Supplementary Appendix Table S1 Electronic searches performed in August 2015

Database, search no.	Search string	Results
Embase		
1	Granulocyte colony stimulating factor.mp. or exp granulocyte colony stimulating factor/	48246
2	(G-CSF$ or GCSF).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	20300
3	filgrastim.mp. or exp filgrastim/	3920
4	(Neupogen or Zarzio or Nivestim or Ratiograstim).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2413
5	Lenograstim.mp. or exp lenograstim/	828
6	Granocyte.mp.	319
7	lipegfilgrastim.mp. or exp lipegfilgrastim/	44
8	Pegfilgrastim.mp. or exp pegfilgrastim/	1177
9	Neulasta.mp.	664
10	(Biograstim or Tevagrastim or Grastofil or Accofil).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	115
11	(Euprotin or r-metHuG-CSF or SD-01 or PEG-rmetHuG-CSFor XM02).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	373
12	(Ro 25-8315m or Nartograstim or Empegfilgrastim or Maxy-G34 or BK0026 or Ro 25-8315m or Nartograstim or Empegfilgrastim or Maxy-G34 or PEG-rHuG-CSF).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	71
13	or/1-12	50833
14	exp neutropenia/ or neutropenia.mp.	91651
15	febrile neutropenia.mp. or exp Febrile Neutropenia/	22954
16	exp severe congenital neutropenia/ or severe congenital neutropenia.mp.	732
17	leukopenia.mp. or exp leukopenia/	155774
18	granulocyte disorder.mp.	4
19	or/14-18	160655
20	(chemotherapy or cancer).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2543716
21	13 and 19	16979
22	20 and 21	11105
23	Clinical study/	113574
24	exp case control study/	104419
25	Longitudinal study/	80175
26	Retrospective study/	418189
27	Prospective study/	301921

Database, search no.	Search string	Results
28	Cohort analysis/	211135
29	(Cohort adj (study or studies)).mp.	144428
30	(Case control adj (study or studies)).tw.	86719
31	(follow up adj (study or studies)).tw.	49735
32	(observational adj (study or studies)).tw.	79782
33	(epidemiologic$ adj (study or studies)).tw.	81479
34	(cross sectional adj (study or studies)).tw.	105972
35	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1369501
36	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/	65527
37	35 not 36	1303974
38	cost$.mp. or exp "cost"/ or "health care cost"/ or "cost of illness"/	751451
39	or/23-34,37-38	3222109
40	22 and 39	3774
41	(animals not (humans and animals)).mp.	616345
42	40 not 41	3765
43	limit 42 to yr="2003 -Current"	2932
Medline		
1	Granulocyte colony stimulating factor.mp. or exp Granulocyte Colony-Stimulating Factor/	18150
2	(G-CSF$ or GCSF).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	13014
3	filgrastim.mp.	2152
4	(Neupogen or Zarzio or Nivestim or Ratiograstim).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	157
5	Lenograstim.mp.	356
6	Granocyte.mp.	19
7	lipegfilgrastim.mp.	9
8	Pegfilgrastim.mp.	550
9	Neulasta.mp.	39
10	(Biograstim or Tevagrastim or Grastofil or Accofil).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7
11	(Euprotin or r-metHuG-CSF or SD-01 or PEG-rmetHuG-CSFor XM02).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	285
12	(Ro 25-8315m or Nartograstim or Empegfilgrastim or Maxy-G34 or BK0026 or	52

Database, search no.	Search string	Results
	Ro 25-8315m or Nartograstim or Empegfilgrastim or Maxy-G34 or PEG-rHuG-CSF).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	
13	or/1-12	21550
14	neutropenia.mp. or exp Neutropenia/	33632
15	febrile neutropenia.mp. or exp Febrile Neutropenia/	4848
16	severe congenital neutropenia.mp.	410
17	leukopenia.mp. or exp Leukopenia/	40374
18	granulocyte disorder.mp.	3
19	or/14-18	56101
20	13 and 19	5079
21	chemotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	329244
22	cancer.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1191481
23	20 and (21 or 22)	2900
24	Clinical study.mp.	42651
25	case control study.mp. or exp Case-Control Studies/	753934
26	Longitudinal study.mp. or exp Longitudinal Studies/	110238
27	Retrospective study.mp. or exp Retrospective Studies/	570389
28	Prospective study.mp. or exp Prospective Studies/	431546
29	Cohort analysis.mp. or exp Cohort Studies/	1477414
30	(Cohort adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	245602
31	(follow up adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	549349
32	(observational adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	64529
33	(epidemiologic$ adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	70715
34	(cross sectional adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique	228088

Database, search no.	Search string	Results
	identifier]	
35	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1074032
36	(random sampl$ or random digit$ or random effect$ or random survey or random regression).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	56899
37	35 not 36	1017133
38	cost*.ti.	89331
39	exp "Costs and Cost Analysis"/	192517
40	or/38-39	225514
41	or/24-34,37,40	3024650
42	41 and 23	1109
43	(animals not (humans and animals)).sh.	3998891
44	42 not 43	1105
45	limit 44 to yr="2003 -Current"	615
Cochrane		
1	Granulocyte colony stimulating factor.mp. or exp Granulocyte Colony-Stimulating Factor/	2284
2	(G-CSF$ or GCSF).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	1800
3	filgrastim.mp.	660
4	(Neupogen or Zarzio or Nivestim or Ratiograstim).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	47
5	Lenograstim.mp.	205
6	Granocyte.mp.	20
7	lipegfilgrastim.mp.	6
8	Pegfilgrastim.mp.	200
9	Neulasta.mp.	15
10	(Biograstim or Tevagrastim or Grastofil or Accofil).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	4
11	(Euprotin or r-metHuG-CSF or SD-01 or PEG-rmetHuG-CSFor XM02).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	108
12	(Ro 25-8315m or Nartograstim or Empegfilgrastim or Maxy-G34 or BK0026 or Ro 25-8315m or Nartograstim or Empegfilgrastim or Maxy-G34 or PEG-rHuG-CSF).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	8
13	or/1-12	3259
14	neutropenia.mp. or exp Neutropenia/	6414
15	febrile neutropenia.mp. or exp Febrile Neutropenia/	1794
16	severe congenital neutropenia.mp.	3
17	leukopenia.mp. or exp Leukopenia/	4414
18	granulocyte disorder.mp.	0
19	or/14-18	8571

Database, search no.	Search string	Results
20	13 and 19	1075
21	chemotherapy.mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	36508
22	20 and 21	844
23	Clinical study.mp.	74228
24	case control study.mp. or exp Case-Control Studies/	12858
25	Longitudinal study.mp. or exp Longitudinal Studies/	106088
26	Retrospective study.mp. or exp Retrospective Studies/	9251
27	Prospective study.mp. or exp Prospective Studies/	88739
28	Cohort analysis.mp. or exp Cohort Studies/	114348
29	(Cohort adj (study or studies)).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	14044
30	(follow up adj (study or studies)).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	49473
31	(observational adj (study or studies)).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	7880
32	(epidemiologic$ adj (study or studies)).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	2571
33	(cross sectional adj (study or studies)).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	5239
34	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	579730
35	(random sampl$ or random digit$ or random effect$ or random survey or random regression).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	16483
36	34 not 35	563247
37	cost*.ti.	19004
38	exp "Costs and Cost Analysis"/	23024
39	or/37-38	28408
40	or/23-33,36,39	626531
41	22 and 40	699
42	limit 41 to yr="2003 -Current" [Limit not valid in DARE; records were retained]	423

Supplementary Appendix Table S2 Electronic searches performed in June 2016

Database, search no.	Search string	Results
Embase		
1	Granulocyte colony stimulating factor.mp. or exp granulocyte colony stimulating factor/	50476
2	(G-CSF$ or GCSF).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	21580
3	filgrastim.mp. or exp filgrastim/	4337
4	(Neupogen or Zarzio or Nivestim or Ratiograstim).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2486
5	Lenograstim.mp. or exp lenograstim/	880
6	Granocyte.mp.	323
7	lipegfilgrastim.mp. or exp lipegfilgrastim/	71
8	Pegfilgrastim.mp. or exp pegfilgrastim/	1391
9	Neulasta.mp.	701
10	(Biograstim or Tevagrastim or Grastofil or Accofil).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	130
11	(Euprotin or r-metHuG-CSF or SD-01 or PEG-rmetHuG-CSFor XM02).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	402
12	(Ro 25-8315m or Nartograstim or Empegfilgrastim or Maxy-G34 or BK0026 or Ro 25-8315m or Nartograstim or Empegfilgrastim or Maxy-G34 or PEG-rHuG-CSF).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	74
13	or/1-12	53564
14	exp neutropenia/ or neutropenia.mp.	98006
15	febrile neutropenia.mp. or exp Febrile Neutropenia/	25070
16	exp severe congenital neutropenia/ or severe congenital neutropenia.mp.	780
17	leukopenia.mp. or exp leukopenia/	165669
18	granulocyte disorder.mp.	4
19	or/14-18	170802
20	(chemotherapy or cancer).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2737202
21	13 and 19	17820
22	20 and 21	11679
23	Clinical study/	122799
24	exp case control study/	115589
25	Longitudinal study/	88464
26	Retrospective study/	469207
27	Prospective study/	337335

