CDI Clinical Designs - Cover Sheet*

Document Type	NCEC Guideline
Document Title	Management of Constipation in Adult Palliative Care Patients
Document Owner (e.g. NCP)	NCP Palliative Care
NCAGL	NCAGL Older Persons
Approved by	CCO Clinical Forum
Unique Identifier Number (UID)	CDI/0166/1.0/2025
Version Number	1.0
Publication Date	November 2015
Recommended Revision Date **	April 2028
Electronic Location	

National Clinical Guidelines must use NCR cover sheet if being uploaded onto NCR. Otherwise this cover sheet applies

***** Refer to *HSE National Framework for developing Policies, Procedures, Protocols and Guidelines (PPPGs)***

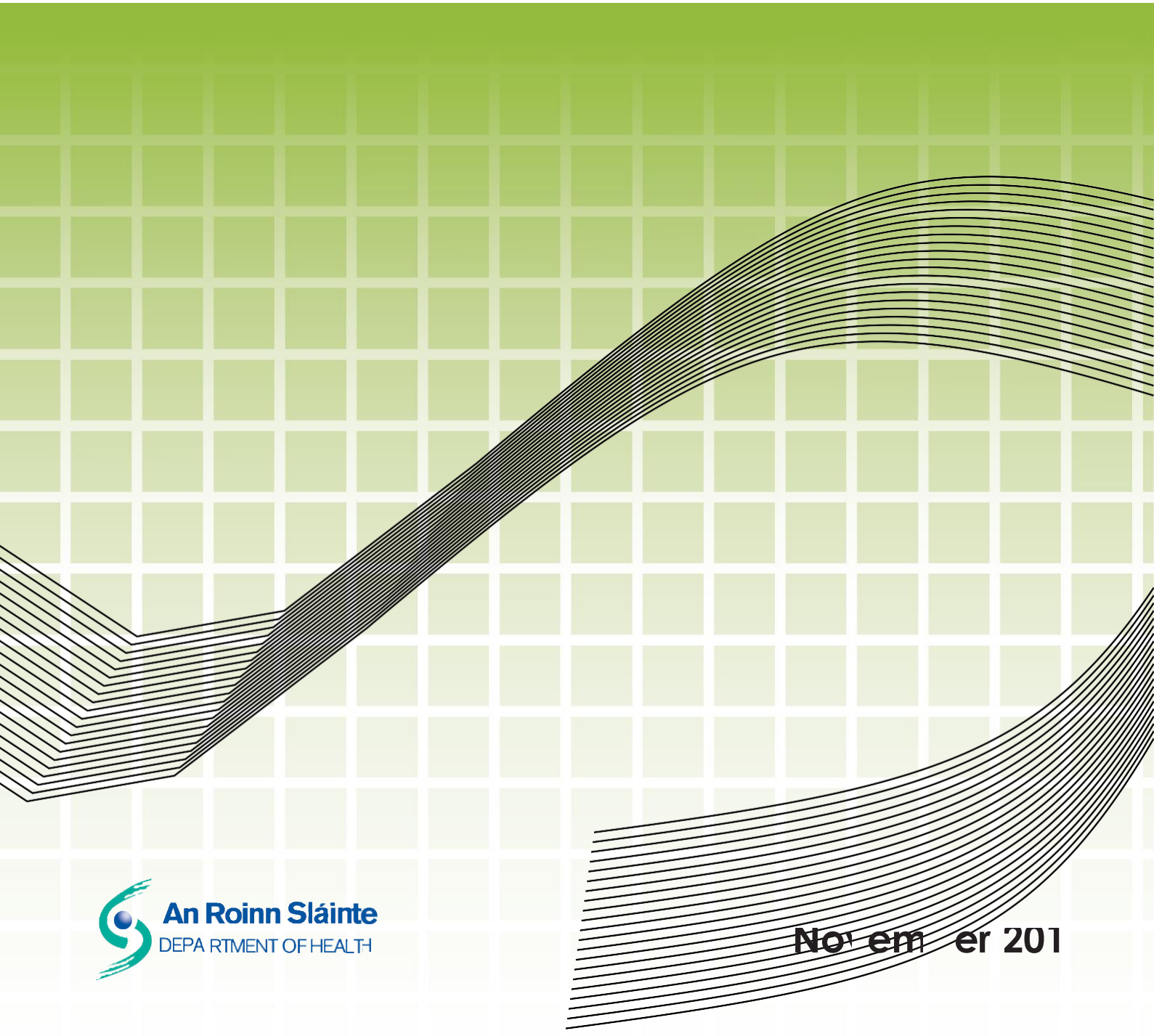
Version	Revision Date	List Section Numbers Changed	Author
1	April 2025	No change	

NATIONAL CLINICAL EFFECTIVENESS COMMITTEE

Tús Áite do Shábháilteacht Othar
Patient Safety First

Management of Constipation in Adult Patients Receiving Palliative Care

National Clinical Guideline No. 10



An Roinn Sláinte
DEPARTMENT OF HEALTH

November 2012

Guideline Development Group
The Management of Constipation in Adult Patients Receiving Palliative Care Guideline was developed by a subgroup of the Health Service Executive (HSE)/Royal College of Physicians of Ireland (RCPI) National Clinical Programme for Palliative Care, known as the Guideline Development Group (GDG). The Guideline Development Group was supported by senior multidisciplinary service leads assembled by the National Clinical Programme for Palliative Care who evaluated the quality of the development process and documentation at key time points. This group was called the Guideline Steering Group.

The All Ireland Institute of Hospice and Palliative Care (AIIHPC) awarded an educational bursary to three members of the Guideline Development Group. The AIIHPC had no editorial influence on the content of this guideline.

PALLIATIVE CARE

AIIHPC
All Ireland Institute of Hospice and Palliative Care

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Using this National Clinical Guideline
This guideline is for use by healthcare professionals providing generalist or specialist palliative care to patients with a life-limiting illness in hospital, hospice and community-based settings (1). This includes specialist palliative care providers, physicians, surgeons, general practitioners, nurses, pharmacists and dietitians. For those providing generalist palliative care, the guideline recommendations indicate where specialist advice should be sought. This guideline may also be of interest to patients with a life-limiting condition and their carers.

This guideline should not be used in patients without a life-limiting illness. This guideline does not apply to children.

The National Clinical Guideline and the summary National Clinical Guideline are available on the websites www.health.gov.ie/patient-safety/NCEC and www.hse.ie/palliativecareprogramme.

Constipation is one of the most frequently encountered symptoms in the palliative care population. It can significantly impact on a patient's quality of life and may necessitate the use of additional medications, emergency visits and hospitalisation.

The consequences of untreated constipation place a significant burden on the healthcare system. Prescribing practice lacks consistency and despite laxative therapy, up to seventy percent of patients receiving palliative care continue to experience symptomatic constipation. The expected outcome of the recommendations made in this guideline is to prevent or reduce constipation and improve quality of life.

This Guideline complements the National Clinical Guideline No 9, Pharmacological Management of Cancer Pain in Adults, also developed by the National Clinical Programme for Palliative Care.

National Clinical Guideline No. 10
ISSN 2009-6259
Published November 2015

National Clinical Effectiveness Committee (NCEC)

The National Clinical Effectiveness Committee (NCEC) is a Ministerial committee established as part of the Patient Safety First Initiative. The NCEC's mission is to provide a framework for national endorsement of clinical guidelines and audit to optimise patient and service user care. The NCEC has a remit to establish and implement processes for the prioritisation and quality assurance of clinical guidelines and clinical audit so as to recommend them to the Minister for Health to become part of a suite of National Clinical Guidelines and National Clinical Audit.

National Clinical Guidelines are **"systematically developed statements, based on a thorough evaluation of the evidence, to assist practitioner and service users' decisions about appropriate healthcare for specific clinical circumstances across the entire clinical system"**. The implementation of clinical guidelines can improve health outcomes, reduce variation in practice and improve the quality of clinical decisions.

The aim of National Clinical Guidelines is to provide guidance and standards for improving the quality, safety and cost effectiveness of healthcare in Ireland. The implementation of these National Clinical Guidelines will support the provision of evidence based and consistent care across Irish healthcare services.

The oversight of the National Framework for Clinical Effectiveness is provided by the National Clinical Effectiveness Committee (NCEC). The NCEC is a partnership between key stakeholders in patient safety and its Terms of Reference are to:

1. Provide strategic leadership for the national clinical effectiveness agenda.
2. Contribute to national patient safety and quality improvement agendas.
3. Publish standards for clinical practice guidance.
4. Publish guidance for National Clinical Guidelines and National Clinical Audit.
5. Prioritise and quality assure National Clinical Guidelines and National Clinical Audit.
6. Commission National Clinical Guidelines and National Clinical Audit.
7. Align National Clinical Guidelines and National Clinical Audit with implementation levers.
8. Report periodically on the implementation and impact of National Clinical Guidelines and the performance of National Clinical Audit.
9. Establish sub-committees for NCEC workstreams.
10. Publish an Annual Report.

It is recognised that the health system as a whole, is likely to be able to effectively implement and monitor only a small number of new national clinical guidelines each year. Not all clinical guidelines will be submitted for national endorsement and clinical guideline development groups can continue to develop clinical guidelines using an evidence based methodology in response to the needs of their own organisations.

Information on the NCEC and endorsed National Clinical Guidelines is available at:
www.health.gov.ie/patient-safety/ncec

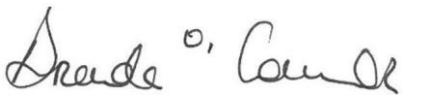
Acknowledgments
The GDG would like to acknowledge the input of Mr Gethin White, Librarian, HSE and Mr Owen Kinsella, Librarian, St. Luke's Hospital, Dublin, who provided assistance in sourcing key reference material for this guideline. We would also like to acknowledge the input of Ms Breffni Smith, Librarian, Beaumont Hospital and Ms Laura Rooney Ferris, Librarian, Irish Hospice Foundation for their assistance with the subsequent literature update. We would like to thank Mr Brendan Leen and his colleagues in the HSE Library for sharing their Systematic Review Protocol.

We were very fortunate that Professor Lukas Radbruch, Chair of Palliative Medicine, University of Bonn: Director of Department of Palliative Medicine, University Hospital Bonn and Director of Palliative Care Centre, Malteser Hospital Bonn/Rhein-Sieg and Associate Professor Max Watson, Consultant in Palliative Medicine/Lecturer in Palliative Care, Northern Ireland Hospice, Belfast reviewed the guideline. We also appreciate the input of Mr Stephen Ward, Clinical Pharmacist for Palliative Care, Northern Ireland Hospice, Belfast and Ms Heather Weir, Director of Nursing and Patient Services, Northern Ireland Hospice, Belfast. We are deeply grateful to them for sharing their time and expertise with the group. We gratefully acknowledge the guidance of Professor Michael Barry from the Medicines Management Programme (HSE) and Ms Michelle O'Neill, Senior Health Economist, Health Information and Quality Authority for the assistance they provided on pharmacoeconomic considerations. We would like to thank Ms Cliona Hayden, Ms Eimear O'Dwyer and Ms Fiona McGrehan, Palliative Meds Info Service, Pharmacy Department, Our Lady's Hospice, Dublin for their expert review and assistance with pharmacoeconomic information. We acknowledge the assistance of Ms June Boulger, National Lead, Service User Involvement, and the staff and service users of the National Advocacy Unit in the development of the patient information booklet that accompanies this guideline.

In particular, we wish to express our gratitude for the support and guidance of the Guideline Development Group of the National Guideline, Pharmacological Management of Cancer Pain in Adults and the All Ireland Institute of Hospice and Palliative Care.

The development of this guideline would not have been possible without the guidance, advice and dedicated input of Dr Karen Ryan, Consultant in Palliative Medicine, St. Francis Hospice, Dublin, and Clinical Lead of the National Clinical Programme for Palliative Care.

Finally we would like to thank the NCEC guideline appraisal team, and Dr Kathleen Mac Lellan, in particular for their assistance in bringing this guideline to completion.



Dr Brenda O'Connor,
Chairperson of the Guideline Development Group,
Clinical Lecturer and Research Fellow in Palliative Medicine, Our Lady's Hospice and Care Services, Harold's Cross, Dublin.

Disclaimer

The Guideline Development Group's expectation is that healthcare staff will use clinical judgement, medical, nursing and clinical knowledge in applying the general principles and recommendations contained in this document. Recommendations may not be appropriate in all circumstances and the decision to adopt specific recommendations should be made by the practitioner taking into account the individual circumstances presented by each patient/ resident and available resources.

Therapeutic options should be discussed with the responsible physician on a case-by-case basis as necessary.

Drug costs may fluctuate and the costs in Tables 4 and 5 were prepared in 2014.

Table of Contents

List of tables

List of Figures

1 Background

1.1 Grading of recommendations

1.1.1 Key to grading method used to highlight quality of evidence and recommendations

This guideline uses a system for grading the quality of evidence based on the Centre for Evidence Based Medicine (CEBM) method of Oxford University as follows(2):

- Level 1a Meta analyses of randomised control trials (RCT)
- Level 1b At least one RCT
- Level 2a At least one well designed controlled study without randomisation or Systematic Review (SR) of cohort studies
- Level 2b A well designed cohort study
- Level 3 Well designed experimental descriptive studies, such as case control or cross sectional studies
- Level 4 Case Series
- Level 5 Expert Committee/Clinical experience

Grading the strength of recommendations:
This guideline also uses the system based on the CEBM approach for grading the strength of recommendations as follows:

- A Level 1 studies
- B Level 2 or 3 studies
- C Level 4 studies
- D Level 5 studies or inconsistent or inconclusive studies of any level

Considered judgement:
The Scottish Intercollegiate Guideline Network (SIGN) introduced the concept of considered judgement when formulating evidence based recommendations in their guideline development handbook (SIGN 50) (3). Through the process of considered judgement, guideline developers are able to downgrade a recommendation if inconsistencies are identified within the evidence base. Potential inconsistencies include a lack of generalisability of the evidence, a lack of direct applicability to the target population, or if the evidence is perceived as being weaker than a simple evaluation of the methodology would suggest. As such, the recommendations made are a reflection of both the strength of the evidence informing the recommendation, and the guideline development group's (GDG) interpretation of the recommendation that can be made based on that evidence. This principle was applied throughout the entire guideline.

1.2 Need for National Clinical Guideline: Management of Constipation in Adult Patients Receiving Palliative Care

1.2.1 Clinical burden

Constipation is one of the most common symptoms experienced by patients with advanced, progressive illness. The prevalence is estimated at 30-90% depending on the population studied (4, 5). In palliative medicine, constipation is the third most frequently encountered symptom after pain and anorexia (6). Common factors which increase the risk of constipation in this population include physical illness, hospitalisation, reduced fluid intake and the use of opioids (7). Constipation can occur at any stage in the disease trajectory, but evidence suggests that constipation is more problematic in advanced disease(8). When present, constipation causes considerable suffering for the affected individual, either as a direct consequence of the physical symptoms or due to related social and psychological complications.

Constipation remains poorly recognised and undertreated by healthcare providers (7, 9). This is driven by the lack of a universally agreed definition of constipation and the disparity between patients and health professionals as to what constitutes constipation (4). Constipation will have a different meaning to each individual. A study of 531 patients attending family clinics demonstrated that 50% of respondents gave a different definition of constipation compared to their physician (10).

There is a wealth of evidence to suggest that the treatment of constipation can and should be improved, however this is frequently delayed until constipation has become a significant problem (11). Failure to diagnose and treat constipation leads to a range of symptoms including anorexia, nausea, abdominal pain, and bowel obstruction. Studies have demonstrated that constipation is inadequately treated in a significant proportion of palliative care patients (12, 13). Prescribing practice lacks consistency and despite laxative therapy, up to 70% of patients receiving palliative care continue to experience symptomatic constipation (14, 15). This suggests that the management of constipation in this population needs to be improved.

1.2.2 Variation in practice and potential for improved health

Apart from cancer-related pain, there is a lack of strong evidence-based guidelines to assist the management of the physical symptoms experienced by patients with advanced progressive illness. Although laxative use is commonplace in palliative care, there is surprisingly little evidence available to guide the choice of laxative (11). A recent Cochrane review conducted by Miles et al, 2006, concluded that "the treatment of constipation in palliative care is based on inadequate experimental evidence". As a result, there persists an uncertainty about "best" management in this group of patients (16).

As scientific evidence is so limited, long years of clinical experience have yielded recommendations based primarily on consensus expert opinion (7, 17-20).

Constipation in advanced illness is clearly a symptom that needs to be addressed. In order to successfully adopt best practice, standardisation of assessment and care processes is critical (21). The development of this guideline aims to inform, aid, and support healthcare professionals to implement this process in Ireland.

1.2.3 Resource implications of constipation in adults receiving palliative care

Constipation affects up to 90% of patients with advanced illness (3, 4). In addition to the well-described impact on quality of life, suboptimal treatment may result in a number of serious complications that often necessitate hospitalization (7).

Although the burden of constipation is well recognised, the economic impact remains difficult to estimate with a paucity of studies evaluating the cost of constipation on health services and society in general (22). This lack of data is particularly true of constipation in advanced life-limiting illness.

As the cost of healthcare continues to rise in the setting of limited resources, clinicians require evidence not only on the efficacy and safety of therapeutics but also their cost to assist them in making an informed selection. Drug therapy of constipation cannot be considered in isolation; patient education, constipation prevention and non-pharmacological measures must also be taken into account (23).

In the development of this guideline, a formal systematic literature search was undertaken to evaluate the economic impact of constipation. Further details on the search may be found in Appendix I. Forty eligible studies were identified but only 10 were deemed suitable for inclusion in the qualitative synthesis. The paucity of studies available for inclusion may be attributed to the fact that there is a historic lack of comparative studies evaluating older laxatives, and that few new laxatives have been produced in recent years.

Only one study, from 2010, evaluated the cost burden of managing constipation in advanced illness (24). This observational study was undertaken in a United Kingdom specialist palliative care inpatient unit and focused on the management of opioid-induced constipation over a 6-month period. Costs associated with the management of constipation were calculated with respect to staff time and consumable items. The direct cost of managing constipation was estimated at €2,707.93 (£2,284.64) with a mean cost per admission of €38.68 (£32.63). The majority of the cost (85%) was for staff time, with only 13% attributed to drug expenditure. The total cost of managing constipation over a 6-month period was estimated at €14,417 (£12,160) once staff discussions about bowel care at handover meetings were taken into account (24). The results of this study are likely to be highly relevant in the Irish inpatient setting as the model of inpatient unit care is similar in both countries, however there are differences between countries in terms of staff and drug costs.

Resource implications for the management of constipation related to advanced illness have yet to be evaluated in the community setting. However, a study from 2014 investigated healthcare resource use and cost of prescription laxatives in 10,371 patients with chronic constipation in a primary healthcare setting in the United Kingdom (25). The mean number of consultations in a 12-month period was 4, with 92% prescribed a laxative (average of 8 prescriptions in 12 months). The mean cost to the National Health Service was estimated at €39.83 (£35.41) per person per year. Higher treatment costs were associated with increased age and co-morbidity (25). A similar study in the United States evaluated 8,745 patients with chronic constipation, of whom 54.9% were identified to have unmet needs, with more healthcare resource utilisation, increased inpatient days and emergency admissions as a result. Indicators of unmet clinical needs were associated with a €2,501.47 incremental annual healthcare cost compared to patients without these indicators. This cost difference was mainly driven by hospitalisation and pharmacy costs (26).

Resource utilisation associated with the diagnosis and management of constipation is a significant driver of increased cost (22). Much additional research is needed to determine the most cost-effective method to treat constipation in advanced illness. To date a limited number of studies have focused on chronic constipation suggesting macrogol preparations as a cost-effective alternative to lactulose (27, 28). Pharmaceutical-sponsored trials have investigated the use of methylnaltrexone and oxycodone/naloxone preparations for laxative resistant opioid-induced constipation. Although these preparations are markedly more expensive than the standard prescription of an opioid with a laxative, these studies demonstrated a marginal cost benefit in terms of quality of life (29, 30). The generalisability of these studies remains unknown. Further trials comparing different classes of laxatives in advanced illness are required. Both the relative impact of laxative classes on constipation symptoms and cost-effectiveness should be evaluated to enable specific recommendations.

This guideline aims to consolidate and improve the quality of current clinical practice regarding the management of constipation. The current national standard of practice in this area is unknown, and therefore it is not possible to quantify with a reasonable degree of certainty what impact the recommendations will have on resources nationally. The guideline might have resource implications at a local level as a result of variation in clinical practice across the country. Therefore, organisations are encouraged to evaluate their own practices against the recommendations in the guideline (using the audit tool provided) and assess costs locally. Some of the resource effects to be considered locally are discussed in the following paragraphs.

The expert opinion of the GDG considers there to be a variation in the current practice of constipation assessment which is addressed in recommendation 1 (1.1-1.5). However, expert opinion is that the recommendation represents a formalisation of best practice for healthcare professionals, and should not need additional resources if continuing professional development activities are used as a means of addressing identified practice gaps. Expert opinion considers that savings may be made by reducing the number of inappropriate diagnostic imaging procedures (i.e. plain film of abdomen) undertaken.

Recommendation 2 (2.1-2.2) focuses on prevention and formalises best practice in this area. It is expected that education of service users would be carried out by the relevant healthcare staff involved in the individual's care (doctor, nurse, and dietitian). The cost of staff time would be included in their existing contractual payments. Regular review of potentially constipating agents and the appropriate prescription of prophylactic laxatives would be expected to be carried out by doctors, pharmacists or nurse prescribers and the cost of staff time would also be included in their existing contractual payments. The healthcare professionals responsible for these activities are already in post and it is not expected that additional staff would be required to implement these recommendations. The expert clinical opinion of the GDG was that the recommendation to appropriately prescribe prophylactic laxatives could lead to increased prescribing costs, (see Table 5 and Table 6 for costs of laxatives in Ireland). However, as improved prevention is expected to reduce incidence of constipation and its associated costs, it was considered that the increased expenditure had the potential to be offset against savings (e.g. hospital admissions will be avoided). Releasing staff time from treating constipation makes it possible to treat more patients within the same capacity, potentially improving the efficiency of the organisation.

Recommendation 3 (3.1-3.2) is not considered to have a resource impact for organisations at a local level as it refers to lifestyle and environmental modifications.

Recommendations 4 (4.1-4.4), 5 (5.1-5.4), 6 (6.1-6.2) and 7 relate to the use of medications in the management of constipation or its complications. No specific medication is recommended and therefore there are no specific costing impacts; rather guidance is provided on best practice in selection, initiation, titration and discontinuation of medications. As a general principle it is advised to use the medication with the lowest cost base where there is no differential benefit between medications, which is supported in feedback from the Medicines Management Programme (see Appendix II). Attention is drawn to the fact that at present, oxycodone/naloxone preparations are significantly more expensive than standard oxycodone prescribed with a regular laxative and it advised that this should be taken into consideration in practice. There is therefore potential for cost savings with promotion of carefully considered and informed practice.

Best Practice Point: Pharmacoeconomics
Where there is no evidence of a differential benefit between different medications in terms of efficacy, tolerability or side effect profile, and where clinical expertise allows, the medication with lowest cost base should be used.

1.3 Aim of National Clinical Guideline

The purpose of this guideline is to provide recommendations based on best available evidence for the management of constipation in adult patients with life-limiting conditions in receipt of generalist or specialist palliative care across all healthcare settings.

The recommendations of this document should not be used in isolation without giving due consideration to individual clinical circumstances and patient preference.

This guideline aims to benefit adult patients with a life-limiting condition who are suffering from constipation. The expected outcome of the recommendations made in this guideline is to prevent or reduce constipation and improve quality of life.

1.4 Scope of National Clinical Guideline, target population and target audience

This guideline applies to adult patients with a life-limiting illness and is for use by healthcare professionals providing generalist or specialist palliative care in hospital, hospice and community-based settings. This includes specialist palliative care providers, physicians, surgeons, general practitioners, nurses, pharmacists and dietitians. For those providing generalist palliative care, the guideline recommendations indicate where specialist advice should be sought.

This guideline may also be of interest to patients with a life-limiting condition and their carers. A patient information leaflet can be accessed on the National Clinical Programme for Palliative Care Website http://www.hse.ie/palliativecareprogramme and NCEC website www.health.gov.ie/patient-safety/ncec.

This guideline should not be used in patients without a life-limiting illness. This guideline does not apply to children.

1.5 Legislation and other related policies

The use of medicines which are unlicensed in Ireland but licensed elsewhere is commonplace in palliative care practice (31). Referred to as "exempt medicinal products" the use of these medications is safeguarded in legislation in accordance with the Medicinal Products (Control of Placing on the Market) Regulations 2007 (32). This is distinct from the "off-label" use of drugs which refers to the use of a licensed medicinal product outside the terms of its product authorisation according to the summary of product characteristics (32). A quarter of all palliative care prescriptions are written for "off-label" use of drugs (33, 34). This may involve the administration of a licensed product via an unlicensed route. The unlicensed use of drugs by prescribers is often appropriate and guided by clinical judgment. Furthermore, drugs prescribed outside license can be dispensed by pharmacists and administered by nurses or midwives (35).

1.6 Roles and responsibilities

It is the role of healthcare line managers (36) to ensure that relevant personnel are aware of this guideline. It is also the role of line managers to ensure that training is available for staff where necessary to ensure that staff possess an appropriate level of palliative care competence and knowledge, as outlined in the Palliative Care Competence Framework of 2014, to put these guidelines into practice (37).

Each healthcare provider is accountable for their own practice and answerable for decisions that he or she makes. Individuals should be prepared to make explicit the rationale for their decisions, and justify them in the context of legislation, evidence-based practice, professional

and ethical conduct. All healthcare staff providing generalist and specialist palliative care in hospital, hospice and community-based settings should:

- comply with this National Clinical Guideline and related policies, procedures and protocols
- adhere to their code of conduct and scope of practice guidelines as appropriate to their role and responsibilities
- maintain competence in the management of constipation in adult palliative care patients
- in using this guideline be aware of the role of appropriate delegation and referral to specialists when necessary.

