Title: Prophylactic Pegfilgrastim to Prevent Febrile Neutropenia Among Patients Receiving Q2W Chemotherapy Regimen: A Systematic Review of Efficacy, Effectiveness, and Safety

Title	Prophylactic Pegfilgrastim to Prevent Febrile Neutropenia Among Patients Receiving Q2W Chemotherapy Regimen: A Systematic Review of Efficacy, Effectiveness, and Safety
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Product Reference	Neulasta
Research Objectives	Among patients treated with Q2W chemotherapy regimens with high or intermediate risk for febrile neutropenia, systematically review the published evidence regarding absolute or relative risk of 1) febrile neutropenia 2) grade 1-4 neutropenia 3) all-cause hospitalization 4) dose delays or dose reductions 5) adverse events, and 6) mortality for patients receiving prophylactic pegfilgrastim versus no prophylactic pegfilgrastim or prophylaxis with other granulocyte colony stimulating factor
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition/Explanation
ANC	Absolute neutrophil count
CI	Confidence Interval
DD	Dose dense
DFS	Disease free survival
EC-P	Epirubicin, cyclophosphamide, and paclitaxel
EORTC	European Organisation for Research and Treatment of Cancer (EORTC)
FEC-P	Fluorouracil, Epirubicin, cyclophosphamide, and paclitaxel
FN	Febrile neutropenia
G-CSF	Granulocyte-colony-stimulating factor
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin's lymphoma
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
OS	Overall survival
Q2W	Every 2 weeks
Q3W	Every 3 weeks

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2. ABSTRACT

- **Title**

  Prophylactic pegfilgrastim to prevent febrile neutropenia among patients receiving Q2W chemotherapy regimen: A systematic review of efficacy, effectiveness, and safety

- **Background and rationale**

  Febrile neutropenia (FN) following myelosuppressive chemotherapy is a potentially life-threatening complication and is associated with loss of treatment efficacy because of dose delays, and dose reductions.(Kuderer, Dale, Crawford, Cosler, & Lyman, 2006; Kuderer, Dale, Crawford, & Lyman, 2007; Lyman et al., 2010; Schilling, Parks, & Deeter, 2011) To prevent FN, the National Comprehensive Care Network (NCCN) guidelines recommends prophylactic use of granulocyte colony stimulating factor (G-CSF) for patients receiving a chemotherapy regimen associated with high risk of developing FN (≥ 20%) or those receiving regimens with intermediate-risk of FN (10-20%) and have at least one patient-level risk factor.(*National Comprehensive Care Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hematopoietic Growth Factors*, 2019) Pegfilgrastim is a long-acting G-CSF that is administered once per cycle and is the most commonly used G-CSF in the US.(Weycker, Bensink, Lonshteyn, Doroff, & Chandler, 2017) The US prescribing information for pegfilgrastim("Food and Drug Administration. Pegfilgrastim [prescribing information].") specifies that Neulasta should not be administered in the period between 14 days before and 24 hours after administration of myelosuppressive chemotherapy. This restriction was placed because of the potential for an increase in sensitivity of rapidly dividing myeloid cells stimulated by pegfilgrastim to myelosuppressive chemotherapy. However, this restriction precludes the prophylactic use of pegfilgrastim among several Q2W chemotherapy regimens associated with high or intermediate risk for FN. The European label for pegfilgrastim("European Medicines Agency. Pegfilgrastim [summary of product characteristics],") does not include the 14-day exclusion period for Neulasta prior to chemotherapy, only exclusion in the 24 hours after cytotoxic chemotherapy is administered.

The latest NCCN guidelines recommend that there should be at least 12 days between the dose of pegfilgrastim and the next cycle of chemotherapy supporting the use of prophylactic pegfilgrastim in patients receiving Q2W regimens.(*National Comprehensive Care Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hematopoietic Growth Factors*, 2019) This is consistent with the guidelines of the European Organisation for Research and Treatment of Cancer (EORTC), which state that pegfilgrastim can be conveniently administered together with chemotherapy in patients receiving treatment at 14 day intervals. (Aapro et al., 2011) The recommendation is based on phase II studies that reported better efficacy and safety profile of pegfilgrastim in reducing FN among patients receiving Q2W regimens for breast cancer,(Burstein et al., 2005; Jones et al., 2009) colorectal cancer,(Hecht et al., 2010) lung cancer,(Pirker et al., 2006) and non-Hodgkin's lymphoma (NHL).(Brusamolino et al., 2006; Watanabe et al., 2011) However, there is a lack of systematic identification, appraisal, and synthesis of the existing evidence base from randomized clinical trials and observational studies that summarizes the efficacy, effectiveness, and safety of prophylactic pegfilgrastim to prevent FN among patients treated with Q2W chemotherapy regimen. The objective of this review is to provide a single-source information for oncologists and payers to make evidence-based decisions. Given the heterogeneity of the studies in terms of tumor types, FN risk of each regimens, and patient population, we will not conduct any meta-analyses.