Database, search no.	Search string	Results
28	Cohort analysis/	246159
29	(Cohort adj (study or studies)).mp.	167573
30	(Case control adj (study or studies)).tw.	94772
31	(follow up adj (study or studies)).tw.	52484
32	(observational adj (study or studies)).tw.	92126
33	(epidemiologic$ adj (study or studies)).tw.	86321
34	(cross sectional adj (study or studies)).tw.	120048
35	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1476018
36	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/	72686
37	35 not 36	1403332
38	cost$.mp. or exp "cost"/ or "health care cost"/ or "cost of illness"/	801013
39	or/23-34,37-38	3501223
40	22 and 39	4048
41	(animals not (humans and animals)).mp.	644109
42	40 not 41	4039
43	limit 42 to dd=20150501-20160530	378
Medline		
1	Granulocyte colony stimulating factor.mp. or exp Granulocyte Colony-Stimulating Factor/	18796
2	(G-CSF$ or GCSF).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	13609
3	filgrastim.mp.	2260
4	(Neupogen or Zarzio or Nivestim or Ratiograstim).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	183
5	Lenograstim.mp.	365
6	Granocyte.mp.	20
7	lipegfilgrastim.mp.	22
8	Pegfilgrastim.mp.	605
9	Neulasta.mp.	51
10	(Biograstim or Tevagrastim or Grastofil or Accofil).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	11
11	(Euprotin or r-metHuG-CSF or SD-01 or PEG-rmetHuG-CSFor XM02).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	298
12	(Ro 25-8315m or Nartograstim or Empegfilgrastim or Maxy-G34 or BK0026 or	51

Database, search no.	Search string	Results
	Ro 25-8315m or Nartograstim or Empegfilgrastim or Maxy-G34 or PEG-rHuG-CSF).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	
13	or/1-12	22438
14	neutropenia.mp. or exp Neutropenia/	35117
15	febrile neutropenia.mp. or exp Febrile Neutropenia/	5289
16	severe congenital neutropenia.mp.	419
17	leukopenia.mp. or exp Leukopenia/	41579
18	granulocyte disorder.mp.	3
19	or/14-18	58353
20	13 and 19	5255
21	chemotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	351195
22	cancer.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1296503
23	20 and (21 or 22)	3034
24	Clinical study.mp.	46747
25	case control study.mp. or exp Case-Control Studies/	810115
26	Longitudinal study.mp. or exp Longitudinal Studies/	118291
27	Retrospective study.mp. or exp Retrospective Studies/	615012
28	Prospective study.mp. or exp Prospective Studies/	455641
29	Cohort analysis.mp. or exp Cohort Studies/	1558545
30	(Cohort adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	269196
31	(follow up adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	570656
32	(observational adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	79298
33	(epidemiologic$ adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	74694
34	(cross sectional adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept	252554

Database, search no.	Search string	Results
	word, unique identifier]	
35	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1142818
36	(random sampl$ or random digit$ or random effect$ or random survey or random regression).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	63278
37	35 not 36	1079540
38	cost*.ti.	96236
39	exp "Costs and Cost Analysis"/	199212
40	or/38-39	236046
41	or/24-34,37,40	3225323
42	41 and 23	1184
43	(animals not (humans and animals)).sh.	4231242
44	42 not 43	1180
45	limit 44 to ed=20150501-20160630	78
Cochrane		
1	Granulocyte colony stimulating factor.mp. or exp Granulocyte Colony-Stimulating Factor/	2424
2	(G-CSF$ or GCSF).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1899
3	filgrastim.mp.	745
4	(Neupogen or Zarzio or Nivestim or Ratiograstim).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	48
5	Lenograstim.mp.	209
6	Granocyte.mp.	18
7	lipegfilgrastim.mp.	11
8	Pegfilgrastim.mp.	227
9	Neulasta.mp.	14
10	(Biograstim or Tevagrastim or Grastofil or Accofil).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	4
11	(Euprotin or r-metHuG-CSF or SD-01 or PEG-rmetHuG-CSFor XM02).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	113
12	(Ro 25-8315m or Nartograstim or Empegfilgrastim or Maxy-G34 or BK0026 or Ro 25-8315m or Nartograstim or Empegfilgrastim or Maxy-G34 or PEG-rHuG-	9

Database, search no.	Search string	Results
	CSF).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	
13	or/1-12	3442
14	neutropenia.mp. or exp Neutropenia/	7161
15	febrile neutropenia.mp. or exp Febrile Neutropenia/	2072
16	severe congenital neutropenia.mp.	3
17	leukopenia.mp. or exp Leukopenia/	4732
18	granulocyte disorder.mp.	0
19	or/14-18	9416
20	13 and 19	1135
21	chemotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	39497
22	cancer.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	78409
23	20 and (21 or 22)	949
24	Clinical study.mp.	86699
25	case control study.mp. or exp Case-Control Studies/	14539
26	Longitudinal study.mp. or exp Longitudinal Studies/	117135
27	Retrospective study.mp. or exp Retrospective Studies/	10704
28	Prospective study.mp. or exp Prospective Studies/	97928
29	Cohort analysis.mp. or exp Cohort Studies/	126884
30	(Cohort adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	15534
31	(follow up adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	54823
32	(observational adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	8880
33	(epidemiologic$ adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2811
34	(cross sectional adj (study or studies)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	6213

Database, search no.	Search string	Results
35	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	628540
36	(random sampl$ or random digit$ or random effect$ or random survey or random regression).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	17217
37	35 not 36	611323
38	cost*.ti.	19736
39	exp "Costs and Cost Analysis"/	23706
40	or/38-39	29547
41	or/24-34,37,40	680143
42	41 and 23	789
43	(animals not (humans and animals)).sh.	19
44	42 not 43	789
45	Limit 44 to yr="2015 -Current" [Limit not valid in DARE; records were retained]	74

Supplementary Appendix Table S3 Conference proceedings searched between 2012 and 2015 (or the most recent 3 years available)

Conference proceeding	Abbreviation
International Society for Pharmacoeconomics and Outcomes Research	ISPOR
European Society for Medical Oncology	ESMO
European Cancer Congress	ECC
American Society of Clinical Oncology	ASCO
American Society of Hematology	ASH
European Association of Hospital Pharmacists	EAHP
American Society of Health-System Pharmacists	ASHP
Multinational Association of Supportive Care in Cancer	MASCC
International Society of Oral Oncology annual meeting on supportive care in cancer	ISOO

Supplementary Appendix Table S4 Eligibility criteria used in the screening for studies of G-CSFs for the reduction of chemotherapy-induced FN

	Inclusion criteria	Exclusion criteria
Populations	• Adults (aged >18 y) with non-myeloid malignancies receiving myelosuppressive anticancer drugs • Adults (aged >18 y) with acute myeloid leukemia receiving induction or consolidation chemotherapy	• Children aged <18 y • Animal/in vitro • Patients with congenital (or nonchemotherapy-induced) neutropenia • Patients with myeloid malignancies (e.g., multiple myeloma)
Interventions	• Primary/secondary G-CSF prophylaxis or treatment with: o Lenograstim (Granocyte) o Filgrastim (Neupogen, Zarzio, Nivestim, Ratiograstim) o Long-acting (pegylated) filgrastim (pegfilgrastim, Neulasta) o Lipegfilgrastim (Longquex) o Ro 25-8315 o Empegfilgrastim o Maxy-G34 o PEG-rHuG-CSF o BK0026	G-CSFs used to increase neutrophils prior to hematopoietic stem cell transplantation
Comparator	Not restricted by comparator; may include any of the above interventions, placebo, or no comparator[a]	Publications that do not report a direct, head-to-head comparison of short- vs. long-acting G-CSFs[a]
Outcomes	• Incidence/risk of FN • FN-related mortality • Neutropenia-related hospitalizations or all cause hospitalizations • Neutrophil profile • Time to neutrophil recovery • Duration of grade 3+ neutropenia • Reduction/delay of chemotherapy dose • Improvements in relative dose intensity • Dosing-response relationships • Compliance • Antibiotic consumption due to FN • Infection-related mortality • Risk reductions of early all-cause mortality • Transfusion and antibiotic requirements (type, dose and duration) • Duration of fever after induction or consolidation chemotherapy • Safety (e.g., bone pain, fever, malaise)	Prognostic factors

	Inclusion criteria	Exclusion criteria
	• Economic impact (e.g., direct costs/resource use associated with clinical outcomes)	
Study design	• Randomized controlled trials • Observational or nonrandomized interventional studies • Cross-sectional surveys • Cohort studies • Case-control studies • Before and after studies • Prospective or retrospective studies • Longitudinal or follow-up studies • Insurance database studies/insurance claim review • Cost studies	• Pooled analyses • Economic evaluations (although were tagged) • Quality of life studies (although were tagged)
Publication type	• Report of primary data • Published from Jan 1, 2003, to date of search run • Published data only	• Reviews/editorials • Letters • Secondary publications • Systematic reviews • Meta-analyses
Language	English language papers or foreign language papers with English abstract	Non-English languages

