiving palliative care, participated.
Results: Oral morphine is frequently used for breakthrough pain across all settings; with transmucosal diamorphine largely limited to use in hospices or given by community nurses, predominantly buccally. Perceived advantages of oral morphine included confidence in its use with no requirement for specific training; disadvantages included tolerability issues, slow onset, unpredictable response and unsuitability for patients with gastrointestinal failure. Perceived advantages of transmucosal diamorphine were quick onset and easy administration; barriers included lack of licensed preparations and prescribing guidance with fears over accountability of prescribers, and potential issues with availability, preparation and palatability. Factors potentially affecting recruitment to a trial were patient suitability and onerousness for families, trial design and logistics, staff time and clinician engagement.
Conclusions: There were perceived advantages to transmucosal diamorphine, but there is a need for access to a safe preparation. A clinical trial would be feasible provided barriers were overcome.

Keywords
Paediatrics, palliative care, terminal care, focus groups, opioids, diamorphine, breakthrough pain, pain management

What is already known in this area
- Oral morphine is the recommended first line treatment for breakthrough pain.
- Intranasal diamorphine is an effective, rapid onset, well tolerated treatment for use in Accident and Emergency (ED) for trauma patients but lacks study in paediatric palliative care.
- It is often assumed that large scale clinical trials are not feasible in a paediatric palliative care population.
Background

The management of pain in the context of palliative or end-of-life care can be challenging. Episodes of sudden onset pain termed ‘breakthrough pain’, are the most difficult to manage effectively because few suitable potent and sufficiently rapidly acting analgesics are available. Breakthrough pain typically occurs in children with cancer but can also occur in children with a wide range of other life-limiting conditions.1

Opioids are the most potent analgesics available and oral immediate-release morphine is a commonly used first-line agent for paediatric breakthrough pain2 but can take up to 40 min to reach its peak concentration.3 Palliative care patients require medications to be administered within their homecare settings to allow them to stay in a familiar environment; however, many medicines for fast symptom relief require injection. Children in pain have a sympathetic response causing vasoconstriction rendering venous access somewhat more technically challenging than usual4 and subcutaneous injections are poorly tolerated. A needle free, fast-acting pain medicine, which is easy to give at home or other place of care, is needed. Transmucosal diamorphine is rapidly absorbed and potentially faster acting for breakthrough pain. Transmucosal routes of drug administration is widely established in paediatrics5 and is useful when children cannot swallow or prefer to avoid injections. Transmucosal intranasal diamorphine is licensed for the treatment of moderate and severe pain in children attending Accident and Emergency departments. Some palliative care prescribers have begun to prescribe this for children with life-limiting illnesses (EH, personal correspondence). Previous studies have shown intranasal diamorphine is as effective as intramuscular morphine for acute pain in A&E settings and has an acceptable safety profile.6,7 Whilst there has not been a clinical study on the efficacy and safety of buccal/sublingual transmucosal diamorphine, its use is increasing in both adult and paediatric palliative care, not least as a result of Covid-19, with fewer district nurses available to administer injections.8

An overview of systematic reviews of pharmacological interventions for chronic pain in children found there were no randomised controlled trials for pharmacological interventions in children with cancer-related pain.9 A systematic review on pharmacological interventions for pain in children and adolescents with life-limiting conditions found that evidence was limited; available research evaluated pain largely as a secondary outcome and the drugs investigated were all adjuvants and not in common use in general paediatric palliative care.10

The National Institute for Health and Care Excellence (NICE) Guideline NG61 (End of Life Care for Infants, Children & Young People)11 identified a paucity of research evidence relating to the administration of breakthrough medication for pain in children, which led to a specific research recommendation.

Conducting RCTs in this group of children is challenging, particularly in regard to maximising recruitment and minimising attrition.12 The DIPPER study is a 4-phase investigation of the feasibility of a randomised controlled trial (RCT) of transmucosal diamorphine versus oral morphine for breakthrough pain in children and young people with life-limiting conditions. In focus groups as part of the DIPPER study, we explored healthcare professionals’ perspectives on the assessment and management of breakthrough pain in palliative care in children, the prescribing and administration of transmucosal diamorphine (buccal, sublingual and intranasal) and oral morphine, and views about patient/carer involvement in a future trial.