- **Objective(s) and research questions**

Primary objective

Among patients treated with Q2W chemotherapy regimens with high or intermediate risk for febrile neutropenia, systematically review the published evidence regarding absolute or relative risk of

1) febrile neutropenia
2) grade 1-4 neutropenia,
3) all-cause hospitalization
4) dose delays or dose reductions
5) adverse events, and
6) mortality

for patients receiving prophylactic pegfilgrastim versus no prophylactic pegfilgrastim or prophylaxis with other granulocyte colony stimulating factor

Research question

What is the published evidence on the efficacy, effectiveness, and safety of prophylactic pegfilgrastim compared to no prophylactic pegfilgrastim or prophylaxis with other granulocyte colony stimulating factor in reducing the risk of febrile neutropenia among patients treated with Q2W chemotherapy regimens with high or intermediate risk for febrile neutropenia?

- **Study eligibility**

  Criteria for the inclusion and exclusion of studies are as follows:

– Inclusion criteria

  Patients: Studies with patients diagnosed with non-myeloid malignancy and treated with a Q2W chemotherapy regimen

  Intervention: Studies with Q2W myelosuppressive chemotherapy regimens associated with high (>20%) or intermediate (10-20%) risk for FN plus prophylactic pegfilgrastim

  Comparator: no prophylactic pegfilgrastim, primary prophylaxis with other G-CSF, or placebo. Studies where the comparator is patients receiving Q3W chemotherapy regimens with primary prophylactic pegfilgrastim will be included

  Outcomes:

  1) FN:
  Definition for RCTs: defined as an absolute neutrophil count [ANC] of $< 0.5 \times 10^9$/L, or a count of $< 1.0 \times 10^9$/L that is predicted to fall to $< 0.5\ 10^9$/L within 48 hours, with fever or clinical signs of sepsis.

  Definition for observational studies: defined as an in-patient stay with a diagnosis claim for neutropenia or fever or infection,

  We will not exclude studies if the FN definition is a variant of the commonly used definitions presented above.
  2) grade 1-4 neutropenia,
  3) all-cause hospitalization,
  4) dose delays or dose reductions, (those occurring as a result of neutropenia will be identified separately)
  5) adverse events, or
  6) mortality

  Study design: studies will include randomized controlled trials, observational studies, and systematic reviews reported in English language

– Exclusion criteria: Single-arm trials that include no comparator, observational studies with no control or comparison group, studies of patients with myeloid malignancy, animal studies, abstracts or publications superseded by more recent publications and editorials or letter to editors. Observational studies with less than 30 patients in the Q2W arm with primary prophylactic pegfilgrastim will be excluded.

– Key studies that are expected to be retrieved from the searches are listed in Appendix A.

- **Study identification**

– Initial search terms are included in Appendix B and will be used in an initial Medline search to obtain an updated list of keywords and MESH terms for the comprehensive search of all the databases.

– Keywords and MESH terms will be used to search Ovid, MEDLINE, Embase, and Cochrane Reviews databases (Appendix B–Appendix D). The literature search will not be limited by publication date to ensure identification of all relevant studies from January 1, 2002 through June 30, 2019. A literature search will be performed for abstracts published in key international congresses (Appendix E) held from January 1, 2015 through June 30, 2019.

- **Study selection**

– A spreadsheet will be used to collate the results of all searches and to facilitate the screening process. A unique identifier will be automatically assigned to every publication retrieved in the broad search to enable tracking of articles. Duplicates will be removed. Based on the initial search, two reviewers will independently screen the titles and abstracts of all publications retrieved to determine eligibility according to the Patients, Intervention, Comparator, Outcomes, Study Design (PICOS) criteria.(Harris, Quatman, Manring, Siston, & Flanigan, 2014) An inter-rater calculation will be performed to reveal the level of agreement.