1.7 Guideline Development Group

1.7.1 Guideline Development Group (GDG)

The GDG, comprised of three palliative medicine physicians and a clinical nurse specialist in palliative care, carried out the work involved in developing the guideline, supported by a mentor and a number of individuals listed in Appendix III.

1.7.2 Conflict of interest

The GDG members were required to complete a conflict of interest form. No conflict of interest was identified.

Professor Philip Larkin is a primary author in the recommendations published by the European Consensus Group on Constipation in Palliative Care in 2008 (7), which was supported by an unrestricted educational grant from Norgine Pharmaceuticals. Although these recommendations are used as a source for this guideline, Professor Larkin was not directly involved in the AGREE and ADAPTE grading which resulted in its selection.

1.7.3 Funding and editorial independence

The All Ireland Institute of Hospice and Palliative Care (AIIHPC) awarded an educational bursary to Dr Brenda O'Connor, Dr Jodie Battley and Ms Louise Duddy to develop the guideline. The AIIHPC had no editorial influence on the content of this guideline.

1.8 Methodology and literature review

1.8.1 The ADAPTE Collaboration

The recommendations of this guideline were developed according to the principles of the ADAPTE process for guideline adaptation. The ADAPTE Collaboration (38) is an international collaboration of researchers, guideline developers, and guideline implementers who aim to promote the development and use of clinical practice guidelines through the adaptation of existing guidelines. They define guideline adaptation as the systematic approach to the endorsement and/or modification of a guideline(s) produced in one cultural and organisational setting for application in a different context. The ADAPTE Collaboration has developed a systematic approach for the adaptation of guidelines. Adaptation may be used as an alternative to the development of a de-novo guideline or to customise an existing guideline to suit the local context.

1.8.2 Process

The GDG was responsible for developing the guideline using the ADAPTE process. A summary of the adaptation process is given in Appendix IV.

Following the completion of the guideline by the GDG, the document was circulated through the National Clinical Programme for Palliative Care for an extensive consultative process. This consultation involved all relevant national and regional stakeholder bodies. The guideline was made available on the National Clinical Programme for Palliative Care website and circulated to the members of the National Clinical Programme for Palliative Care Working Group (including medical, nursing, pharmacy and allied health representation) and the RCPI Clinical Advisory Group for Palliative Care. Information was circulated through the All Ireland Institute of Hospice and Palliative Care contact database. Formal feedback was received and tabulated by the GDG, and responses to any suggestions made were documented (see Appendix XIII).

1.8.3 Existing guidelines

There are a number of international guidelines on the management of constipation in advanced illness. These guidelines have been identified through a formal systematic literature search facilitated by the HSE library, graded for methodological rigour, and considered for inclusion in the development of this guideline. Through a search of electronic databases (Medline, CINAHL, EMBASE and Google Scholar), and websites of known guideline clearinghouses, as suggested by the ADAPTE Collaboration(38), eleven existing guidelines/recommendations were identified.

In order to identify the most rigorously developed recommendations, these documents were assessed and scored by two members of the GDG according to the Appraisal of Guidelines through Research and Evaluation (AGREE II) tool (39). The AGREE II instrument is an internationally recognised means of assessing the quality of a clinical guideline. An overall assessment score is assigned once the guideline has been appraised for rigour of development and quality of reporting. The AGREE II scores are presented in Appendix V.

Using the AGREE II instrument, the following five guidelines were identified to have sufficient methodological rigour to be considered for adaptation to the Irish context:

1. Consensus Recommendations for the Management of Constipation in Patients with Advanced Progressive Illness. The Canadian Consensus Development Group for Constipation in Patients with Advanced Progressive Illness (17).
2. The Management of Constipation in Palliative Care: Clinical Practice Recommendations. The European Consensus Group on Constipation in Palliative Care (7).
3. Putting Evidence into Practice: Evidence-based Interventions for the Prevention and Management of Constipation in Patients with Cancer. Oncology Nursing Society (19).
4. Palliative Care for the Patient with Incurable Cancer or Advanced Disease Part 2: Pain and Symptom Management Constipation (20).
5. Constipation Nationwide Guideline. Oncoline (18).

In order to assess the clinical content of each guideline, a recommendations matrix was constructed in accordance with the ADAPTE process. The recommendations matrix was most useful when more than one source guideline was under consideration. This enabled the reviewers to compare the wording and level of evidence of similar recommendations made within each guideline. This table was used as a resource by the reviewers when formulating recommendations. The reviewers then assessed the guidelines for currency, consistency, acceptability, and applicability of these recommendations.

A copy of the recommendations matrix is available in Appendix VI.

1.8.4 Source guidelines

Following assessment with the AGREE II and ADAPTE tools, two high quality guidelines were selected for adaptation. These guidelines were deemed as being of an acceptable standard to

directly refer to in our adapted guideline. These source guidelines may be directly referenced in this document, without a requirement to cite a primary evidence source.

1.8.4.1 Consensus Recommendations for the Management of Constipation in Patients with Advanced, Progressive Illness; The Canadian Consensus Development Group for Constipation in Patients with Advanced Progressive Illness [17]

The Canadian Consensus Development Group for Constipation in Patients with Advanced Progressive Illness is comprised of a multidisciplinary group of leading Canadian palliative care specialists. They developed the consensus recommendations in an effort to define best practices in palliative care constipation management that are relevant and useful to healthcare professionals. As there is a limited body of evidence evaluating pharmacological interventions in constipation, the recommendations are based on the best of the existing evidence, combined with expert opinion derived from experience in clinical practice. They were developed according to the ADAPTE protocol, and published in 2010.

This document is considered by the GDG to reflect best evidence, up to the date of publication and is therefore the primary source for adaptation.

1.8.4.2 The Management of Constipation in Palliative Care: Clinical Practice Recommendations: The European Consensus Group on Constipation in Palliative Care [7]

The European Consensus Group on Constipation in Palliative Care is comprised of pan-European healthcare professionals with significant experience in the management of constipation in palliative care. In 2008, they developed and published recommendations to provide clear practical guidance on the management of constipation in palliative care. These recommendations reflect best clinical practice in the countries represented. Following assessment using the AGREE II and ADAPTE tools this document was also chosen to inform the development of this guideline as the recommendations are particularly relevant to the Irish context.

1.8.5 Definition of health questions

In parallel with the above guideline search process, the GDG identified relevant health questions related to key areas of importance in the management of constipation in patients with life-limiting conditions. These health questions reflected areas to be addressed within the guideline. They were reviewed, adjusted and finalised in consultation with the Guideline Steering Group (See Appendix VII).

1.8.6 Literature search

Once the two source guidelines were selected, the GDG commenced the process of updating this document by identifying recent literature. As the European Consensus Group completed their literature search in 2006, this was considered an appropriate starting point. The GDG undertook a literature search on each of the defined health questions for the period between January 2006 and July 2014.

The databases used for the literature search were the Cochrane Database of Systematic Reviews, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline (PubMed), Embase and Google Scholar.

A sample search diagram is included in Appendix VIII. A summary of the literature search for each health question is available in Appendix IX.

1.8.7 Reviewing the evidence and consensus techniques

On completion of a literature search for each health question, the resulting search abstracts were reviewed. Ineligible abstracts were excluded, and the remaining articles reviewed in their entirety by two members of the GDG. Relevant articles were identified. This search, alongside the source guidelines, provided the evidence base from which the guideline recommendations were derived. A level of evidence was then assigned to each recommendation.

A value-based consensus decision-making model was decided upon in the event of any significant issues relating to the formation of a consensus (40). However no significant issues arose and consensus was achieved without resorting to the model.

1.9 External review

The guideline was reviewed by two international experts. Professor Lukas Radbruch, Chair of Palliative Medicine, University of Bonn; Director of Department of Palliative Medicine, University Hospital Bonn, Director of Palliative Care Centre, Malteser Hospital Bonn/Rhein-Sieg and Associate Professor Max Watson, Consultant in Palliative Medicine/Lecturer in Palliative Care, Northern Ireland Hospice, Belfast provided their expertise without gratuity.

The external reviewers evaluated the draft document and provided commentary at key stages of the process. A thematic summary of their review is presented in Appendix X.

1.10 Implementation of National Clinical Guideline

1.10.1 Dissemination

The National Clinical Programme for Palliative Care Working Group and the GDG will take responsibility for guideline dissemination through the following actions:

- The guideline document summary will be published on the National Clinical Programme for Palliative Care website and other forums such as the RCPI and NCEC websites.
- Local and national media will be used to publicise both the development process and the availability of the guidelines.
- Professional journals will be used to inform about the guideline development and to promote the completed guideline.
- Communication links developed by the HSE, specialist palliative care service providers and specialty societies, service user groups, and universities will be used to promote guideline dissemination and utilisation in all areas. This encompasses hospitals, hospices, community palliative care services, GPs and charitable foundations.
- The educational processes of relevant colleges, professional organisations, healthcare providers and consumer groups, (including conferences, workshops and Continuing Professional Development activities) will be used to promote guideline dissemination and utilisation.
- Potential users and clinical leaders have been involved throughout the guideline development and consultation process, ensuring community ownership of the guideline.

1.10.2 Facilitation of action

It is recognised that there is significant variation in multidisciplinary team structure and responsibilities between care settings. However, the recommendations are deemed relevant for implementation in all healthcare settings. A favourable implementation climate has been created through the work of the National Clinical Programme for Palliative Care to date.

- Stakeholder advisory groups have been established for medical, nursing and allied health professional groups, and members are actively engaged in supporting Clinical Programme activities. Communication pathways exist between the Clinical Programme and the

stakeholder advisory groups that will allow for regular communication with staff throughout the process and trouble-shooting of any possible implementation problems.
- A number of implementation tools have been developed and will be made available on the National Clinical Programme for Palliative Care and NCEC websites.
- Audit of important components will be promoted and encouraged, with feedback of the results, to highlight successes as well as challenges in their full implementation.
- Development of an online learning module would support implementation and is planned in collaboration with the AIIHPC.
- Regulators and education providers should give consideration to the education requirements highlighted by the guideline recommendations. Current curricula should be reviewed to incorporate these requirements.

1.11 Audit and monitoring

To ensure that this guideline positively impacts on patient care, it is important that implementation is audited. Audit is recommended to support continuous quality improvement in relation to the implementation of the National Clinical Guideline.

Quality assurance and quality improvement activities have a complementary relationship with clinical guidelines. Quality assurance activities encourage the implementation of guidelines which in themselves are a crucial component of such activities. A number of Excel-based resources have been developed to assist in audit activities:
- Baseline assessment tool
- Audit tool
- Action plan template.

These tools may be found on the National Clinical Programme for Palliative Care website and the NCEC website.

Table 1 Suggested recommendations for audit

Recommendation	Number
Assessment	
A thorough history and physical examination are recommended as essential components of the assessment process.	**1.1**
A digital rectal examination (DRE) should be considered to exclude faecal impaction if it has been more than 3 days since the last bowel movement or if the patient complains of incomplete evacuation (following appropriate DRE training).	**1.3**
A plain film of the abdomen (PFA) is **not** recommended for routine evaluation but may be useful in combination with history and examination in certain patients.	**1.5**
Prevention	
Education on the importance of pharmacological and non-drug measures is essential to enable patients and caregivers to take an active role in constipation prevention.	**2.1**
Non-pharmacological Management	
Attention should be paid to the provision of optimised toileting while ensuring adequate privacy and dignity for all patients.	**3.1**
Consideration should be given to lifestyle modification including the adjustment of diet and activity levels within a patient's limitations.	**3.2**
Pharmacological Management	
The combination of a softening and a stimulating laxative is often required. Optimisation of a single laxative is recommended prior to the addition of a second agent.	**4.3**
The laxative dose should be titrated daily or alternate days according to response.	**4.4**
Opioid Induced Constipation	
The development of opioid induced constipation should be anticipated. A bowel regimen should be initiated at the commencement of opioid therapy.	**5.1**
In the management of opioid induced constipation, optimised monotherapy with a stimulant laxative is essential followed by the addition of a softener if required. The current evidence is too limited to provide evidence-based recommendations for the choice of stimulant laxative and selection should be made on an individual basis.	**5.2**
The use of opioid receptor antagonists under specialist guidance should be considered in patients whose treatment is resistant to conventional laxative therapy.	**5.4**
Intestinal Obstruction	
A stool softener should be considered in partial intestinal obstruction. Stimulant laxatives should be avoided.	**6.1**
In complete intestinal obstruction, the use of all laxatives should be avoided as even softening laxatives have some peristaltic action.	**6.2**

1.12 Further research

The GDG has highlighted a number of areas that they consider of interest when considering future research in the area of constipation management in life-limiting conditions:

- Correlation between patients and healthcare professionals' definition of constipation in palliative care.
- The sensitivity and specificity of constipation assessment tools in patients with life-limiting illness.
- An evaluation of the patient experience and patient outcomes of using symptom assessment tools.
- An evaluation of the patient experience of using symptom assessment tools at different stages of their illness trajectory.
- The value of radiology in the assessment of constipation in palliative care patients.
- Evaluation of the interface between pharmacological and non-pharmacological management of constipation.
- Evaluating the effectiveness of complementary therapies in treating constipation.
- The economic impact of constipation management in palliative care.
- Randomised controlled trials:
  - Comparing the relative efficacy of different oral laxatives in patients with constipation.
  - Comparing the relative efficacy of different rectal laxatives in patients with constipation.
  - Investigating the optimal management of opioid-induced constipation.

1.13 Procedure for update of National Clinical Guideline

This guideline was published in November 2015 and is due for review in three years. The evidence and recommendations will be reviewed and updated every three years by the National Clinical Programme for Palliative Care with support and will be reported through the National Clinical Programme for Palliative Care website. These are formal evidence searches on the clinical questions and the recommendations that follow a standardised methodology. In doing this, it is anticipated that the guideline will be maintained in terms of currency and relevance. Any updates will be submitted to NCEC for review and inclusion in the National Clinical Guideline.

1.14 Glossary of Terms, Definitions and Abbreviations

The main referenced definitions are in the relevant sections as they arise. A glossary of abbreviations is available in Appendix XI.

1.15 Further resources and accompanying documents

The following documents and resources are available at www.hse.ie/palliativecareprogramme and numbers 1, 2, 3, 4 and 5 are also available from www.health.gov.ie/patient-safety/NCEC

1. National Clinical Guideline No 10 Management of Constipation in Adult Patients Receiving Palliative Care Summary of Key Recommendations
2. National Clinical Guideline No 10 Management of Constipation in Adult Patients Receiving Palliative Care Guideline Audit Tool
3. National Clinical Guideline No 10 Management of Constipation in Adult Patients Receiving Palliative Care Guideline Audit Tool Guidance
4. *Relief from Constipation* Patient Information Leaflet
5. National Clinical Guideline No 9 Pharmacological Management of Cancer Pain in Adults
6. Palliative Care Competence Framework (37)
7. Glossary of terms (1)
8. Role Delineation Framework (41)

2 National Clinical Guideline recommendations

2.1 Summary of National recommendations

Key recommendations are outlined below numbered **Recommendation1-7**; with the strength of evidence for the recommendation to follow (A/B/C/D), based on the CEBM method of Oxford University. Grade A recommendations represent the strongest level of recommendation based on the strongest evidence, and Grade D recommendations are based on lower levels of evidence.

Best practice point
Where possible, the assessment and management of constipation should be delivered within a multidisciplinary team with a clearly identified clinical lead and active communication between all team members.

This guideline is for use by healthcare professionals providing generalist or specialist palliative care to patients with a life-limiting illness in hospital, hospice and community-based settings. This includes specialist palliative care providers, physicians, surgeons, general practitioners, nurses, pharmacists and dietitians. For those providing generalist palliative care, the guideline recommendations indicate where specialist advice should be sought.

Responsibility for implementation

CEO/General Managers/Line Managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with palliative care needs are responsible for implementation of recommendations 1-7.

Recommendation 1 Constipation assessment

Key finding A comprehensive assessment is required to accurately diagnose the presence and potential causes of constipation in patients with life-limiting illnesses.	
Key recommendations	
D	**1.1** A thorough history and physical examination are recommended as essential components of the assessment process.
D	**1.2** Constipation assessment scales may be useful in encouraging patient self-assessment or when communication is difficult. Due to a lack of evidence in the use of constipation assessment scales in day-to-day clinical practice they are **not** recommended for routine use.
D	**1.3** A digital rectal examination (DRE) should be considered to exclude faecal impaction if it has been more than 3 days since the last bowel movement or if the patient complains of incomplete evacuation (following appropriate DRE training).
D	**1.4** Caution is advised when considering a DRE in immuno-compromised or thrombocytopaenic patients.
D	**1.5** A plain film of the abdomen (PFA) is **not** recommended for routine evaluation but may be useful in combination with history and examination in certain patients.

Recommendation 2 Prevention

Key finding Preventative measures for constipation should be ongoing throughout the patient's disease trajectory.	
Key recommendations	
D	**2.1** Education on the importance of pharmacological and non-drug measures is essential to enable patients and caregivers to take an active role in constipation prevention.
D	**2.2** Medications should be reviewed in order to identify potentially constipating agents and prophylactic laxatives prescribed when appropriate. Unless there are existing alterations in bowel patterns (bowel obstruction or diarrhoea) all patients prescribed regular opioids should be started on a laxative regimen and receive education on bowel management.

Recommendation 3 Non-pharmacological management

Key finding Non-pharmacological strategies in the management of constipation are at least as important as the use of pharmacological agents.	
Key recommendations	
D	**3.1** Attention should be paid to the provision of optimised toileting while ensuring adequate privacy and dignity for all patients.
D	**3.2** Consideration should be given to lifestyle modification including the adjustment of diet and activity levels within a patient's limitations.

Recommendation 4 Pharmacological management

In particular, physicians, surgeons, general managers, nurses, pharmacists and dietitians caring for patients with palliative care needs are responsible for the implementation of recommendation 4.

Key finding a. Pharmacological agents are a necessary component of the management of established constipation in life-limiting illness. b. There is a lack of evidence to support the use of any one laxative over another.	
Key recommendations	
D	**4.1** The choice of laxative should be guided by individual patient preference and circumstances.
D	**4.2** Where there is no evidence to differentiate between medications in terms of efficacy, tolerability and side effect profile, and where clinical expertise allows, the medication with lowest cost base should be used.
D	**4.3** The combination of a softening and a stimulating laxative is often required. Optimisation of a single laxative is recommended prior to the addition of a second agent. The ratio of softener: stimulant should be guided by faecal consistency.
D	**4.4** The laxative dose should be titrated daily or alternate days according to response.

Recommendation 5 Opioid induced constipation

Key finding Constipation is a common and distressing side effect of opioid therapy.	
Key recommendations	
D	**5.1** The development of opioid induced constipation should be anticipated. A bowel regimen should be initiated at the commencement of opioid therapy.
D	**5.2** In the management of opioid induced constipation, optimised monotherapy with a stimulant laxative is essential followed by the addition of a softener if required. The current evidence is too limited to provide evidence-based recommendations for the choice of stimulant laxative and selection should be made on an individual basis.
D	**5.3** Where there is no evidence to differentiate between medications in terms of efficacy, tolerability and side effect profile, and where clinical expertise allows, the medication with lowest cost base should be used.
D	**5.4** The use of opioid receptor antagonists under specialist guidance should be considered in patients whose treatment is resistant to conventional laxative therapy.

Recommendation 6 Intestinal obstruction

Key findings a. If intestinal obstruction is suspected, this should be evaluated by history, examination and appropriate radiological investigations. b. Specialist referral for either surgical or medical management should be considered.	
Key recommendations	
D	**6.1** A stool softener should be considered in partial intestinal obstruction. Stimulant laxatives should be avoided.
D	**6.2** In complete intestinal obstruction, the use of all laxatives should be avoided as even softening laxatives have some peristaltic action.

Recommendation 7 Management of constipation in the dying patient

Key finding In the last days of life, bowel movements become less frequent as a consequence of proximity to death.	
Key recommendation	
D	**7.** As a patient's level of consciousness deteriorates, oral laxatives should be discontinued. Rectal intervention is rarely required at this stage.

2.2 Constipation in palliative care

The primary goal of palliative care is the optimisation of patient quality of life. Collaboration between healthcare providers, the patient and family is essential in the development of management strategies that promote comfort and maintain dignity (17). Treatment of burdensome symptoms such as constipation is an essential part of palliative care.

2.2.1 Prevalence

Constipation is one of the most frequently encountered symptoms in the palliative care population and has the potential to significantly impair quality of life (5). Estimated prevalence rates of constipation in palliative care patients vary from 30% to 90% (42). Such wide variation is likely to reflect the lack of an agreed-upon definition of constipation and is dependent on the population of patients assessed (5).

Constipation remains poorly recognised and undertreated by healthcare providers (7, 9). In some cases, constipation may even be considered a low priority in the overall management of patients with advanced illness (7). The lack of a universally agreed definition of constipation and the disparity between patients and health professionals as to what constitutes constipation significantly contribute to the challenge of managing constipation in this population (43).

2.2.2 Defining constipation

Constipation is a highly subjective symptom and what constitutes normal bowel habit varies between individuals. In general, two aspects should be taken into consideration in defining constipation in patients with advanced illness (44).

- The first of these are measurable objective symptoms including frequency of defecation and stool characteristics.
- The second is the patient's perception of constipation including ease of defecation and associated level of discomfort.

For the purpose of this guideline, constipation is considered to be the infrequent (relative to a patient's normal bowel habit), difficult passage of small, hard faeces (44). However, the use of these criteria alone in defining constipation may fail to capture associated subjective symptoms which should also be taken into account. These include pain on defecation, flatulence, bloating, straining, unproductive urges or a sensation of incomplete evacuation (7, 17, 44). Although bowel frequency varies between individuals, if a patient is defecating less than three times per week, as used in the Rome III criteria for defining chronic constipation, assessment is recommended (17).

Level 5

2.2.3 Impact of constipation in palliative care

The negative impact of constipation should not be underestimated. Constipation has been reported to rival the distress caused by pain (45). Constipation-related sequelae include nausea, vomiting, anorexia, haemorrhoids, anal fissures, bowel obstruction and urinary retention. Furthermore, constipation itself is an independent cause of delirium (46). These factors can significantly impact on a patient's quality of life and may necessitate the use of additional medications, emergency visits and hospitalisation (47).

The consequences of untreated constipation are not limited to those experienced by patients and carers. It also places a significant burden on the healthcare system. Constipated palliative care patients receive more community nursing support and are 20% more likely to be hospitalised (48, 49). Hospitalised patients with constipation require increased nursing time. A study undertaken with hospice patients suggests that earlier and more effective interventions for this group will result in significant clinical and economic benefits (24). **Level 3**

2.2.4 Causal factors of constipation in palliative care

Multiple factors, both organic and functional, place patients with advanced illness at greater risk of constipation. The evidence that underlies opioids as a cause for constipation in palliative care is robust but the literature for other important causative factors is limited. Table 2 lists the common causes of constipation affecting palliative care patients. **Level 5**

Table 2 Contributing factors to constipation in patients with advanced progressive illness
(Adapted with permission from Sykes* 2004 (44))

Organic Factors	
Pharmacological agents	Opioid analgesics, anti-cholinergics, antacids, anti-convulsants, anti-emetics, anti-tussives, anti-diarrhoeals, anti-parkinsonians, neuroleptics, anti-depressants, iron, diuretics, chemotherapeutic agents
Metabolic disturbances	Dehydration, hypercalcaemia, hypokalaemia, uraemia, hypothyroidism, diabetes mellitus
Weakness/fatigue	Proximal and central myopathy
Neurological disorders	Cerebral tumours, spinal cord impingement or infiltration, autonomic dysfunction
Structural abnormalities	Pelvic tumour mass, radiation fibrosis
Pain	Painful anorectal conditions, uncontrolled bone pain and other cancer pain
Functional Factors	
Diet	Anorexia, reduced food intake, poor fluid intake, low fibre diet
Environmental/cultural	Lack of privacy, comfort or assistance with toileting, cultural sensitivities regarding defecation
Other factors	Advanced age, inactivity, decreased mobility, depression, sedation

*Source: Oxford Textbook of Palliative Medicine 3E edited by Derek Doyle, Geoffrey Hanks, Nathan Cherny & Sir Kenneth Calman (2004) Ch. 8.3.3 "Constipation and diarrhoea" by Nigel Sykes pp. 483–496, Table 2 (p. 485) and Table 6 (p. 487) adapted. See www.oup.com

2.2.5 Disciplines responsible for the management of constipation in palliative care

Collaborative and informed discussions between the patient, family and all healthcare professionals, particularly the disciplines of medicine, nursing and pharmacy, are essential to create an optimal multidisciplinary strategy for the assessment and management of constipation.

Best practice point
Where possible, the assessment and management of constipation should be delivered within a multidisciplinary team with a clearly identified clinical lead and active communication between all team members.

This guideline is for use by healthcare professionals providing generalist or specialist palliative care to patients with a life-limiting illness in hospital, hospice and community-based settings(1). This includes specialist palliative care providers, physicians, surgeons, general practitioners, nurses, pharmacists and dietitians. For those providing generalist palliative care, the guideline recommendations indicate where specialist advice should be sought.

2.3 Constipation assessment

A comprehensive history and physical examination is required.

2.3.1 Bowel history

The history should include a systematic assessment taking into account the patient's overall illness including their physical, psychosocial and functional needs.

A thorough history should establish the difference between the patient's current and usual bowel pattern. Particular attention should be paid to the common causes of constipation in patients with advanced progressive disease (see Table 2).

It is important to recognise that constipation may lead to paradoxical or 'overflow' diarrhoea, with leakage of fluid faeces past an impacted mass.

Assessment of current bowel performance should include the following:

- Onset of symptoms
- Aggravating and alleviating factors
- Frequency and pattern of bowel motions
- Stool volume and appearance (consistency, colour, odour, blood, mucous)
- Nausea
- Abdominal discomfort
- Bloating or flatus
- Tenesmus.