Methods and design

Our overall research question was to highlight the challenges of running a future trial of oral morphine versus transmucosal diamorphine for breakthrough pain in children and young people with life-limiting conditions receiving palliative care. This study was approved by University

What this research adds

- Highlights the variation in experience of use of transmucosal diamorphine for breakthrough pain.
- Reports clinicians’ experience of the benefits of transmucosal diamorphine in the absence of data for breakthrough pain in children receiving palliative care and highlights their concerns in regard to the feasibility of running a randomised controlled trial of oral morphine versus transmucosal diamorphine.
- Evidence that many of the identified barriers to wider use of transmucosal diamorphine could be overcome by offering education and undertaking research, potentially leading to a licensed preparation.

Implications for clinical practice

- Clinicians identified clinical scenarios where transmucosal diamorphine may be preferable but identified several current barriers to its use. Access to a safe and effective preparation of transmucosal diamorphine would provide a range of options with which clinicians could flexibly target breakthrough pain in different clinical scenarios.
- This adds to the case for undertaking research in this population despite perceived challenges.
A qualitative focus group methodology reported in accordance with the consolidated criteria for reporting qualitative research (COREQ) guidelines.13 Focus groups facilitate group discussions allowing participants to deliberate on their own position in the context of the views of others.14

Participants
Healthcare professionals with experience of paediatric palliative care or caring for children with life-limiting conditions working in hospitals, hospices or in the community (prescribers and non-prescribers) and those with experience of medicines prescribed for breakthrough pain, for example, pharmacists.

Setting and sampling
Three focus groups were held in June 2019 in three geographical regions to ensure diversity of participants and prevent local practice bias. One was held at an academic institution in Liverpool, one at a hospice in Oxford and the third at a public venue in London.

Purposive sampling was used to achieve maximum variation in each of the groups (including professional role of participants and settings of care). An a priori decision was made that three groups of 8–10 people would generate sufficient data to achieve data saturation.

Recruitment
The focus groups were advertised through professional organisations: Together for Short Lives, the APPM (Association for Paediatric Palliative Medicine) newsletter and NPPG (Neonatal and Paediatric Pharmacists’ Group). A link to the advertised information was also emailed to clinicians in the field (from EH and MJ). Participants were paid £240 to cover a locum fee plus travel costs and lunch/refreshments were provided.

Data collection
Each focus group was led by a facilitator (RFH) with support from a research team member (LJ), an experienced qualitative researcher. Some members of the project management team attended as non-participant observers. Each participant provided written, informed consent. Open-ended questions were used to encourage discussion. RFH as a specialist in pain medicine, but not a palliative medicine specialist, encouraged participants to express their views on the topic freely. Each focus group lasted for 120 min, was audio-recorded and transcribed verbatim. LJ also took field notes. A semi structured topic guide covered the following:

- Experiences and barriers of prescribing transmucosal diamorphine and oral morphine for breakthrough pain in children and young people with life-limiting conditions receiving palliative care
- Barriers and facilitators to taking part in an end-of-life RCT involving children and young people
- Recruitment of participants in a feasibility study/trial
- Challenges of running the DIPPER trial

Data analysis
The framework method of analysis,15 appropriate for managing large data sets involving multiple stakeholders, was applied to facilitate comparison between and within professional subgroups. Transcripts of the focus groups were read several times and data relevant to the aims identified. Two researchers (LJ and KO) independently coded the transcripts and discussed codes to ensure that all relevant codes were identified and grouped into categories using an Excel spreadsheet to generate a matrix (framework) which was agreed by consensus and applied across all focus group data. Data were ‘charted’ into the matrix including references to illustrative quotations. Constant comparative analysis was used to reveal similarities and differences in the data. The transcripts were not returned to participants for their comments.

Results
Twenty-eight participants attended (Table 1). The sample included nurses, doctors and pharmacists, with experience of caring for children with life-limiting illnesses receiving palliative care in both primary and secondary care. The groups included prescribers, including some nurse-prescribers, and those who relied on others to prescribe.

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College London (UCL) Ethics Committee, reference no. 8277/002 on 29 March 2019; data protection registration number Z6364106/2019/03/32.
The groups started with a general discussion about the assessment and management of breakthrough pain before discussing the five topics. Within each high-level theme there were emergent sub-themes which are presented below using illustrative verbatim quotes.