– The spreadsheet will be used to track the screening process. Of the studies identified for inclusion, the full publications will be retrieved and reviewed by two authors to confirm eligibility. A third review of full-text of selected studies will be performed by a board-certified hematologist-oncologist to assess eligibility and risk of bias. Following review of the full text, the inclusion/exclusion status and rationale will be recorded for each study. All disagreements regarding inclusion/exclusion will be resolved through consensus. The PRISMA flow diagram will be used for reporting the screening process (Appendix F).(Moher, Liberati, Tetzlaff, Altman, & Group, 2009)

- **Data abstraction**

– A data collection form adapted from the Cochrane Collaboration Data Collection (Appendix G) will be used for recording the extracted data.(Higgins et al., 2011) One reviewer will independently extract data from each included publication. Extracted data will include: year, authors, publication title, research question or study purpose, study design, context, subjects/participants, sample size, intervention, definition of concepts, data collection methods, reliability coefficients, validity measures, and relevant results. Extracted data will be checked for accuracy and completeness by a second reviewer and any discrepancies resolved by consensus.

- **Assessment of methodological quality**

– Each included publication will be independently assessed for quality by two reviewers. The risk of bias tool recommended by the Cochrane Collaboration tool (Appendix H) will be used for randomized control trials.(Higgins et al., 2011) This tool addresses six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Within each domain, assessments are made for one or more items, which may cover different aspects of the domain, or different outcomes. Each domain will be graded as either 'low risk', 'high risk' or 'unclear risk' for bias.

– A quality assessment tool designed to assess bias in non-randomized, observational studies - Cochrane Robins-I tool (Appendix I) recommended by the GRADE working group will be utilized.(Schunemann et al., 2018) The Robins-I tool consists of eight domains which include: bias due to confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. In addition, the Robins-I tool allows for comparison of final ratings of bias for RCTs and non-randomized studies since they utilize the same metrics.

– Risk of bias and quality rating will be considered in the data summarization but will not determine a study's inclusion or exclusion. For evidence of potential reporting biases, funnel plots will be used.

- **Data synthesis (descriptive only)**

– Where studies report dichotomous outcomes, results will be reported as absolute and relative risk ratios with 95% confidence intervals (CI). For continuous outcomes, mean, median. 25th and 75th percentiles and standard deviations will be reported. For randomized controlled trials, we will note the level of attrition. For all outcomes, we will consider an intent to treat basis and sample sizes will be reported for all studies.

3. AMENDMENTS AND UPDATES

Not applicable

4. BACKGROUND AND RATIONALE

4.1 Disease or Therapeutic Area

Febrile neutropenia (FN) following myelosuppressive chemotherapy is a potentially life-threatening complication and is associated with loss of treatment efficacy because of dose delays, and dose reductions.(Kuderer et al., 2006; Kuderer et al., 2007; Lyman et al., 2010; Schilling et al., 2011) To prevent FN, the National Comprehensive Care Network (NCCN) guidelines recommends prophylactic use of granulocyte colony stimulating factor (G-CSF) for patients receiving chemotherapy regimen associated with high risk of developing FN (≥ 20%) or those receiving regimens with intermediate-risk of FN (10-20%) and have least one patient-level risk factor.(*National Comprehensive Care Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hematopoietic Growth Factors*, 2019) Pegfilgrastim is a long-acting G-CSF that is administered once per cycle and is the most commonly used G-CSF in the US.(Weycker et al., 2017) The US prescribing information of pegfilgrastim,("Food and Drug Administration. Pegfilgrastim [prescribing information].") specifies that Neulasta should not be administered in the period between 14 days before and 24 hours after administration of myelosuppressive chemotherapy. This restriction was placed because of the potential for an increase in sensitivity of rapidly dividing myeloid cells stimulated by pegfilgrastim to myelosuppressive chemotherapy. However, this restriction precludes the prophylactic use of pegfilgrastim among severalQ2W chemotherapy regimens associated with high or intermediate risk for FN.

The latest NCCN guidelines recommend that there should be at least 12 days between the dose of pegfilgrastim and the next cycle of chemotherapy supporting the use of prophylactic pegfilgrastim in patients receiving Q2W regimens.(*National Comprehensive Care Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hematopoietic Growth Factors*, 2019) This recommendation is based on phase II studies that reported better efficacy and safety profile of pegfilgrastim in reducing FN among patients receiving Q2W regimens for breast cancer,(Burstein et al., 2005; Jones et al., 2009) colorectal cancer,(Hecht et al., 2010) lung cancer,(Pirker et al., 2006) and non-Hodgkin's lymphoma (NHL).(Brusamolino et al., 2006; Watanabe et al., 2011) However, there is a lack of systematic identification, appraisal, and synthesis of the existing evidence base from randomized clinical trials and observational studies that

summarizes the efficacy, effectiveness, and safety of prophylactic pegfilgrastim to prevent FN among patients treated with Q2W chemotherapy regimen. The objective of this review is to provide a single-source information for oncologists and payers to make evidence-based decisions. Given the heterogeneity of the studies in terms of tumor types, FN risk of each regimens, and patient population, we will not conduct any meta-analyses