FN febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor

[a] Following the initial full paper review, a decision was taken to restrict publications of interest to those reporting a direct, head-to-head comparison of short- vs. long-acting G-CSFs, and to exclude publications that did not report a direct, head-to-head comparison of short- vs. long-acting G-CSFs

Supplementary Appendix Table S5 Description of RCTs identified from the SLR that compared short- vs long-acting G-CSFs for the reduction of chemotherapy-induced FN

Inclusion criteria	Chemotherapy regimen (max. no. of cycles; cycle length)	Cancer type	Age, mean (±SD); [median] y	Interventions analyzed (no. of patients)
Bozzoli et al., 2015 [1]; prospective, randomized study; Italy				
Pts 60–75 y that were considered suitable for treatment with R-CHOP-14	R-CHOP-14 (4–8; NR)[a]	DLBCL	[66] [67]	Filgrastim, 300 µg QD from days 8–11 of each cycle (*n* = 24) Pegfilgrastim, 6 mg single dose on day 2 of each cycle (*n* = 27)
Filon et al., 2015 [2]; Nechaeva et al., 2015 [3]; phase III, double-dummy randomized, clinical study; Russia				
NR	Docetaxel + doxorubicin (NR; NR)	BC	NR NR NR NR	Filgrastim, 5 µg/kg QD until ANC ≥10×10^9/L (*n* = NR) Empegfilgrastim, 6 mg single dose/cycle (*n* = NR) Empegfilgrastim, 7.5 mg single dose/cycle (*n* = NR) Total, both groups: *N* = 135 (randomized 1:1:1 to each group)
Green et al., 2003 [4]; randomized, double-blind, multicenter phase III study; worldwide				
Pts aged >18 y; chemotherapy-naive or adjuvant therapy only or only 1 chemotherapy regimen for metastatic disease; ECOG PS ≤2; ANC ≥1.5×10^9/L; platelet count ≥100×10^9/L; serum creatinine <1.5×ULN	Doxorubicin + docetaxel (4; 21 days)	High-risk stage II or stage III/IV BC	52.8 (11.5) 52.1 (9.2)	Filgrastim, 5 µg/kg QD from day 2 of each cycle until post-nadir ANC ≥10×10^9/L or for 14 days (*n* = 75) Pegfilgrastim, 6 mg single dose on day 2 of each cycle (*n* = 77)
Grigg et al., 2003 [5]; multicenter, open-label, randomized, phase II, dose-finding study; worldwide				
Pts aged ≥60 y; ECOG PS ≤2; ANC ≥2×10^9/L; platelet count ≥100×10^9/L; bilirubin concentration ≤2×ULN	CHOP (6; 21 days)	NHL	67.5 (5.7) 70.5 (5.3)	Filgrastim, 5 µg/kg QD from day 2 of each cycle until post-nadir ANC ≥10×10^9/L or for 14 days (*n* = 13) Pegfilgrastim, 60 µg/kg single dose

Inclusion criteria	Chemotherapy regimen (max. no. of cycles; cycle length)	Cancer type	Age, mean (±SD); [median] y	Interventions analyzed (no. of patients)
				on day 2 of each cycle (*n* = 13)
			68.8 (6.3)	Pegfilgrastim, 100 µg/kg single dose on day 2 of each cycle (*n* = 14)
			65.9 (5.5)	No cytokine support in cycle 1 followed by filgrastim 5 µg/kg QD in all other cycles (*n* = 9)
Lopez et al., 2005 [6]; multicenter, parallel-group, open label Ph II study; Europe				
Pts aged 18–70 y; histologically confirmed, aggressive B-cell NHL with <30% bone marrow involvement and age-adjusted IPI score of 0–2; no prior treatment with chemotherapy or radiation therapy	R-CHOP-14 (6; 14 days)	B-cell NHL	NR	Filgrastim 5 µg/kg QD from days 2–13 of each cycle or until the ANC $\geq 10 \times 10^9$/L (*n* = 26)
			NR	Pegfilgrastim 6 mg single dose on day 2 of each cycle (*n* = 32)
Park et al., 2013 [7]; multicenter, dose-finding, open-label, randomized Ph II study; Korea				
Pts aged >18 y; chemotherapy-naive; ECOG PS 0–1; ANC $\geq 1.5 \times 10^9$/L; platelet count $\geq 100 \times 10^9$/L; bilirubin <1.5×ULN; AST, ALT, or both <1.5×ULN and alkaline phosphatase <2.5×ULN	Docetaxel + doxorubicin + cyclophosphamide (6; 21 days)	High-risk stage II or III BC	45.29 (6.13) [47]	Filgrastim, 100 µg/m^2 QD on day 2 of each cycle until post-nadir ANC 5×10^9/L or up to 10 days (*n* = 21)
			42.50 (5.62) [43]	Pegfilgrastim (DA-3031) 3.6 mg single dose on day 2 of each cycle (*n* = 20)
			46.95 (9.19) [46]	Pegfilgrastim (DA-3031) 6 mg single dose on day 2 of each cycle (*n* = 20)
Ramkumar et al., 2013 [8]; multicenter, open-label, randomized study; India				
Pts aged >18 y; chemotherapy-naive	NR (6; NR)	NSCLC or BC	NR	Filgrastim (Grafeel®) (*n* = NR)
			NR	Peg G-CSF (*n* = NR)
			NR	Total, both groups: *N* = 162
Salafet et al., 2013 [9]; randomized, open-label active-comparator, non-inferiority phase II study; Russia				
NR	Doxorubicin + docetaxel (NR; NR)	BC	NR	Filgrastim 5 mg/kg QD until ANC $\geq 10 \times 10^9$ cells/L (maximum of 14

Inclusion criteria	Chemotherapy regimen (max. no. of cycles; cycle length)	Cancer type	Age, mean (±SD); [median] y	Interventions analyzed (no. of patients)
				days), start day of G-CSF administration NR (*n* = 19)
			NR	Empegfilgrastim (BCD-017) 3 mg, start day of G-CSF administration NR (*n* = 21)
			NR	Empegfilgrastim (BCD-017) 6 mg, start day of G-CSF administration NR (*n* = 20)
Satheesh et al., 2009 [10]; randomized; India				
Pts aged <65 y with ECOG PS 0–1	Doxorubicin + cyclophosphamide + docetaxel (NR; 21 days)	BC	[57]	Filgrastim 5 mg/kg QD, start day and duration of G-CSF administration NR (*n* = 43)
			[58]	Pegfilgrastim, 6 mg single dose, start day of G-CSF administration NR (*n* = 28)
Shi et al., 2006 [11]; randomized, multicenter, matched cross-over, open-label phase II study; China				
NR	2 cycles received, regimen NR (NR; NR)	NSCLC, BC, or NHL	NR	rhG-CSF 5 μg/kg QD from day 3 of cycle until ANC >5×10^9/L twice after nadir or for 14 days
			NR	PEG-rhG-CSF 100 μg/kg single dose on day 3 of cycle
			NR	Total, both groups: *N* = 104
Shi et al., 2013 [12]; phase III, randomized, multicenter, open-label, crossover, noninferiority study; China				
Pts aged 18–70 y; chemotherapy-naive; Karnofsky PS ≥70; normal WBC and platelet counts; adequate renal, hepatic, and cardiac function; normal bone marrow function	Paclitaxel + carboplatin or cisplatin; doxorubicin, pirarubicin, or epirubicin + cyclophosphamide; paclitaxel + doxorubicin, pirarubicin, or epirubicin; CHOP[b] (2; 21 days)	NSCLC, BC, NHL, head and neck cancer, or other	49.06 (10.35) [51]	Filgrastim 5 μg/kg/ QD from day 3 of cycle until post-nadir ANC ≥10×10^9/L or for 14 days (*n* = 157)
			50.37 (10.47) [51]	Pegfilgrastim 100 μg/kg single dose on day 3 of cycle (*n* = 169)

Inclusion criteria	Chemotherapy regimen (max. no. of cycles; cycle length)	Cancer type	Age, mean (±SD); [median] y	Interventions analyzed (no. of patients)
Sierra et al., 2008 [13]; phase II, randomized, double-blind multicenter study; worldwide				
Pts aged ≥18 y with ECOG PS ≤2 and life expectancy ≥3 mo	**Induction:** idarubicin + cytarabine; **Consolidation:** cytarabine (NR; NR)	De novo AML	[54]	Filgrastim, 5 μg/kg QD from day 2 of each cycle until post-nadir ANC $\geq 1\times10^9$/L for 3 consecutive days or $\geq 10\times10^9$/L for 1 day (*n* = 41)
			[51]	Pegfilgrastim, 6 mg single dose on day 2 of each cycle (*n* = 42)
Vose et al., 2003 [14]; phase II, randomized, open-label, multicenter study; USA				
Pts aged ≥18 y; ECOG PS ≤2; ANC $\geq 1.5\times10^9$/L; platelet count $\geq 100\times10^9$/L; adequate renal function	ESHAP (NR; NR)	Relapsed or refractory Hodgkin or NHL	48.4 (15.9)	Filgrastim 5 μg/kg QD until post-nadir ANC $\geq 10\times10^9$/L or for 12 days (*n* = 31)
			50.6 (13.9)	Pegfilgrastim 100 μg/kg single dose per cycle (*n* = 29)
Zhang et al., 2015 [15]; randomized, open-label, multicenter dose-finding study; China				
Pts aged 18–-65 y; ECOG PS ≤1; ANC $\geq 2\times10^9$/L; WBC $\geq 4\times10^9$/L; platelet count $\geq 100\times10^9$/L; adequate renal, hepatic and cardiac function	Docetaxel + doxorubicin + cyclophosphamide (NR; 21 days)	High-risk BC	47.35 (8.14)	Filgrastim 5 μg/kg QD from day 3 of chemotherapy cycle until post-nadir ANC $\geq 10\times10^9$/L or for 14 days (*n* = 43)
			47.03 (7.66)	Pegfilgrastim 60 μg/kg single dose on day 3 of chemotherapy cycle (*n* = 43)
			48.18 (8.09)	Pegfilgrastim 100 μg/kg single dose on day 3 of chemotherapy cycle (*n* = 43)
			46.71 (6.80)	Pegfilgrastim 120 μg/kg single dose on day 3 of chemotherapy cycle (*n* = 42)
Zhang et al., 2014 [16]; randomized, match and crossover study; China				
NR	NR (2; NR)	NR	NR	rhG‑CSF 5 μg/kg QD SC injection