Assessment and management of breakthrough pain

Participants agreed that breakthrough pain is frequently encountered across the spectrum of patients in all settings and that the number of episodes for individual patients was very variable. Participants shared the view that determining the type of pain experienced was not straightforward, and there were particular challenges in those who were non-verbal, sedated and/or ventilated or with cognitive impairment:

**Doctor, Hospice:** “You actually also have issues about defining what you mean by pain . . . because if you have a child with neurological problems, they don’t say ‘I’m in pain’, which is one of the weaknesses of all these pain tools and within the hospice sector we probably have two-thirds neurological, one-third oncological. So we manage distress, it just so happens that sometimes we can manage the distress with opioids and sometimes we have to manage the distress with other medication.”

Under-reporting of pain by younger children was highlighted, as was distinguishing breakthrough pain from distress associated with other symptoms:

**Doctor, Hospital:** “You’ve got children [that] have got seizures, the seizures by themselves are not painful but you have tonic seizures every, you know, in the next 10 minutes, the distress is what causes them and it looks like pain”.

The challenges of distinguishing anxiety from breakthrough pain was also raised:

**Doctor, Hospital:** “It’s always very difficult to decide what’s pain and what’s anxiety and if it’s anxiety how you manage that because what we’re trying to get people to do is not just jump for drugs because there’s other ways to manage anxiety”.

Whilst the important role parents/carers played in the assessment of breakthrough pain was highlighted, it was noted that this involved education:

**Nurse Community:** . . . “I used to find it was really helpful to be able to talk through the different scenarios with parents”.

**Doctor, Hospice:** “really good information and working with parents and carers to explain what they might see and give them the information they need to be able to report, that will inform what we do”.

There was a consistent view that no one pain assessment tool is suitable for all patients. Many participants from different settings have created personalised scoring systems, which are a composite of various observations and tools.

**Doctor, Hospice:** “I’m not aware of any one tool that is going to be suitable for all the kinds of patients that we might be talking about. And even if we do find a tool I’m not sure that we will necessarily know it’s pain we’re talking about”.

Hospital pharmacists spoke of problems using pain assessment tools for telephone outreach services, making it difficult to gauge how effective treatment had been. Hospice and community nurses commented that whilst staff are quite good at assessing and ‘scoring’ pain pre-treatment, they are less good at scoring afterwards or documenting the effectiveness of pain relief. However, one hospital nurse shared a contrasting experience of *having* to record pain scores to inform subsequent decisions:

**Nurse, Hospital:** “Well we have to record because if we don’t record it, if we don’t know how effective it is we’re not going to give it again. We have to look at some of the things, you know, we won’t just go in and then go back a week later, you know, we’re either in the house or we’re ringing up later or they’re ringing us. So it is important to record that because it influences what you’re going to give next”.

The link between the assessment and management of breakthrough pain is articulated well in this example:

**Doctor, Hospital:** “It matters if the distress is caused by constipation for example. Very simple terms if your pain is caused by constipation and you give opioids you will only make the pain worse, and you need to give them Movicol, you know . . .”

Hospice nurses highlighted the importance of having something that works quickly for breakthrough pain but does not necessarily last a long time. The difference between treating unpredictable, very acute onset pain, pain that wakes children from sleep or flash headaches in children with brain tumours, and predictable, incident related pain, when washing or dressing were highlighted, with various methods of pain management described.

**Oral morphine use**

Oral morphine was frequently prescribed for breakthrough pain. Community nurses felt it worked well for families. It has a long-lasting effect and is useful when waiting for an analgesic infusion to achieve therapeutic levels. Hospital doctors agreed that oral morphine was very good for incident-related pain. However, the time to onset of pain relief and the fact that as time goes on ‘it doesn’t hit the spot’, meant that oral morphine was not
viewed as being suitable for all types of breakthrough pain:

Nurse Hospice: “I think it’s good for some things, and it’s good to begin with, but it does lose its, as time goes on it tends to, yeah, it doesn’t hit the spots”.

Its unpredictable nature also meant it was not suitable for all patients:

Doctor, Hospital: “So 1) it takes a very long to work and 2) it’s got a very unpredictable response, it can flatten some people and have no effect on others and I think there’s a physiology basis for that as well as what we see and people metabolise at different rates, so. And it’s also, people that have oral morphine say it can be quite an unpleasant feeling, it’s not a nice groggy sedation, sick, nausea. . .”

The potential side-effects of oral morphine, which include sickness, nausea, constipation and unpalatable taste, and the need for patients to have good oral absorption, were highlighted as factors which might necessitate a switch to another medication.