2.3.2 Constipation assessment scales

A number of constipation assessment scales have been developed to evaluate the presence and severity of constipation. They can be particularly useful in encouraging patient self-assessment or when communication is difficult. The use of images to describe stool consistency has been shown to be meaningful to patients (17). Although these scales are useful, validated tools for research and training, further prospective analysis in day-to-day practice is needed to confirm the clinical utility and as such, they are not recommended for routine practice. In order to be useful in clinical practice, essential elements of any scale include readability and completion time (7).

Level 5

2.3.3 Physical examination

Conduct a thorough physical examination for signs of constipation, taking into account cultural sensitivities and privacy.

The important elements of abdominal examination include the following:

- Distension
- Visible peristalsis
- Abdominal tenderness
- Faecal masses
- Nature of bowel sounds.

2.3.4 The use of digital rectal examination

The 2007 National Institute for Health and Care Excellence (NICE) guidelines recommend that a digital rectal examination (DRE) be included as an essential component of bowel assessment (50). This practice is underutilised in both non-palliative and palliative care patients (51). In supporting implementation of the guideline and if not already doing so, it is expected that providers of education and training in constipation management will include DRE training in existing and future programmes, with reference to this guideline, local practice, procedures, protocols and guidance (see section 1.10.2).

A DRE should be considered to exclude faecal impaction if it is more than 3 days since the last bowel movement, or the patient complains of incomplete evacuation (7). Individual patient circumstances should guide this decision. DRE should not be routinely conducted in actively dying patients. **Level 5**

Issues that should be assessed during a DRE include the following:

- Anal fissures or tears
- Haemorrhoids
- Anal sphincter tone
- Rectal dilatation
- Presence or absence of stool
- Stool consistency
- Rectal masses.

As the normal state of the rectum is empty, the absence of faecal matter on DRE does not necessarily exclude constipation (52). One study found that 30% of patients with an empty rectum had faecal loading in the sigmoid colon on x-ray (53). **Level 4**

Caution should be exercised in performing a DRE in thrombocytopaenic (Platelets $<20 \times 10^9$/L) or immuno-compromised patients (52). **Level 5**

2.3.5 The use of radiology

A plain film of the abdomen (PFA) is a simple, inexpensive and widely available test that is frequently used in patients in whom constipation is suspected (54).

However, the evidence assessing the validity and reliability of a PFA in the routine evaluation of constipation is contradictory (55-57).

There is little evidence specific to the palliative care population. A retrospective study by Bruera et al 1994, reviewed the assessment and diagnosis of constipation in 103 terminal cancer patients admitted to a palliative care unit. All patients underwent a PFA that scored for the presence of stool in the colon. There was good correlation between blinded assessments by two physicians (0.78). The authors suggest that a PFA might allow for faster diagnosis and treatment of constipation for inpatients and outpatients, potentially preventing or shortening hospital admissions (58). **Level 3**

A PFA may be particularly useful in patients who cannot provide a reliable bowel history, for example, patients with cognitive impairment. It may also provide clarification in suspected "overflow diarrhoea" (57). **Level 5**

Recent developments including manometric, neurophysiologic and radiologic techniques have been assessed in the diagnosis of chronic constipation. There are no studies investigating the use of these techniques in a palliative setting and their role is likely to be limited.

Recommendation 1 Constipation assessment

The following are responsible for implementation of recommendation 1

CEO/General Managers/Line managers are responsible for ensuring all healthcare staff are aware of this guideline. All healthcare staff caring for patients with palliative care needs are responsible for implementation.

Key Finding A comprehensive assessment is required to accurately diagnose the presence and potential causes of constipation in patients with life-limiting illnesses.	
Key recommendations	
D	**1.1** A thorough history and physical examination are recommended as essential components of the assessment process.
D	**1.2** Constipation assessment scales may be useful in encouraging patient self-assessment or when communication is difficult. Due to a lack of evidence in the use of constipation assessment scales in day-to-day clinical practice they are **not** recommended for routine use.
D	**1.3** A digital rectal examination (DRE) should be considered to exclude faecal impaction if it has been more than 3 days since the last bowel movement or if the patient complains of incomplete evacuation (following appropriate DRE training).
D	**1.4** Caution is advised when considering a DRE in immuno-compromised or thrombocytopaenic patients.
D	**1.5** A plain film of the abdomen (PFA) is **not** recommended for routine evaluation but may be useful in combination with history and examination in certain patients.

2.4 Prevention

In order to prevent or reduce constipation, patient and caregiver education is essential. Patients should be encouraged to take a proactive role in the prevention of constipation, however, research has highlighted that this strategy cannot be solely relied upon (7). **Level 5**

Prevention, like assessment, should be carried out on a continuous basis. Key elements of prevention should include (7):

- Ensuring maintenance of patient privacy and comfort to enable normal defecation
- Encourage physical activity within the patient's limits
- Increasing fluid and fibre intake where appropriate
- Recognition of potential constipating pharmacological agents with discontinuation when possible or provision of prophylactic laxative therapy for patients prescribed opioids.

Recommendation 2 Prevention

The following are responsible for implementation of recommendation 2

CEO/General Manager/Line managers are responsible for ensuring all healthcare staff are aware of this guideline. All healthcare staff caring for patients with palliative care needs are responsible for implementation.

Key finding Preventative measures for constipation should be ongoing throughout the patient's disease trajectory.	
Key recommendations	
D	**2.1** Education on the importance of pharmacological and non-drug measures is essential to enable patients and caregivers to take an active role in constipation prevention.
D	**2.2** Medications should be reviewed in order to identify potentially constipating agents and prophylactic laxatives prescribed when appropriate. Unless there are existing alterations in bowel patterns (bowel obstruction or diarrhoea) all patients prescribed regular opioids should be started on a laxative regimen and receive education on bowel management.

2.5 Non-pharmacological management

Once a diagnosis of constipation has been confirmed the degree of intervention should be guided by a patient's clinical status. Factors to consider include performance status, stage of disease and disease trajectory, the level of distress resulting from constipation and the patient's preference. The clinician's paramount concern should be the maintenance of patient comfort and dignity (17).

The primary objective of preventing and treating constipation should be to re-establish comfortable bowel habit to the patient's satisfaction and avoid constipation-related complications (7). Education, dietary recommendations and non-pharmacological interventions are at least as important as pharmacological treatment (18). However, once constipation is established, a combination of these measures is generally required (17).

Level 5

2.5.1 *Optimised toileting*

The physical environment should be reviewed to facilitate good sitting position and ensure privacy (visual, auditory and olfactory). Positioning both feet on a solid surface maximises abdominal muscle function to aid defecation. Sitting decreases the acuity of the anorectal angle facilitating faecal propulsion from the rectum into the anal canal, hence toilets and commodes should be used in preference to bedpans (59, 60). The most powerful gastro-colic reflex occurs in the morning, the patient should be encouraged to use the toilet twenty minutes after breakfast (17, 52). **Level 5**

2.5.2 *Fluid and fibre intake*

Insoluble fibre (e.g. bran, vegetables, whole grains) increases stool bulk and plasticity leading to colonic distension and promotion of peristalsis. When combined with adequate fluid it can help prevent constipation. Fibre-containing oral nutritional supplements are available.

Many palliative care patients suffer from anorexia leading to reduced dietary fibre intake. The amount of fibre required may be beyond the capabilities of patients in this population. A study undertaken in cancer patients undergoing radiotherapy demonstrated that a 450% increase in fibre intake would be required to produce a 50% increase in bowel frequency (7). **Level 2b**

Adequate fluid intake is an important factor in promotion of normal bowel function, however the ability to consume fluids deteriorates with disease progression. Fluid intake can be improved using foods containing a large amount of water such as soups, fruit, gelatin desserts, yogurt, mousses, sauces, milky desserts and fortified supplements (17). Research in chronic functional constipation suggests that prevention of constipation requires at least 2 litres of fluid per day (61). **Level 1b**

A minimum of 1.5 litres is required for the effective and safe use of dietary fibre supplements. For these reasons, the use of fluid and fibre supplementation may not be an appropriate choice in the management of constipation in palliative care patients (7, 17). **Level 5**

2.5.3 *Mobility*

Literature suggests a correlation between exercise and improved bowel transit time (62). In a palliative care population the capacity for physical activity may be reduced. Activity should be encouraged within the patient's limits, however; the aim of maximising mobility should primarily be the improvement of quality of life (63). **Level 5**

2.5.4 Abdominal massage

Abdominal massage, also referred to as bowel or colonic massage, may be beneficial for some patients in the prevention and treatment of constipation. This remains an unproven intervention with a limited evidence base.

- A recent RCT of 60 Swedish patients with idiopathic constipation demonstrated that massage decreased the severity of gastrointestinal symptoms and increased bowel frequency, but did not lead to a reduction in laxative requirements. Abdominal massage initially produced a high healthcare cost per Quality-Adjusted Life Year (QALY) of €60,000- €75,000, depending on whether it was administered by the healthcare professional or patient. The authors suggest that abdominal massage should be seen as a complement to laxative use rather than a replacement (64, 65). **Level 1b**
- A small RCT in multiple sclerosis patients (n=30) with constipation suggested a positive effect of massage on symptoms of constipation (66).

Despite recent studies there remains a lack of clear direction in the existing literature on the most efficacious type, intensity or timing of massage. Although added advantages of this technique are that patients perceive it as relaxing and that it can be taught to patients and carers to enable it to be carried out at home, the cost involved must be taken into account (52, 65).

Recommendation 3 Non-pharmacological management

The following are responsible for implementation of recommendation 3

CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with palliative care needs are responsible for implementation.

Key finding Non-pharmacological strategies in the management of constipation are at least as important as the use of pharmacological agents.	
Key recommendations	
D	**3.1** Attention should be paid to the provision of optimised toileting while ensuring adequate privacy and dignity for all patients.
D	**3.2** Consideration should be given to lifestyle modification including the adjustment of diet and activity levels within a patient's limitations.

2.6 Pharmacological management

Although non-pharmacological measures will help many patients, pharmacological treatment is often necessary. Laxatives are commonly prescribed in palliative care, with 50% of patients receiving two or more laxatives simultaneously (67). However, little evidence-based data exists in relation to the efficacy and safety of laxatives in this patient population. Where studies exist, laxatives are usually compared to placebo with little evidence available to establish differential efficacy. Much of the published research pertains specifically to chronic constipation and many therapeutic recommendations remain based on clinical experience.

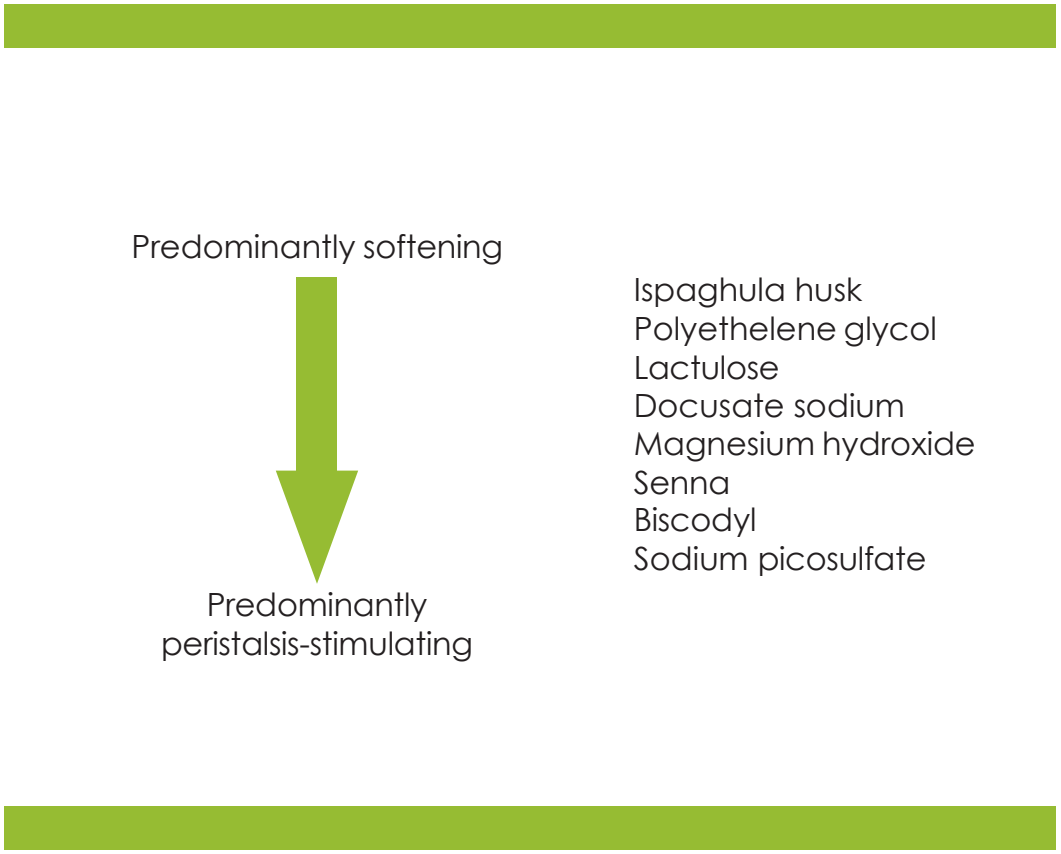
A review undertaken by the Cochrane Collaboration explored the use of laxatives for the management of constipation in palliative care patients. Only four trials fit the Cochrane criteria for evaluation, where minimal differences were shown in effectiveness between individual laxatives. The authors conclude that due to a lack of comparative randomised controlled trials (RCTs), the treatment of constipation in palliative care patients is based on inadequate evidence. "There persists an uncertainty about the "best" management of constipation in this group of patients" (16).

Level 1a

Laxatives can be classified into two broad categories; those that act to predominantly soften faecal matter and those that stimulate gut peristalsis (7) (see Figure 1). Within each category, there is no conclusive evidence to support any specific laxative preparation and individual patient characteristics, their preference and laxative cost are essential considerations. The assessment process will help to identify which type of laxative is indicated but a combination of the two categories may be most effective and is the recommendation made for general use in the United Kingdom Palliative Care Formulary (68, 69). The Management Algorithm (Appendix XII) can be used as a guide for treatment.

Level 5

Figure 1 Oral laxative classification
(Adapted with permission from Skyes*, 2004, (44))



*Source: Oxford Textbook of Palliative Medicine 3E edited by Derek Doyle, Geoffrey Hanks, Nathan Cherny & Sir Kenneth Calman (2004) Ch. 8.3.3 "Constipation and diarrhoea" by Nigel Sykes pp. 483–496. See www.oup.com

If single-agent oral laxative treatment is given alone, a bowel motion should be expected within 3 days. If this does not occur, the combination of softening and stimulating laxatives is essential; the dose of which should be titrated daily or alternate days according to response. The development of faecal leakage suggests a need to reduce the softener and perhaps increase the stimulant. If bowel colic occurs the dose of the softening laxative should be increased relative to the stimulant dose (7). **Level 5**

The different laxatives available and the cost of commonly used laxatives in palliative care are shown in Tables 3-6.

2.6.1 Classification of laxatives

2.6.1.1 Bulk-forming laxatives

Bulk-forming laxatives are fibre supplements, e.g. Ispaghula husk and methylcellulose. These hydrophilic agents absorb water from the intestinal lumen, softening stool consistency and increasing stool bulk, thus promoting peristalsis. Their onset of action is approximately 10-24 hours. Adequate fluid intake must be maintained when using these agents in order to avoid mechanical bowel obstruction. Bulk-forming agents can also interfere with the absorption of several common medications including warfarin, aspirin and calcium (70).

- The American College of Gastroenterologists chronic constipation task force deemed that there was sufficient evidence to support a Grade B recommendation for the use of Ispaghula to increase stool frequency in patients with chronic constipation (71). **Level 2**
- In the palliative care population their use is largely limited by tolerance (44).

2.6.1.2 Osmotic Laxatives

Osmotic laxatives can be subdivided into saline laxatives, sugars and polyethylene glycols (PEG).

Saline laxatives e.g. magnesium salts, draw water into the intestinal lumen from the bowel wall and thereby promote peristalsis. Their use can result in dehydration and electrolyte imbalance. Magnesium hydroxide may interfere locally with the absorption of other drugs by increasing gastric pH. This can be avoided by giving other medications 2-3 hours before the administration of magnesium hydroxide.

Lactulose, a synthetic sugar remains unabsorbed until it reaches the colon, where it is metabolised by bacteria. This results in a decrease in the intraluminal pH value and subsequently promotes peristalsis. The fermenting process leads to flatulence as a result of gas production. Patients may find the sweet taste unpalatable.

High molecular weight PEGs are non-absorbable, non-metabolised soluble polymers that form hydrogen bonds with water in the gut. Due to high osmotic pressure PEGs act as both a softening and bulk-forming agent due to water retention within the bowel.

- Numerous RCTs have demonstrated the sustained efficacy of PEG in the treatment of chronic constipation. Superiority of PEG in comparison with lactulose has also been demonstrated in increasing stool frequency and reducing straining. PEG has also been shown to be effective in faecal impaction (72, 73). **Level 1a**

2.6.1.3 Surfactants

These laxatives moisten the stool through a detergent action, thereby softening it e.g. docusate sodium. The onset of action is approximately 24-72 hours. Although relatively well tolerated, docusate is not completely free of side effects (74). Administration is recommended 2 hours before or after other medication to avoid disturbance in their absorption. There is a lack of evidence supporting the use of docusate in advanced illness.

- In a systematic review of docusate in the chronically ill conducted in 2000, Hurdon et al. concluded that the use of docusate for constipation in palliative care is based on inadequate experimental evidence (75). **Level 2a**
- A recent RCT exploring the use of docusate and sennosides compared to placebo and sennosides in hospice patients; reported no significant difference in stool frequency, volume or consistency between both groups (76). **Level 1b**

2.6.1.4 Lubricants/emollients

Lubricants, such as liquid paraffin, ease defecation by softening the stool. Caution should be used in this patient population due to the risk of anal seepage, irritation and granuloma formation in chronic use, reduced absorption of fat soluble vitamins and the potential for lipoid pneumonia if aspirated (77).

2.6.1.5 Stimulants

Stimulant laxatives work by stimulating the myenteric nerve plexus resulting in rhythmic muscle contractions and increased intestinal motility. They also inhibit sodium and water reabsorption and increase secretion of water into the bowel lumen. Stimulant laxatives provide a logical approach to opioid-induced slowing of colonic transit time by increasing propulsive activity. The most widely used stimulant laxatives are anthracenes (sennosides and dantron) and polyphenolics (bisacodyl and sodium picosulfate). Onset of action typically occurs within 6-12 hours. As a result of their peristaltic activity, stimulant laxatives can cause abdominal cramping, pain, diarrhoea and electrolyte imbalance.

Senna is a naturally occurring plant-derived anthranoid. Hydrolisation by bacterial flora in the colon yields active compounds. Individual responses vary and may be a result of differences in bacterial flora.

- Limited evidence, but much clinical consensus in palliative care, demonstrates that sennosides are as effective as lactulose (78). **Level 3**

Bisacodyl is a prokinetic with a hydrogogue effect, which acts locally in the large bowel by directly enhancing motility, reducing transit time and increasing the water content of the stool.

- A limited number of RCTs have demonstrated that bisacodyl is effective in increasing stool frequency and improving consistency when compared with placebo in patients with chronic constipation (79, 80). **Level 1b**

Sodium picosulfate has a similar mode of action to bisacodyl. Taken orally in liquid form, it is hydrolysed by the colonic microflora.

- A limited number of RCTs have demonstrated the efficacy of sodium picosulfate compared to placebo in the acute management of chronic constipation (81, 82). **Level 1b**

- One RCT compared the efficacy and safety of bisacodyl and sodium picosulfate. Both treatments were equally effective in treating constipation, providing a sustained improvement in symptoms. There was a trend towards better tolerability of bisacodyl based on the number of drug-related adverse events (82). **Level 1b**

Dantron is a synthetic anthranoid, which acts on the small and large bowel. It is used in combination with stool softening agent poloxamer, e.g. Co-danthramer. Dantron containing laxatives are only licensed for use in advanced illness due to evidence of carcinogenesis in animal studies. These agents should not be used in patients with urinary or faecal incontinence due to local dermatitis and excoriation.

- One study undertaken in 51 cancer patients demonstrated that patients had a higher stool frequency when taking lactulose plus senna compared to dantron combined with poloxamer. Patients with reduced constipation following lactulose plus senna subsequently reported an increase in constipation on changing to the dantron plus poloxamer arm (83). **Level 1b**

Of note, Dantron-containing products are due to be discontinued and withdrawn from the market in 2015.

2.6.1.6 Rectal Laxatives

Patients and carers may find rectal measures uncomfortable and undignified and in general, oral laxatives should be used in preference. However their rapid mode of action can be useful. They may have a necessary role (alone or in combination with oral laxatives), in patients with faecal impaction, in patients with spinal cord lesions disrupting bowel innervation or patients who cannot tolerate or swallow oral laxatives.

Digital rectal examination is required to assess the type of stool in the rectum and guide appropriate therapy (See Table 4). Rectal treatments can be given as either suppositories or enemas. These work by a combination of stool softening/lubrication and stimulation of the defecation reflex through rectal distension.

Bisacodyl is the only suppository that works by pharmacologically stimulating peristalsis and therefore needs to be in direct contact with the rectal wall to have effect.

Limited evidence suggests that microenemas may have almost equal efficacy and a more favourable side effect profile when compared with phosphate enemas. They could therefore be considered in preference (44, 84). **Level 3**

2.6.2 Adjuvant Therapies

2.6.2.1 Neostigmine

Neostigmine is an acetylcholinesterase inhibitor that can rapidly reverse intestinal atony by facilitating the transmission of impulses through the neuromuscular junction, stimulating intestinal tone and peristalsis. Its use has been studied in acute colonic pseudo-obstruction (85). Neostigmine is associated with adverse effects such as abdominal cramps, nausea, salivation, bronchoconstriction and bradycardia when administered at high doses without antimuscarinic drugs.

- Experience using neostigmine in advanced cancer patients is limited to case series. Reports suggest efficacy and tolerability when used at low doses in the treatment of refractory constipation (86, 87). **Level 4**

2.6.2.2 *Amidotrizoate (Gastrografin)*

Amidotrizoate (AM) is an anionic mixture of sodium diatrizoate, meglumine diatrizoate and a wetting agent, polysorbate 80. It is a hyperosmolar water-soluble contrast medium, which has been used for diagnostic purposes. It has been found to be effective in recovery of bowel transit in malignant bowel obstruction in combination with other agents (88).

- A single observational, open-label, prospective study evaluated the use of AM as a rescue treatment in constipation unresponsive to conventional laxative therapy in 99 patients with advanced cancer. This preliminary study suggests that AM is effective and well tolerated, inducing a bowel motion within 24 hours of administration in 44% of patients (89). Further controlled studies are needed.

Level 3

Table 3 Oral laxatives for the treatment of constipation in palliative care

(Adapted from Larkin, 2008 (7))

Prescribers notice: Healthcare staff should use clinical judgement and knowledge in prescribing and give due regard to individual circumstances presented by each patient and available resources.

Category	Examples	Formulation	*Starting dose	Mechanism of action	Onset of action	Common side effects	Contraindications	Volume of liquid required
Bulking agents	Ispaghula	Powder for oral solution	Variable 1-2 sachets daily	Increase in stool bulk and water content, increasing colonic transit time	Initially 24-72h, later 8-24h	Distension, bloating, abdominal pain	May be poorly tolerated in patients unable to tolerate adequate fluid volume, Intestinal obstruction	150 mL daily
Predominantly Softening Laxatives								
Non-digestible sugars	Lactulose (10g/15mL)	Syrup	10-15 mL BD	Increases faecal weight	1-2 days	Flatulence, cramps, abdominal discomfort	Galactosaemia, Intestinal obstruction	15-30 mL daily
Saline laxatives	Magnesium hydroxide BP (415mg/ 5mL)	Syrup	15-30 mL BD	Increases intestinal wall secretion and stimulates peristalsis	12h	Electrolyte and fluid imbalance	Risk of hypermagnesaemia in patients with renal impairment, Intestinal obstruction	30-60 mL daily
Macrogol	Polyethylene glycol	Powder for oral solution	1-3 sachets daily in divided doses	Increases stool water content and stool volume stimulating peristalsis	1-3 days	Abdominal distension and pain, nausea, borborygmi, mild diarrhoea that usually responds to dose reduction	Intestinal perforation or intestinal obstruction, severe gastrointestinal inflammatory conditions (Crohn's, Ulcerative colitis, toxic megacolon)	125 mL per sachet
Surfactants	Docusate sodium	Liquid (50mg/ 5mL) Capsule 100 mg	10mL BD 100 mg BD	Increases water penetration and softens stools	1-3 days	Diarrhoea, nausea, abdominal cramps, or skin rash	Abdominal pain, nausea, vomiting, intestinal obstruction Hereditary problems with fructose intolerance	20 mL daily Water required for ingestion of capsules
Lubricants/ Emollients	Liquid paraffin	Oral Emulsion, BP	5-15 mL BD	Lubricates and softens stools	1-3 days	Anal seepage, perianal irritation, risk of lipoid pneumonia	Abdominal pain, nausea or vomiting, Intestinal obstruction	10-30 mL daily
Predominantly Stimulant Laxatives								
Sennosides	Senna	Syrup: Sennosides 7.5mg/5 mL (240 mL) Tablet: Sennosides (7.5 mg)	15 mL nocte 1-2 tablets nocte	Alters intestinal mucosal permeability and reduces absorption of water from the gut, increases intestinal motility through direct stimulation of the nerve endings in the colonic mucosa	8-12h	Watery diarrhoea, may cause abdominal cramping, electrolyte imbalance, dermatitis	Intestinal obstruction	15-30mL daily Volume required for ingestion of tablets
Sodium Picosulfate	Dulcolax Pico Liquid Dulcolax Perles	Syrup (5mg/5mL) Capsules (2.5mg)	5-10mg nocte 2 capsules BD	Increases intestinal motility through direct stimulation of the nerve endings in the colonic mucosa	6-12h	Abdominal cramps, diarrhoea, electrolyte disturbance	Avoid in active inflammatory bowel disease, severe dehydration, Intestinal obstruction	5-10mL Volume required for ingestion of tablets
Bisacodyl		Tablet (enteric coated): 5 mg	10-20 mg BD	Increases intestinal motility through direct stimulation of the nerve endings in the colonic mucosa	6-12h	Abdominal cramps, diarrhoea, electrolyte disturbance	Intestinal obstruction	Volume required for ingestion of tablets
Combination Softener/Stimulant Laxatives								
Softener and stimulant	Poloxamer and dantron**	Codalax Suspension (200/25) Codalax Forte Suspension (1000/75) Codalax Capsule (200/25) Codalax Forte Capsule (500/35.5)	5-10 mL nocte 5mL nocte 1-2 capsules nocte 1-2 capsules nocte	Acts on nerve endings of myenteric plexus and stimulates muscles of large intestine	6-12h	Temporary pink or red urine and skin discoloration, excoriation of perianal area	Intestinal obstruction	5-10 mL daily 5-10 mL daily Water required for ingestion of capsules Water required for ingestion of capsules

*Always consult the product literature for starting dose recommendations

**Dantron-containing products are due to be discontinued and withdrawn from the market in 2015

Table 4 Rectal laxatives for the treatment of constipation in palliative care
(Adapted from Larkin, 2008 (7))

Prescribers notice: Healthcare staff should use clinical judgement and knowledge in prescribing and give due regard to individual circumstances presented by each patient and available resources.