4.2 Scope for Analysis

This review will include randomized trials and observational studies of patients diagnosed with non-myeloid malignancies receiving Q2W myelosuppressive chemotherapy regimen and a primary prophylactic pegfilgrastim. Comparators will include “no primary prophylactic pegfilgrastim”, “primary prophylaxis with other G-CSF”, or “placebo”. We will also include studies where comparator is patients receiving Q3W chemotherapy regimens with primary prophylactic pegfilgrastim. Only publications that address relevant outcomes such as FN, grade 3 or 4 neutropenia, all-cause hospitalization, dose delays or dose reductions, adverse events, or mortality will be included. Systematic reviews that include studies of patients receiving Q2W chemotherapy regimens with primary prophylactic pegfilgrastim will also be reviewed for additional data that include the relevant outcomes.

5. OBJECTIVES

Among patients treated with Q2W chemotherapy regimens with high or intermediate risk for febrile neutropenia, systematically review the evidence regarding absolute or relative risk of

1) febrile neutropenia
2) grade 1-4 neutropenia,
3) all-cause hospitalization
4) dose delays or dose reductions (those occurring as a result of neutropenia will be identified separately)
5) adverse events, and
6) mortality

for patients receiving prophylactic pegfilgrastim versus no prophylactic pegfilgrastim or prophylaxis with other granulocyte colony stimulating factor

6. RESEARCH QUESTIONS

What is the published evidence on the efficacy, effectiveness, and safety of prophylactic pegfilgrastim compared to no prophylactic pegfilgrastim or prophylaxis with other granulocyte colony stimulating factor in reducing the risk of febrile neutropenia among patients treated with Q2W chemotherapy regimens with high or intermediate risk for febrile neutropenia?

7. METHODS FOR DATA COLLECTION

The study protocol will be registered at PROSPERO (https://www.crd.york.ac.uk/prospero/) an international register for systematic reviews after it is approved by Amgen's internal governance review ie, ORRG.

7.1 Study Eligibility

Criteria for the inclusion and exclusion of studies are as follows:

- Inclusion criteria: Published randomized clinical trials or observational studies in English language where patients were treated with a Q2W myelosuppressive chemotherapy regimen and received prophylactic pegfilgrastim. Studies will only be included if the regimens were associated with high (>20%) or intermediate (10-20%) risk for FN. Studies that address FN, grade 1 to 4 neutropenia, all-cause hospitalization, dose delays or dose reductions, adverse events, or mortality will be included.
- Exclusion criteria: Single-arm trials that include no comparator, observational studies with no control or comparison group, studies of patients with myeloid malignancy, case studies, case reports, animal studies, abstracts or publications superseded by more recent publications and editorials or letter to editors. Observational studies with less than 30 patients in the Q2W arm with primary prophylactic pegfilgrastim will be excluded.
- Study Design: Studies will include randomized controlled trials, observational studies, and systematic reviews.
- Population: Patients diagnosed with non-myeloid malignancy and treated with a Q2W chemotherapy regimen with high (>20%) or intermediate (10-20%) risk for FN and receiving prophylactic pegfilgrastim.
- Outcomes:
  1) FN:

     Definition for RCTs: defined as an absolute neutrophil count [ANC] of $< 0.5 \times 10^9$/L, or a count of $< 1.0 \times 10^9$/L that is predicted to fall to $< 0.5\ 10^9$/L within 48 hours, with fever or clinical signs of sepsis.

     Definition for observational studies: defined as an in-patient stay with a diagnosis claim for neutropenia or fever or infection,

We will not exclude studies if the study uses a variant of commonly used FN definition that is presented above.

2) grade 1-4 neutropenia,

3) all-cause hospitalization,

4) dose delays or dose reductions, (those occurring as a result of neutropenia will be identified separately)

5) adverse events, or

6) mortality

- Comparators: No prophylactic pegfilgrastim, primary prophylaxis with other G-CSF, or placebo. We will also include studies where comparator is patients receiving Q3W chemotherapy regimens with primary prophylactic pegfilgrastim.
- Based on these inclusion and exclusion criteria, key studies expected to be retrieved from the searches can be found in Appendix A.