Preconceived views about opioids were raised, with hospice nurses revealing that some families, particularly extended families, may refuse them fearing they cause respiratory depression or may make their child die sooner, whilst other families want oral morphine to ‘speed things up’. It was felt that oncology patients may believe that oral morphine use is indicative of end-of-life treatment; more so than in children with complex needs who may have been introduced to it gradually. Outside palliative care there is resistance and fear about opioids amongst professionals.

Transmucosal diamorphine use

There was a range of experience of using transmucosal diamorphine. Nurses generally agreed that best practice would be to start with oral morphine and move on to diamorphine. Advantages of transmucosal diamorphine were said to be speed of action (around 5 min), and the fact that it was appropriate for patients with gastrointestinal (GI) failure. Transmucosal Diamorphine was felt to be useful for patients with escalating symptoms, experiencing trauma or receiving a large volume of medication. Transmucosal diamorphine does not require much patient co-operation and it may delay the point at which an infusion is required. One community nurse said that if the pain was severe or required a fast-acting medicine, she would use buccal diamorphine. Some hospital doctors said they used buccal agents, such as midazolam, for anxiety in the neurometabolic population.

Participants felt that hospital pharmacists overseeing formulary entries in hospital, and lack of GP shared care protocols, could be barriers to prescribing transmucosal diamorphine. Factors affecting prescribing included inexperience, lack of pain management education, a perception that diamorphine is strong, professional accountability or fear of being blamed:

Doctor, Hospital: “I think that’s strongly linked to the lack of licensed preparations because if we had licensed preparations I think Primary Care would be more willing to prescribe them because obviously the degree of legal responsibility we take if we prescribe an unlicensed drug is high”.

Several doctors agreed that policies usually indicate oral morphine first line in secondary care (mainly due to lack of licensed alternatives) making it difficult to prescribe diamorphine. Concerns about professional accountability and drug stability meant that community nurses must discard and replace pre-prepared syringes left in the family home daily. It was noted that some hospital pharmacists did not allow nurses to leave prepared diamorphine in the home, and parents have to manipulate the intravenous preparation, often making up very tiny doses per weight from glass vials.

Another barrier was said to be the bitter taste of transmucosal diamorphine with a need to mask this in a bespoke buccal preparation. Many participants expressed concerns about different, or more severe, side effects and drug interactions. One hospice doctor felt that terminology might be a problem as diamorphine is seen as something that goes in a syringe driver (infusion). Barriers to the intranasal formulation included possible irritation to the nasal lining, especially if given repeatedly. The cost of the licensed intranasal formulation of diamorphine for Accident & Emergency use, Ayendi, was said to be prohibitive, and there were issues with its supply, stability, exposure to light, temperature and 7-day expiry. A hospice doctor felt that it was not helpful that it only had two strengths as dosing should be based on weight. Also, its use can be challenging in children who have a nasogastric tube and/or lots of mucous.

Barriers to buccal diamorphine include the possibility of increased oral secretions and potential need for suction, and concerns about absorption when patients dribble or have fragile oral mucosa. Pharmacists felt that the preparation would require viscosity to stay under the tongue, but noted that, in practice, side effects were minimal, particularly respiratory depression.

There was limited experience of using intranasal (mainly in A&E for trauma/fractures) and sublingual routes for transmucosal diamorphine, in comparison to the buccal route which was used more widely. Experience with buccal midazolam increased professionals’ confidence in using this route, and was thought to increase acceptability, as well as ease of administration for the family and a lack of need for training:

Doctor, Hospice: “So like [the hospice doctor], the intranasal would be the last resort for us. I’ve used it sublingual but I’ve used it intranasally once when the buccal just seemed to
increase their oral secretions and caused all sorts of trouble but generally would use buccal. A lot of the families have got experience of giving buccal midazolam, so they know how to give it, there isn’t a training issue”.

Barriers and facilitators for taking part in an end-of-life RCT

Trial duration, logistics and randomisation were reported concerns. The duration of a trial would be important to consider in relation to patient survival; with a concern that if the child passed away soon after starting, families may blame the new drug.