Category	Examples	*Starting dose	Mechanism of action	Speed of action	Common side effects
Lubricant laxative	Mineral oil enema Vegetable oil enema	60-120 mL	Allows penetration of water into faeces to soften stool	Up to 1h	Local irritation
Osmotic laxative	Glycerin suppository (softening and irritant properties)	1	Increases water in intestinal lumen and faecal weight	15-60 minutes	Local irritation
Stimulant (irritant) laxative	Bisacodyl suppository	1-2 (10 mg per suppository)	Increases intestinal motility, directly stimulates the nerve endings in the colonic mucosa	15-60 minutes (must come into contact with the bowel wall to be effective)	Abdominal cramping and pain, diarrhoea, local irritation
Saline laxative	Phosphate enema (Microlax-proprietary) Each mL contains: sodium citrate, sodium lauryl sulfoacetate, glycerin, sorbitol, sorbic acid, purified water in a disposable plastic tube fitted with a flexible enema tip about 5 cm long. Tubes of 5 mL	1 1	Increases intestinal water secretion and stimulates peristalsis	15-30 minutes 30-60 minutes	Local irritation (phosphate enema) Excessive use may cause diarrhoea and fluid loss

*Always consult the product literature for starting dose recommendations

Table 5 Cost of oral laxatives in Republic of Ireland and Northern Ireland

Drug	Brands available	GMS/DPS	Cost per dosage unit (€)	Cost per dosage unit (£)
Co-danthramer**	Codalax capsules Poloxamer '188' 200mg +Dantron 25mg per capsule	Yes	€14.40/60	£12.86/60
	Codalax Forte Capsules Poloxamer '188' 500mg +Dantron 35.5mg per capsule	Yes	€15.65/60	£15.55/60
	Codalax Suspension Poloxamer '188' 200mg +Dantron 25mg per 5mls	Yes	€26.09/300mL	£11.27/300mL
	Codalax Forte Suspension Poloxamer '188' 1g +Dantron 75mg per 5mls	Yes	€7.80/300mL	£30.13/300mL
Polyethylene Glycol	Movicol 13g	Yes	€7.07/20 €10.62/30	£4.45/20 £6.68/30 £11.13/50
	Molaxole	Yes	€7.02/20 €8.91/30	N/A
	Laxido	Yes	€8.29/30	N/A
Lactulose	Duphalac 3.335g/5ml	Yes	€1.23/300mL €3.72/1000mL	N/A
	Laxose 3.335g/5ml	Yes	€1.20/300mL €3.64/500mL €4.07/1000mL	£2.04/300mL £2.28/500mL
Docusate Sodium	Dioctyl	No	€24.83/100	£6.40/100
Magnesium Hydroxide	Milk of Magnesia	No	€3.00/100mL €5.63/200mL	N/A
Senna	Senokot tablets (7.5mg)	No	€2.62/20 €5.46/60	£1.44/60
	Senokot 15mg/10mg	No	€7.26/100 €18.77/500mL €5.19/150mL	£2.69/500mL
Bisacodyl	Bisacodyl 5mg tablets	No	€1.21/10 €2.01/40 €3.89/50 €4.64/60	£3.27/100
Sodium Picosulfate	Dulcolax Pico Perles	No	€4.28/50	N/A
	Dulcolax Pico Liquid 5mg/5ml	No	€2.76/100mL €7.78/300mL	£1.89/100mL
Ispaghula Husk	Fybogel Citrus	Yes	€2.68/30 €5.35/60	£1.84/30
	Fybogel Mebeverine (Mebeverine 135mg + Ispaghula husk 3.5g)	Yes	€3.15/10 €18.93/60	N/A
Methylcellulose	Celevac 500mg	No	€3.58/112	£3.22/112

****Dantron-containing products are due to be discontinued and withdrawn from the market in 2015**

Table 6 Cost of rectal laxatives in Ireland

Drug	Brands available	GMS/DPS	Unit Cost (€)	Unit Cost (£)
Bisacodyl	Dulcolax 5mg Dulcolax 10mg	No No	€1.49/5 (5mg) €2.75/12 (10mg) €5.10/20 (10mg)	£1.15/12 (10mg)
	Toilax	No	€3.73/5 €29.76/50	N/A
Arachis Oil Enema	Arachis Oil Enema	Unlicensed	N/A	£7.98/130mL
Docusate Enema	Norgalax Micro-enema	Unlicensed	€14.47	57p/10g unit
Glycerine (Glycerol)	Babylax* (Enema) Glycerin Suppositories	No	€8.95/3	£1.14/(1g) £1.16 (2g) £1.40 (4g)
Sodium Citrate	Microlax* (Enema)	No	€29.15/50	41p/5mL (single dose pack)
	Micolette* (Enema)	No	€8/12	42p/5mL (single dose pack)

*Contains other active ingredients

Recommendation 4 Pharmacological management

The following are responsible for implementation of recommendation 4

CEO/General Managers/Line managers are responsible for ensuring all healthcare staff are aware of this guideline. All healthcare staff and in particular physicians, surgeons, general practitioners, nurses, pharmacists and dietitians, caring for patients with palliative care needs are responsible for implementation.

Key finding a. Pharmacological agents are a necessary component of the management of established constipation in life-limiting illness. b. There is a lack of evidence to support the use of any one laxative over another.	
Key recommendations	
D	**4.1** The choice of laxative should be guided by individual patient preference and circumstances.
D	**4.2** Where there is no evidence to differentiate between medications in terms of efficacy, tolerability and side effect profile, and where clinical expertise allows, the medication with lowest cost base should be used.
D	**4.3** The combination of a softening and a stimulating laxative is often required. Optimisation of a single laxative is recommended prior to the addition of a second agent. The ratio of softener: stimulant should be guided by faecal consistency.
D	**4.4** The laxative dose should be titrated daily or alternate days according to response.

Prescribers notice: Healthcare staff should use clinical judgement and knowledge in prescribing and give due regard to individual circumstances presented by each patient and available resources.

2.7 Opioid induced constipation

2.7.1 Definition and incidence

Pain occurs in 50-90% of patients with advanced cancer and approximately 65% of patients suffering from terminal non-malignant disease (90). Opioids remain the mainstay in the treatment of cancer pain and are increasingly used in the management of chronic non-cancer pain. Evidence-based recommendations on the management of cancer pain can be found in the National Clinical Guideline No 9, Pharmacological Management of Cancer Pain in Adults (www.hse.ie/palliativecareprogramme or www.health.gov.ie/patient-safety/NCEC).

The therapeutic benefits of opioids are compromised by adverse effects, which include opioid-induced bowel dysfunction (OIBD). This comprises a constellation of gastrointestinal (GI) symptoms and signs such as gastro-oesophageal reflux, abdominal distension, incomplete evacuation, straining and constipation (91, 92). Opioid-induced constipation (OIC) is the most common clinical aspect of OIBD, affecting up to 90% of patients on opioid therapy (93). Uncontrolled symptoms of OIBD can have a profound effect on quality of life, rivalling the distress caused by pain (45). Yet these symptoms remain underappreciated by healthcare professionals (94). Constipation is one of the most common reasons that patients avoid or discontinue opioids, compromising effective analgesia (95). Unlike other side-effects,

such as nausea and sedation, patients rarely develop tolerance to opioid-induced constipation (96).

The constipating effect of opioids is predominantly mediated by their action on mu-opioid receptors in the submucosa of the GI tract. Binding of opioids to these receptors reduces GI motility, promotes fluid reabsorption and inhibits fluid secretion into the intestinal lumen causing delayed colonic transit and dry, hard stools (97).

2.7.2 General principles

In the palliative care setting, the use of analgesic medications, despite their side effects, is a necessity for the majority of patients. The WHO recommends preventive measures against constipation for all palliative care patients receiving opioid medications (98). The initiation of a bowel regimen early in the course of opioid therapy is considered to be the standard of care (91,99). Although all opioids are associated with a degree of bowel dysfunction, there is limited evidence that some, including fentanyl and methadone, are less constipating than others. Further prospective studies are required to confirm this. In a single small series (n=4), opioid switching of morphine to methadone resulted in a reduction in constipation(100). Changing the route of opioid administration to transdermal fentanyl or buprenorphine has been shown to have better GI tolerability (101-103) however, contradictory data also exists (104). Whether the decrease in laxative usage is clinically significant, and whether the decrease relates to the opioid type or the route of administration needs to be demonstrated.

Level 5

Level 4

Tapentadol, a combined mu-opioid agonist and noradrenaline reuptake inhibitor, has been shown to have a more favourable gastro-intestinal side effect profile due to a reduced level of mu-opioid agonism.

- A double-blinded randomised clinical trial investigating gastro-intestinal tolerability of oxycodone compared to tapentadol in patients with non-malignant joint disease, demonstrated superior outcomes for nausea, vomiting and constipation in the tapentadol arm (105).

Level 1b

The EAPC recommends the following strategies for managing established opioid-induced side effects: reduction of opioid dose, opioid rotation, changing the route of administration and symptomatic management (106).

Level 2a

Currently the most viable option for relieving OIC is symptomatic management. In practice, non-pharmacological strategies are rarely sufficient and most individuals will require aggressive pharmacological management (99).

- Sykes et al, 1996 conducted a volunteer model study comparing laxative use in OIC (n=25). This study concluded that the combination of a stimulant laxative and a stool softener was most likely to maintain bowel function at the lowest dose with the least adverse effects (107). This recommendation was endorsed by the European Consensus Group on Constipation in Palliative Care, 2008 (7).

Level 5

- Recent evidence in patients with advanced illness and OIC supports the optimisation of a stimulant laxative as first line prior to the addition of a softener or osmotic agent (108,109). There is no evidence to favor the choice of one particular stimulant laxative over another.

Level 2b

Maximal conventional laxative therapy may only provide partial benefit, as the underlying opioid-receptor mediated mechanism is not addressed. Evidence

suggests that of those receiving standard treatments, over half will remain dissatisfied with the outcome (110). If OIC has not responded to standard laxative treatment, the use of opioid receptor antagonists may be considered.

2.7.3 Opioid receptor antagonists

Initial attempts to block opioid-induced adverse effects led to the development of naloxone.

Efficacy of naloxone in restoring laxation during opioid therapy has been demonstrated in small studies (111-113). When given orally, immediate release naloxone undergoes extensive first-pass hepatic metabolism leading to negligible systemic bioavailability (<2%) (114). However, because of its ability to cross the blood-brain barrier, despite its low oral bioavailability, reversal of centrally mediated analgesia and precipitation of withdrawal can occur. Its use is therefore limited by a narrow therapeutic index due to the need to titrate peripherally versus centrally active doses (115). A prolonged-release formulation of naloxone may reduce these risks.

2.7.3.1 Prolonged release opioid-receptor agonist/antagonist combination

A combination of prolonged-release naloxone with prolonged-release oxycodone has been licensed in 13 European countries since 2008. This was formulated to counteract OIC development through the antagonistic effect of naloxone on mu-opioid receptors in the bowel wall while maintaining analgesia due to the slow absorption of the formulation and the low bioavailability of naloxone (114).

- Phase III studies have confirmed that the combination of prolonged-release naloxone and oxycodone (OXN PR) provides safe and effective pain relief with superior bowel function over oxycodone alone in cancer and non-cancer patients (116-120). **Level 1b**

- The majority of adverse effects observed in these trials were mild or moderate and consistent with the adverse effect profile of opioid analgesics. The long-term analgesic efficacy has been demonstrated in open-label extension studies in patients with chronic non-cancer pain for up to 52 weeks (121). **Level 1b**

- The optimal ratio of oxycodone to naloxone identified in trials is 2:1 (122). The dose studied in the majority of clinical trials has been limited to a maximum dose of 80/40mg per day. Doses were extended to 120/60mg daily in a randomised controlled trial in cancer patients, without reported loss of analgesia (123). **Level 1b**

- A case report of a cancer patient receiving 240/120mg per day observed declining analgesia at this dose; substitution with the same dose of regular prolonged-release oxycodone resulted in recovery of adequate analgesia (124). Further studies are needed, particularly in cancer patients where the analgesic requirement may be higher. **Level 5**

At present, oxycodone/naloxone preparations are significantly more expensive than standard oxycodone prescribed with a regular laxative. This should be taken into consideration in practice.

2.7.4 Selective peripheral opioid-receptor antagonists

In order to avoid the centrally mediated effects of opioid receptor antagonists, selective peripherally acting agents have been developed. A recent Cochrane review conducted a meta-analysis on mu-opioid receptor antagonists for OIBD. This demonstrated that methylnaltrexone and alvimopan were better than placebo in reversing OIC (125).

2.7.4.1 Methylnaltrexone

Methylnaltrexone bromide is a quaternary N-methyl derivative of the opioid receptor antagonist naltrexone. The addition of a methyl group at the nitrogen ring increases polarity and reduces lipid solubility, thus restricting ability to cross the blood-brain barrier (126, 127).

Subcutaneous methylnaltrexone was initially demonstrated to reverse opioid-induced delays in gastric emptying and oral-caecal transit time and to induce laxation in chronic methadone users with OIC (128). Efficacy and tolerability of methylnaltrexone in patients with advanced illness has subsequently been demonstrated in phase III trials.

- A randomised-controlled trial by Portenoy et al (2008) included 22 patients with advanced illness on chronic opioid therapy. In this dose-ranging study patients received doses of methylnaltrexone between 1 and 20mg. No dose response relationship was observed beyond 5mg. Of those patients who received 5mg or above, almost half had a laxation response within 4 hours (129).

- Similar results were observed in a double blind, randomised placebo-controlled trial by Thomas et al (n=133), in 2008. This demonstrated that 48% of patients had a laxation response within 4 hours of first dosing of methylnaltrexone (0.15 mg/kg) as compared with 15% in the placebo arm. In a three-month open-label extension phase, 82 patients with OIC who did not respond to laxatives received methylnaltrexone as needed for up to 3 months. Mean laxation response rates in the methylnaltrexone group (DB phase, months 1, 2, 3 open-label phase) were 45.3%, 45.5%, 57.7%, and 57.3%, respectively, for patients treated with DB methylnaltrexone and 10.8%, 48.3%, 47.6%, and 52.1%, respectively, for patients treated with DB placebo. Approximately 50% of patients reported improvement in constipation-related distress (130, 131). **Level 1b**

- In 2009, a multi-centre, double-blind, randomised, placebo-controlled trial comparing two dosages (0.15 mg/kg and 0.3 mg/kg) of methylnaltrexone in 154 patients with advanced illness and OIC found a significant reduction in time to laxation in both methylnaltrexone groups compared with placebo ($p<0.0001$; each dose vs. placebo). Approximately half of the methylnaltrexone responders defecated within 30 minutes of administration. Notably, increasing the dose to 0.3 mg/kg did not show improved laxation response and was associated with more abdominal pain (132). **Level 1b**

No trial has demonstrated evidence of reduced analgesic efficacy or opioid withdrawal with methylnaltrexone. The most frequent adverse event reported was abdominal cramping, with flatulence, nausea and dizziness at higher doses. As yet no clinical trials directly comparing methylnaltrexone to conventional laxatives have been conducted.

2.7.4.2 Methylnaltrexone dosage and administration

Methylnaltrexone is administered by subcutaneous injection on alternate days. In adults over 18 years, the dose of methylnaltrexone is 8mg for a body weight of 38-61kg and 12mg for a body weight of 62-114kg. Outside this range, a dose of 150mcg/kg on alternate days is recommended. The interval between administrations can be varied, although is not recommended more than once daily(69).

Methylnaltrexone is contraindicated in patients with known or suspected intestinal obstruction or acute abdominal distress. Pharmacokinetic studies have resulted in a recommendation to reduce the methylnaltrexone dose by 50% in patients with severe renal impairment (CrCl <30mls/min). No dose adjustment has been deemed necessary for patients with mild or moderate renal impairment or hepatic impairment (69).

2.7.4.3 Alvimopan

Alvimopan, an orally administered peripherally acting mu-opioid receptor antagonist has been investigated in the management of post-operative ileus and in patients taking opioids for chronic non-cancer pain. In a limited number of studies alvimopan has been shown to counter opioid-induced delays in GI transit. However, further clinical studies in OIC have been suspended due to an apparent increase in cardiovascular events, neoplasms and fractures in patients on alvimopan compared to placebo (125).

2.7.5 Novel pharmacological approaches

2.7.5.1 Prokinetic agents

Serotonin is a major mediator of bowel contractility; 5HT receptors (particularly $5HT_{1P}$ and $5HT_4$ receptors subtypes) are therefore compelling targets for prokinetic agents (99). Metoclopramide, a dopamine antagonist and partial $5HT_4$ agonist, is primarily effective in gastric motility but is believed to have little colonic effect and is not useful as a laxative (133).

Prokinetic agents, cisapride and tegaserod, previously showed promise in the management of constipation, however have demonstrated clinically significant cardiac toxicity limiting their use. Prucalopride is a new selective $5HT_4$ agonist, which has shown promising early results in the relief of OIC in chronic constipation without cardiac toxicity (134). Further studies are awaited.

Level 1b

2.7.5.2 Erythromycin

Erythromycin acts by stimulating motilin receptors in the upper gastrointestinal tract and has been shown to be effective in diabetic gastroparesis (135). There are no data for its use in palliative care.

2.7.5.3 Selective chloride channel agonist

Lubiprostone is a chloride-channel (CIC-2) agonist, which enhances intestinal secretion and augments intestinal motility. Clinical studies have demonstrated the efficacy and safety of this agent in the management of OIBD in chronic, non-cancer pain (136). The most frequent adverse effect is nausea, which has been reported in up to 30% of patients in clinical studies (137). Its role in the palliative care population is yet to be investigated.

Level 1b

2.7.6 New developments

A number of peripherally restricted opioid receptor antagonists are currently in development and have shown favourable results in clinical trials. These include Pegylated naloxone (Naloxegol [previously known as NKTR-118]), and other orally administered mu-opioid receptor antagonists including methylnaltrexone (138). **Level 1b**

- Two randomised controlled trials in patients with OIC have demonstrated significantly improved stool frequency with a rapid onset of action with the investigational, oral, peripherally-acting, μ-opioid receptor antagonist Naloxegol (139-141). **Level 1b**

Recommendation 5 Opioid induced constipation

The following are responsible for implementation of recommendation 5:

CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with palliative care needs are responsible for implementation.

Key finding Constipation is a common and distressing side effect of opioid therapy.	
Key recommendations	
D	**5.1** The development of opioid induced constipation should be anticipated. A bowel regimen should be initiated at the commencement of opioid therapy.
D	**5.2** In the management of opioid induced constipation, optimised monotherapy with a stimulant laxative is essential followed by the addition of a softener if required. The current evidence is too limited to provide evidence-based recommendations for the choice of stimulant laxative and selection should be made on an individual basis.
D	**5.3** Where there is no evidence to differentiate between medications in terms of efficacy, tolerability and side effect profile, and where clinical expertise allows, the medication with lowest cost base should be used.
D	**5.4** The use of opioid receptor antagonists under specialist guidance should be considered in patients whose treatment is resistant to conventional laxative therapy.

2.8 Intestinal obstruction

2.8.1 Aetiology and prevalence

Intestinal obstruction is a frequent complication in patients with advanced cancer, especially of gastrointestinal or gynaecological origin. The obstruction may be mechanical or functional, partial or complete, and may occur at one or more sites. The global prevalence is estimated to be 3-15% of cancer patients (142).

2.8.2 Assessment

If clinically suspected, radiological investigation (including PFA and/or computed tomography (CT) scan of abdomen) may be appropriate depending on the goals of care for each individual patient.

2.8.3 Laxative use in bowel obstruction

In the case of partial bowel obstruction, the introduction of a stool softener should be considered. Stimulant laxatives should be avoided due to potential exacerbation of bowel colic. If the obstruction is complete, laxatives should not be used and consideration should be given to specialist referral for either surgical or conservative medical management (7). **Level 5**

Full explanation of the medical management of intestinal obstruction is outside the scope of this guideline but health professionals caring for adult palliative care patients should consider specialist referral when intestinal obstruction is diagnosed.

Recommendation 6 Intestinal obstruction

The following are responsible for implementation of recommendation 6:

CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with palliative care needs are responsible for implementation.

Key findings a. If intestinal obstruction is suspected, this should be evaluated by history, examination and appropriate radiological investigations. b. Specialist referral for either surgical or medical management should be considered.	
Key recommendations	
D	**6.1** A stool softener should be considered in partial intestinal obstruction. Stimulant laxatives should be avoided.
D	**6.2** In complete intestinal obstruction, the use of all laxatives should be avoided as even softening laxatives have some peristaltic action.

2.9 Management of constipation in the dying patient

In the last days of life, regardless of the use of laxatives, bowel movements become less frequent as a consequence of proximity to death (143). During this phase, numerous factors lead to reduced bowel transit time. These include deteriorating performance status, impaired oral intake and the use of medications including opioid analgesia and anticholinergic agents (144). **Level 5**

It is important to regularly assess the aims of management at this stage. With deteriorating functional status patients may become less aware of the symptoms of constipation and its management becomes a lower priority in their overall care (7). As a patient's level of consciousness deteriorates, oral laxatives should be discontinued. Rectal intervention is rarely required at this stage. **Level 5**

Recommendation 7 Management of constipation in the dying patient

The following are responsible for implementation of recommendation 7:

CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with palliative care needs are responsible for implementation.

Key finding In the last days of life, bowel movements become less frequent as a consequence of proximity to death.	
Key recommendation	
D	**7.** As a patient's level of consciousness deteriorates, oral laxatives should be discontinued. Rectal intervention is rarely required at this stage.

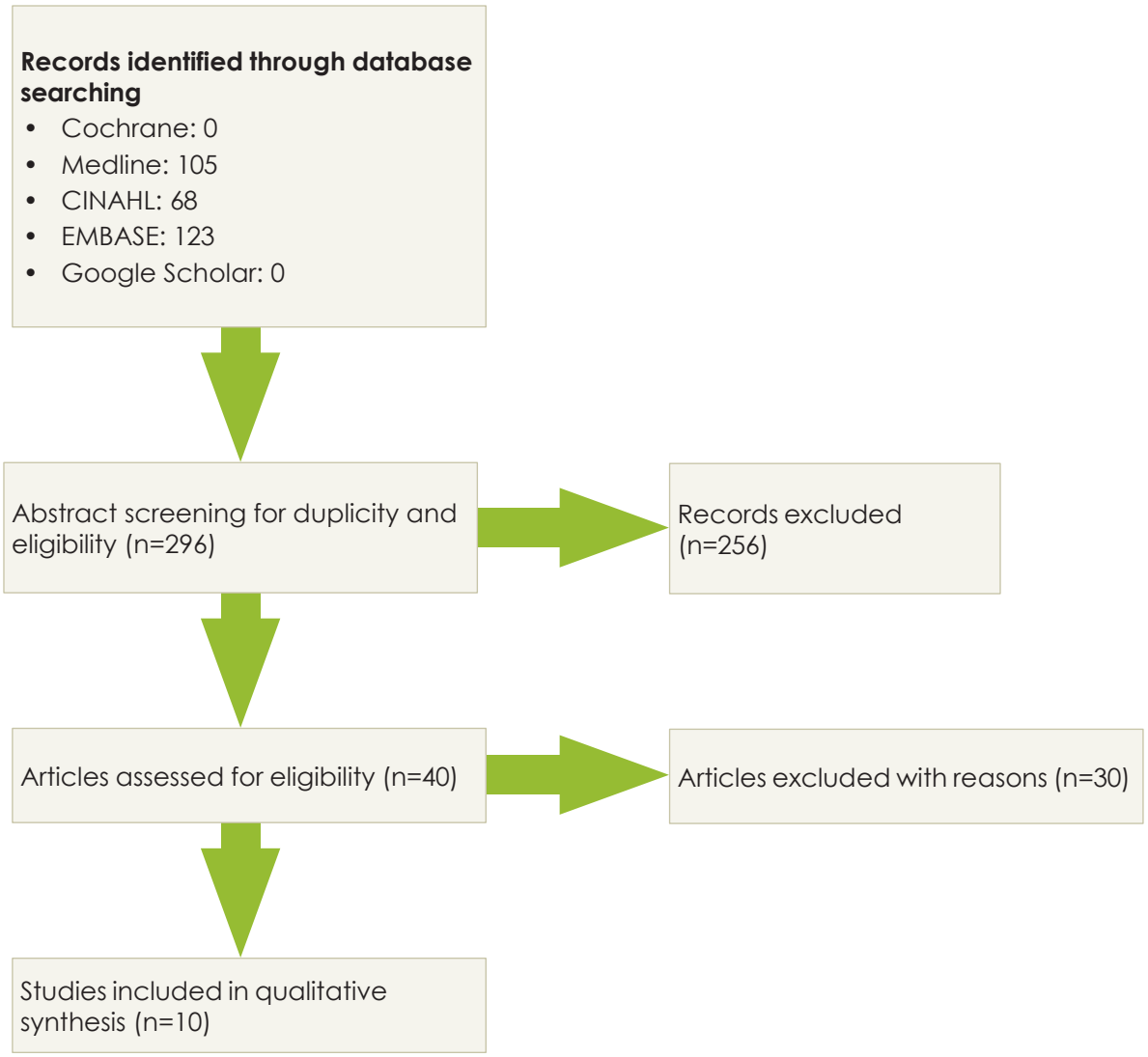
3 Appendices and References

Appendix I: Budget impact assessment

Economic search

Date 17/7/2014

Figure 2 Economic Search diagram



Economic search filter

Table 7 Economic search filter

Search ID#	Economic Search Terms
S27	S25 AND S26
S26	opioid induced
S25	S8 AND S24
S24	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23
S23	TI budget*
S22	AB budget*
S21	TI (value N1 money)
S20	AB (value N1 money)
S19	TI (expenditure* not energy)
S18	AB (expenditure* not energy)
S17	TI economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*
S16	AB economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*
S15	(MH "Economics, Pharmaceutical")
S14	(MH "Economics, Nursing")
S13	(MH "Economics, Medical")
S12	(MH "Economics, Hospital+")
S11	(MH "Cost-Benefit Analysis")
S10	(MH "Costs and Cost Analysis+")
S9	(MH "Economics")
S8	S6 AND S7
S7	S4 OR S5
S6	S1 OR S2 OR S3
S5	(MH "Laxatives")
S4	laxative*
S3	constipation management
S2	(MH "Constipation")
S1	Constipation

Economic impact report

Constipation affects up to 90% of patients with advanced illness, with the exact prevalence determined by the population studied (3, 4). Apart from the well-described impact on quality of life, suboptimal treatment of constipation may result in a number of serious complications, which include intestinal obstruction or perforation, faecal impaction, anal tears and fissures. These complications often necessitate hospitalisation (6).