7.2 Study Identification

7.2.1 Identifying Citations (Literature Searches)

An initial search of Medline will be conducted using the search terms included in Appendix B. Based on this initial search, retrieved articles will be reviewed for additional keywords and MESH terms. A subsequent electronic search of the following databases will then be conducted including Ovid and PubMed MEDLINE, Embase, and Cochrane Reviews using the updated list of search terms (Appendix B-Appendix D). The literature search will not be limited by publication date to ensure identification of all relevant studies from January 1, 2002 through June 30, 2019. We included a longer assessment window because we do not expect many studies given the restriction of Neulasta use among patients receiving Q2W regimens. A literature search will be performed for abstracts published in key international congresses (Appendix E) held from June 30, 2016 through June 30, 2019. Previous systematic reviews evaluating the primary objectives of this review will also be identified to ensure that all relevant data have been identified in the search. Sources of 'grey' literature, such as clinical trial registries, will not be searched due to the high likelihood that any relevant data will be identified in the searches of the Ovid Embase and PubMed databases and the defined congress abstract books.

7.3 Study Selection

A spreadsheet will be used to collate the results of all searches and to facilitate the screening process. A unique identifier will be automatically assigned to every publication retrieved in the broad search to enable tracking of articles. Duplicates will be removed.

Based on the second search, two reviewers will independently screen the titles and abstracts of all publications retrieved to determine eligibility according to the PICOS criteria. An inter-rater calculation will be performed to reveal the level of agreement. Of the studies identified for inclusion, the full publications will be retrieved and reviewed by two authors to confirm eligibility. Following review of the full text, the inclusion/exclusion status and rationale will be recorded for each study. A third review of full-text of selected studies will be performed by a board-certified hematologist-oncologist to assess eligibility and risk of bias. All disagreements regarding inclusion/exclusion will be resolved through consensus. Eligibility for inclusion of a study will be assessed using the outlined Inclusion/exclusion criteria (Section 7.1). This information will be captured in data collection form adapted from the Cochrane Collaboration Data Collection Form (Appendix F).(Higgins et al., 2011) The PRISMA flow diagram will be used for reporting the screening process.(Moher et al., 2009)

7.4 Data Abstraction and Quality Control Procedures

One reviewer will independently extract data from each included publication and include in the data collection form. Extracted data will include: year, authors, publication title, research question or study purpose, study design, context, subjects/participants, sample size, intervention, definition of concepts, data collection methods, validity measures, and relevant results (ie, absolute and relative risk of FN, grade 3 or 4 neutropenia, chemotherapy dose delays and dose reductions, and mortality). Data will be extracted from the full texts of the included studies into a purpose-created Microsoft® Excel® date extraction table and will then be quality checked by a separate analyst.

DATA SYNTHESIS

7.5 Narrative Summary (Qualitative Synthesis)

Summary of the results of the systematic review will be presented in tabular form consisting of the availability of the data to address each research question including the population(s), interventions, outcomes and quality. Final ratings of bias and quality will be based on the quality assessment tools for both randomized and non-randomized studies.(Higgins et al., 2011; Schunemann et al., 2018) Based on previous experience, we expect substantial heterogeneity between studies by type of tumor and regimen; therefore, no meta-analysis will be performed.

8. STUDY LIMITATIONS

- Generalizability of the results: We expect substantial heterogeneity in terms of types of tumors and Q2W regimens used to treat them. The results from a study with specific tumor type or Q2W regimen may not be extrapolated to other tumors or regimens. We will summarize the results stratified by type of tumor and regimens.
- Publication bias: We do not have access to unpublished data and no attempt will be made to obtain unpublished results. It is well established that results that are published may be different from the ones that do not get published. We cannot quantify the direction or magnitude of this publication bias.

9. ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Adverse Events

Reporting of individual adverse events (AE), product complaints (PCs) and other safety findings is not applicable for systematic literature reviews which involve published literature sources, as the safety data from the studies identified will have been previously reported to regulatory agencies, institutional review boards, and ethics committees in accordance with local regulations and routine pharmacovigilance practices.

9.1.1 Amgen Medical Information/Global Patient Safety

Phone:

US Only: +1-800-772-6436 (+1-800-77-Amgen)

9.2 Data Management and Quality Control Procedures

The summary of systematic literature search will be shared with Amgen by the study partner mentioned in the collaboration section. The risk of bias analysis will be done by Amgen in collaboration with study partner and subject matter experts. These documents along with the final manuscript will be stored on Amgen servers and on Box for at least 3 years.

9.3 Subject Confidentiality

This study will comply with all applicable laws regarding subject privacy. No direct subject contact or collection of additional subject data will occur. Study results will be in tabular form and aggregate analyses that omits subject identification. Any publications and reports will not include subject identifiers.

10. ADMINISTRATIVE AND LEGAL OBLIGATIONS

10.1 Study Amendments and Study Termination

Amendments must be made only with the prior approval of Amgen. Amgen reserve the right to terminate participation in the study according to the study contract.