Hospice doctors suggested that families could perceive the trial as an ‘experiment’, and that their child might not be receiving the best treatment. If the trial involves patients being given one or other drug, families will need to be reassured that it will not make their child worse. A cross-over design might be preferable, so families feel they are trialling two ways of giving the same type of medicine (opioid) for the same type of effect (pain relief). Participants felt this would be a more positive explanation than if the child were given a placebo. They also felt that it should be made clear that both drugs are very effective pain medications, but the study is looking at which is more effective in a given situation. It was felt that the increased monitoring/reporting of adverse events in trials together with the medicine being available afterwards, would encourage people to take part.

Other perceived barriers included obtaining ethics approval and finance, and hospice staff felt there was a lack of time for research. Another concern was how onerous the trial would be for the family and intrusiveness if a researcher did the observations. Gaining consent from families could be challenging where there was family conflict, separation, or if the child were fostered.

Engaging clinicians was said to be important. There was an awareness of potential gatekeeping by professionals to protect families from being over-burdened, and recognition that education was needed. Doctors recognised that they underestimated families’ ability to see research as positive and that parents may feel empowered by contributing to the evidence-base with their child leaving a legacy:

Nurse, Hospice: “If Children have an illness or a problem which is life-limiting, families are very altruistic a lot of the time in wanting to help other families and we hear that many, many times”.

It was felt that all children with life-limiting illnesses should be invited to participate, but oncology patients would be more familiar with trials but could also see them as ‘saviours’.

Someone who knew the family well, possibly a key worker, should introduce the trial. There were varied views about the best time to approach families about participation. Some felt that there may never be a good time, while others felt families should be told as soon as possible. However, caution was advised about approaching families too soon before opioids are indicated for their child. Suggested good times included when there was a discussion about the range of pain control measures, at the symptom management stage when complex drugs are discussed, at the Advanced Care Planning stage, or when patients are starting on long-acting, background analgesia.

Challenges to running a trial

It was suggested that a clear working definition of breakthrough pain was needed:

Doctor, Hospice: “I think the Association of Palliative Medicine but we would need to check it, would talk about breakthrough pain as the umbrella and incident pain is within breakthrough pain, it’s one type of breakthrough pain. So breakthrough pain is, in my understanding would be any pain that breaks through is an exacerbation on top of their background and that might be an incident in response to some trigger or it might be just spontaneously when they’re asleep”.

‘End-of-life’ also needs to be defined; whilst this is usually six to twelve months (gold standard) it may not always be the case. All agreed that care should be taken with the language used.

Other challenges included variable numbers of eligible patients across organisations and patient stability.

Nurse Community: “Yeah. I think one of the problems is that if you’ve got someone who is stable, you can probably establish them on a stable pain ratio and the likelihood of them needing breakthrough is minimal because they are stable. And it is the patients who are changing that we have problems with breakthrough, with a need for breakthrough pain relief. So we’ve almost got a tension here if you want them to be stable so that we know that we’re not losing because of the condition change but actually if they’re really stable they won’t have breakthrough pain and we won’t be able to give them anything”.

Many children have progressive conditions and it could be impossible to say whether the treatment was effective as doses would be escalated. A trajectory can be defined better for a patient with cancer than with a neurological problem and it could be difficult for clinicians and families to switch medicines if patients were comfortable. Oral morphine (Oramorph 10 mg/5 ml) is not a controlled drug and can be administered by school staff, whereas diamorphine cannot. Patients with GI failure would have to be excluded from any trial, but if GI failure occurred during the trial, information up to that point could be used.
Discussion

Main findings

Participants agreed that breakthrough pain is very frequently seen across the spectrum of patients in different settings and that no one pain tool was suitable for the different types of breakthrough pain.

Oral morphine is frequently used first line for breakthrough pain across all settings in the UK, and staff and families were confident in its use. For hospice doctors and nurses, Oramorph was their ‘bread and butter’ as most children are not immediately ‘end-of-life’, do not have gastrointestinal failure but do have long term pain. Oral morphine can also be used at end-of-life, when the pain is not being controlled during a hospital admission, or afterwards for moderate pain. Using oral morphine was said to be easier than buccal or intranasal. There is no training issue, it is not a controlled drug and it is likely to be in stock. However, it takes a long time to work when a child has sudden onset pain. Experience of transmucosal diamorphine was very variable, mainly limited to the buccal route, with some hospice nurses never having used it. Buccal diamorphine was said to be useful when children are on infusions where there is reduced GI absorption and for acute, sudden onset pain. Advantages of transmucosal diamorphine such as its quick onset and easy administration were noted, but the main barrier to its use was a lack of a suitable licensed preparation. Taste was also a major barrier for the buccal and sublingual routes. As Anderson warned, children will not retain the drug under the tongue unless the taste is satisfactory and may result in more swallowed drug or drug spat out, than in adults.