Although the burden of constipation is well recognised, the economic impact remains difficult to estimate with a paucity of studies evaluating the cost of constipation on health services and society in general (22). This lack of data is particularly true of constipation in advanced life-limiting illness.

As the cost of healthcare continues to rise in the setting of limited resources, clinicians require evidence not only on the efficacy and safety of therapeutics but also their cost to assist them in making an informed selection. Drug therapy of constipation cannot be considered in isolation; patient education, constipation prevention and non-pharmacological measures must also be taken into account (23).

In the development of this guideline, a formal systematic literature search was undertaken to evaluate the economic impact of constipation. Forty eligible studies were identified but only 10 studies were deemed suitable for inclusion in the qualitative synthesis. It is worth noting that there have been few new laxatives produced in recent years and a lack of comparative studies evaluating older products.

This guideline aims to consolidate and improve the quality of current clinical practice regarding the management of constipation. The current national standard of practice in this area is unknown, and therefore it is not possible to quantify with a reasonable degree of certainty what impact recommendations will have on resources nationally. The guideline might have resource implications at a local level as a result of variation in clinical practice across the country. Therefore, organisations are encouraged to evaluate their own practices against the recommendations in the guideline (using the audit tool provided) and assess costs locally. Some of the resource effects to be considered locally are discussed in the following paragraphs:

The expert opinion of the guideline development group considers there to be a variation in current practice pertaining to assessment and history taking with regard to constipation which is addressed in recommendations 1.1-1.5. However, expert opinion is that the recommendation represents a formalisation of best practice for healthcare professionals, and should not need additional resources if continuing professional development activities are used as a means of addressing identified practice gaps. Expert opinion considers that savings may be made by reducing the number of inappropriate diagnostic imaging procedures (i.e. plain film of abdomen) undertaken.

Recommendations 2.1-2.2 focus on prevention and formalises best practice in this area. It is expected that education of service users is carried out by relevant healthcare staff involved in the care of the individual (doctor, nurse, dietitian) and the cost of staff time would be included in their existing contractual payments. Regular review of potentially constipating agents and the appropriate prescription of prophylactic laxatives would be expected to be carried out by doctors, pharmacists or nurse prescribers and the cost of staff time would be included in their existing contractual payments. The healthcare professionals responsible for these activities are already in post and it is not expected that additional staff would be required to implement these recommendations. The expert clinical opinion of the guideline development group was that the recommendation to appropriately prescribe prophylactic laxatives could lead to increased prescribing costs. However, as improved prevention is expected to reduce incidence of constipation and its associated costs, it was considered that the increased expenditure had the potential to be offset against savings (e.g. hospital admissions will be avoided). Releasing staff time from treating constipation makes it possible to treat more patients within the same capacity, potentially improving the efficiency of the organisation.

Recommendations 3.1-3.2 are not considered to have a resource impact for organisations at a local level as it refers to lifestyle and environmental modifications.

Recommendations 4.1-4.4, 5.1-5.4, 6.1-6.2 and 7 relate to the use of medications in the management of constipation or its complications. No specific medication is recommended and therefore there are no specific costing impacts; rather guidance is provided on best practice in selection, initiation, titration and discontinuation of medications. As a general principle it is advised to use the medication with the lowest cost base where there is no differential benefit between medications. Attention is drawn to the fact that at present, oxycodone/naloxone preparations are significantly more expensive than standard oxycodone prescribed with a regular laxative and it advised that this should be taken into consideration in practice. There is therefore potential for cost saving with promotion of carefully considered and informed practice.

Best Practice Point: Pharmacoeconomics
Where there is no evidence of a differential benefit between different medications in terms of efficacy, tolerability or side effect profile, and where clinical expertise allows, the medication with lowest cost base should be used.

See section 1.2.3 for more information on budget impact and Tables 5-6 for cost of laxatives in Ireland

Appendix II Feedback from the Medicines Management Programme

Medicines Management Programme:
Comments approved by Prof. Michael Barry, MMP Clinical Lead, 1/4/2014.
Management of Constipation in Adult Palliative Care Patients

Suggestions:
Table 3. Oral laxatives for the treatment of constipation in palliative care
Combination softener/stimulant laxatives
Align bottom two rows, product with dose (currently misaligned):
Codalax capsules 1-2 capsules
Codalax forte 1-2 capsules

Table 4. Rectal laxatives for the treatment of constipation
Faeces versus. feces/faecal versus. fecal.
Both are referred to in table 4. Suggest using one or the other.

Table 5. Cost of oral laxatives available in Ireland
Where a preparation is not available in Northern Ireland, suggest inserting 'N/A' into 'cost per dosage unit (£)' where it has been left blank.

Appendix XII: Constipation Management Algorithm
Opioid-induced constipation
'Consider methylnaltrexone AND/OR oxycodone/naloxone combination AND/OR consider switching to a less constipating opioid, e.g. fentanyl or methadone'.

- Is it appropriate to administer methlynaltexone with naloxone/oxycodone? – is there therapeutic duplication with opioid receptor antagonists? i.e. should it be 'consider methylnaltrexone OR switching to oxycodone/naloxone'?
- Would oxycodone/naloxone not be considered a less constipating laxative, albeit because of the addition of an opioid receptor antagonist?

A suggestion to consider the cost of the various laxatives is included and the MMP believes this is sufficient.

Action:
The feedback informed a "Best Practice Point: Pharmacoeconomics" which was added to section 1.2.3, Appendix I and development of recommendation 4.2.

Appendix III: Guideline Development Group membership

The following lists the GDG members who contributed to the drafting and amending of the guideline.

- **Dr Brenda O'Connor**: Chairperson, Clinical Lecturer and Research Fellow in Palliative Medicine, Our Lady's Hospice and Care Services, Harold's Cross, Dublin.
  Conflicts of Interest: nothing to declare

- **Dr Jodie Battley**: Specialist Registrar in Palliative Medicine, Royal College of Physicians of Ireland
  Conflicts of Interest: nothing to declare

- **Ms Louise Duddy**: Clinical Nurse Specialist in Palliative Care, Donegal Homecare Team, Letterkenny, Donegal
  Conflicts of Interest: nothing to declare

- **Dr Karen Ryan**, National Lead of the National Clinical Programme for Palliative Care, HSE/ RCPI & Consultant in Palliative Medicine, St Francis Hospice, Dublin.
  Conflicts of Interest: nothing to declare

- **Professor Philip Larkin**, Professor of Palliative Care, School of Nursing, Midwifery and Health Systems, University College Dublin. (Mentor)
  Conflicts of Interest: nothing to declare.

Guideline Steering Group
A larger group, termed the Guideline Steering Group reviewed the draft material and provided commentary at key stages of the process (see Appendix IV). The additional members were:

- Mr Stephen Ward, Clinical Pharmacist for Palliative Care, Northern Ireland Hospice, Belfast
- Ms Heather Weir, Director of Nursing and Patient Services, Northern Ireland Hospice, Belfast

The GDG was supported by:

- Mr Gethin White, Librarian, HSE and Mr Owen Kinsella, Librarian, St. Luke's Hospital, Dublin, who provided assistance in sourcing key reference material for this guideline.
- Ms Breffni Smith, Librarian, Beaumont Hospital and Ms Laura Rooney Ferris, Librarian, Irish Hospice Foundation for their assistance with the subsequent literature update.
- Mr Brendan Leen and his colleagues in the HSE Library for sharing their Systematic Review Protocol.
- Mr Brian Lee, Programme Manager, National Clinical Programme for Palliative Care, replaced by Ms Sinéad Fitzpatrick in December 2013 co-ordinated meetings, managed the consultation process and formatted the document.
- Mr Louis Lavelle, Programme Co-ordinator, Clinical Care, RCPI developed the baseline assessment tool, audit tool and action plan template.

There was no commercial input or external funding source input in the development of the guideline.

The All Ireland Institute of Hospice and Palliative Care (AIIHPC) awarded an educational bursary to Dr Brenda O'Connor, Dr Jodie Battley and Ms Louise Duddy. The AIIHPC had no editorial influence on the content of this guideline.

Professor Philip Larkin is a primary author in the recommendations published by the European Consensus Group on Constipation in Palliative Care in 2008 (7), which was supported by an unrestricted educational grant from Norgine Pharmaceuticals. Although these recommendations are used as a source for this guideline, Professor Larkin was not directly involved in the AGREE and ADAPTE grading which resulted in its selection.

Appendix IV: Guideline development: adaptation plan (based on the ADAPTE Collaboration process)

Figure 3 Guideline development adaptation plan

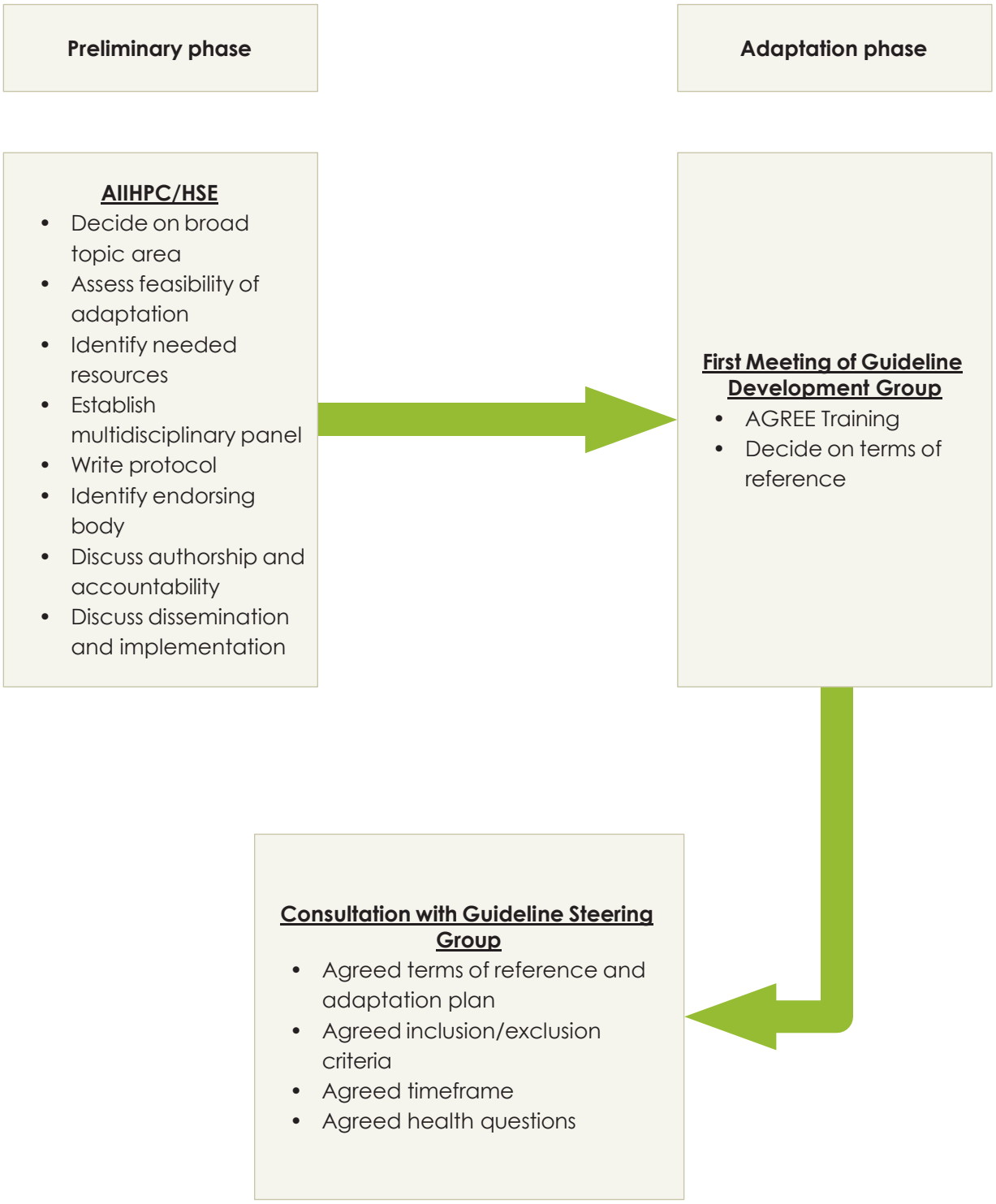
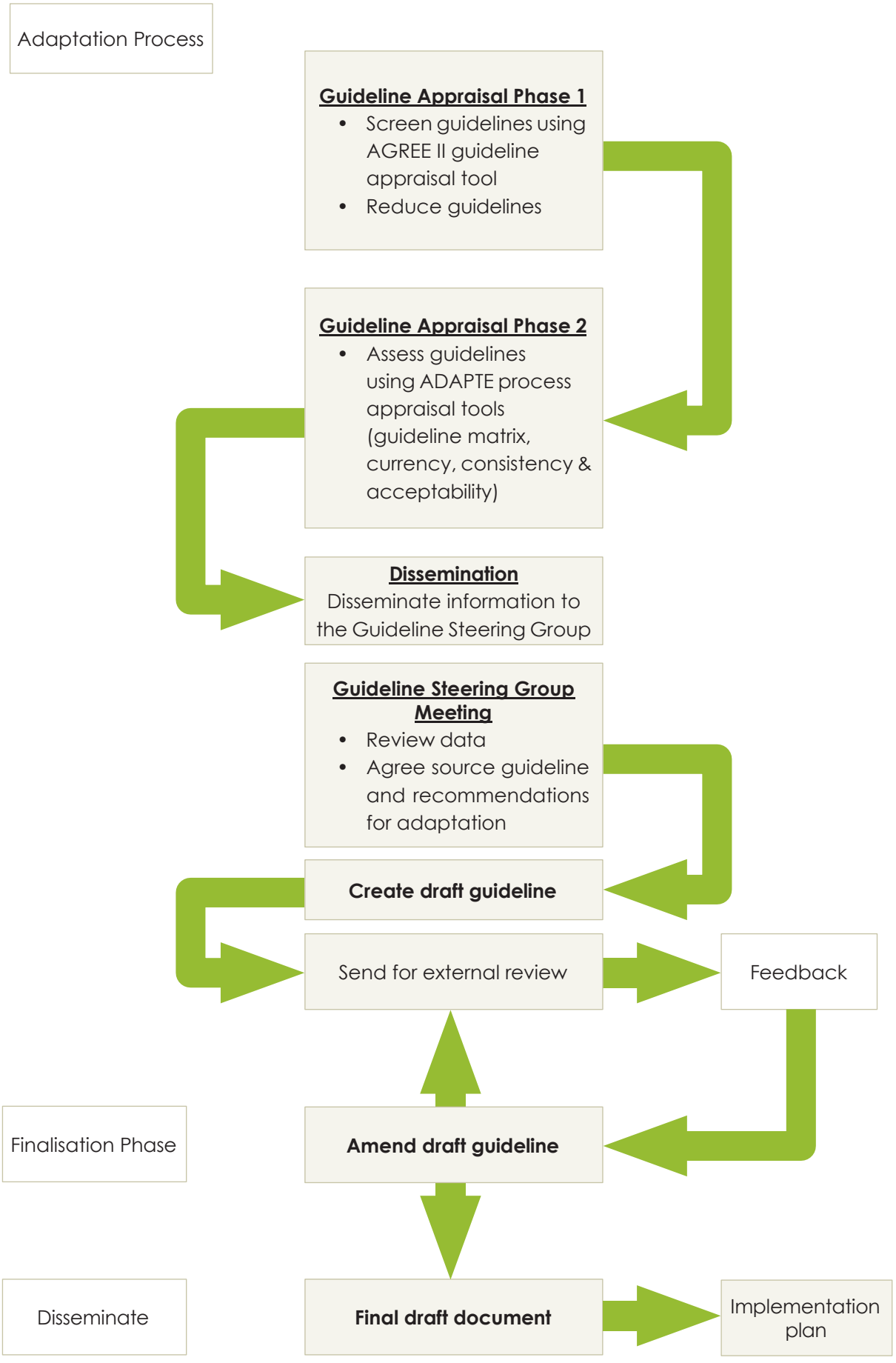


Figure 4 Adaptation process



Appendix V AGREE II scores

Appraiser 1 = Brenda O'Connor
Appraiser 2 = Louise Duddy

Table 8 AGREE II Scores

Title: Canadian Guidelines (17)	
DOMAIN 1 (Scope & Purpose): 77.8% DOMAIN 2 (Stakeholder Involvement): 58.3% DOMAIN 3 (Rigour of Development): 58%	DOMAIN 4 (Clarity of Presentation): 83.3% DOMAIN 5 (Applicability): 37.5% DOMAIN 6 (Editorial Independence): 87.5%

Title: EU Guideline (7)	
DOMAIN 1(Scope & Purpose): 69.4% DOMAIN 2 (Stakeholder Involvement): 66.6% DOMAIN 3 (Rigour of Development): 48.9%	DOMAIN 4 (Clarity of Presentation): 80.5% DOMAIN 5 (Applicability): 43.75% DOMAIN 6 (Editorial Independence): 50%

Title: Oncoline Guidelines (18)	
DOMAIN 1 (Scope & Purpose): 38.9% DOMAIN 2 (Stakeholder Involvement): 44.4% DOMAIN 3 (Rigour of Development): 39.5%	DOMAIN 4 (Clarity of Presentation): 58.3% DOMAIN 5 (Applicability): 31.25% DOMAIN 6 (Editorial Independence): 16.6%

Title: Guidelines Protocols British Columbia (20)	
DOMAIN 1 (Scope & Purpose): 61.6% DOMAIN 2 (Stakeholder Involvement): 55.5% DOMAIN 3 (Rigour of Development): 51.04%	DOMAIN 4 (Clarity of Presentation): 52.8% DOMAIN 5 (Applicability): 60.4% DOMAIN 6 (Editorial Independence): 58%

Title: Putting Evidence into Practice (US Guideline) (19)	
DOMAIN 1 (Scope & Purpose): 75% DOMAIN 2 (Editorial Independence): 55.6% DOMAIN 3 (Rigour of Development): 58.3%	DOMAIN 4 (Clarity of Presentation): 19.4% DOMAIN 5 (Applicability): 25% DOMAIN 6 (Editorial Independence): 58.3%

Title: Fraser Healthcare Guidelines (145)	
DOMAIN 1 (Scope & Purpose): 86.1% DOMAIN 2 (Stakeholder Involvement): 55.5% DOMAIN 3 (Rigour of Development): 37.5%	DOMAIN 4 (Clarity of Presentation): 55.5% DOMAIN 5 (Applicability): 14.6% DOMAIN 6 (Editorial Independence): 0%

Title: 14 Palliative Care 3 Symptom (Perth Guideline) (146)	
DOMAIN 1 (Scope & Purpose): 41.7% DOMAIN 2 (Stakeholder Involvement): 36% DOMAIN 3 (Rigour of Development): 13.5%	DOMAIN 4 (Clarity of Presentation): 19.4% DOMAIN 5 (Applicability): 10.4% DOMAIN 6 (Editorial Independence): 0%

Title: Tasmania Guidelines (147)	
DOMAIN 1 (Scope & Purpose): 55.5% DOMAIN 2 (Stakeholder Involvement): 13.8% DOMAIN 3 (Rigour of Development): 10.4%	DOMAIN 4 (Clarity of Presentation): 52.7% DOMAIN 5 (Applicability): 14.6% DOMAIN 6 (Editorial Independence): 0%

Title: St Richards Guideline (148)	
DOMAIN 1 (Scope & Purpose): 52.8% DOMAIN 2 (Stakeholder Involvement): 55.5% DOMAIN 3 (Rigour of Development): 24%	DOMAIN 4 (Clarity of Presentation): 63.9% DOMAIN 5 (Applicability): 22.9% DOMAIN 6 (Editorial Independence): 16.7%

Title: PANG Guidelines (149)	
DOMAIN 1 (Scope & Purpose): 36% DOMAIN 2 (Stakeholder Involvement): 55.5% DOMAIN 3 (Rigour of Development): 32.2%	DOMAIN 4 (Clarity of Presentation): 58.3% DOMAIN 5 (Applicability): 22.9% DOMAIN 6 (Editorial Independence): 50%

Title: Lothian Guidelines (150)	
DOMAIN 1 (Scope & Purpose): 44.4% DOMAIN 2 (Stakeholder Involvement): 36% DOMAIN 3 (Rigour of Development): 21.9%	DOMAIN 4 (Clarity of Presentation): 52.7% DOMAIN 5 (Applicability): 18.75% DOMAIN 6 (Editorial Independence): 4%

Appendix VI: Recommendation matrix

Table 9 Recommendations matrix

Constipation Guidelines – Grouped by recommendation	Canada CPG1
AGREE rigour scores	**6**
Overall quality assessment	**Strongly Recommended and most current**
1. Definitions A & B	**A. Grade D/Level 5** reference EU guidelines, Oxford Textbook and ABC PC (ABC has no ref for definition) Definition in algorithm <3 BM/week &/or sense of incomplete evacuation &/or hard stools &/or straining **B. Level 5** Not defined p766 mentions aetiology of opioid induced constipation, not referenced
2. Responsible disciplines	**Grade D/Level 5** p763 Refers to "the clinician" in assessment of constipation p765 "Healthcare providers" p765 Consistent, regular monitoring by patient, family and healthcare providers is vital…"
3. Assessment Tools	**Grade D/Level 5** **A.** Regular screening with a validated assessment tool at least every three days in all patients with advanced progressive illness "with inquiry and a validated assessment scale" p763 **B.** The group supported a portion of the Victoria Hospice Bowel Performance Scale (BPS), (excludes portion relevant to diarrhoea). Other recommended scales listed are the Bristol Stool Form Scale and Constipation Assessment Scale (CAS) p764 **C.** No reason for use of one tool over another given. Scales given are those currently in use in Canada. "The use of images has been shown to be meaningful to patients" – **Grade B/Level 3** **D.** All 3 scales validated p764 (2, 11, 12) & p770 **E.** All patients with advanced progressive illness should be monitored frequently (at least every three days), no other guidance on adjusting to type or stage of disease. p763
4. Radiology	**A. Grade D/Level 5** p765 Radiology described as an underused diagnostic tool (no ref), useful in quantifying constipation and excluding faecal impaction. Abdominal flat plate recommended in cases of severe constipation (not defined), or constipation unresponsive to treatment. Should be performed in all patients well enough to undergo radiography (ABC PC). **B.** Abdominal flat plate (supine position) (check this is equivalent to PFA)
5. Use of DRE	**Grade D/Level 5** No discussion of evidence for use "Privacy and cultural sensitivities should be taken into account." p764 DRE listed as an "important element" in physical examination Caution advised when performing DRE in immunocompromised patients due to risk of anal fissures or abscesses (no mention of frailty etc) (Kyle)

Constipation Guidelines – Grouped by recommendation	**Canada CPG1**
6. Risk reduction in palliative care patients	**Grade D/Level 5** Encourage patients to be as mobile as possible within their capabilities Encourage adequate fluid intake (Kyle) Awareness of drugs likely to cause constipation – either avoid, or laxative available at time of first prescription (Consensus best practice) p770 (no references) Increased fibre intake may not be appropriate in this population (Kyle)
7. Management options for established constipation in patients with palliative care needs	**Grade D/Level 5** Specific for palliative population Bulking agents not recommended in bedridden patients due to extra need for fluid Docusate and mineral oil not recommended
8. Drug adjustment	Selection based on individual patient symptoms, PS and preference VH 2-3 Osmotic PEG/Lactulose ± stimulant senna/bisacodyl if not resolved, consider MNTX, VH4 maximize laxative doses then ADD as necessary suppositories (bisacodyl/glycerin), rectal enemas (phosphate) or high enemas (oil±saline/tap water) European guidelines & VH referenced, p 766, 771
9. Is a step-wise approach recommended?	Yes Pharmacological interventions based on American College of Gastroenterologists meta-analysis 2005 and are consistent with Cochrane review 2006 but overall treatment in palliative care is based on inadequate evidence Decision points – Figure 2 p771 Bulk forming laxatives **Grade B** evidence Osmotic laxatives, lactulose and PEG supported by **Grade A** evidence Stimulants can be used despite 'insufficient evidence' Rectal intervention if constipation persists MNTX to be considered if opioids felt to be a factor
10. Managing opioid induced constipation in palliative care patients	**Grade A/Level 1b (Pharma Sponsored)** MNTX listed as an option for patients on opioids who fail to respond to optimal laxative therapy (unable to draw firm conclusions of safety at time of development). (McNichol – a small number of RCTs supporting use in this population)
11. Pharma vs non-pharm interface	**Grade D/Level 5** Emphasized prior to pharmacological intervention Adequate fluid intake including foods containing large amounts of water as ability to consume fluids decreases with debility (Kyle) Consideration of dignity, individual preferences, cultural sensitivities, privacy recommended Ongoing assessment/evaluation including family input Optimized regular toileting, positioning Use of fibre advised with caution because inadequate fluid intake is often a problem P765 & 770 Need for concomitant medications often required despite above
12. Alternative route of administration	**Grade D/Level 5** CBP Management 5e – if constipation persists, an enema or suppository may be needed (harder feces - mineral/vegetable oil or phosphate enema +/- higher saline enema may be needed; softer feces – a suppository or phosphate enema may suffice) – EU guidelines referenced

Constipation Guidelines – Grouped by recommendation	Canada CPG1
13. Management in setting of bowel obstruction	Recommend patients with signs of obstruction should be considered for surgical intervention (if consistent with goals of care), no references p765
14. Discontinuation of treatment in terminal phase	**Not mentioned,** selection of laxatives should be based on PS p766
15. Side Effects	**P 767, ref = EU, OTPM, Canadian Pharmacists Association** **Oral Laxatives** Bulking agents – may cause distension, bloating, abdominal pain Surfactant laxatives/softeners – Diarrhoea, nausea, cramps, skin rash, bitter taste Lubricants/emollients – May decrease absorption of fat-soluble vitamins, anal seepage and irritation, risk of lipoid pneumonia Stimulant (irritant) laxatives – Watery diarrhoea, cramping, electrolyte imbalance and dermatitis Osmotic laxatives – Lactulose: flatulence or colic, abdominal distension, discomfort, need for monitoring in DM, taste intolerance; Sorbital: less nauseating than lactulose (nausea not listed for lactulose) Saline laxatives – Electrolyte imbalance – caution advised in cardiac and renal disease PEG: Abdominal distension and pain, borborygmi, nausea, mild diarrhoea **Rectal laxatives** Lubricant laxatives – local irritation Osmotic laxative – local irritation Stimulant laxative – abdominal cramping and pain, diarrhoea, local irritation Saline laxative – local irritation, excessive use may cause diarrhoea and fluid loss
16. Cost implications	**Grade D/Level 5** "Recommendations for laxative use can be related to costs as much as to efficacy." (taken from Cochrane Review – 14), no other mention of cost.