Inclusion criteria	Chemotherapy regimen (max. no. of cycles; cycle length)	Cancer type	Age, mean (±SD); [median] y	Interventions analyzed (no. of patients)
				for 7 days until ANC >5 x 10^9/L (*n* = NR)
			NR	PEG‑rhG‑CSF 100 μg/kg single SC injection (*n* = NR)
			NR	Total, both groups: *N* = 42
Zhou et al., 2011 [17]; randomized, open-label, match and crossover study; China				
NR	NR (2; NR)	NSCLC, BC, or NHL	46.51 (12.31)	rhG-CSF 5 μg/kg QD from day 3 of chemotherapy cycle until ANC >5×10^9/L twice post-nadir or for 14 days (*n* = 38)
			46.44 (11.98)	PEG-rhG-CSF 100 μg/kg single SC injection on day 3 of chemotherapy cycle (*n* = 40)
Zhou et al., 2013 [18]; randomized, open-label phase I study; China				
Chemotherapy- and radiotherapy-naive patients	Paclitaxel + carboplatin; epirubicin + cyclophosphamide (3; NR)	NR	NR	rHuG-CSF 150 μg QD SC injection (*n* = 15)
			NR	rHuG-CSF 300 μg QD SC injection (*n* = 15)
			NR	YPEG-rHuG-CSF 10 μg/kg single SC injection (*n* = 3)
			NR	YPEG-rHuG-CSF 20 μg/kg single SC injection (*n* = 6)
			NR	YPEG-rHuG-CSF 30 μg/kg single SC injection (*n* = 6)
			NR	YPEG-rHuG-CSF 45 μg/kg single SC injection (*n* = 9)
			NR	YPEG-rHuG-CSF 60 μg/kg single SC injection (*n* = 6)

ALT alanine aminotransferase, *AML* acute myeloid leukemia, *AST* aspartate aminotransferase, *ANC* absolute neutrophil count, *BC* breast cancer, *CHOP/R-CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone/CHOP and rituximab, *DLBCL* diffuse large B-cell lymphoma, *ECOG* Eastern Cooperative Oncology Group, *ESHAP* etoposide, methylprednisolone, cytarabine, and cisplatin, *FN* febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor, IPI International Prognostic Index, *NHL* non-Hodgkin lymphoma, *NR* not reported, *NSCLC* non-small cell lung cancer, *PEG-rhG-CSF/YPEG-rHuG-CSF* recombinant human pegylated granulocyte colony-stimulating factor, *PS* performance score, *Pts* patients, *QD* once daily, *RCT* randomized controlled trial, *R-CHOP-14* cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab administered every 14 days, *rhG-CSF/rHuG-CSF* recombinant human granulocyte colony-stimulating factor, *SC* subcutaneous, *SD* standard deviation, *SLR* systematic literature review, *ULN* upper limit of normal, *WBC* white blood cell

[a] Antibiotic prophylaxis with cotrimoxazole-sulfonamide for *Pneumocystis carinii*. Levofloxacin was added if neutrophil counts were $<0.5\times10^9$/L on day 8 and stopped upon recovery of neutrophil count [1]

[b] CHOP consisted of cyclophosphamide, doxorubicin (or pirarubicin) or epirubicin, vincristine, and prednisone [12]

Supplementary Appendix Table S6 Description of non-RCTs identified from the SLR that compared short- vs long-acting G-CSFs for the reduction of chemotherapy-induced FN

Inclusion criteria	Chemotherapy regimen	Cancer type	Age, mean (±SD), [median] y	Interventions analyzed (sample size)
Almenar Cubells et al., 2013 [19]; multicenter, retrospective, observational two-cohort study; Spain				
Aged ≥18 y, pts who had undergone chemotherapy with ≥1 concomitant G-CSF (daily or non-daily) administration >2 mo prior	Platinum agent, taxane, mustard analogs, pyrimidine analog, or cytotoxic antibiotics	Lung, gastrointestinal, gynecologic, head and neck, or other cancer	61.7 (12.2)	G-CSF QD (dose NR) starting within 3 days after chemotherapy (42.2% of patients) and continuing for ≥7 (10.5% of patients), ≥6 (14.3% of patients), and ≥5 (45.9% of patients) days (*n* = 211: filgrastim, *n* = 196; lenograstim, *n* = 15)
			57.9 (13.7)	Pegfilgrastim single injection (dose NR) within 3 days after chemotherapy (46.2% of patients) (*n* = 180)
Almenar et al., 2009 [20]; multicenter, retrospective, observational; Spain				
Pts who underwent chemotherapy supported by G-CSF treatment	**BC:** Anthracycline-based or taxane-based combination regimens, CMF, others **Lung cancer:** platinum-based or taxane-based combination regimens, platin + etoposide, gemcitabine, or vinorelbine; platin-taxane combination regimens; others **NHL:** R-CHOP-14, R-CHOP-21, others **Hodgkin's lymphoma:** doxorubicin + bleomycin +	NHL, Hodgkin lymphoma, multiple myeloma, breast, lung, gastrointestinal, gynecologic, or other cancer	55.4 (14.5)	G-CSF QD (dose NR); median (range) of 6 (1–13) injections/cycle (*n* = 111: filgrastim, *n* = 99; lenograstim, *n* = 12)
			57.0 (14.8)	Pegfilgrastim single injection (dose or cycle day NR) (*n* = 75)
			59.3 (15.6)	Both daily G-CSF and pegfilgrastim (*n* = 62)[a]

Inclusion criteria	Chemotherapy regimen	Cancer type	Age, mean (±SD), [median] y	Interventions analyzed (sample size)
	vinblastine + dacarbazine; others **Multiple myeloma:** vincristine + carmustine + melphalan + cyclophosphamide + prednisolone; vincristine + carmustine + doxorubicin + dexamethasone; melphalan + prednisolone; others			
Brito et al., 2012 [21]; Brito et al., 2016 [22]; single-center, retrospective study; Portugal				
Women who completed ≥1 cycle of chemotherapy	Adjuvant or neoadjuvant docetaxel + doxorubicin + cyclophosphamide	Early BC	[52] (range, 27–70)	Reference filgrastim QD 300 or 480 µg in patients ≤75 and >75 kg, respectively; median (range) of 7 (1–-10) administrations/cycle (11% of patients had <7 administrations); 833 total chemotherapy cycles (*n* = 147)
			[52] (range, 28–76)	Pegfilgrastim 6 mg single dose (cycle day NR); 761 total chemotherapy cycles (*n* = 139)
			[48] (range, 25–67)	Biosimilar filgrastim QD 300 or 480 µg in patients ≤75 and >75 kg, respectively; median (range) of 7 (3–9) administrations/cycle (12% of patients had <7 administrations); 761 total chemotherapy cycles (*n* = 134)
Chan et al., 2011 [23]; single-center, retrospective cohort; Asia				
Pts who underwent chemotherapy and received G-CSF as primary prophylaxis against FN[b]	**Chemotherapy with FN risk <20%:** R-CHOP-21, R-CEPP, R-CEOPP,	NHL	56.7 (13.1)	Filgrastim QD (dose NR); median (interquartile range) of 7 (5–8.25) administrations (*n* = 81)

