STUDY PROTOCOL

Current management of adults receiving oral anti-cancer medications: A scoping review protocol [version 1; peer review: 2 approved with reservations]

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Abstract
Oncology has been undergoing a profound transition in the last ten years or more with the increase in oral anti-cancer medications. Approximately 25% of all anti-cancer medication is now designed for oral use and this is likely to increase prospectively. These treatments are convenient for patients and are often preferred by them, yet there are similar safety and toxicity concerns as there are to intravenous treatment. Oral anti-cancer medications (OAMs) have the potential to alleviate capacity issues in cancer treating units as patients receive their treatment at home, however there remains a requirement for safe and efficient assessment and care. Consequently, the management of patients on oral anti-cancer is of paramount importance but as to the location of such patient assessment and monitoring and by which health care professional is subject to ongoing debate.

This paper presents a protocol for a scoping review which aims to systematically and comprehensively map the available literature on the current management of adults receiving oral anti-cancer medications. The scoping review will follow the published guidance to direct the various steps involved. The report will be guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) framework to ensure methodological and reporting quality. The review will be performed by two reviewers and checked by a third reviewer and will be iterative in the process.

This scoping review will provide a narrative synthesis and map the extent of available literature on the management of individuals receiving oral anti-cancer medication. This work is an appropriate initial stage in presenting the literature to inform the subsequent

Open Peer Review

Reviewer Status ??

Invited Reviewers

1. Andrew Darley, University College Dublin, Dublin, Dublin, Ireland
2. Eileen Furlong, University College Dublin, Dublin, Ireland
1. Paolo Tralongo, Ospedale Umberto I, RAO, Siracusa, Italy

Any reports and responses or comments on the article can be found at the end of the article.
steps in a multi-phased research study which aims to establish and analyse the safety and efficacy of an integrated care model for the management of patients receiving OAM in the community by an advanced nurse.

**Keywords**
cancer, oral anticancer medications, care, management, assessment

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Author roles: **Richmond JP**: Conceptualization, Funding Acquisition, Investigation, Methodology, Writing – Original Draft Preparation; **Kelly MG**: Conceptualization, Funding Acquisition, Investigation, Methodology, Writing – Original Draft Preparation; **Johnston A**: Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation; **Hynes L**: Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation; **Murphy PJ**: Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation; **Murphy AW**: Formal Analysis, Funding Acquisition, Investigation, Methodology, Writing – Original Draft Preparation

Competing interests: No competing interests were disclosed.

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**Introduction**

The introduction of novel oral anti-cancer medications (OAM) is a paradigm shift in cancer care and these are being approved at a record-setting pace (Meier et al., 2018) with almost 20 new approvals over the past three years in oncology (U.S. Food & Drug Administration, 2018). Oral anticancer medications are a sub-set of systemic anti-cancer treatments (SACT) and have a narrow therapeutic window with a unique mechanism of action which includes pro-drugs and targeted therapies, and excludes endocrine therapy (National Cancer Institute, 2020). The National Cancer Control Programme (NCCP) (2018) defines OAMs as all medications with direct anti-tumour activity administered by mouth (enteral route) for the treatment of cancer. They are increasingly common; a review of the NCCP website shows more than 50 different OAMs are currently in use alongside a suite of guidelines for health care professionals to direct safe and standardised patient care.

OAMs have the same benefits and risks as SACT given parenterally in terms of positive disease outcomes, treatment-related toxicities or potential for serious medication errors leading to patient harm (NCCP, 2018). Consequently individuals receiving OAMs require frequent (at least monthly) holistic patient assessment, and serum and/or urine analysis. While these medications are convenient for individuals, it shifts the responsibility for medication management from the oncology healthcare professionals to the patient. Consequently there are concerns regarding adherence and management of toxicities or adverse effects (Greer et al., 2016; Hammond et al., 2012; NCCP, 2018; Paolella et al., 2018; Wood, 2012). Evidence suggests that current health care practices globally do not ensure safe administration or patient adherence (Griffiths & Pasco, 2014; LeFebvre & Felice, 2016; Le Saux et al., 2018; Redelico et al., 2018; Zerillo et al., 2015). Following a review of OAM practices in North America, Zerillo et al. (2015) identified unmet patient needs of 43–49% for patient education and 19–25% for adherence/toxicity monitoring. Individuals prescribed OAMs often experience a high burden of cancer related symptoms which corresponds to reduced adherence and quality of life (Jacobs et al., 2019).