Constipation Guidelines – Grouped by recommendation	**EU CPG2**
AGREE rigour scores	**5.5**
Overall quality assessment	**Strongly Recommended (Potential conflict of interest identified)**
1. Definitions A & B	**Grade D / Level 5** **A.** Takes into account measurable symptoms and patient perception, definition used (Sykes OTPM), no frequency specified - Added note if defecating <3 x per week (ROME II) an assessment is recommended. **B.** Listed as a causative factor but not specifically defined
2. Responsible disciplines	**Grade D / Level 5** Healthcare professional referred to in assessment and management. Separate paragraph addressing the role of nurses – anticipation and evaluation as key nursing role, nurses as ideally placed to assess risk of constipation and evaluate the efficacy of constipation prophylaxis or treatment. Regular assessment of 9 factors listed p 806. Algorithm as a guide for all medical and nursing staff involved in the management of constipation in PC patients.
3. Assessment Tools	**Grade D / Level 5** **A. Not recommended for routine clinical practice.** Useful for encouraging patients to assess their own bowel movements or when communication between the healthcare professional and patient is difficult. (Heaton) **B.** 4 most commonly used scales listed (Bristol Stool Form Scale; Constipation Assessment Scale; Constipation Visual Analogue Scale; Eton Scale Risk Assessment for Constipation) No evidence given that these are the most commonly used. **C.** Importance of readability and time necessary for completion emphasized but no evidence given to support one over another **D.** No, those listed are validated **E.** No comment
4. Radiology	**Grade D / Level 5** **A.** May be recommended for specific patients p 799 not elaborated on **B.** Plain film of abdomen, if necessary, to exclude bowel obstruction
5. Use of DRE	Recommended in patients with more than 3 days since last bowel movement, or the patient describes incomplete evacuation. Unless the history clearly suggests acute infection – no references

Constipation Guidelines – Grouped by recommendation	EU CPG2
6. Risk reduction in palliative care patients	Importance of ongoing continuing aspects of management/assessment to monitor improvements or deterioration and helping management decisions by identifying modifiable causative factors. Promoting change in lifestyle or other underlying factors that may reduce or prevent constipation. Patient education as a central part of prevention. – Ensuring privacy and comfort **Grade D/Level 5** – Increasing fluid and fibre intake within the patient's limits (note made that amount of dietary fibre and fluid intake required to have an effect is an unrealistic expectation in this patient population secondary to anorexia and ability to consume fluids. Conclude that reliance on dietary fibre for relief of constipation in PC is inappropriate **Grade B/Level 3** – Encouraging activity and mobilization within the patient's limits **Grade D/Level 5** – Anticipating the constipating effect of pharmacological agents and prescribing prophylactic laxatives – Use of abdominal massage, usually in combination with other methods **Level 1b (Chronic Constipation)** – Individuals may find personal benefit from other complimentary therapies – Duty of care of health professionals to encourage these changes although research suggests that there is a limit to their influence and should not be solely relied upon (not referenced ?point of this statement)
7. Management options of established constipation in patients with palliative care needs	3 published clinical trials in this population show minimal differences in effectiveness between individual laxatives Generally a softener and a stimulant recommended in PC **(Level 5)** Advise not to use danthron-containing preparations in incontinent patients **(Level 5)** Bulking agents not recommended in patients unable to consume large volumes of fluid **(Level 5)** Enema or suppository may be needed in faecal impaction **(Level 5)**
8. Drug adjustment	**Grade D/Level 5** If no BM in 3 days after oral laxatives commenced (not stated if regular or what type), then use combination of stimulant and softener, then titrate dose on a daily or alternate day basis until BM achieved. If practicable and acceptable a rectal examination should be done periodically during this up-titration and an enema or suppository may be needed. Occurrence of colic – recommend increasing the dose of softener > stimulant, faecal leakage reduce softener and possibly increase stimulant. Acknowledge that certain patient groups i.e. cognitive impairment/SCC have different needs/management – out of scope of guideline
9. Is a step-wise approach recommended?	**Grade D/Level 5** Yes p805 Pt complains of constipation (or in some cases BM < 3 x wk) Assess to confirm and exclude obstruction Assessment of cause and treatment of correctable causes First line – Oral laxative: combination of softener and stimulant Second line – Rectal suppository and enema +/- MNTX if on opioid Third line – Manual evacuation +/- MNTX
10. Managing opioid induced constipation in palliative care patients	**Level 1b (Pharma sponsored)** Double-blind RCT showed MNTX superiority to placebo in PC patients (Thomas et al NEJM) The therapeutic role of MNTX initially felt likely to be the treatment of opioid-induced constipation that has been resistant to conventional laxative interventions

Constipation Guidelines – Grouped by recommendation	**EU CPG2**
11. Pharma vs non-pharm interface	**Grade D/Level 5** Preventative measures = education, ensuring privacy and comfort to allow normal defecation, increasing fluid and fibre intake within the patient's limits, encouraging activity and increased mobility within the patients limits, individuals may find personal benefit from complimentary therapies, abdominal massage may be useful for prophylaxis and treatment in some patients
12. Alternative route of administration	**Grade D/Level 5** Need for rectal care at end of life is rare Rectal intervention should be avoided where possible but may be necessary in patients who cannot swallow or tolerate oral laxatives or when oral medication has been unsuccessful at re-establishing a regular bowel pattern, where there is fecal impaction or in spinal cord lesions and disrupted innervation to the lower bowel.
13. Management in setting of bowel obstruction	**Grade D/Level 5** Investigate by history, examination, and if necessary radiology (e.g. plain film of the abdomen). If the obstruction is partial, a softener should be used alone. If complete, laxatives should not be used and consideration given to surgical or conservative management.
14. Discontinuation of treatment in terminal phase	**Grade D / Level 5** Importance of regularly reassessing the goals of management during the last days of life. A patient's deteriorating functional status can mean that the symptoms of constipation become less apparent as they become comatose and therefore management of constipation becomes a lower priority. Once unable to receive medication, oral laxatives should be discontinued. The need for rectal care is likely to be rare at this stage. P806 No references.
15. Side Effects	See tables
16. Cost implications	(refs 19-21) **Grade B/Level 3** Systematic review – Cost of laxatives in the elderly in UK = £43 million per year. Study in US NH suggested an annual cost of treating constipation (drugs plus nursing staff) US $2253 per long-term resident. UK study 80% of community nurses spend up to half a day each week treating patients with constipation Another study 5.5% of calls to an out-of-hours district nursing service directly related to constipation No direct study in PC pop'n, suggest that figures are likely to be higher in PC setting because of increased risk factors for constipation.

Constipation Guidelines – Grouped by recommendation	Oncoline CPG3 Aimed at oncology patients
AGREE rigour scores	**4**
Overall quality assessment	
1. Definitions A & B	**A.** ROME criteria used. "The passage of faeces infrequently and with difficulty" (from Sykes but not referenced) p2 **B.** Description of pathophysiology p4
2. Responsible disciplines	No mention Consider dietitian, consider stoma nurse input
3. Assessment Tools	None recommended or mentioned, list of history taking points p6 and advising patient to keep a diary may be worthwhile
4. Radiology	**A.** X-ray may be done if there are doubts about the presence of constipation or to exclude obstruction **B.** 'abdominal x-ray' listed. Or USS/CT/endoscopic examination may be performed in obstruction p6 Lumbar MRI (NOT GOLD STANDARD) if spinal cord or cauda equina suspected
5. Use of DRE	**Grade D/Level 5**- no references Recommended routinely p 6
6. Risk reduction in palliative care patients	**Grade D/Level 5** – no references Create a favourable sanitary environment If possible, let the patient take enough fluid (at least 1500ml per day) Aim for a varied and fibre-rich diet and regular eating pattern, often not attainable in "palliative phase" Use of fibres "contraindicated" in patients who cannot take enough fluid and in the case of (impending) bowel obstruction Advise as much physical exercise as is feasible Consider abdominal massage Preventative laxatives recommended at: the start of a treatment with opioids, in the presence of two or more risk factors (bedridden, exhaustion, insufficient fluid and/or food intake, cognitive dysfunction, anticholinergic meds, PD, neurological loss of function, partial intestinal obstruction, hypercalcaemia
7. Management options in palliative care patients	Treatment of causative factors only if worthwhile and desirable
8. Drug adjustment	See below

Constipation Guidelines – Grouped by recommendation	**Oncoline CPG3** **Aimed at oncology patients**
9. Is a step-wise approach recommended?	**Grade D/Level 5** Yes p13 Prevention, treatment of causative factors If constipation has occurred application and/or optimization of non-pharmacologic measures If faecal compaction: – microenema or phosphate enema – PEG up to 8 sachets for max 3 days – Manual removal if necessary Only use oral laxatives once defaecation has occurred If insufficient effect of non-pharmacologic measures or hard faeces, start pharmacologic treatment – 1st choice monotherapy with PEG 1-2 daily – 2nd choice Mg oxide/hydroxide 500/724-1000/1448 3 x daily – Alternatives lactulose 20-30ml 1-2 x day or lactitol 10-20g 1-2 x daily – If insufficient add bisacodyl 5-10mg PRN or suppository or senna 10-20ml OD – If PO not possible use bisacodyl suppository mane – If soft faeces use bisacodyl PO or PR
10. Managing opioid induced constipation in palliative care patients	Routine prescription of laxatives, softener +/- stimulant. Consider switching to fentanyl or other opioid (clear indications less constipating than morphine) MNTX 8mg or 12mg SC every other day if oral laxatives insufficient effect (not referenced at all, but levels of evidence table provided later)
11. Pharma vs non-pharm interface	All measures stated as prevention then add pharmacological measures
12. Alternative route of administration	Oral route as preferred route Rectal laxative or enema if full rectum or impaction, micro-enema, then phosphate if ineffective Enemas can be given via colostomy MNTX in severe opioid induced constipation Manual removal described using midazolam 7.5mg SC, 10ml lidocaine gel 1% rectally, or rectal lavage with saline solution
13. Management in setting of bowel obstruction	Oral laxatives contraindicated in (impending) bowel obstruction Consider surgery/stent
14. Discontinuation of treatment in terminal phase	In the last few days prior to death, and if oral medication is no longer taken, laxatives can be discontinued
15. Side Effects	Table format PEG – foul taste (recommend dissolving in iced water) Magnesiumoxide/hydroxide – not for use in severe renal impairment, not for use with tetracyclines. Lactulose – foul taste, bloated feeling, flatulence (lactitol doesn't have) Bisacodyl – may induce stomach cramps Senna – foul taste, stomach cramps – suggest mixing with chocolate milk or apple juice Methycellulose – CI in insufficient fluid intake, faecal impaction, presence of adhesions and or stenosis (abdominal operations in the history)
16. Cost implications	Cost mentioned as a factor in choosing one oral laxative over another but not qualified.

Constipation Guidelines – Grouped by recommendation	BC CPG4
AGREE rigour scores	**4**
Overall quality assessment	
1. Definitions A & B	**A.** Not defined **B.** Not defined
2. Responsible disciplines	Not mentioned
3. Assessment Tools	No tool recommended Assessment includes – understanding the patients bowel habit, both current and when previously well
4. Radiology	**A.** Abdominal x-ray can be useful when examination inconclusive **B.**
5. Use of DRE	
6. Risk reduction in palliative care patients	For lower PS patients, lower BM frequency is acceptable as long as there is no associated discomfort
7. Management options in palliative care patients	Regular laxatives when risk factors are ongoing
8. Drug adjustment	
9. Is a step-wise approach recommended?	Yes Sennosides as first choice for prevention and treatment, unless IBS – then osmotic Weak evidence that lactulose and sennosides are equally effective, however lactulose limited by side effects Recommend a palliative care consult if unsuccessful
10. Managing opioid induced constipation in palliative care patients	After a trial of first-line recommended stimulant laxatives and osmotic laxatives, switch to a less constipating opioid i.e. methadone or fentanyl. Then consider MNTX. Cancer, GI malignancy, GI ulcer, Ogilvie's Syndrome and concomitant use of NSAIDs, steroids and bevacizumab may increase the risk of GI perforation with MNTX
11. Pharma vs non-pharm interface	Not mentioned
12. Alternative route of administration	Avoid rectal interventions except in crisis management. But then listed as 1st line if full rectum. Rectal measures CI in neutropenia/thrombocytopenia (PLT <20) or rectal/ anal disease If required, recommend a stimulant suppository then an enema
13. Management in setting of bowel obstruction	FPON guideline advised
14. Discontinuation of treatment in terminal phase	Not mentioned
15. Side Effects	Sennosides – patients with IBS may experience painful cramps Lactulose – tastes unpleasant, bloating
16. Cost implications	Cost comparison listed in appendix B

Constipation Guidelines – Grouped by recommendation	**US CPG5** **Aimed at cancer patients** **Clear search history and summery of literature**
AGREE rigour scores	**3.5**
Overall quality assessment	
1. Definitions A & B	**A.** "A decrease in the passage of formed stool characterized by stools that are hard and difficult to pass" (not referenced), they note lack of a consistently accepted definition and that most relate to chronic constipation. **B.** Terms opioid bowel dysfunction and opioid induced bowel dysfunction also mentioned. "Opioids bind to the mu receptors of the GI tract, delaying gastric emptying and causing symptoms of constipation." (Friedman & Dello Buono 2001, Tamayo & Diaz-Zuluaga 2004)
2. Responsible disciplines	Oncology nurses
3. Assessment Tools	Not addressed **A.** **B.** **C.** **D.** **E.**
4. Radiology	**A.** Neither addressed **B.**
5. Use of DRE	Recommended in evaluation of impaction. Discouraged in myelosuppressed patients due to risk of development of portals of infection (NCI 2006) (Expert committee – Level 5/D)
6. Risk reduction in palliative care patients	Not addressed
7. Management options in palliative care patients	Stimulant or osmotic laxatives for patients who have persistent constipation **at the end of life**
8. Drug adjustment	Not addressed due to lack of evidence
9. Is a step-wise approach recommended?	After 3 days of BNO a patient should initiate a bowel management program. "Insufficient high-quality evidence exists to recommend a systematic approach…" = based on evidence. No interventions which could be recommended for nursing practice in oncology population. NCCN guidance is quoted p 328 LTBE: – PEG for persistent constipation, (as per NCCN 2006a), high level of evidence for safety and efficacy in non-oncology population, evidence not specific for cancer patients – Stimulant or osmotic laxatives for patients who have persistent constipation **at the end of life**, "some patients may need both" – Agra et al 1998 no difference in senna v lactulose in terminal cancer patients

Constipation Guidelines – Grouped by recommendation	US CPG5 Aimed at cancer patients Clear search history and summery of literature
10. Managing opioid induced constipation in palliative care patients	– Strong evidence and expert opinion support the initiation of a prophylactic bowel management regimen and monitoring when opioids are prescribed – (Bisanz 2005, Kalso, McNichol Miaskowski 2005, NCCN 2006a, Robinson 2000) however paucity of research re which regimen. – Opioid rotation to Fentanyl – 3 crossover studies from MR morphine to transdermal fentanyl significant decline in constipation (Radbruch 2000, Ahmedzai 1997, Allan 2001, McNichol, Miaskwski 2005) – Naloxone = inconsistent reliability and mixed efficacy, recommended in Benefits balanced with harms category – MNTX and Alvimopan listed under "Effectiveness not established" – 1 RCT & 2 phase III trials for MTNX Grade D/Level 5 – Tegaserod – FDA restricted to refractory constipation in IBS – significant cardiac risks
11. Pharma vs non-pharm interface	Non-pharmacologic interventions listed as "Effectiveness not established" – Privacy, comfort, access – Activity and increased mobility – Adequate fluid intake (warm fluids may benefit NCI 2006, Consortium for Spinal Cord Medicine 1998) – Valsalva maneuver in patients with neurogenic problems – Aromatherapy, massage therapy and aromatherapy massage – Biofeedback (training body and mind to change bodily function) – Dietary fibre (research inconclusive, not recommended in advanced disease due to fluid requirements) – Fresh baker's yeast (not recommended in neutropenia, storage issue) – Herbal supplements – Paraffin – Seeds/dils/arachis oil – Stercullia (type of fibre)
12. Alternative route of administration	Not addressed
13. Management in setting of bowel obstruction	Not addressed Prokinetic agents should be avoided
14. Discontinuation of treatment in terminal phase	Not addressed
15. Side Effects	– Castor oil not recommended because of severe cramps – Prokinetics should be limited for severe constipation and those resistant to bowel programs? Why (Mancini and Bruera 1998, NCCN 2006a, Consortium for Spinal Medicine 1998). Should be avoided in large abdominal tumours ?why – Oral mineral oil may interfere with absorption of some nutrients – Lactulose cramping and flatus
16. Cost implications	Lactulose costs more than sorbitol (same ingredients and efficacy)

Appendix VII: Health questions

Relevant Population:
Adult populations with life-limiting conditions in receipt of palliative care (both generalist and specialist)

Health Question Development:
The following structure was used in the development of health questions to be addressed within the guideline:

P - **P**opulation
I - **I**ntervention
P - **P**rofessionals
O - **O**utcome
H - **H**ealthcare setting

Health Questions:

General:
(1) What is the definition of constipation/opioid induced constipation?
(2) What disciplines are responsible for the assessment, plan of management and treatment of patients?

Assessment/ Diagnosis:
(3) Assessment tools:
  a) When is it appropriate to use an assessment tool?
  b) What assessment tools are available?
  c) Is there any evidence to support the use of one tool over another?
  d) Is there any evidence on the validity/reliability of any of the assessment tools?
  e) Does this need to be adjusted according to the type and stage of disease?
(4) Radiology:
  a) What is the evidence for the use and timing of radiological investigations (PFA in particular) in assessment?
  b) What radiological investigations are recommended to assess for constipation?
(5) What is the evidence for the use of digital rectal examination?

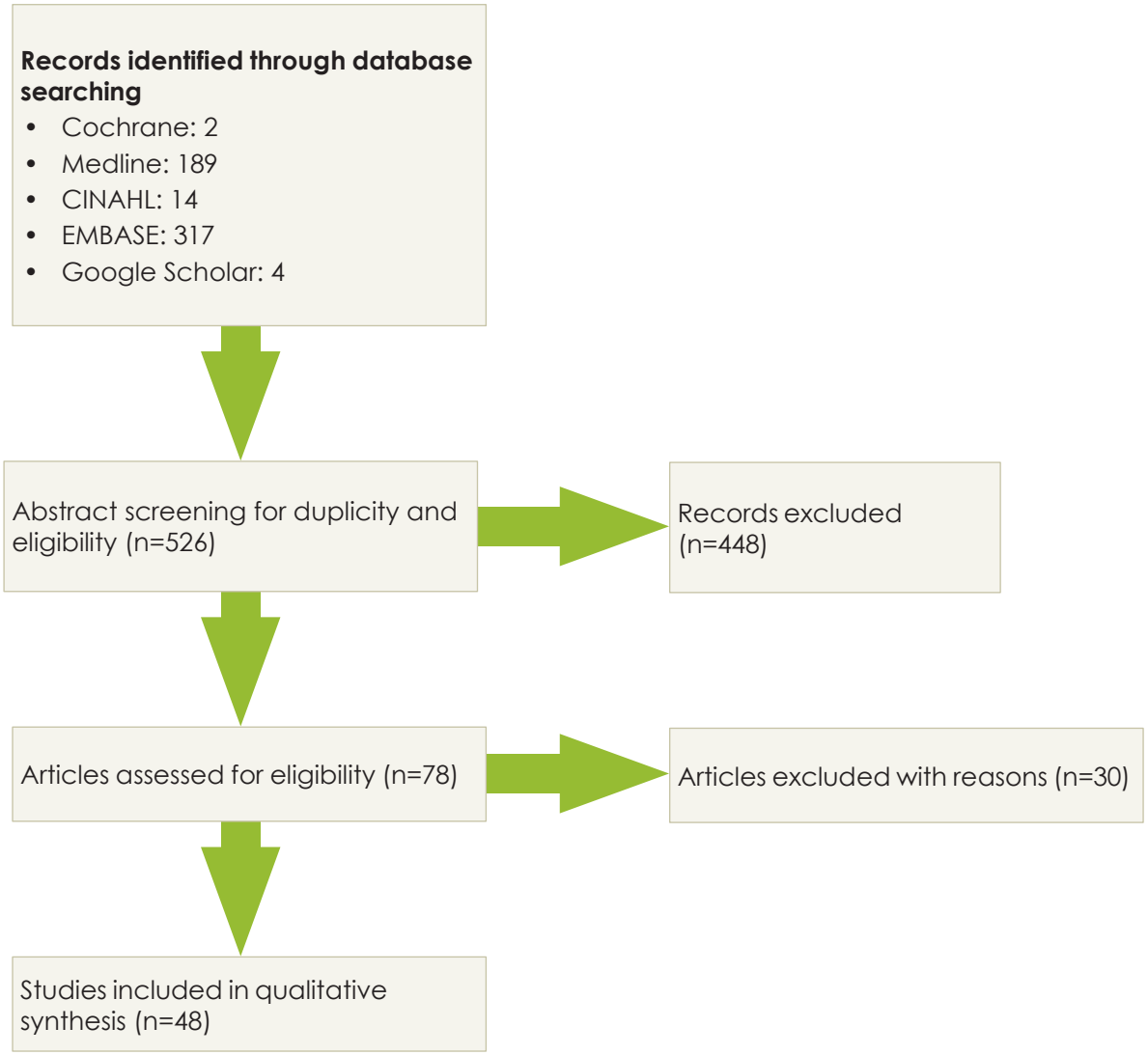
Management:
(6) What are the recommended management options to reduce the risks of constipation developing in patients with palliative care needs?
(7) What are the recommended management options for the treatment of established constipation in patients with palliative care needs?
(8) When is it appropriate to adjust drug therapy i.e. intervene with new/changed drug therapy?
(9) Is there a step-wise approach that can be recommended?
(10) What measures are recommended for managing opioid-induced constipation in patients with palliative care needs?
(11) Where is the interface between non-pharmacological versus pharmacological intervention?
(12) When is it appropriate to use an alternative to the oral route for laxative administration (PR/SC)?
(13) What is the role of constipation management in patients who have developed bowel obstruction i.e. what are the indications for not treating?
(14) When should treatment be stopped in the terminal stages/last days of life?
(15) What are the side-effects/complications of laxative treatment?
(16) What are the cost implications of the recommended treatments for constipation in this guideline?

Appendix VIII: Sample health question literature search

Health Question Number 10
What measures are recommended for managing opioid-induced constipation in patients with palliative care needs?