Inclusion criteria	Chemotherapy regimen	Cancer type	Age, mean (±SD), [median] y	Interventions analyzed (sample size)
	R-CVP, or R-GDC **Chemotherapy with FN risk ≥20%:** GIFOX, HyperCVAD, R-CHOP-14, R-EPOCH, R-ESHAP, R-ICE, or SMILE		55.3 (14.8)	Pegfilgrastim (dose or cycle day NR) single injection (*n* = 123)
Hadji et al., 2012 [24]; Germany				
Pts with ≥1 G-CSF prescription between Jan 2008 and Jul 2010 and observation period ≥6 mo prior to and after G-CSF prescription	NR	NR	NR NR NR NR	Originator filgrastim (*n* = 8726) Biosimilar filgrastim (*n* = 4240) Pegfilgrastim (*n* = 9939) Lenograstim (*n* = 6456)
Heaney et al., 2009 [25]; retrospective matched cohort study; USA				
Pts aged >18 y continuously enrolled in a health plan with ≥1 cancer claim, ≥2 filgrastim or ≥1 pegfilgrastim claim, and ≥1 chemotherapy claim	NR	BC, lung cancer, NHL	57.6 (11.6) 58.6 (11.5)	Filgrastim QD (dose NR) for 31 days (*n* = 990) Pegfilgrastim (dose and dosing NR) for 58 days (*n* = 982)
Henk et al., 2013 [26]; retrospective analysis; USA				
Pts aged ≥18 y; treated with myelosuppressive chemotherapy; and ≥1 claim for filgrastim, and/or pegfilgrastim, and/or sargramostim during chemotherapy course (two databases included HIRD^{SM} and OptumInsight)	NR	NHL, Hodgkin lymphoma, breast, lung, colorectal, ovarian or solid tumors	**HIRD^{SM}:** 56.59 (11.32) 56.05 (11.33) **Optum-Insight:** 54.97 (11.20) 54.84 (10.61)	 Filgrastim QD (dose NR) for a mean (±SD) of 6.41 (5.85) days (*n* = 621) Pegfilgrastim (dose and dosing NR) (*n* = 8569) Filgrastim QD (dose NR) for a mean (±SD) of 4.73 (2.98) days (*n* = 628) Pegfilgrastim (dose and dosing NR) (*n* = 6719)
Hershman et al., 2009 [27]; retrospective, cohort study; USA				

Inclusion criteria	Chemotherapy regimen	Cancer type	Age, mean (±SD), [median] y	Interventions analyzed (sample size)
Pts who initiated chemotherapy in 2003	NR	Breast, lung, ovarian, or colon cancer, or lymphoma	NR	Filgrastim QD (dose NR) for a mean (±SD) of 6.5 (3.9) days in cycle 1 and 6.7 (4.0) days in subsequent cycles (*n* = 101)
			NR	Pegfilgrastim (dose and dosing NR) (*n* = 721)
Kourlaba et al., 2015 [28]; retrospective cohort study; Greece				
Participants from two randomized trials and an observational study treated with dose-dense sequential chemotherapy and supported by use of G-CSF	Epirubicin → paclitaxel → CMF; Epirubicin + paclitaxel → CMF; epirubicin → CMF → docetaxel or paclitaxel	BC	All pts: 52.3 (11.3)	Filgrastim 5 µg/kg QD from days 2–7 of each cycle (*n* = 529) Pegfilgrastim 6 mg single dose (cycle day NR) (*n* = 529)
Kubista et al, 2003 [29]; retrospective study; worldwide				
Pts aged ≥18 y; either chemotherapy-naive or received adjuvant therapy and/or completed ≤1 regimen of chemotherapy for metastatic disease; completed any previous chemotherapy >3 wk before randomization; adequate hepatic and cardiac function; ECOG PS ≤2; ANC ≥15,000/µL; platelet count ≥100,000/µL	Doxorubicin → docetaxel was administered on day 1 of each cycle every 3 wk for maximum 4 cycles, unless a dose delay was necessary for low neutrophil or platelet counts. Pts were required to have recovered ANC >10,000/µL and platelet >100,000/µL counts before receiving next full dose of chemotherapy	High-risk stage II-IV BC	**Study 1:** 52.7 (11.5) 51.9 (9.3) **Study 2:** 51.9 (11.1) 50.9 (11.6)	 Filgrastim 5 µg/kg QD SC injection from day 2 of each cycle until post-nadir ANC ≥10,000/µL or for 14 days (*n* = 76) Pegfilgrastim, 6 mg single SC injection on day 2 of each cycle (*n* = 79) Filgrastim 5 µg/kg QD SC injection from day 2 of each cycle until post-nadir ANC ≥10,000/µL or for 14 days (*n* = 151) Pegfilgrastim 100 µg/kg single SC injection on day 2 of each cycle (*n* = 150)
Leonard et al., 2009 [30]; Leonard et al., 2015 [31]; multicenter trial (G-CSFs nonrandomized); UK				
Women aged >18 y who received standard chemotherapy, including	Standard-dose adjuvant chemotherapy	BC	NR	Filgrastim 5 µg/kg QD from days 3–9 of each cycle (*n* = 129)

Inclusion criteria	Chemotherapy regimen	Cancer type	Age, mean (±SD), [median] y	Interventions analyzed (sample size)
neoadjuvant chemotherapy			NR	Pegfilgrastim, 6 mg single dose on day 2 of each cycle (*n* = 75)
Leung et al., 2012 [32]; prospective, observational and ethics-approved study; Canada				
Women who received neoadjuvant or adjuvant chemotherapy and pegfilgrastim or filgrastim	58% of pts received docetaxel-based chemotherapy	BC	NR	Filgrastim 300 µg QD SC injection initiated 24 hr after chemotherapy and continuing for 7–8 days (*n* = NR; publication states one-third received filgrastim)
			NR	Pegfilgrastim, 6 mg single SC injection 24 hr after chemotherapy (*n* = NR; publication states two-thirds received pegfilgrastim)
			52	Total, both groups: *N* = 140
Leung et al., 2015 [33]; prospective, observational and comparative study; Canada				
Pts who received adjuvant or neoadjuvant chemotherapy with initiation of pegfilgrastim or filgrastim as primary prophylaxis for FN	Docetaxel ± cyclophosphamide; docetaxel + carboplatin + trastuzumab; other docetaxel-based regimens; cyclophosphamide + doxorubicin; FEC[c]	Non-metastatic BC	51	Filgrastim 300 µg QD for a mean of 6.9 days (*n* = 48)
			52	Pegfilgrastim, 6 mg single dose on day 2 of chemotherapy cycle (*n* = 94)
Marina et al, 2009 [34]; multicenter, prospective, observational study; Spain				
Patients who initiated a chemotherapy regimen associated with ≥10% FN risk	Docetaxel or paclitaxel-containing regimens	BC	NR	Filgrastim (dose and dosing NR) (*n* = NR)
			NR	Pegfilgrastim (dose and dosing NR) (*n* = NR)
			[51]	Total, both groups: *N* = 735
Mates et al., 2012 [35]; retrospective cohort study; Canada				
Pts who received ≥1 cycle of modern adjuvant chemotherapy	Anthracycline-taxane or taxane regimens	Early BC	All patients: [55]	Filgrastim (dose and dosing NR) (*n* = 47)

Inclusion criteria	Chemotherapy regimen	Cancer type	Age, mean (±SD), [median] y	Interventions analyzed (sample size)
(taxane-containing regimens ± anthracyclines) between Jan 2009 and Dec 2011				Pegfilgrastim (dose and dosing NR) (*n* = 98)
Mazo et al., 2009 [36]; comparative study; Spain				
Pts with high-grade NHL	R-CHOP-14 or R-EDOCH-14; 56 cycles administered	NHL	All pts: [63]	Filgrastim 5 µg/kg QD for 5 days (*n* = NR) Pegfilgrastim 6 mg single dose on day 4 of each cycle (*n* = NR)
Morrison et al., 2007 [37]; retrospective cohort study; USA				
Patients aged ≥18 y; treated with chemotherapy and new users of filgrastim in 2001 (prior to approval of pegfilgrastim by FDA in Jan 2002), or filgrastim or pegfilgrastim in 2003	NR	Breast, lung, ovarian, or colon cancer; or lymphoma	NR NR NR	Filgrastim 2001 cohort, QD (dose NR) for a mean (±SD) of 5.2 (3.5) days in cycle 1 and 6.0 (3.5) days in subsequent cycles (*n* = 583) Filgrastim 2003 cohort, QD (dose NR) for a mean (±SD) of 3.7 (2.8) days in cycle 1 and 4.6 (3.2) days in subsequent cycles (*n* = 868) Pegfilgrastim, single injection (dose NR) initiated, on average (±SD), 2.4 (3.2) days after chemotherapy in cycle 1 and 1.9 (3.0) days after chemotherapy in subsequent cycles (*n* = 1412)
Naeim et al., 2010 [38]; retrospective US claims analysis; USA				
Filgrastim and pegfilgrastim-treated pts who received chemotherapy Jan 1, 2004, to Feb 28, 2009. Cycles were included if they were 20–60	NR	NHL, breast, lung, ovarian, or colorectal cancer	NR NR	Filgrastim QD (dose and dosing NR); 852 cycles; (*n* = NR) Pegfilgrastim, once-per-cycle (dose and dosing NR); 12,218