10.2 Study Documentation and Archive

Retention of study documents will be governed by the contractual agreement with the vendor and will be maintained pursuant to Amgen's records retention schedule.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this systematic review will be submitted for publication. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Oxford Pharmagenesis agreement will detail the procedures for, and timing of, Amgen's review of publications.

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13. APPENDICES

Appendix A. Key Studies That can be Expected to be Retrieved Based on the Eligibility Criteria

1. Cameron *et al.* Lancet Oncol 2017; 18:929–945
2. Del Mastro *et al.* Lancet 2015; 385:1863–1872
3. Hecht *et al.* Clin Colorectal Cancer 2010; 9:95–101
4. Hendler *et al.* Am J Clin Oncol 2011; 34:619–624
5. Jones *et al.* BJC 2009; 100:305–310
6. Kourlaba *et al.* Support Care Cancer 2015: 23:2045–2051
7. Kurbacher *et al.* JCO 2015 3:15_suppl, e20693–e20693
8. Lane *et al.* L&L 2006; 47:1813–1817
9. Lopez *et al.* Poster presented at ASH Dec 4–7 2004 Ab 3311
10. Mizuno *et al.* JJCO 2017; 47:12–17
11. Ng *et al.* Acta Haematol 2011; 125:107–114
12. Pinter *et al.* Clinical Colorectal Cancer 2017; 16:103–114
13. Skarlos *et al.* Oncology 2009; 77:107–112
14. Untch *et al.* Annals of Oncology 2011; 22:1988-1998
15. Wildiers *et al.* Breast Cancer Res Treat 2009; 114:103–112

Appendix B. Initial Medline Search Terms, January 1, 2002 – June 30, 2019

	Medline Search Terms[a,b,c]	Results
1	Exp granulocyte colony stimulating factor OR recombinant granulocyte colony stimulating factor.mp	15325
2	(G-CSF OR GCSF or granulocyte stimulating factor).mp	23699
3	Pegylat*.mp	15860
4	1 or 2	23820
5	3 and 4	354
6	($pegfilgrastim or SD01 or neulasta or neulastim or imupeg).mp	842
7	Pegfilgrastim.mp	796
8	(Peg-rmetHuG-CSF or polyethylene glycol-conjugated filgrastim).mp	2
9	5 or 6 or 7 or 8	1095
10	(Tumor$ OR tumour$ OR cancer OR malignant neoplasm)	2937354
11	Cancer chemotherapy.mp.	11113
12	ABVD.mp	1509
13	Hyper-CVAD.mp	242
14	(ACT or adoptive cellular therapy).mp	273224
15	(CHOP 14 OR R-CHOP-14).mp	98
16	FOLFOX.mp	2702
17	FOLFIRI.mp	1341
18	(Leucovorin calcium and fluorouracil and irinotecan).mp	8
19	(((Fluorouracil and leucovorin) or calcium) and oxaliplatin).mp	2886
20	(Cyclophosphamide and vincristine and doxorubicin and dexamethasone).mp	901
21	Epirubicin and cyclophosphamide and methotrexate and fluorouracil and docetaxel).mp	46
22	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	3176116
23	Exp febrile neutropenia/ or neutropenia.mp or exp neutropenia/	40002
25	9 and 22 and 23	396
26	Limit 25 to English language	370

[a] An asterisk at the end of the search term will retrieve publications with the search term or any other search terms for which that is the root eg, fortnight* will retrieve fortnight or fortnightly
[b] In search-term combinations OR will retrieve publications where there is at least one of the combined terms, and it does not exclude hits where more than one term is present.
[c] Search terms in the list will be combined with OR or AND search operators in order to retrieve relevant publications with combinations of content meeting the search objectives.

Appendix C. Embase Search Terms, January 1, 2002 – June 30, 2019

	Embase Search Terms[a,b,c]	Results
1	Recombinant Granulocyte colony stimulating factor.mp OR exp recombinant granulocyte colony stimulating factor/	17058
2	(G-CSF OR GCSF or granulocyte stimulating factor).mp	60614
3	Pegylat*.mp	25371
4	1 or 2	62517
5	3 and 4	1131
6	($pegfilgrastim or SD01 or neulasta or neulastim or imupeg).mp	2717
7	Exp pegfilgrastim/	1163
8	(Peg-rmetHuG-CSF or polyethylene glycol-conjugated filgrastim).mp	2
9	5 or 6 or 7 or 8	3505
10	(Tumor$ OR tumour$ OR cancer OR malignant neoplasm)	4652921
11	Cancer chemotherapy.mp. OR exp cancer chemotherapy/	428685
12	ABVD.mp	2865
13	Hyper-CVAD.mp	666
14	(ACT or adoptive cellular therapy).mp	319786
15	(CHOP 14 OR R-CHOP-14).mp	318
16	FOLFOX.mp	4479
17	FOLFIRI.mp	3273
18	(Leucovorin calcium and fluorouracil and irinotecan).mp	13
19	(((Fluorouracil and leucovorin) or calcium) and oxaliplatin).mp	3896
20	(Cyclophosphamide and vincristine and doxorubicin and dexamethasone).mp	8862
21	Epirubicin and cyclophosphamide and methotrexate and fluorouracil and docetaxel).mp	1830
22	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	4933440
23	Exp neutropenia/ or neutropenia.mp or exp febrile neutropenia/	120933
24	9 and 22 and 23	1614
25	Limit 24 to English language	1538