Due to the potential toxicity of these medications and associated safety challenges, the care and monitoring of patients receiving OAMs remains largely within the acute hospital setting by specialist health care teams (Department of Health, 2017; Hammond et al., 2012; Kinaer et al., 2019; NCCP, 2018). A medication safety review in Ireland noted a recurring theme of diversity and often lack of processes for the management of OAM (Heckmann et al., 2014). Furthermore, anecdotal evidence from the authors suggest that in the hospital environment individuals on OAMs receive disproportionately less input that those on parenteral treatment as the former are incorrectly perceived as being less acute and as the medication is administered at home there is less requirement to expediently progress their care at their hospital visit. To try to maximise the safety of OAMs and improve hospital efficiency, the National Cancer Strategy (Department of Health, 2017) recommended the development of a model of care for OAM. Subsequently a guidance document for this was published by the NCCP (2018). The NCCP (2018) made 16 recommendations for the care of individuals receiving OAMs in an attempt to maximise safe practice. The focus was on safe and efficient care of individuals rather than prescriptive directions for which location that care should be delivered or by which health care professional. The authors of the NCCP (2018) report recognised that there was a requirement for change within the Irish health care service to fully realise the recommendations. There is scope for these to be built upon to standardise and improve safe practice for the care of individuals receiving OAMs.

There is universal consensus in international healthcare policy documents regarding the crucial and central role which primary care should play in health care delivery. Systems with strong primary care have better health outcomes at lower costs (House of the Oireachtas, 2017; Randall et al., 2017; Starfield, 1998; World Health Organisation, 2018). Within Ireland, a shift from hospital to community based care is being strongly promoted with the aim of delivering care closer to the person’s home within an integrated care context. This is evident in the Sláintecare health reform programme (Government of Ireland, 2018) which endorses efforts to transform health care to maximise hospital efficiency and patient convenience. The nursing profession is recognised as critical to implementing this. Specifically, nurse-led clinics for management of chronic diseases have emerged as an ideal means to achieve improved organisation in the health service (Government of Ireland, 2018; Randall et al., 2017).

Patient satisfaction levels are high with specialist or advanced practice in nursing clinics (Liljeroos & Stromberg, 2019; Linedale et al., 2020). In Ireland, Advanced Nurse Practitioners (ANP) have scope for physical examination and medicinal prescribing (Department of Health, 2019). They have the required expertise and skills to undertake caseload management of a cohort of patients requiring advanced level decision making, such as those receiving OAMs. Currently, however advanced nursing assessment in cancer care is largely performed within a hospital context. Of particular relevance is a recent systematic review which assessed the impact of community based nurse-led clinics on patient outcomes, and none of the studies included in the final review were oncological (Randall et al., 2017) indicating that oncology nurse-led care in the community is in its’ infancy. This review concluded that community based nurse-led clinics have largely shown positive impact on patient outcomes, patient satisfaction and access to care despite the evidence base for such a key universal policy aim being limited. Extrapolating this to more specific care of individuals receiving OAMs, community-based care or integrated care models for this cohort of patients do not appear to be well established in national or international healthcare landscapes.

The coronavirus 2019 (COVID-19) pandemic has brought into sharp focus the requirement to reduce unnecessary hospital visits (Cucinotta & Vanelli, 2020). This is especially pertinent to individuals receiving cancer treatment due to potential immunosuppression and concomitant risk of infection. Those patients being treated with OAM require on-going
assessment and monitoring but this does not necessarily require them to repeatedly attend the hospital. Consequently, within the COVID-19 context this is an opportune time to transform the care of this cohort of patients. This would be in line with the transformative vision of a shift beyond the acute hospital, yet at the same time implement the NCCP recommendations (2018).

The document by the NCCP (2018), the Sláintecare health reform programme (Government of Ireland, 2018), the context of the COVID-19 pandemic alongside other literature promoting robust OAM patient monitoring provides the opportunity for a nurse-led integrated model of care to be developed for this patient cohort.

To consider the management of this subset of cancer patients, it is necessary to initially identify the specific aspects that constitute their care assessment and care. The NCCP (2018) outlined five stages for generic SACT care which include: decision to treat, prescribing, dispensing, medication administration and patient monitoring (Figure 1).