Inclusion criteria	Chemotherapy regimen	Cancer type	Age, mean (±SD), [median] y	Interventions analyzed (sample size)
days, as defined by chemotherapy claims. G-CSF use was designated 'prophylactic' if initiated in 1st 5 days of chemotherapy cycle, or 'delayed' if after day 5				cycles; (*n* = NR) Total, both groups: *N* = 3958
Naeim et al., 2013 [39]; retrospective US claims analysis; USA				
Pts with chemotherapy medical claims between Jan 1, 2005, and Feb 28, 2009; had ≥2 medical claims (≥7 days apart) with ICD-9 code(s) for NHL, or breast, lung, ovarian, or colorectal cancer from 30 days prior to up to 30 days after index date; and ≥1 claim for filgrastim or pegfilgrastim (not both) during chemotherapy course	NR	NHL, breast, lung, ovarian, or colorectal cancer	57.5 (12.6) 55.1 (10.7)	Filgrastim QD (dose NR) for a mean (±SD) of 4.8 (3.3) injections/cycle (*n* = 163) Pegfilgrastim single injection (dose and cycle day NR) per-cycle (*n* = 3372)
Phillips et al., 2012 [40]; cost analysis and utilization management opportunity assessment; USA				
Filgrastim and pegfilgrastim pharmacy and medical claims data were queried among 1.2 million commercially insured members from Jan 1, 2010, to Dec 31, 2010	NR	Lymphoma, or breast, lung, colon, or other cancer	NR NR	Filgrastim 300 or 480 µg QD injection; 44.8% of pts had <7 cumulative days' supply (*n* = 259) Pegfilgrastim 6 mg single injection to last 14 days (*n* = 612)
Salar et al., 2009 [41]; multicenter, prospective, observational, single-cohort study; Spain				
Adult pts who initiated new chemotherapy regimen associated with >10% FN risk; ≥4 planned cycles; and ≥3 mo expected survival time	Most common regimen was CHOP or R-CHOP	Hodgkin's or NHL	NR NR [58]	Filgrastim (dose and dosing NR) (*n* = NR) Pegfilgrastim (dose and dosing NR) (*n* = NR) Total, both groups: *N* = 294
Schippinger et al., 2006 [42]; retrospective study; Austria				

Inclusion criteria	Chemotherapy regimen	Cancer type	Age, mean (±SD), [median] y	Interventions analyzed (sample size)
Pts who received neoadjuvant or adjuvant chemotherapy between Oct 1993 and Nov 2005	Epirubicin + docetaxel or paclitaxel	BC	All filgrastim pts: 47.3	Filgrastim 300 or 480 µg (based on body weight) or lenograstim 340 µg, QD for median (range) of 6 (1–11) days (*n* = 82)
				Filgrastim 300 or 480 µg (based on body weight) + lenograstim 340 µg QD for median (range) of 6 (1–11) days (*n* = 6)
			50.9	Pegfilgrastim, 6 mg single dose on day 2 of cycle (*n*=30)
Skarlos et al., 2009 [43]; retrospective, matched case-control study; Greece				
Pts who participated in 2 randomized trials (HE10/00 and HE10/05); treated with dose-dense sequential chemotherapy and G-CSF support	**Protocol HE10/00:** Epirubicin → paclitaxel → CMF; epirubicin + paclitaxel → CMF; epirubicin → CMF → docetaxel or paclitaxel	BC	55	Filgrastim, 5 µg/kg QD on days 2–10 of each cycle (*n* = 107)
			54	Pegfilgrastim 6 mg single dose on day 1 of each cycle (*n* = 107)
Tan et al., 2011 [44]; retrospective cohort study; USA				
Pts aged ≥18 y treated with chemotherapy between Jul 1, 2004, and Jan 31, 2008	NR	NHL, or breast or lung cancer	58.4 (11.0) [60]	Filgrastim (dose NR) QD injection for ≤6 days (74% of cycles) and ≥9 days (18% of cycles); 616 filgrastim cycles; (*n* = NR)
			57.1 (11.6) [57]	Pegfilgrastim, single injection (dose NR) on day 3 of cycle; 4955 pegfilgrastim cycles; (*n* = NR)
			NR	Total, both groups: *N* = 1618
von Minckwitz et al., 2008 [45]; post-hoc analysis of data from RCT (GEPARTRIO study [46]); Germany				
Pts aged ≥18 y; chemotherapy-naive; normal hematopoietic, liver,	Doxorubicin → docetaxel + cyclophosphamide (six or eight	BC	NR	Filgrastim 5 µg/kg or lenograstim 150 µg/m^2, QD from days 5–10

Inclusion criteria	Chemotherapy regimen	Cancer type	Age, mean (±SD), [median] y	Interventions analyzed (sample size)
renal, and cardiac function	21-day cycles administered)			per cycle (*n* = 377)
			NR	Pegfilgrastim 6 mg single dose on day 2 of each cycle (*n* = 305)
			NR	Pegfilgrastim 6 mg single dose on day 2 of each cycle + ciprofloxacin (*n* = 321)
			NR	Ciprofloxacin alone (*n* = 253)
Wetten et al., 2015 [47]; retrospective cohort study; Germany				
Pts aged ≥18 y who received 1st-line chemotherapy associated with high/intermediate risk for FN from Jan 1, 2009, to Dec 31, 2013	**Most common for BC:** docetaxel + doxorubicin + cyclophosphamide; FEC-docetaxel **Most common for NHL:** R-CHOP-21	BC or NHL (identified by ICD-10-GM)	**Patients with BC:** 52.66 (11.35)	Filgrastim QD (dose NR); duration ≤5 (75.58%), >5 to 10 (22.77%), and >10 days (1.65%); (*n* = 606) Pegfilgrastim (dose and dosing NR) (*n* = 1569)
			Patients with NHL: 62.76 (15.09)	Filgrastim QD (dose NR); duration ≤5 (54.02%), >5 to 10 (39.08%), and >10 days (6.90%); (*n* = 87) Pegfilgrastim (dose and dosing NR) (*n* = 164)
Weycker et al., 2009 [48]; retrospective cohort study; USA				
Pts with cancer who received pegfilgrastim, filgrastim, or sargramostim during their first course of chemotherapy	NR	NR	NR	Filgrastim (dose and dosing NR) (*n* = 2704)
			NR	Pegfilgrastim (dose and dosing NR) (*n* = 18,361)
Weycker et al., 2012 [49]; retrospective cohort study; USA				
Pts aged ≥18 y with solid tumors who received chemotherapy between Jul 1, 2001, and Jun 30, 2007, and filgrastim, pegfilgrastim, or sargramostim prophylaxis during	**Most common for BC:** cyclophosphamide + doxorubicin **Most common for lung cancer:** carboplatin + etoposide **Most common for NHL:**	BC; NHL; trachea, bronchus and lung; prostate; colon/rectum; and other	60 (12) [60]	Filgrastim QD (dose NR) for mean (±SD) 4.8 (3.4) days; 67% of patients received <7 days and 88% received <10 days; 8286 filgrastim cycles; (*n* = NR)

Inclusion criteria	Chemotherapy regimen	Cancer type	Age, mean (±SD), [median] y	Interventions analyzed (sample size)
1st course of chemotherapy	cyclophosphamide + doxorubicin + vincristine		58 (12) [58]	Pegfilgrastim (dose NR) single injection by day 3 of cycle in 94% of pegfilgrastim cycles; 67,247 pegfilgrastim cycles; (*n* = NR)
			NR	Total, both groups: *N* = 208,401

ANC absolute neutrophil count, *BC* breast cancer, *CEOPP/R-CEOPP* cyclophosphamide, etoposide, vincristine, prednisone and procarbazine/CEOPP and rituximab, *CEPP/R-CEPP* cyclophosphamide, etoposide, procarbazine and prednisone/CEPP and rituximab, *CHOP/R-CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone/CHOP and rituximab, *CHOP-14/R-CHOP-14* cyclophosphamide, doxorubicin, vincristine, and prednisone administered every 14 days/CHOP and rituximab administered every 14 days, *CHOP-21/R-CHOP-21* cyclophosphamide, doxorubicin, vincristine, and prednisone administered every 21 days/CHOP and rituximab administered every 21 days, *CMF* cyclophosphamide, methotrexate and 5-fluorouracil, *CVP/R-CVP* cyclophosphamide, vincristine, prednisone/CVP and rituximab, *GDC/R-GDC* gemcitabine, doxorubicin and cyclophosphamide/GDC and rituximab, *ECOG PS* Eastern Cooperative Oncology Group performance status, *R-EDOCH-14* etoposide, doxorubicin, vincristine, cyclophosphamide, dexamethasone and rituximab every 14 days, *EPOCH/R-EPOCH* etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin/EPOCH and rituximab, *ESHAP/R-ESHAP* etoposide, methylprednisolone, cytarabine, and cisplatin/ESHAP and rituximab, *FDA* US Food and Drug Administration, *FEC* fluorouracil, epirubicin, and cyclophosphamide, *FN* febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor, *GIFOX* gemcitabine, ifosfamide, and oxaliplatin, *HIRD* HealthCare Integrated Research Database, *HyperCVAD* hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, *ICD-9-CM* The International Classification of Diseases, Ninth Revision, Clinical Modification, *ICD-10-GM* The International Classification of Diseases, Tenth Revision, German Modification, *ICE/R-ICE* ifosfamide, carboplatin, etoposide/ICE and rituximab, *IV* intravenous, *NHL* non-Hodgkin lymphoma, *non-RCT* non-randomized controlled trial, *NR* not reported, *pts* patients, *QD* once daily, *SC* subcutaneous, *SD* standard deviation, *SLR* systematic literature review, *SMILE* steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase, and etoposide