[a] An asterisk at the end of the search term will retrieve publications with the search term or any other search terms for which that is the root

[b] In search-term combinations OR will retrieve publications where there is at least one of the combined terms, and it does not exclude hits where more than one term is present.

[c] Search terms in the list will be combined with OR or AND search operators in order to retrieve relevant publications with combinations of content meeting the search objectives.

Appendix D. Cochrane Library Search String, January 1, 2002 – June 30, 2019

	Cochrane Search Terms[a,b,c]	Results
1	Recombinant Granulocyte colony stimulating factor.mp	1447
2	(G-CSF OR GCSF or granulocyte stimulating factor).mp	5744
3	Pegylat*.mp	2974
4	1 or 2	5744
5	3 and 4	166
6	($pegfilgrastim or SD01 or neulasta or neulastim or imupeg).mp	561
8	(Peg-rmetHuG-CSF or polyethylene glycol-conjugated filgrastim).mp	1
9	5 or 6 or 7 or 8	665
10	(Tumor$ OR tumour$ OR cancer OR malignant neoplasm).mp	194546
11	Cancer chemotherapy.mp.	58531
12	ABVD.mp	587
13	Hyper-CVAD.mp	59
14	(ACT or adoptive cellular therapy).mp	12412
15	(CHOP 14 OR R-CHOP-14).mp	567
16	FOLFOX.mp	1072
17	FOLFIRI.mp	960
18	(Leucovorin calcium and fluorouracil and irinotecan).mp	55
19	(((Fluorouracil and leucovorin) or calcium) and oxaliplatin).mp	2358
20	(Cyclophosphamide and vincristine and doxorubicin and dexamethasone).mp	274
21	Epirubicin and cyclophosphamide and methotrexate and fluorouracil and docetaxel).mp	46
22	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	205637
23	neutropenia.mp	13007
24	febrile neutropenia.mp	4360
25	23 or 24	13007
26	9 and 22 and 25	336

[a] An asterisk at the end of the search term will retrieve publications with the search term or any other search terms for which that is the root