PIPOH format
Population: Adult populations (greater than 18) with life-limiting conditions in receipt of palliative care (both generalist and specialist)
Intervention: Pharmacological agents for the management of opioid-induced constipation
Professionals: All healthcare professionals caring for patients with life-limiting conditions
Outcomes: Resolution of opioid-induced constipation
Healthcare Setting: Generalist & specialist palliative care setting

Figure 5 Search diagram



Appendix IX: Summary searches

Table 10 Summary Searches

Health Question	Search terms	Search dates	Records identified through database searching	Articles excluded and included
Question 1: Constipation Definition	Constipation; Opioid induced constipation; Definition; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life-limiting; Advanced disease; Advanced illness; **Limits:** English; Human; Adult; Dates: 01/01/06-11/01/13	10/12/12 & 11/1/13 **Search Update:** 18/07/14	Cochrane: 0 Medline: 56 CINAHL: 23 EMBASE: 64 Google Scholar: 3 (n = 146)	**Excluded:** 123 **Included:** 23
Question 2: Responsible Health Professionals	Constipation, Disciplines; Multidisciplinary; Multidisciplinary team; Health professional; Healthcare professional; Medical; Doctor; Nursing; Nurses; Pharmacy; Pharmacist; Physiotherapy; Occupational Therapy; Complementary Therapy; Assessment; Management; Treatment; Monitoring; Planning; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life limiting; Advanced disease; Advanced illness **Limits:** English; Human; Adult; Dates: 01/01/06-20/01/13	07/01/13 & 20/01/13 **Search Update:** 18/07/14	Cochrane: 0 Medline: 114 CINAHL: 14 EMBASE: 89 Google Scholar: 1 (n = 218)	**Excluded:** 212 **Included:** 6
Question 3: Assessment Tool	Constipation; Assessment; Tools; Assessment tools; Assessment scale; Screening tools; Instrument; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life limiting; Advanced disease; Advanced illness **Limits:** English; Human; Adult; Dates: 01/01/06-11/01/13	11/12/12 & 11/01/13 **Search Update:** 18/07/14	Cochrane: 0 Medline: 76 CINAHL: 12 EMBASE: 94 Google Scholar: 2 (n = 184)	**Excluded:** 171 **Included:** 13
Question 4: Radiological Assessment	Constipation Assessment; Investigation; Radiology; Radiological Investigation; Plain film of abdomen; Abdominal x-ray; Abdominal film; Plain film of abdomen; Film of abdomen; Ultrasound; Computerised Tomography; CT, Magnetic Resonance Imaging; MRI; Barium, Gastrograffin; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life limiting; Advanced disease; Advanced illness **Limits:** English; Human; Adult; Dates: 01/01/06-12/01/13	12/12/12 & 12/01/13 **Search Update:** 19/07/14	Cochrane: 0 Medline: 33 CINAHL: 9 EMBASE: 49 Google Scholar: 2 (n = 93)	**Excluded:** 85 **Included:** 8

Health Question	Search terms	Search dates	Records identified through database searching	Articles excluded and included
Question 5: Digital Rectal Examination	Constipation; Digital rectal examination; Rectal examination; Rectal exam; Per rectum examination; PR examination, Digital Examination; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life limiting; Advanced disease; Advanced illness **Limits:** English; Human; Adult; Dates: 01/01/06-12/01/13	17/12/12 & 12/01/13 **Search Update:** 19/07/14	Cochrane: 0 Medline: 57 CINAHL: 22 EMBASE: 42 Google Scholar: 1 (n = 122)	**Excluded:** 117 **Included:** 5
Question 6: Constipation Prevention/Risk Reduction	Constipation; Prevention; Prophylaxis; Reduction; Risk reduction; Avoid; Avoidance; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life limiting; Advanced disease; Advanced illness **Limits:** English; Human; Adult; Dates: 01/01/06-16/01/13	05/01/12 & 16/01/13 **Search Update:** 19/07/14	Cochrane: 0 Medline: 60 CINAHL: 23 EMBASE: 82 Google Scholar: 3 (n = 168)	**Excluded:** 156 **Included:** 12
Question 7: Pharmacological Management Of Constipation	Constipation; Treatment; Management; Laxative; Laxatives; Medications; Prescription; Therapy; Therapeutics; Regimen; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life limiting; Advanced disease; Advanced illness **Limits:** English; Human; Adult; Dates: 01/01/06-13/01/13	15/12/12 & 13/01/13 **Search Update:** 24/07/14	Cochrane: 1 Medline: 323 CINAHL: 67 EMBASE: 457 Google Scholar: 8 (n = 856)	**Excluded:** 778 **Included:** 78
Question 8: Drug Therapy Adjustment	Constipation; Treatment; Management; Laxatives; Medication; Stop; Stopped; Discontinue; Discontinued; Discontinuation; Adjust; Adjusted; Adjustment; **Limits:** English; Human; Adult; Dates: 01/01/06-13/01/13	29/12/12 & 13/01/13 **Search Update:** 24/07/14	Cochrane: 0 Medline: 312 CINAHL: 49 EMBASE: 392 Google Scholar: 2 (n = 755)	**Excluded:** 752 **Included:** 3
Question 9: Step-Wise Pharmacological Approach	Constipation; Treatment; Management; Medications; Management; Step-wise; Stepped approach; Step-wise approach; Path; Pathway; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life limiting; Advanced disease; Advanced illness **Limits:** English; Human; Adult; Dates: 01/01/06-13/01/13	29/12/12 & 13/01/13 **Search Update:** 24/07/14	Cochrane: 0 Medline: 61 CINAHL: 13 EMBASE: 72 Google Scholar: 0 (n = 146)	**Excluded:** 139 **Included:** 7
Question 10: Opioid Induced Constipation Management	Opioid induced constipation; Management; Treatment; Laxatives; Medications; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life limiting; Advanced disease; Advanced illness **Limits:** English; Human; Adult; Dates: 01/01/06-28/12/12	28/12/12 & 15/01/13 **Search Update:** 28/07/14	Cochrane: 2 Medline: 189 CINAHL: 14 EMBASE: 317 Google Scholar: 4 (n = 526)	**Excluded:** 478 **Included:** 48

Health Question	Search terms	Search dates	Records identified through database searching	Articles excluded and included
Question 11: Non-Pharmacological versus Pharmacological	Constipation; Non pharmacological; Non drug; Diet; Exercise; Physical activity; Complementary therapy; Massage; Alternative therapy; Natural therapy; Management; Treatment; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life limiting; Advanced disease; Advanced illness **Limits:** English; Human; Adult; Dates: 01/01/06-16/01/13	05/01/13 & 16/01/13 **Search Update:** 21/07/14	Cochrane: 1 Medline: 35 CINAHL: 24 EMBASE: 53 Google Scholar: 3 (n = 116)	**Excluded:** 95 **Included:** 21
Question 12: Alternative To Oral Route	Constipation; Treatment; Management; Rectal; Rectal interventions; Rectal measures; Suppository; Suppositories; Enema; Enemas; Subcutaneous laxative; Injection; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life limiting; Advanced disease; Advanced illness **Limits:** English; Human; Adult; Dates: 01/01/06-14/01/13	29/12/12 & 14/01/13 **Search Update:** 24/07/14	Cochrane: 1 Medline: 92 CINAHL: 25 EMBASE: 107 (n = 227	**Excluded:**203 **Included:**24
Question 13: Laxatives In Bowel Obstruction	Constipation; Cancer; Bowel obstruction; Malignant bowel obstruction; Management; Medical management; Treatment; Laxative; Enema; Enemas; Suppository; Suppositories; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life limiting; Advanced disease; Advanced illness **Limits:** English; Human; Adult; Dates: 01/01/06-19/01/13	06/01/13 & 19/01/13 **Search Update:** 24/07/14	Cochrane: 0 Medline: 47 CINAHL: 12 EMBASE: 39 Google Scholar: 0 (n = 98)	**Excluded:** 84 **Included:** 14
Question 14: Pharmacological Therapy In Last Days Of Life	Constipation; Stop; Stopped; Discontinue; Discontinuation; Discontinued; Adjusted; Adjustment; Last days; Last days of life; Terminal stage; Terminal days; Terminal phase; Final days; Final stage; End of life; End stage; End phase; Final phase; Palliative; Supportive Care; Hospice; **Limits:** English; Human; Adult; Dates: 01/01/06-20/01/13	06/01/13 & 19/01/13 **Search Update:** 28/07/14	Cochrane: 0 Medline: 19 CINAHL: 7 EMBASE: 15 Google Scholar: 2 (n = 43)	**Excluded:** 37 **Included:** 6
Question 15: Laxative Side-Effects/ Complications	Constipation; Treatment; Management; Medication; Laxative; Enema; Suppository; Suppositories; Side-effect; Adverse effect; Adverse reaction; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life limiting; Advanced disease; Advanced illness **Limits:** English; Human; Adult; Dates: 01/01/06-30/12/12	30/12/12 & 14/01/13 **Search Update:** 24/07/14	Cochrane: 0 Medline: 903 CINAHL: 111 EMBASE: 827 Google Scholar: 7 (n = 1,848)	**Excluded:**1,811 **Included:** 37

Health Question	Search terms	Search dates	Records identified through database searching	Articles excluded and included
Question 16: Cost Implications	Constipation; Laxatives; Treatment; Management; Monitoring, Nursing; Cost; Economics; Finance; Financial; Health economics; Palliative; Supportive Care; Terminal; Hospice; End of life; End stage; Life limiting; Advanced disease; Advanced illness **Limits:** English; Human; Adult; Dates: 01/01/06-20/01/13	08/01/13 & 20/01/13 **Updated Search:** 17/07/14 (see more comprehensive pharmacoeconomic search)	Cochrane: 0 Medline: 19 CINAHL: 8 EMBASE: 23 Google Scholar: 0 (n = 50)	**Excluded:** 47 **Included:** 3

Appendix X: External review

External Reviewers:
The external reviewers evaluated the draft document and provided commentary summarised below.

- Professor Lukas Radbruch (Key Collaborator to AIIHPC), Chair of Palliative Medicine, University of Bonn; Director of Department of Palliative Medicine, University Hospital Bonn; Director of Palliative Care Centre, Malteser Hospital Bonn/Rhein-Sieg.
- Associate Professor Max Watson, Consultant in Palliative Medicine/Lecturer in Palliative Care, Northern Ireland Hospice, Belfast.

External Review thematic feedback

Table 11 External Review Thematic Feedback

Has the appropriate evidence been identified and reviewed in line with the scope and clinical questions posed by these guidelines?	The key questions that you asked are addressed and a real synthesis of the current literature and practice demonstrated. *Suggestion*: provide more detail regarding which recommendations were new and those based on the source guidelines. *Action:* Suggestion incorporated
Are there specific links between decisions and scientific evidence?	*Suggestion*: emphasise recognition that management of constipation is an integral component of palliative care and that there is evidence that palliative care can improve quality of life, quality of care and reduce health expenditure. *Action:* Suggestion incorporated
Have the risks and potential harms of recommendations been fully considered in the context of clinical practice, including any medico-legal implications (insofar as you are able to comment on the Irish context)?	*Suggestion*: describe how specific recommendations apply in the palliative care setting and emphasise the need to recognise the urgency of managing suspected gastro-intestinal obstruction. Also consider that pharmacological and non-pharmacological management options are not necessarily mutually exclusive and can be used in combination. *Action:* Suggestion incorporated
Are the guidelines clearly written, user friendly and allow for individual clinician decisions?	Your draft is clear, easy to read and well formatted. *Suggestion*: Review the consistency of terminology used for laxatives. *Action:* Suggestion incorporated
Are the guidelines suitable for routine use as intended (insofar as you are able to comment on the Irish situation)?	*Suggestion*: Consider there may be a challenge in implementing the recommendation in palliative care setting for digital rectal examination (DRE) after three days of constipation. *Action:* The Guideline Development Group acknowledges this challenge but considered this an essential recommendation. It has been included in the audit tool to encourage implementation.

Appendix XI: Abbreviations

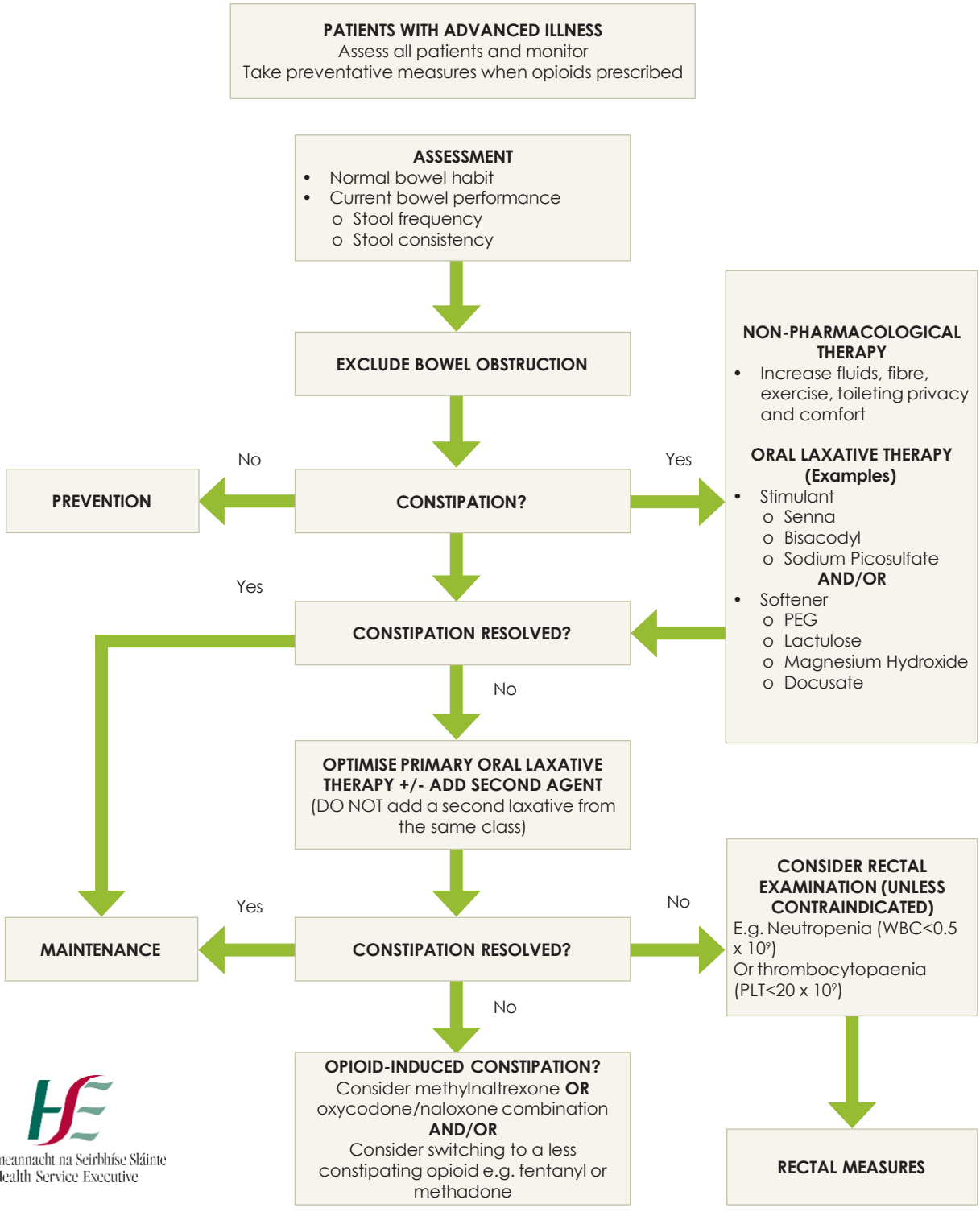
Table 12 Abbreviations

AGREE	Appraisal of Guidelines for Research & Evaluation
AIIHPC	All Ireland Institute for Hospice & Palliative Care
BD	Twice Daily
BFI	Bowel Function Index
BSFS	Bristol Stool Form Scale
CAS	Constipation Assessment Scale
CIC-2	Chloride-Channel
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CrCL	Creatinine Clearance
CT	Computed Tomography
DIOS	Distal Intestinal Obstruction Syndrome
DRE	Digital Rectal Examination
EAPC	European Association for Palliative Care
5HT Receptors	5-Hydroxytryptamine Receptors
GI	Gastrointestinal
HIQA	Health Information and Quality Authority
HSE	Health Service Executive
Kg	Kilogram
MBO	Malignant Bowel Obstruction
MDT	Multidisciplinary Team
Mcg	Microgram
Mg	Milligram
ML	Millilitres
N/A	Not Applicable
NCEC	National Clinical Effectiveness Committee
NICE	National Institute for Health and Care Excellence
NKTR-118	Naloxegol
OD	Once Daily
OIBD	Opioid Induced Bowel Dysfunction
OIC	Opioid-Induced Constipation
PEG	Polyethylene Glycol
PFA	Plain Film of Abdomen
PRN	As Required
PR	Per Rectum
QALY	Quality-Adjusted Life Year
QDS	Four Times Daily
QOL	Quality of Life
RCPI	Royal College of Physicians of Ireland
RCT	Randomised Controlled Trial
SC	Subcutaneous
UK	United Kingdom
VBPS	Victoria Bowel Performance Scale
WHO	World Health Organisation

Appendix XII: Constipation management algorithm

Figure 6 Constipation Management Algorithm

(Adapted from Librach (2010)(17))



Appendix XIII: Details of consultation process

The draft document was uploaded to the HSE National Clinical Programme for Palliative Care website for public consultation for a six week period in July 2013.

Through the National Clinical Programme for Palliative Care Working Group and the RCPI Clinical Advisory Group, a broad and extensive consultation process was undertaken including professional organisations for health and social care professions and patient representative groups. All relevant stakeholders received a draft of the document with a covering letter requesting feedback and comment.

Individual and group responses were collected and collated in a tabular fashion noting changes to the document based on suggestions received. The feedback received was generally positive and reviewers were supportive of the guideline development. The majority of suggestions related to formatting and terminology. The importance of patient and family education in the prevention and management of constipation was highlighted and incorporated as a key recommendation. Invaluable suggestions from several dietitians informed the non-pharmacological management section of the Guideline and the patient information booklet. Adjustments were also made to the constipation management algorithm and laxative tables to ensure clarity based on the feedback received.

Table 13 Consultation Process

Date	July/August 2013
Patients and members of the public	Public consultation on National Clinical Programme for Palliative Care website August 2013. HSE National Patient Advocacy Unit (August/September 2013).
External review	Professor Lukas Radbruch (Key Collaborator to AllHPC), Chair of Palliative Medicine, University of Bonn; Director of Department of Palliative Medicine, University Hospital Bonn; Director of Palliative Care Centre, Malteser Hospital Bonn/Rhein-Sieg. Associate Professor Max Watson, Consultant in Palliative Medicine/Lecturer in Palliative Care, Northern Ireland Hospice, Belfast.
Clinical leaders and healthcare managers	Dr Lucy Balding, Consultant in Palliative Care, Our Lady's Hospice and Care Services and St James's Hospital, Dublin. Ms Claire Browne, Clinical Nutrition Manager, St. James's Hospital. Ms Eileen Donovan - Regional Continence Co-ordinator, HSE. Ms Julie Goss, St Vincent's Private Hospital (CNS Palliative care 0.5WTE) and Our Lady's Hospice and Care Services (Nurse Tutor 0.5WTE). Ms Cliona Hayden- Senior Pharmacist, Our Lady's Hospice & Care Services. Ms Geraldine Keane Campbell, Palliative Care Nurse Specialist, Roscommon Hospital. Dr Michael Lucey, Consultant in Palliative Care, Milford Care Centre and St John's Hospital, Limerick.

Clinical leaders and healthcare managers – *continued*	Ms Helena McCloskey, Senior Palliative Care Dietitian, Regional Specialist Palliative Care Services, Dochas Centre, Our Lady of Lourdes Hospital, Drogheda, Co Louth. Dr Regina McQuillan, Consultant in Palliative Care, St Francis Hospice, Raheny, Dublin. Ms Carmel O'Donnell, Palliative Care Nurse Specialist, Letterkenny General Hospital, Letterkenny, Co. Donegal. Ms Cathy Payne MSc RD, Doctoral Fellow All Ireland Institute of Hospice and Palliative Care and the HSC R&D Division, Public Health Agency , University of Ulster. Dr Feargal Twomey, Consultant in Palliative Care, Milford Care Centre, Limerick. Ms Maria Tynan, Macmillan Specialist Dietitian in Palliative Care, Southern Health and Social Care Trust, Craigavon Area Hospital, Portadown, Co. Armagh.
National committees/ organisations	All Ireland Institute of Hospice and Palliative Care, Our Lady's Hospice and Care Services. Marie Curie Cancer Care, Marie Curie Hospice, Belfast, Northern Ireland. Northern Ireland Hospice, Adult Community Service, Northern Ireland Hospice, Belfast. RCPI Clinical Advisory Group for the National Clinical Programme for Palliative Care. Specialist Palliative Care Service Regional Medicines Review Group, HSE North East, Dochas Centre, Our Lady of Lourdes Hospital, Drogheda, County Louth. Dr Tracy Anderson, Palliative Medicine Consultant, on behalf of the Regional Palliative Medicine Group, Southern Health and Social Care Trust, Craigavon Area Hospital,Portadown, Co. Armagh. Medicines Management Programme. (see Appendix II)
Professional groups	Feedback channelled through representatives on the National Clinical Programme for Palliative Care Working Group.

References

1. Glossary of Terms Version 2 2014 [17.11.2014]. Available from: www.hse.ie/palliativecareprogramme.
2. Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, et al. Levels of Evidence. Oxford: Oxford Centre for Evidence-Based Medicine, 2001.
3. Forming guideline recommendations. 2012 [05.01.2013]. Available from: http://www.sign.ac.uk/guidelines/fulltext/50/section7.html.
4. Clark K, Urban K, Currow DC. Current approaches to diagnosing and managing constipation in advanced cancer and palliative care. Journal of palliative medicine. 2010 Apr;13(4):473-6. PubMed PMID: 20384510. Epub 2010/04/14.
5. Clark K, Smith JM, Currow DC. The prevalence of bowel problems reported in a palliative care population. J Pain Symptom Manage. 2012 Jun;43(6):993-1000. PubMed PMID: 22651945. Epub 2012/06/02.
6. Potter J, Hami F, Bryan T, Quigley C. Symptoms in 400 patients referred to palliative care services: prevalence and patterns. Palliative medicine. 2003;17:310-4.
7. Larkin PJ, Sykes NP, Centeno C, Ellershaw JE, Elsner F, Eugene B, et al. The management of constipation in palliative care: clinical practice recommendations. Palliative medicine. 2008;22:796-807.
8. Fallon MT, Hanks GW. Morphine, constipation and performance status in advanced cancer patients. Palliative medicine. 1999;13:159-60.
9. Laugsand EA, Jakobsen G, Kaasa S, Klepstad P. Inadequate symptom control in advanced cancer patients across Europe. Support Care Cancer. 2011 Dec;19(12):2005-14. PubMed PMID: 21116653. Epub 2010/12/01.
10. Herz MJ, Kahan E, Zalevski S, Aframian R, Kuznitz D, Reichman S. Constipation: A different entity for patients and doctors. Fam Pract. 1996;13(2):156-9.
11. Smith S. Evidence-based management of constipation in the oncology patient. European Journal of Oncology Nursing. 2001;5(1):18-25. PubMed PMID: 2001091367.
12. Droney J, Stevens A-M, Riley J. Constipation in palliative care patients: Audit of Assessment and Management. Palliative Medicine. 2008; 22(1 suppl):504.
13. Van den Beuken-van Everdingen MHJ, De Rijke JM, Kessels AG, Schouten HC, Van Kleef M, Patijn J. Quality of life and non-pain symptoms in patients with cancer. J Pain and Symptom Manage. 2009;38:216-33.
14. Clark K, Currow DC. Plain abdominal radiographs to diagnose constipation patients with advanced progressive illness? J Pain Symptom Manage. 2011 Apr;41(4):e2-3. PubMed PMID: 21481734. Epub 2011/04/13.
15. Davis MP. Cancer constipation: are opioids really the culprit? Support Care Cancer. 2008;16:427-9.
16. Miles CL, Fellowes D, Goodman ML, Wilkinson S. Laxatives for the management of constipation in palliative care patients. The Cochrane database of systematic reviews. 2006 (4):CD003448.
17. Librach SL, Bouvette M, De Angelis C, Farley J, Oneschuk D, Pereira JL, et al. Consensus Recommendations for the Management of Constipation in Patients with Advanced, Progressive Illness. J Pain Symptom Manage. 2010;40(5):761-73.
18. De Graeff A, Krol RJA. Constipation. Nation-wide guideline, Version: 2.0. Integraal Kankercentrum Nederland, 2010.

19. Woolery M, Bisanz A, Lyons HF, Gaido L, Yenulevich M, Fulton MS, et al. Putting Evidence Into Practice: Evidence-Based Interventions for the Prevention and Management of Constipation in Patients with Cancer. Clinical journal of oncology nursing. 2008;12(2):317-37.

20. British Columbia Ministry of Health. Palliative Care for the Patient with Incurable Cancer or Advanced Disease. Part 2: Pain and Symptom Management *Constipation*. Guidelines and Protocols Advisory Committee 2011.

21. Yonek J, Hines S, Joshi M. A Guide to Achieving High Performance in Multi-Hospital Health Systems. Chicago: Health Research & Educational Trust, 2010.

22. Dennison C, Prasad M, Lloyd A, Bhattacharyya SK, Dhawan R, Coyne K. The health-related quality of life and economic burden of constipation. PharmacoEconomics. 2005;23(5):461-76. PubMed PMID: 15896098. Epub 2005/05/18.

23. Passmore AP. Economic aspects of pharmacotherapy for chronic constipation. PharmacoEconomics. 1995 Jan;7(1):14-24. PubMed PMID: 10155290. Epub 1994/12/09.

24. Wee B, Adams A, Thompson K, Percival F, Burslem K, Jobanputra M. How much does it cost a specialist palliative care unit to manage constipation in patients receiving opioid therapy? J Pain Symptom Manage. 2010 Apr;39(4):644-54. PubMed PMID: 20226620. Epub 2010/03/17.

25. Radford M, Bloomfield E, Joseph A. PWE-178 Impact of chronic constipation on healthcare resource use in the UK: an analysis based on electronic medical records. Gut. 2014;63:A203-A204.