For parental SACT these stages are all performed within the hospital setting but for OAM, dispensing is performed by the community pharmacy and medication administration is within the patients’ home. Similarly Zerillo et al. (2018) outlines the care delivery domains for oral chemotherapy care process in their systematic review on the safety and quality of OAM. The authors do not specifically identify decision to treat as a specific stage and they include patient education occurring prior to drug administration which is a logical inclusion. Furthermore, storage and disposal are added as a final aspect of care (Zerillo et al., 2018) (Figure 2).

For the purposes of this scoping review, the processes outlined by the NCCP (2018) and Zerillo et al. (2018) will be used as a framework to guide the analysis and categorisation of literature. There will be a particular emphasis on literature pertaining to prescribing, dispensing, patient education and patient monitoring as these are encompassed within the concept of patient management. Treatment decision is a baseline initial assessment based on the individuals’ suitability for treatment to commence and is not part of the daily ongoing management of care and consequently will be excluded from this review.

Aim

A preliminary search of relevant databases, CINAHL, Medline and Web of Science was conducted, and no published systematic reviews on the overall management or continued monitoring of individuals receiving OAM were identified. Therefore, the aim of this scoping review is to identify existing international literature regarding the current management of patients receiving oral anti-cancer medications with the aim of making recommendations for a suitable integrated model of care that could be performed by an ANP. This approach could help maximise hospital efficacy, reduce hospital overcrowding, increase patient convenience and continuity of care yet provide safe cost-effective care.

Objectives

The specific objectives of the review are to:

- Complete a systematic search of the literature to explore the current clinical management practices for the ongoing assessment and monitoring of patients receiving OAM.
- Map existing patient management practices for those receiving OAMs.
- From the research literature, identify any best-practice patient care recommendations that exist within current frameworks of OAM management.

This organization of information is the initial stage in a multi-phased research study which aims to establish and analyse...
the safety and efficacy of an integrated care model for the management of patients receiving OAM by an ANP. The scope of the review will be deliberately broad so as not to exclude the identification of best practice from any one health care professional group or any country/health service. In addition, the iterative nature of this work allows for a repetitive process that can be adapted to ensure it is fit for the desired endpoint. Guidance produced by Peters et al. (2015) will be used to direct the various stages of this scoping review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist will be followed throughout (Tricco et al., 2018).

Protocol design

A search will be conducted for published and appropriate literature on the research subject. The PCC mnemonic will be used as a guide to frame the scoping review question and refers to ‘Population, Concept and Context (Joanna Briggs Institute, 2019). In this scoping review adult cancer patients are the population, ‘oral anticancer medications’ are the concept and the context is management of care.

The three-step method for searching for studies will be applied as recommended by the Joanna Briggs Institute (2019). The databases CINAHL, Medline and Web of Science will be used for this scoping review as crucially they collectively contain a vast range of medical, nursing and allied health literature; enabling this review to be comprehensive by capturing the majority of relevant references. Relevant grey literature will be included. The keywords with Medical Subject Headings (MeSH) and proximity operators will be identified appropriate for each database.

An initial limited search will be conducted in these databases, followed by an analysis of text in the title and abstract, and of the index terms used to describe the article. A comprehensive search strategy will be formulated, in consultation with a university librarian, to identify relevant studies. The search strategy, including natural language, identified keywords and index terms, will be adapted for each included database as syntax of search strategies are database specific. A second search using all identified keywords and index terms will then be undertaken across all included databases. To keep the search broad no specific search fields will be applied and all study designs will be included. The third search will be of the reference list of all identified articles that are relevant to identify any potential additional further studies. Search results will be imported into a reference management software programme and duplicates removed. Any deviation from the protocol will be made clear and explained in the complete scoping review report as advocated by the Joanna Briggs Institute (2019).

Search selection

The inclusion and exclusion criteria for this review are shown in Table 1. Only English language articles published in the years 2010–2020 will be included; justification for this being English is the vernacular of the authors and OAM are a recent development (NCCP, 2018). The systematic review by Zerillo et al. (2018) of OAM safety and quality encompassed the past 20 years but all included articles were published after 2007 with 75% (n = 12) in the last 3 years. The authors note that the types of OAM medications have became more diverse over time and most of the earlier publications focused on capecitabine in patients with breast or colorectal cancers. Therefore, as this scoping review aims to consider contemporary management of care for this patient population who are receiving all OAMs it is sufficient to focus on studies published from 2010–2020 inclusive.