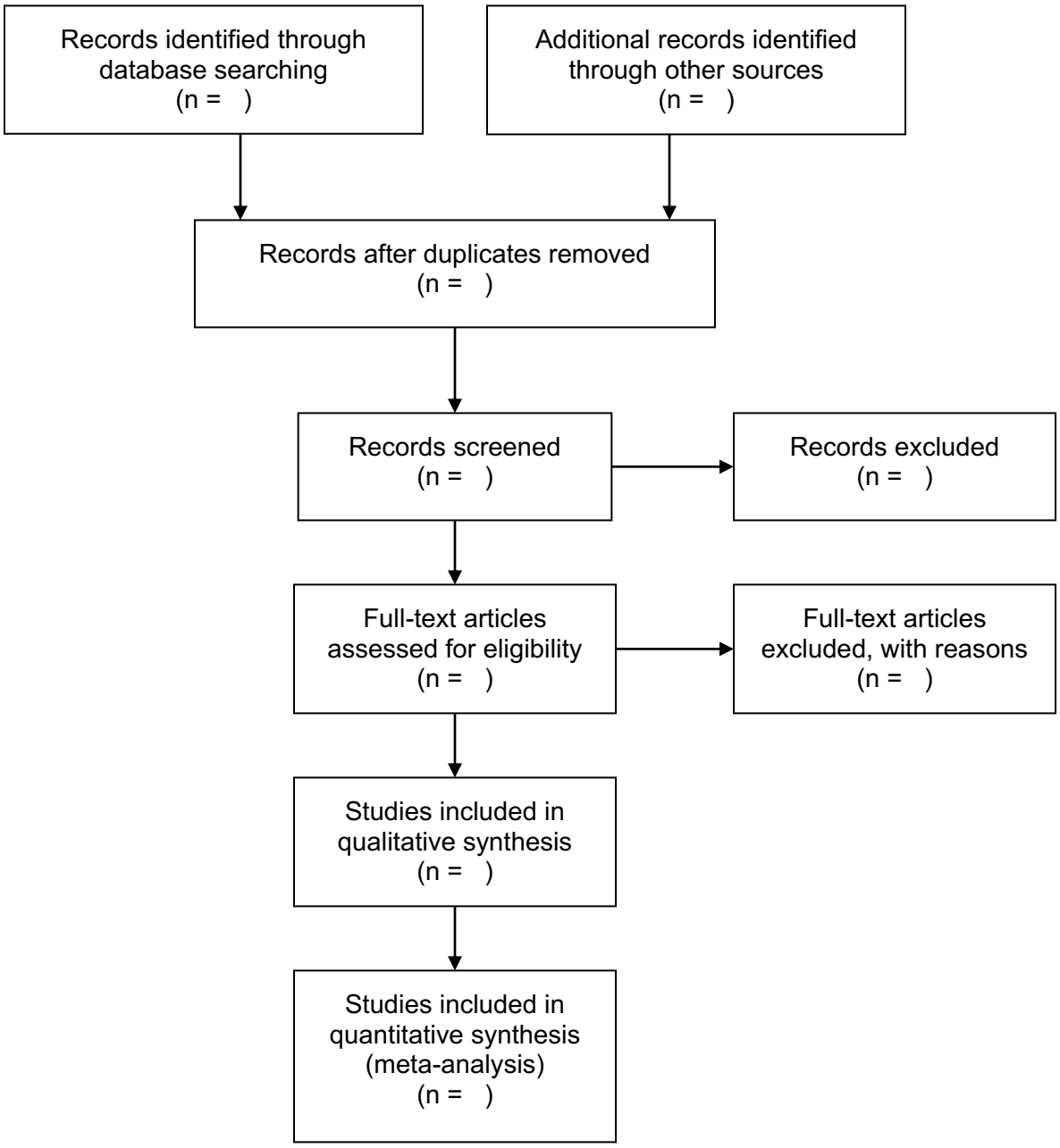
[b] In search-term combinations OR will retrieve publications where there is at least one of the combined terms, and it does not exclude hits where more than one term is present.

[c] Search terms in the list will be combined with OR or AND search operators in order to retrieve relevant publications with combinations of content meeting the search objectives.

Appendix E. Potential List of Congresses for Abstract Search, January 1, 2015 Through June 30, 2019

Academy of Managed Care Pharmacy
American College of Clinical Pharmacy
American Pharmacists Association
American Society of Clinical Oncology
American Society of Hematology
American Society of Hospital Pharmacists
European Hematology Association
European Society for Medical Oncology
The European Multidisciplinary Cancer Congress
Hematology/Oncology Pharmacy Association
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)including European, North American and Latin American conferences
Multinational Association of Supportive Care in Cancer
Oncology Nursing Society
San Antonio Breast Cancer Symposium

Appendix F. Prisma Flow Diagram



Source: http://www.prisma-statement.org/

Appendix G. Systematic Review Data Collection Form

Review title or ID	
Study ID *(surname of first author and year first full report of study was published eg, Smith 2001)*	
Report ID	
Report ID of other reports of this study	
Abstract or Full-text Review	☐ Abstract ☐ Full-text
Notes	

General Information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation	
Study author contact details	
Publication type *(eg, full report, abstract, letter)*	
Notes:	

Study eligibility

Study Characteristics	Eligibility criteria *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	Eligibility criteria met? Yes	No	Unclear	Location in text or source *(pg & ¶/fig/table/other)*
Type of study	Randomised Controlled Trial	☐	☐	☐	
	Non-randomized Observational Study	☐	☐	☐	
Participants		☐	☐	☐	
Types of intervention		☐	☐	☐	
Types of comparison		☐	☐	☐	
Types of outcome measures		☐	☐	☐	
INCLUDE ☐		EXCLUDE ☐			
Reason for exclusion					
Notes:					

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Appendix H. Cochrane Collaboration Tool

Bias domain	Source of bias	Support for judgement	Review authors' judgement (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should product comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel*	Describe all lmeasures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias	Blinding of outcome assessment*	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review	Attrition bias due to amount, nature, or handling of incomplete outcome data
Reporting bias	Selective reporting	State how selective outcome reporting was examined and what was found	Reporting bias due to selective outcome reporting
Other bias	Anything else, ideally prespecified	State any important concerns about bias not covered in the other domains in the tool	

*Assessments should be made for each main outcome or class of outcomes.

Appendix I. Cochrane Robins-I Table

Study name	Confounding	Selection	Measurement of intervention	Missing data	Measurement of outcomes	Reported result