[a] Patients randomized to both daily G-CSF and pegfilgrastim were excluded from analyses of G-CSF use and chemotherapy-related complications [20]

[b] Primary prophylaxis was defined as administration of G-CSF during the first cycle of chemotherapy in patients who had no documented history of neutropenia or FN. The G-CSF had to have been administered ≥24 h after the end of chemotherapy administration [23]

[c] All patients received antiemetic prophylaxis with ondansetron and dexamethasone, prior to chemotherapy and continuing for 2–3 days. With docetaxel-based regimens, dexamethasone commenced >24 h prior [33]

Supplementary Appendix Table S7 List of relevant publications: Short- vs long-acting G-CSFs for the reduction of chemotherapy-induced FN[a]

Reference	FN	Hospitalizations	Dose reduction or delay	G-CSF duration <7 days/NR
RCT				
Bozzoli *et al*., 2015 [1]	✓	✓[b]	✓[c]	Yes
Filon *et al*., 2015 [2]; Nechaeva *et al*., 2015 [3]	✓			No
Green *et al*., 2003 [4]	✓	✓	✓[c]	No
Grigg *et al*., 2003 [5]	✓	✓	✓[c]	No
Lopez *et al*., 2005 [6]			✓[c]	No
Park *et al*., 2013 [7]	✓			No
Salafet *et al*., 2013 [9]	✓			No
Satheesh *et al*., 2009 [10]	✓	✓		No
Shi *et al*., 2006 [11]	✓			No
Shi *et al*., 2013 [12]	✓			No
Sierra *et al*., 2008 [13]	✓	✓[d]		No
Zhang *et al*., 2015 [15]	✓			No
Non-RCT				
Almenar Cubells *et al*., 2013 [19]	✓	✓	✓	Yes <7 days
Almenar *et al*., 2009 [20]	✓	✓	✓	Yes <7 days
Brito *et al*., 2012 [21]; Brito *et al*., 2016 [22]	✓	✓	✓	No
Chan *et al*., 2011 [23]	✓		✓	No
Heaney *et al*., 2009 [25]		✓		No
Henk *et al*., 2013 [26]		✓[d]		Yes <7 days
Hershman *et al*., 2009 [27]	✓			Yes <7 days
Kourlaba *et al*., 2015 [28]	✓		✓	Yes <7 days
Leonard *et al*., 2009 [30]; Leonard *et al*., 2015 [31]			✓[d]	No
Leung *et al*., 2015 [33]	✓		✓	Yes <7 days
Marina *et al*., 2009 [34]		✓[d]		Yes NR
Mates *et al*., 2012 [35]	✓			Yes NR
Mazo *et al*., 2009 [36]		✓[d]		Yes <7 days
Morrison *et al*., 2007 [37]	✓			Yes <7 days
Naeim *et al*., 2010 [38]		✓[d]		Yes NR
Naeim *et al*., 2013 [39]		✓		Yes <7 days
Salar *et al*., 2009 [41]		✓[d]	✓[d]	Yes NR
Schippinger *et al*., 2006 [42]	✓			Yes <7 days
Skarlos *et al*., 2009 [43]	✓[e]		✓[e]	No PEG given day 1
Tan *et al*., 2011 [44]	✓	✓		Yes <7 days
von Minckwitz *et al*., 2008 [45]	✓	✓	✓[d]	Yes <7 days
Wetten *et al*., 2015 [47]		✓[d]		Yes <7 days
Weycker *et al*., 2009 [48]		✓		Yes NR
Weycker *et al*., 2012 [49]		✓		Yes <7 days

CIN chemotherapy-induced neutropenia, *FN* febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor, *NR* not reported, *non-RCT* non-randomized controlled trial, *PEG* pegylated, *RCT* randomized controlled trial

[a] Primary outcome (where stated) is highlighted in bold

[b] Excluded from meta-analysis due to hospitalizations being FN-related (compared with “all cause” in other RCTs)

[c] Meta-analysis not performed because dose reduction/delay/relative dose intensity was reported differently in each study

[d] Not included in meta-analysis because no individual numerical data were provided or because outcome was reported in non-comparable format

[e] Not included in meta-analysis as pegfilgrastim administered <24 hours after chemotherapy

Supplementary Appendix Table S8 Short- vs long-acting G-CSFs for the reduction of chemotherapy-induced FN: Summary of FN outcomes

Reference	Definition of FN	Incidence and duration of FN	Summary statistics reported
RCT			
Bozzoli *et al.*, 2015 [1]	NR	**Incidence, *n* (%)** *Per patient, overall cycles* Filgrastim (*n* = 24): 5 (21) Pegfilgrastim (*n* = 27): 4 (15) *FN events per cycle* Filgrastim (*n* = 96 cycles): 7 (7.2) Pegfilgrastim (*n* = 105 cycles): 6 (5.7)	Filgrastim vs pegfilgrastim, *P* = 0.7 Filgrastim vs pegfilgrastim, *P* = 0.8
Filon *et al*., 2015 [2]; Nechaeva *et al*., 2015 [3]	NR	**Incidence, *n*** Filgrastim (*n* = NR): *n* = 1 Empegfilgrastim, 6 mg (*n* = NR): *n* = 1 Empegfilgrastim, 7.5 mg (*n* = NR): *n* = 1 Total no. of patients in all groups: *N* = 135 (randomized 1:1:1 to each group)	
Green *et al.*, 2003 [4]	ANC $<0.5\times10^9$/L with a coincidental oral equivalent temperature ≥38.2°C	**Incidence, *n* (%)** *First cycle* Filgrastim (*n* = 75): 11 (15) Pegfilgrastim (*n* = 77): 7 (9) *Overall cycles (1–4)* Filgrastim (*n* =75): 15 (20) Pegfilgrastim (*n* = 77): 10 (13)	The incidence of FN was not statistically different between pegfilgrastim and filgrastim
Grigg *et al.*, 2003 [5]	ANC $<0.5\times10^9$/L and temperature >38.2°C	**Incidence, *n* (%)** *First cycle* Filgrastim (*n* = 13): 0 (0) No cytokine support then filgrastim (*n* = 9): 0 (0) Pegfilgrastim, 60 µg/kg (*n* = 13): 2 (15) Pegfilgrastim, 100 µg/kg (*n* = 14): 0 (0) *Total no. of FN events* Filgrastim (*n* = 13): 1 (8) No cytokine support then filgrastim (*n* = 9): 0 (0) Pegfilgrastim, 60 µg/kg (*n* = 13): 4 (31) Pegfilgrastim, 100 µg/kg (*n* = 14): 0 (0)	Incidence of FN was low
Park *et al.*, 2013 [7]	Grade 4 neutropenia	**Incidence, *n* (%)**	Filgrastim vs pegfilgrastim,

Reference	Definition of FN	Incidence and duration of FN	Summary statistics reported
	ANC <0.5×10^9/L	*Total no. of FN events, first cycle* Filgrastim (*n* = 21): 2 (9.5) Pegfilgrastim, 3.6 mg (*n* = 20): 3 (15) Pegfilgrastim, 6 mg: (*n* = 20): 1 (5)	*P* = 0.681
Salafet *et al.*, 2013 [9]	NR	**Incidence, *n*** *Total no. of FN events* Filgrastim (*n* = 19): 0 Empegfilgrastim, 3 mg (*n* = 21): 1 Empegfilgrastim, 6 mg (*n* = 20): 1	Differences between empegfilgrastim groups and filgrastim group were not significant
Satheesh *et al.*, 2009 [10]	NR	**Incidence, %** *Total no. of FN events* Filgrastim (*n* = 43): 18.6 Pegfilgrastim (*n* = 28): 10.7	A trend towards a lower incidence of FN was noted across all cycles with pegfilgrastim compared with filgrastim
Shi *et al.*, 2006 [11]	NR	**Incidence, *n* (%)** *Total no. of FN events* rhG-CSF (*n* = NR): 0 (0) PEG-rhG-CSF (*n* = NR): 0 (0) Total no. of patients: 104	None of the patients experienced FN
Shi *et al.*, 2013 [12]	ANC <0.5×10^9/L and auxiliary temperature >38.0°C	**Incidence, *n* (%)** *Total no. of FN events* Filgrastim (*n* = 313): 0 (0) Pegfilgrastim (*n* = 313): 1 (0.3)	Filgrastim vs pegfilgrastim, *P* = 1.00
Sierra *et al.*, 2008 [13]	ANC <0.5×10^9/L and oral temperature ≥38.0°C	**Incidence, *n* (%)** *FN events* during induction chemotherapy Filgrastim (*n* = 41): 36 (88) Pegfilgrastim (*n* = 42): 34 (81) **Duration, median (IQR) days** *FN duration* during induction chemotherapy Filgrastim (*n* = 41): 14 (11.5–18.5) Pegfilgrastim (*n* = 42): 15 (11–20)	No clinically meaningful difference between filgrastim and pegfilgrastim
Zhang *et al.,* 2015 [15]	An oral or oral equivalent temperature of ≥38.2°C for ≥1	**Incidence, *n* (%)** *First cycle*	Filgrastim vs pegfilgrastim, *P* = 0.504