26. Carson RT, Guerin A, Lewis B, Yin D, Kaminsky M, Ramakrishnan K, et al. PGI15 The Economic Burden of Unmet Treatment Needs in Medicaid Patients with Chronic Constipation. Value in Health. 2012; 15(4):A137.

27. Guest JF, Clegg JP, Helter MT. Cost-effectiveness of macrogol 4000 compared to lactulose in the treatment of chronic functional constipation in the UK. Current Medical Research and Opinion. 2008;24(7):1841-52.

28. Taylor RR, Guest JF. The cost-effectiveness of macrogol 3350 compared to lactulose in the treatment of adults suffering from chronic constipation in the UK. Alimentary Pharmacology & Therapeutics. 2010;31(2):302-12.

29. Earnshaw SR, Klok RM, Iyer S, McDade C. Methylnaltrexone bromide for the treatment of opioid-induced constipation in patients with advanced illness--a cost-effectiveness analysis. Aliment Pharmacol Ther. 2010 Apr;31(8):911-21. PubMed PMID: 20096019. Epub 2010/01/26.

30. Dunlop W, Uhl R, Khan I, Taylor A, Barton G. Quality of life benefits and cost impact of prolonged release oxycodone/naloxone versus prolonged release oxycodone in patients with moderate-to-severe non-malignant pain and opioid-induced constipation: a UK cost-utility analysis. Journal of medical economics. 2012;15(3):564-75. PubMed PMID: 22313329. Epub 2012/02/09.

31. Using licensed drugs for unlicensed purposes. [Internet]. 2012 [cited 07.05.2013]. Available from: http://palliativedrugs.com/using-licensed-drugs-for-unlicensed-purposes.

32. Irish Statute Book Medicinal Products (Control of Placing on the Market) Regulations S.I. 540/2007 (2007).

33. Todd J, Davies A. Use of unlicensed medication in palliative medicine. Palliative medicine. 1999;13:466.

34. Atkinson CV, Kirkham SR. Unlicensed uses for medication in a palliative care unit. Palliative medicine. 1999;13:145-52.

35. Prescribing unlicensed drugs or using drugs for unlicensed indications. Drugs and therapeutics bulletin. 1992;30:97-9.

36. HSE. Procedure for developing Policies, Procedures, Protocols and Guidelines. Dublin: Health Service Executive, 2009 Contract No.: OQR029.

37. Ryan K, Connolly M, Charnley K, Ainscough A, Crinion J, Hayden C, et al. Palliative Care Competence Framework. Dublin: Health Service Executive. Palliative Care Competence Framework Steering Group, 2014.

38. The ADAPTE process: resource toolkit for guideline adaptation. Version 2.0 2009 [02/06/2012]. Available from: http://www.g-i-n.net.

39. Brouwers K, Kho M, Browman G, Cluzeau F, Feder G, Fervers B, et al. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. Can Med Assoc J. 2010;182:E839-42.

40. Butler C, Rothstein A. On Conflict and Consensus: a handbook on Formal Consensus decisionmaking: Portland: Food Not Bombs Publishing; 1987.

41. Role Delineation Framework 2014 [17.11.2014]. Available from: www.hse.ie/palliativecareprogramme.

42. Clark K, Currow DC. Constipation in Palliative Care: What Do We Use as Definitions and Outcome Measures? Journal of Pain and Symptom Management. 2013;45(4):753-62.

43. Ross H. Constipation: cause and control in an acute hospital setting. British journal of nursing (Mark Allen Publishing). 1998;7(15):907-13.

44. Sykes NP. Constipation and diarrhoea. In: Doyle D, Hanks GWC, Cherny N, Calman K, editors. Oxford Textbook of Palliative Medicine. 3rd ed. Oxford: Oxford University Press; 2004. pp 483-496.

45. Holmes S. Use of a modified symptom distress scale in assessment of the cancer patients. Int J Nurs Stud. 1989;26:69-79.

46. Thomas J. Cancer-related constipation. Current oncology reports. 2007 Jul;9(4):278-84. PubMed PMID: 17588352. Epub 2007/06/26.

47. Clark K, Currow DC. Assessing constipation in palliative care within a gastroenterology framework. Palliative medicine. 2012 Sep;26(6):834-41. PubMed PMID: 21775408. Epub 2011/07/22.

48. Addington-Hall J, Altmann D, McCarthy M. Which terminally ill cancer patients receive hospice in-patient care? Social science & medicine (1982). 1998;46:1011-6.

49. Addington-Hall J, Altmann D. Which terminally ill cancer patients in the United Kingdom receive care from community specialist palliative care nurses? J Adv Nursing. 2000;32:799-806.

50. National Institute for Health and Clinical Excellence. Faecal Incontinence: The Management of Faecal Incontinence in Adults. London: National Institute for Health and Clinical Excellence, 2007.

51. Clark K, Currow DC, Talley NJ. The use of digital rectal examinations in palliative care inpatients. Journal of palliative medicine. 2010 Jul;13(7):797. PubMed PMID: 20636145. Epub 2010/07/20.

52. Kyle G. Constipation and palliative care - where are we now? International journal of palliative nursing. 2007 Jan;13(1):6-16. PubMed PMID: 17353846. Epub 2007/03/14.

53. Smith RG, Lewis S. The relationship between digital rectal examination and abdominal radiographs in elderly patients. Age Aging. 1990;19:142-3.

54. Remes-Troche JM, Rao SS. Diagnostic testing in patients with chronic constipation. Current gastroenterology reports. 2006 Oct;8(5):416-24. PubMed PMID: 16968610. Epub 2006/09/14.

55. Rao SS, Meduri K. What is necessary to diagnose constipation? Best practice & research Clinical gastroenterology. 2011 Feb;25(1):127-40. PubMed PMID: 21382584. Epub 2011/03/09.

56. Cowlam S, Vinayagam R, Khan U, Marsden S, Minty I, Moncur P, et al. Blinded comparison of faecal loading on plain radiography versus radio-opaque marker transit studies in the assessment of constipation. Clinical radiology. 2008 Dec;63(12):1326-31. PubMed PMID: 18996262. Epub 2008/11/11.

57. Gau JT. Advantages of using abdominal radiography for evaluating constipation in older adults. Journal of the American Geriatrics Society. 2010 Jan;58(1):212-3. PubMed PMID: 20122077. Epub 2010/02/04.

58. Bruera E, Suarez-Almanzor M, Velasco A, Bertolino M, MacDonald SM, Hanson J. The assessment of constipation in terminal cancer patients admitted to a palliative care unit: a retrospective review. Journal of Pain & Symptom Management. 1994;9(8):515-9. PubMed PMID: 1995033518.

59. Folden SL. Practice Guidelines for the Management of Constipation in Adults. Rehabilitation Nursing. 2002;27(5):169-75.

60. Brown E, Henderson A, McDonagh A. Exploring the causes, assessment and management of constipation in palliative care. International journal of palliative nursing. 2009 Feb;15(2):58-64. PubMed PMID: 19247220. Epub 2009/02/28.

61. Anti M, Pignataro G, Armuzzi A, Valenti A, Iascone E, Marmo R, et al. Water supplementation enhances the effect of high-fiber diet on stool frequency and laxative consumption in adult patients with functional constipation. Hepatogastroenterology. 1998;45:727-32.

62. Cordain L, Latin RW, Behnke JJ. The effects of an aerobic running program on bowel transit time. J Sports Med Phys Fitness. 1986;26:101-4.

63. Sykes NP. The pathogenesis of constipation. The journal of supportive oncology. 2006 May;4(5):213-8. PubMed PMID: 16724641. Epub 2006/05/27.

64. Lamas K, Lindholm L, Stenlund H, Engstrom B, Jacobsson C. Effects of abdominal massage in management of constipation- A randomized controlled trial. International Journal of Nursing Studies. 2009;46(6):759-67.

65. Lamas K, Lindholm L, Engstrom B, Jacobsson C. Abdominal massage for people with constipation: a cost utility analysis. Advanced Nursing. 2010;66(8):1719-29.

66. McClurg D, Hagen S, Hawkins S, Lowe-Strong A. Abdominal massage for the alleviation of constipation symptoms in people with multiple sclerosis: a randomized controlled feasibility study. Multiple Sclerosis (Houndmills, Basingstoke, England). 2011;17(2):223-33. PubMed PMID: 20940182.

67. Clark K, Lam LT, Agar M, Chye R, Currow DC. Retrospective analysis of contributing factors to laxative prescription in hospitalized palliative care patients. Palliative medicine. 2010;24(4):410-18.

68. Andrews A, Morgan G. Constipation management in palliative care: treatments and the potential of independent nurse prescribing. International journal of palliative nursing. 2012 Jan;18(1):17-22. PubMed PMID: 22306715. Epub 2012/02/07.

69. Palliative Care Formulary. 4th ed. Twycross R, Wilcock A, editors. Nottingham: Palliativedrugs.com Ltd.; 2011.

70. Gallagher P, O'Mahony D. Constipation in old age. Best Practice & Research Clinical Gastroenterology. 2009;23(6):875-87. PubMed PMID: 19942165.

71. American College of Gastroenterology Chronic Constipation Task Force. An evidence-based approach to the management of chronic constipation in North America. Am J Gastroenterol. 2005;100:S1-S22.

72. Belsey JD, Geraint M, Dixon TA. Systematic review and meta-analysis: Polyethylene glycol in adults with non-organic constipation. International journal of clinical practice. 2010;64(7):944-55.

73. Zurad EG, Johanson JF. Over-the-counter laxative polyethylene glycol 3350: an evidence-based appraisal. Curr Med Res Opin. 2011 Jul;27(7):1439-52. PubMed PMID: 21604961. Epub 2011/05/25.

74. Gattuso JM, Kamm MDS-. Adverse effects of drugs used in the management of constipation and diarrhoea. Drug Safety. 1994;10:47-65.

75. Hurdon V, Viola R, Schroder C. How useful is docusate in patients at risk for constipation? A systematic review of the evidence in the chronically ill. Journal of Pain & Symptom Management. 2000;19(2):130-6. PubMed PMID: 2000044436.

76. Tarumi Y, Wilson MP, Szafran O, Spooner GR. Randomized, double-blind, placebo-controlled trial of oral docusate in the management of constipation in hospice patients. J Pain Symptom Manage. 2013 Jan;45(1):2-13. PubMed PMID: 22889861. Epub 2012/08/15.

77. Xing JH, Soffer E. Adverse effects of laxatives. Dis Colon Rectum. 2001;44:1201-9.

78. Agra Y, Sacristan A, Gonzalez M, Ferrari M, Portugues A, Calvo MJ. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. Journal of Pain & Symptom Management. 1998;15(1):1-7. PubMed PMID: 1998010852.

79. Kienzle-Horn S, Vix JM, Schuijt C, Peil H, Jordan CC, Kamm MA. Efficacy and safety of bisacodyl in the acute treatment of constipation: a double-blind, randomized, placebo-controlled study. Aliment Pharmacol Ther. 2006 May 15;23(10):1479-88. PubMed PMID: 16669963. Epub 2006/05/04.

80. Kamm MA, Mueller-Lissner S, Wald A, Richter E, Swallow R, Gessner U. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. Clinical gastroenterology and hepatology. 2011 Jul;9(7):577-83. PubMed PMID: 21440672. Epub 2011/03/29.

81. Wulkow R, Vix JM, Schuijt C, Peil H, Kamm MA, Jordan C. Randomised, placebo-controlled, double-blind study to investigate the efficacy and safety of the acute use of sodium picosulphate in patients with chronic constipation. International journal of clinical practice. 2007 Jun;61(6):944-50. PubMed PMID: 17504357. Epub 2007/05/17.

82. Kienzle-Horn S, Vix JM, Schuijt C, Peil H, Jordan CC, Kamm MA. Comparison of bisacodyl and sodium picosulphate in the treatment of chronic constipation. Curr Med Res Opin. 2007 Apr;23(4):691-9. PubMed PMID: 17407625. Epub 2007/04/05.

83. Sykes N. A clinical comparison of laxatives in a hospice. Palliative medicine. 1991;5:307-14.

84. Sweeney WJ. The use of disposable microenema in obstetrical patients. Proceedings of a Symposium on the Clinical Evaluation of a New Disposable Microenema; New Brunswick1963. p. 7-8.

85. Ponec TJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. N Engl J Med. 1999;341:137-41.

86. Papa P, Turconi L. Neostigmine for the treatment of gastrointestinal atony: a report of one case. Journal of palliative medicine. 2011 Nov;14(11):1270-3. PubMed PMID: 21631369. Epub 2011/06/03.

87. Rubiales AS, Hernansanz S, Gutierrez C, Del Valle ML, Flores LA. Neostigmine for refractory constipation in advanced cancer patients. J Pain Symptom Manage. 2006 Sep;32(3):204-5. PubMed PMID: 16939843. Epub 2006/08/31.

88. Mercadante S, Ferrera P, Villari P, Marrazzo A. Aggressive pharmacological treatment for reversing malignant bowel obstruction. J Pain and Symptom Manage. 2004;28:412-6.

89. Mercadante S, Ferrera P, Casuccio A. Effectiveness and tolerability of amidotrizoate for the treatment of constipation resistant to laxatives in advanced cancer patients. J Pain Symptom Manage. 2011 Feb;41(2):421-5. PubMed PMID: 20833504. Epub 2010/09/14.

90. Abernethy AP, Samsa GP, Matchar DB. A clinical decision and economic analysis model of cancer pain management. The American journal of managed care. 2003 Oct;9(10):651-64. PubMed PMID: 14572175. Epub 2003/10/24.

91. Kurz A, Sessler DI. Opioid induced bowel dysfunction: pathophysiology and potential new therapies. Drugs. 2003;63:649-71.

92. Pappagallo M. Incidence, prevalence and management of opioid bowel dysfunction. Am J Surg. 2001;182 (5Asuppl):11S-18S.

93. Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. International journal of clinical practice. 2007;61(7):1181-7.

94. Cook S, Bell T, Sweeney C, Fehnel S, Hollis K. Impact on quality of life of constipation-associated GI symptoms related to opioid treatment in chronic pain patients: PAC-QOL results from the opioid survey. J Pain. 2007;8:[Abstract 833]s71.

95. Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). Pain Medicine (Malden, Mass). 2009;10(1):35-42. PubMed PMID: 18721170.

96. Walsh TD. Prevention of opioid side effects. J Pain and Symptom Manage. 1990;5:362-7.

97. Holzer P. Opioid receptors in the gastrointestinal tract. Regul Pept 2009;155:11-17.

98. World Health Organisation. Cancer pain relief. 2nd ed: Geneva: WHO; 1996.

99. Thomas JR, Cooney GA, Slatkin NE. Palliative care and pain: new strategies for managing opioid bowel dysfunction. Journal of palliative medicine. 2008 Sep;11 Suppl 1:S1-19; quiz S21-2. PubMed PMID: 18800914. Epub 2008/10/31.

100. Daeninck PJ, Bruera E. Reduction in constipation and laxative requirements following opioid rotation to methadone: a report of four cases. Journal of Pain And Symptom Management. 1999;18(4):303-9.

101. Radbruch L, Sabatowski R, Loick G, Kulbe C, Kasper M, Grond S, et al. Constipation and the use of laxatives: a comparison between transdermal fentanyl and oral morphine. Palliative medicine. 2000;14(2):111-9. PubMed PMID: 10829145.

102. Shipton EA. Safety and tolerability of buprenorphine. In: Budd K, Raffa R, editors. Buprenorphine: the unique opioid analgesic. Stuttgart: Thieme Verlag KG; 2005. p. 92-101.

103. Ahmedzai SH, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. J Pain and Symptom Manage. 1997;13(5):254-61.

104. Weschules D, Bain K, Reifsnyder J, McMath J, Kupperman D, Gallagher R, et al. Toward Evidence-Based Prescribing at End of Life: A Comparative Analysis of Sustained-Release Morphine, Oxycodone, and Transdermal Fentanyl, with Pain, Constipation, and Caregiver Interaction Outcomes in Hospice Patients. Pain Medicine July/August. 2006;7(4):320-9.

105. Etropolski M, Kelly K, Okamoto A, Rauschkolb C. Comparable efficacy and superior gastrointestinal tolerability (nausea, vomiting, constipation) of tapentadol compared with oxycodone hydrochloride. Adv Ther. 2011;28(5):401-17.

106. Dale O, Moksnes K, Kaasa S. European Palliative Care Research Collaborative pain guidelines: opioid switching to improve analgesia or reduce side effects. A systematic review. Palliative medicine. 2011;25:494-503.

107. Sykes NP. A volunteer model for the comparison of laxatives in opioid-related constipation. J Pain Symptom Manage. 1996 Jun;11(6):363-9. PubMed PMID: 8935140. Epub 1996/06/01.

108. Hawley PH, Byeon JJ. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. Journal of palliative medicine. 2008 May;11(4):575-81. PubMed PMID: 18454610. Epub 2008/05/06.

109. Twycross R, Sykes N, Mihalyo M, Wilcock A. Stimulant laxatives and opioid-induced constipation. J Pain Symptom Manage. 2012 Feb;43(2):306-13. PubMed PMID: 22248790. Epub 2012/01/18.

110. Mancini I, Bruera E. Constipation in advanced cancer patients. Support Care Cancer. 1998;6:356-64.

111. Sykes NP. An investigation of the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer. Palliative medicine. 1996;10:135-44.

112. Sykes NP. Oral naloxone in opioid-associated constipation. Lancet. 1991;337:1475.

113. Liu M, Wittbrodt E. Low-dose oral naloxone reverses opioid-induced constipation and analgesia. J Pain and Symptom Manage. 2002;23:48-53.

114. Holzer P. Opioid antagonists for prevention and treatment of opioid-induced gastrointestinal effects. Current opinion in anaesthesiology. 2010 Oct;23(5):616-22. PubMed PMID: 20543677. Epub 2010/06/15.

115. Lowenstein O, Leyendecker P, Lux EA, Blagden M, Simpson KH, Hopp M, et al. Efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials. BMC clinical pharmacology. 2010;10:12. PubMed PMID: 20920236. Epub 2010/10/06.

116. Meissner W, Schmidt U, Hartmann M, Kath R, Reinhart K. Oral naloxone reverses opioid-associated constipation. Pain. 2000;84:105-9.

117. Vondrackova D, Leyendecker P, Meissner W, Hopp M, Szombati I, Hermanns K, et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. Journal of Pain. 2008;9(12):1144-54. PubMed PMID: 2010141765.

118. Lowenstein O, Leyendecker P, Hopp M, Schutter U, Rogers PD, Uhl R, et al. Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: a randomised controlled trial. Expert opinion on pharmacotherapy. 2009 Mar;10(4):531-43. PubMed PMID: 19243306. Epub 2009/02/27.

119. Clemens KE, Quednau I, Klaschik E. Bowel function during pain therapy with oxycodone/naloxone prolonged-release tablets in patients with advanced cancer. International journal of clinical practice. 2011 Apr;65(4):472-8. PubMed PMID: 21401835. Epub 2011/03/16.

120. Ahmedzai SH, Nauck F, Bar-Sela G, Bosse B, Leyendecker P, Hopp M. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. Palliative medicine. 2012 Jan;26(1):50-60. PubMed PMID: 21937568. Epub 2011/09/23.

121. Sandner-Kiesling A, Leyendecker P, Hopp M, Tarau L, Lejcko J, Meissner W, et al. Long-term efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of non cancer chronic pain. Int J Clin Pract. 2010;64:763-74.

122. Meissner W, Leyendecker P, Mueller-Lissner S, Nadstawek J, Hopp M, Ruckes C, et al. A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. European Journal of Pain. 2009;13(1):56-64.

123. Ahmedzai SH, Boland J. Constipation in people prescribed opioids. BMJ clinical evidence. 2010;2010. PubMed PMID: 21718572. Epub 2010/01/01.

124. Mercadante S, Ferrera P, Adile C. High doses of oxycodone-naloxone combination may provide poor analgesia. Support Care Cancer. 2011 Sep;19(9):1471-2. PubMed PMID: 21656338. Epub 2011/06/10.

125. McNicol ED, Boyce D, Schumann R, Carr DB. Mu-opioid antagonists for opioid-induced bowel dysfunction. The Cochrane database of systematic reviews. 2008 (2):CD006332. PubMed PMID: 18425947. Epub 2008/04/22.

126. Brown DR, Golberg LI. The use of quaternary narcotic antagonists in opiate research. Neuropharmacology. 1985;24.

127. Russel J, Bass P, Golberg LI, Schuster CR, Merz H. Antagonism of gut, but not central effects of morphine with quaternary narcotic antagonists. Eur J Pharmacol. 1982;78:255-61.

128. Rotshteyn Y, Boyd TA, Yuan CS. Methylnaltrexone bromide: research update of pharmacokinetics following parenteral administration. Expert opinion on drug metabolism & toxicology. 2011 Feb;7(2):227-35. PubMed PMID: 21222554. Epub 2011/01/13.

129. Portenoy RK, Thomas J, Moehl Boatwright ML, Tran D, Galasso FL, Stambler N, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. J Pain Symptom Manage. 2008 May;35(5):458-68. PubMed PMID: 18440447. Epub 2008/04/29.

130. Lipman AG, Karver S, Cooney GA, Stambler N, Israel RJ. Methylnaltrexone for opioid-induced constipation in patients with advanced illness: a 3-month open-label treatment extension study. Journal of pain & palliative care pharmacotherapy. 2011;25(2):136-45. PubMed PMID: 21657861. Epub 2011/06/11.

131. Thomas J, Karver S, Cooney GA, Chamberlain BH, Watt CK, Slatkin NE, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med. 2008 May 29;358(22):2332-43. PubMed PMID: 18509120. Epub 2008/05/30.

132. Slatkin N, Thomas J, Lipman AG, Wilson G, Boatwright ML, Wellman C, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. The journal of supportive oncology. 2009 Jan-Feb;7(1):39-46. PubMed PMID: 19278178. Epub 2009/03/13.

133. Thomas J. Opioid-induced bowel dysfunction. Journal of Pain and Symptom Management. 2008;35(1):103-13.

134. Gervitz C. Update on the management of opioid-induced constipation. Topics in Pain Management. 2007;23(3):1-12.

135. Abrahamsson H. Treatment options for patients with severe gastroparesis. Gut. 2007 Jun;56(6):877-83. PubMed PMID: 17519490. Epub 2007/05/24.

136. Cryer BL, Katz S, Vallejo R, Scott CB, Joswick TR, Dolecek G, et al. A phase 3, randomized, double-blind, placebo-controlled clinical trial of lubiprostone for the treatment of opioid-bowel dysfunction in patients with chronic, non-cancer pain. Gastroenterology 2010;138 (Suppl 1):S129.

137. Johansen JF, Ueno R. Lubiprostone, a locally acting chloride channel activator, in adult patients with chronic constipation: a double-blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety. Aliment Pharmacol Ther. 2007;25:1351-61.

138. Brock C, Olesen SS, Olesen AE, Frøkjaer JB, Andresen T, Drewes AM. Opioid-induced bowel dysfunction: pathophysiology and management. Drugs. 2012;72(14):1847-65. PubMed PMID: 22950533.

139. Tack J, Gralla R, Webster L, Sostek M, Lappalainen J, Barker PN, et al. Efficacy and safety of naloxegol in patients with opioid induced constipation (OIC): Results from 2 identical phase 3, prospective, randomized, multicenter, double-blind, controlled trials. Supportive Care Cancer. 2013;21:S260.

140. Webster L, Dhar S, Eldon M, Masuoka L, Lappalainen J, Sostek M. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. Pain. 2013 Sep;154(9):1542-50. PubMed PMID: 23726675. Epub 2013/06/04.

141. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. N Engl J Med. 2014 Jun 19;370(25):2387-96. PubMed PMID: 24896818. Epub 2014/06/05.

142. Tuca A, Guell E, Martinez-Losada E, Codorniu N. Malignant bowel obstruction in advanced cancer patients: Epidemiology, management, and factors influencing spontaneous resolution. Cancer Management and Research. 2012;4(1):159-69. PubMed PMID: 2012463797.

143. Clark K, Hipwell A, Byfieldt N. A retrospective pilot study to explore the timing of cessation of laxatives before death in a palliative care unit. International journal of palliative nursing. 2012;18(7):326-30. PubMed PMID: 2011639331.

144. Clark K, Lam L, Currow D. Exploring the relationship between the frequency of documented bowel movements and prescribed laxatives in hospitalized palliative care patients. The American journal of hospice & palliative care. 2011 Jun;28(4):258-63. PubMed PMID: 21057139. Epub 2010/11/09.

145. Fraserhealth. Hospice Palliative Care Program Symptom Guidelines. Bowel Care https://www.fraserhealth.ca/media/04FHSymptomGuidelinesBowelCare.pdf; 2006 [31/5/2012].

146. King Edward Memorial Hospital. Palliative Care Clinical Guidelines. Management of Constipation: http://kemh.health.wa.gov.au/development/manuals/O&G_guidelines/sectionc/14/c14.3.2.pdf; 2010 [31/05/2012].

147 Department of Health and Human Services Tasmania. Care Management Guidelines. Constipation http://www.dhhs.tas.gov.au/__data/assets/pdf_file/0003/36939/Constipation_Final290909_PCSSubComm.pdf; 2009 [31/05/2012].

148. Grundy J, Husbands E. St Richard's Hospice. Clinical Care Guidelines. Constipation Guidelines: http://virtualhospice.ca/Assets/Constipation%20Guideline_with%20appendices_St%20Richard%27s%20Hospice.%20pdf_20100505160131.pdf; 2008 [31/05/12].

149. Constipation. In: Watson M, Lucas C, Hoy A, Back I, Armstrong P, editors. Palliative Adult Network Guidelines. 3rd ed. http://book.pallcare.info2011.

150. Lothian NHS. Constipation in Palliative Care http://cln-palliativecare.org/files/lothian_guideline_constipation.pdf; 2009 [31/05/12].

Department of Health, Hawkins House, Hawkins Street, Dublin, D02 VW90, Ireland
Tel: +353 1 6354000 • Fax: +353 1 6354001 • www.health.gov.ie