Two reviewers will independently review the retrieved articles for inclusion based on title and abstract review. The articles selected at this stage will then undergo a further independent

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**Table 1. Inclusion and exclusion criteria.**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>English language articles</td>
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<tr>
<td>Articles published 2010-2020</td>
</tr>
<tr>
<td>Adults: individuals of 18 years old or more</td>
</tr>
<tr>
<td>- Allow inclusion of relevant studies with mean age over 18 years of age</td>
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<tr>
<td>Studies pertaining to the ongoing management of adults receiving oral anti-cancer</td>
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<tr>
<td>medication.</td>
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<table>
<thead>
<tr>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Non-English language articles</td>
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<tr>
<td>Articles published prior to 2010</td>
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<tr>
<td>Articles pertaining to studies involving individuals whose study sample all are</td>
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<tr>
<td>younger than 18 years old</td>
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<tr>
<td>Non-human studies</td>
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full text review by the reviewers to determine relevance. Any disagreement will be resolved through discussion with a third reviewer.

Data extraction
Data extraction will be performed by two reviewers independently. Microsoft Excel 2010 will be used for the management of the screening and data extraction stages of the scoping review. A data extraction table (Table 2) will be used to capture the characteristics relating to the aims and objectives of the scoping review. Pre-testing with a pilot of up to five studies will be performed by two reviewers to evaluate the appropriateness and suitability of the headings used in the data extraction tool.

Data analysis
Descriptive numerical summaries and narrative synthesis, that aligns with the scoping review aim and objectives, will be presented in appropriate formats e.g. maps, tables. Narrative synthesis refers to an approach to the systematic review and synthesis of findings from multiple studies that relies primarily on the use of words and text to summarise and explain the findings and utilises a textual approach to ‘tell the story’ of the findings from included studies (Popay et al., 2006). Search results, selection process results, additions from reference searching, etc. and the final number of included sources will be presented in a PRISMA-ScR flow chart.

Dissemination of information
The results of the scoping review is critical as a means to gather the relevant evidence base and inform further aspects of the study. As the research team plan to produce an nurse-led community model for care of individuals on OAMs, the scoping review will provide an overview of the current management of this cohort of patients a identify essential aspects of care required for safe practice. Furthermore, any recommendations for practice identified by existing literature will be included to enable any model of care developed by this work to practice to best practice standards. Once the scoping review has been completed, the findings will be disseminated in two ways. Firstly the results will be presented to a study advisory panel, consisting of the applicants and collaborators and invited national experts to discuss models of potential processes and outcomes, and produce a proposal for an ANP integrated oncology care model in the community. Furthermore, the results will be disseminated by publication in a peer-reviewed journal.

Study status
At the time of publication of this protocol, informal preliminary searches of the literature have been commenced primarily to help to identify key search terms.

Discussion
The scoping review protocol is an essential component in the process of performing a scoping review of a chosen topic.

Table 2. Definitions for data extraction.

<table>
<thead>
<tr>
<th>Descriptive term</th>
<th>Definition for the purpose of the scoping review</th>
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<tbody>
<tr>
<td>Author(s)</td>
<td>Name of individual(s) writing the paper</td>
</tr>
<tr>
<td>Year</td>
<td>Year paper was published</td>
</tr>
<tr>
<td>Country/countries</td>
<td>Country/countries in which the paper was published</td>
</tr>
<tr>
<td>Publication type</td>
<td>List whether it is paper, conference presentation, website or other</td>
</tr>
<tr>
<td>Aims</td>
<td>List the aims of the paper</td>
</tr>
<tr>
<td>Type of study/methodology</td>
<td>List the method used to gather the data e.g. Randomised controlled trial, ethnographic, intervention, descriptive etc.</td>
</tr>
<tr>
<td>Study population</td>
<td>Type of malignant pathology that the paper primarily focuses on for the study population</td>
</tr>
<tr>
<td></td>
<td>Select if the cancer(s) studied is haematological (non-solid) or oncology (solid) or both.</td>
</tr>
<tr>
<td></td>
<td>For solid malignancies select the best option to describe the primary cancer as breast/colorectal/prostate/gastric/variety of cancers or unspecified</td>
</tr>
<tr>
<td>Sample size</td>
<td>Number of participants in the study</td>
</tr>
<tr>
<td>Health Care Professionals (HCP) primarily involved</td>
<td>The health care professional(s) primarily involved in the study e.g. nurse/medical/pharmacist/variety</td>
</tr>
<tr>
<td>Model of care identified</td>
<td>Is a defined or established framework for delivery care identified?</td>
</tr>
<tr>
<td>Patient monitoring</td>
<td>Is on-going scheduled monitoring/assessment of patients on OAMs described or outlined?</td>
</tr>
<tr>
<td>Recommendation(s)</td>
<td>Identify any recommendation(s) for improvement of patient care on OAMs</td>
</tr>
</tbody>
</table>
(Moloney et al., 2020) and provides an outlined method for exploring and mapping relevant literature (Lafferty et al., 2019). Individuals being treated with OAM require on-going assessment and monitoring (NCCP, 2018) yet with increasing numbers of patients on OAMs there is a requirement to improve hospital efficiency and reduce overcrowding in cancer units yet provide safe, appropriate and timely patient care. The results of this scoping review will inform the subsequent steps in a multi-phased research study which aims to establish and analyse the safety and efficacy of an integrated care model for the management of patients receiving OAM in the community by an ANP.