Factors raised in relation to a future randomised controlled trial of oral morphine versus transmucosal diamorphine included trial design, with a cross-over design being preferable, patient stability over time in the trial, logistics including when to introduce the trial and who to introduce it, eligibility criteria, and potential burden for families. Clinician engagement and education was essential to avoid potential gatekeeping.

Strengths and limitations

To our knowledge this is the first study to examine the experience and perspectives of healthcare professionals in palliative care with oral morphine and transmucosal diamorphine for breakthrough pain in children with life limiting illnesses. The high level of participation in the focus groups demonstrates that this is an important topic for healthcare professionals. However, this study also highlights the need to agree a working definition of breakthrough pain. This is probably because international consensus on the definition of breakthrough pain has still not yet been achieved and there is a lack of validated tools for assessing breakthrough pain.

Most participants were from London or Oxford, but some travelled from further afield, for example, Cornwall. However, the size of the Liverpool group was small in comparison. There were only two pharmacists, but there are few specialist pharmacists in paediatric palliative care. These factors may influence the generalisability of the findings.

Diamorphine is not used in some countries, but this could change if the UK were to obtain a licensed formulation. The UK Association for Paediatric Palliative Medicine (APPM) Formulary is an international reference point. A randomised controlled trial would be a first step in providing an evidence base and has been identified as research with high priority in the NHS. However, the concerns raised in the focus groups would need to be addressed.

What this research adds and further research

The focus groups provided evidence of clinicians’ positive opinions and experience of the benefits of transmucosal diamorphine for breakthrough pain in this setting, yet highlighted the variation in experience. Clinicians identified scenarios where transmucosal diamorphine may be preferable but mentioned barriers to its use, especially concerns over professional accountability and the lack of a licensed preparation. This could be overcome by running a randomised controlled trial of oral morphine versus transmucosal diamorphine, potentially leading to a licensed preparation providing a range of options so clinicians could flexibly target breakthrough pain in different clinical scenarios. The need for this research is even more timely now as the demand for transmucosal products is greater in both adult and paediatric palliative care, not least because Covid-19 makes district nurses unavailable to administer injections. A recent editorial in relation to families administering end-of-life drugs at home during the crisis, acknowledged that the buccal and sublingual routes are less commonly used with evidence coming primarily from professional experience and paediatric palliative care. To enable high-quality needle-free palliative care, particularly in the community, a guide, summarising the evidence on orodispersible and transmucosal alternative medications for symptom control in adults, has recently been published to assist healthcare professionals to choose medications to control symptoms when patients do not have an oral route and when injectable medications are not available. The authors identified medications through review of drug formularies, review of the published evidence and their experience. Despite the challenges of conducting research in the vulnerable paediatric palliative care population, there is a need for evidence-based studies.
Acknowledgements
The authors would like to thank all the participants who took part in the focus groups. Kate Oulton is a National Institute for Health Research (NIHR) Senior Nurse and Midwife Research Leader. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care.

Author contributions
IW is the Chief Investigator of the DIPPER study and conceived the project and takes overall responsibility for the conduct of the study. RFH contributed to the conception and design of the study, chaired the focus groups, contributed to the analysis and revised the manuscript critically for important intellectual content. LJ contributed to acquisition of data, led on the analysis of data; prepared the first draft of the manuscript; revised the manuscript for submission after feedback. KO led on the analysis with LJ and revised the manuscript critically for important intellectual content. Cl, EH, SS and MJ contributed to the conception and design of the study, data acquisition and analysis and revised the manuscript critically for important intellectual content. CM revised the manuscript for submission providing an international perspective. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of conflicting interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: IW is the founder of Therakind Ltd which was funded by Wockhardt Pharmaceutical to conduct the clinical studies for Ayendi®. (diamorphine hydrochloride) licensing application.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This project is funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RPB) Programme (Grant Reference Number PB-PG-0317-20036). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

ORCID iDs
Liz Jamieson https://orcid.org/0000-0002-3667-0423
Christina Liossi https://orcid.org/0000-0003-0627-6377
Christine Mott https://orcid.org/0000-0002-2538-2530
Simons S. Skene https://orcid.org/0000-0002-7828-3122

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