Data availability
No data are associated with this article.

References


Paolo Tralongo
Medical Oncology Unit, Ospedale Umberto I, RAO, Siracusa, Italy

The paper on the protocol proposed belongs to a fascinating and important issue in the oncology field and daily debated.

1. The rationale and objectives of the study are clearly described. However, the aim of making any recommendations for the clinicians should undergo to a valid and shared by scientific community method, to assess and grading quality of evidence and strength of any potential recommendation.

2. The study design appears appropriate for the research question. However I would modify the exclusion criteria, they should not be only the opposite of inclusion criteria.

3. I would suggest to gather and summarize the findings of the studies included, categorizing them by the quality and strength of the evidence, through the type of studies (i.e. randomized controlled trial, observational studies, etc..).

4. The manuscript is extremely concise and it does not provide all details of the proposed research.

Is the rationale for, and objectives of, the study clearly described?
Partly

Is the study design appropriate for the research question?
Partly

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes
Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medica oncologist

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 17 February 2021
https://doi.org/10.21956/hrbopenres.14360.r28770

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Andrew Darley
School of Medicine, University College Dublin, Dublin, Ireland

Eileen Furlong
School of Nursing, Midwifery and Health Systems, University College Dublin, Dublin, Ireland

Thank you for the opportunity to review your submission. Oral anti-cancer medication is a very pertinent healthcare issue for advanced nurse practitioners and this scoping review is very timely in light of the initiative towards enhancing integrated care. The protocol is well-written and the reviewers have some comments for consideration.

Abstract
  ○ In the first sentence specify “increase” regarding oral anti-cancer medications, i.e., availability or usage.

  ○ Consider rewording and clarifying the points in the last sentence in the first paragraph of the Abstract i.e., “patients on oral anti-cancer”, “as to the location of such patient assessment”.

  ○ Use “protocol” rather than report.

  ○ Last sentence: suggest using “advanced nurse practitioner” for consistency.

Introduction
  ○ Please specify the concept in this sentence “The nursing profession is recognised as critical to implementing this.”

Aim/Objectives
  ○ Clearly state the research question of the scoping review.

  ○ Consider changing “This approach” to “The knowledge obtained in this review could...”

  ○ Please specify the patient management practices as mentioned in the Objectives.
Methodology

- Are you using a screening tool e.g., Covidence?

- How will study selection be recorded? Is this being done through Excel or are the authors using a reference manager?

- Will duplicates be removed manually by the author team?

- In the abstract it states that the review will be performed by two reviewers and checked by a third reviewer, however on P8 that 'any disagreement will be resolved through discussion with a third reviewer'. Please confirm the process.

- Provide more specific detail on “relevant grey literature” and justify why it is being included. It would be helpful if the authors provided the search strategy for the grey literature and how it will be limited. e.g. search terms, sources.

- Consider using initials of the author team when referring to the reviewers.

- Statement regarding “desired endpoint” – consider using “replicable” process rather than repetitive.

- Consider removing “crucially” in Protocol Design.

- Consider changing “natural language” to “English”.

- Reword sentence beginning with “To keep the search broad...”

- Did the authors consider using SCOPUS in their search?

- Will the authors conduct a quality appraisal on the identified studies? If not, provide justification.

- Consider including Limitations of the studies reported in Table 2, which will help analysis.

- Please use “A nurse-led...” not “an”.

Conclusion

- Consider reframing the final two sentences to address the value of this scoping review in light of the aims and objectives.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly
Are the datasets clearly presented in a useable and accessible format?
Not applicable

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Cancer care; patient outcomes; integrated care; scoping reviews

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.