Reference	Definition of FN	Incidence and duration of FN	Summary statistics reported
	h concurrent with an ANC $<0.5\times10^9$/L	Filgrastim (*n* = 43): 5 (11.63) Pegfilgrastim, 60 μg/kg (*n* = 43): 3 (6.98) Pegfilgrastim, 100 μg/kg (*n* = 43): 2 (4.65) Pegfilgrastim, 120 μg/kg (*n* = 42): 5 (11.90)	
Non-RCT			
Almenar Cubells *et al*., 2013 [19]	ANC $<0.5\times10^9$/L and fever ≥38°C within the same day	**Incidence, *n* (%)** Daily G-CSF (*n* = 211): 28 (13.3) Pegfilgrastim (*n* = 180): 12 (6.7)	Filgrastim vs pegfilgrastim, *P* = 0.032
Almenar *et al.,* 2009 [20]	NR	**Incidence, *n* (%) [95% CI]** Daily G-CSF (*n* = 111): 27 (24.3) [17.2–33.1] Pegfilgrastim (*n* = 75): 8 (10.7) [5.3–19.9]	Patients who were treated with pegfilgrastim appeared to have a numerically lower incidence of FN than those who received daily G-CSF; however, due to the descriptive nature of the analysis in this study, a conclusion of the significance cannot be made
Brito *et al*., 2012 [21]; Brito *et al*., 2016 [22]	Body temperature ≥38°C concurrent with ANC ≤500 cells/μL	**Incidence, *n* (%)** *No. of patients with ≥1 FN episode* Reference filgrastim (*n* = 147): 23 (16) Biosimilar filgrastim (*n* = 134): 21 (16) Pegfilgrastim (*n* = 140): 12 (9) *No. of cycles with FN* Reference filgrastim (*n* = 833 cycles): 27 (3) Biosimilar filgrastim (*n* = 761 cycles): 28 (4) Pegfilgrastim (*n* = 761 cycles): 17 (2)	No significant differences were found between the three groups in exploratory analyses of FN incidence
Chan *et al.,* 2011 [23]	Oral temperature ≥38.3°C and ANC $<0.5\times10^9$/L	**Incidence, *n* (%)** *First cycle* Filgrastim (*n* = 81): 6 (7.4) Pegfilgrastim (*n* = 123): 11 (8.9) *Overall cycles* Filgrastim (*n* = 81): 11 (13.6) Pegfilgrastim (*n* = 123): 20 (16.3)	Filgrastim vs pegfilgrastim, *P* = 0.8 Filgrastim vs pegfilgrastim, *P* = 0.69

Reference	Definition of FN	Incidence and duration of FN	Summary statistics reported
Hershman *et al.,* 2009 [27]	NR	**Incidence, %** Filgrastim (*n* = 101): 6.9 Pegfilgrastim (*n* = 721): 4.2 No primary prophylaxis (*n* = 1523): 7.5	Filgrastim vs pegfilgrastim, not compared statistically
Kourlaba *et al.,* 2015 [28]	Body temperature >38.2°C and neutrophil count $<0.5\times10^9$/L	**Incidence, *n* (%) [95% CI]** Filgrastim (*n* = 529): 18 (3.4) [2.0, 5.3] Pegfilgrastim (*n* = 529): 23 (4.3) [2.8, 6.4]	Filgrastim vs pegfilgrastim, *P* = 0.500
Leung *et al.,* 2015 [33]	NR	**Incidence, *n* (%)** Filgrastim (*n* = 48) Pegfilgrastim (*n* = 94)	No difference observed between filgrastim and pegfilgrastim
Mates *et al.,* 2012 [35]	NR	**Incidence, *n* (%)** Filgrastim (*n* = 47): 13 (28) Pegfilgrastim (*n* = 98): 8 (8)	Filgrastim vs pegfilgrastim; OR 4.3, *P* = 0.003
Morrison *et al.,* 2007 [37]	Single oral temperature of ≥38.3°C (101°F), or ≥38.0°C (100.4°F) for ≥1 h and neutropenia	**Incidence, *n* (%)** Filgrastim (cohort 1; *n* = 583): 31 (5.3) Filgrastim (cohort 2; *n* = 868): 63 (7.3) Pegfilgrastim (*n* = 1412): 67 (4.7)	Filgrastim (cohort 1) vs pegfilgrastim, *P* = 0.591 Filgrastim (cohort 2) vs pegfilgrastim, *P* = 0.012
Schippinger *et al.,* 2006 [42]	ANC <1000/μL and fever >38°C measured ≥2× in 24 h, or 1 fever episode of ≥38.3°C in 24 h	**Incidence, *n* (%)** *First cycle* Filgrastim or lenograstim (*n* = 88): 8 (9.1) Pegfilgrastim (*n* = 30): 1 (3.3) *Total FN events in all cycles* Filgrastim or lenograstim (*n* = 476 cycles): 13 (2.7) Pegfilgrastim (*n* = 172 cycles): 2 (1.2)	Filgrastim or lenograstim vs pegfilgrastim, *P* = 0.445 Filgrastim or lenograstim vs pegfilgrastim, *P* = 0.376
Skarlos *et al.,* 2009 [43]	Body temperature >38.2°C and neutrophil count $<0.5\times10^9$/L	**Incidence, *n* (%)** Filgrastim (*n* = 107): 1 (1) Pegfilgrastim (*n* = 107): 14 (13)	Filgrastim vs pegfilgrastim, *P* = 0.001
Tan *et al.,* 2011 [44]	NR	**Incidence, %** *FN or infection* Filgrastim (*n* = 616 cycles): 42 Pegfilgrastim (*n* = 4955 cycles): 49	Filgrastim vs pegfilgrastim, *P* = 0.002

Reference	Definition of FN	Incidence and duration of FN	Summary statistics reported
von Minckwitz *et al.*, 2008 [45]	Three oral temperature determinations >38°C during a 24-h period/single elevation >38.5°C and ANC <1.0×10^9/L	**Incidence, *n* (%)** *Overall cycles (1–5)* Daily G-CSF (*n* = 374): 67 (18) Pegfilgrastim (*n* = 303): 22 (7) Pegfilgrastim + ciprofloxacin (*n* = 314): 17 (5) Ciprofloxacin (*n* = 253): 55 (22)	Filgrastim vs pegfilgrastim, *P* < 0.001

ANC absolute neutrophil count, *CI* confidence interval, *FN* febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor, *IQR* interquartile range, *NR* not reported, *non-RCT* non-randomized controlled trial, *OR* odds ratio, *PEG-rhG-CSF* pegylated recombinant human granulocyte colony-stimulating factor, *rh-G-CSF* recombinant human granulocyte colony-stimulating factor, *RCT* randomized controlled trial

Supplementary Appendix Table S9 Short- vs long-acting G-CSFs for the reduction of chemotherapy-induced FN: Summary of hospitalization outcomes

Reference	Hospitalization outcome	Summary statistics reported
RCT		
Bozzoli *et al*., 2015 [1]	**Unplanned hospitalization, all cycles, *n* (%)** Filgrastim (*n* = 96 cycles): 5 (5.2) Pegfilgrastim (*n* = 105 cycles): 7 (6.7) Total (*n* = 201 cycles): 12 (6)	Filgrastim vs pegfilgrastim, *P* = 0.8
Green *et al*., 2003 [4]	**Rate of hospitalization, %** Filgrastim (*n* = 75): 31 Pegfilgrastim (*n* = 77): 18	Rates of hospitalization were generally consistent with the results obtained for the incidence of FN
Grigg *et al*., 2003 [5]	**Rate of hospitalization, *n* (%)** Filgrastim (*n* = 22): 12 Pegfilgrastim (*n* = 27): 10 **Hospitalization due to AEs, *n*** Filgrastim (*n* = 22): 4 (18) Pegfilgrastim (*n* = 27): 6 (22)	Comparable numbers between filgrastim and pegfilgrastim groups were hospitalized with similar numbers due to AEs; other hospitalizations were for routine procedures or chemotherapy administration
Satheesh *et al*., 2009 [10]	**Rate of hospitalization, %** Filgrastim (*n* = 43): 25.6 Pegfilgrastim (*n* = 28): 17.8	No statistical analysis reported
Sierra *et al*., 2008 [13]	**Incidence and duration** Filgrastim (*n* = 41) Pegfilgrastim (*n* = 42)	The incidence and duration of hospitalization was similar in the 2 treatment groups, with nearly all patients being hospitalized, as per routine clinical practice
Non-RCT		
Almenar Cubells *et al*., 2013 [19]	**Outcome, *n* (%)** *Total hospitalization incidents* Daily G-CSF (*n* = 211): 71 (33.6) Pegfilgrastim (*n* = 180): 46 (25.6) *Hospitalization due to FN* Daily G-CSF (*n* = 211): 23 (10.9) Pegfilgrastim (*n* = 180): 5 (2.8) *Hospitalization due to neutropenia* Daily G-CSF (*n* = 211): 31 (14.7)	Daily G-CSF vs pegfilgrastim, *P* = 0.002

Reference	Hospitalization outcome	Summary statistics reported
	Pegfilgrastim (*n* = 180): 7 (3.9)	
	Hospitalization due to severe neutropenia	Daily G-CSF vs pegfilgrastim,
	Daily G-CSF (*n* = 211): 26 (12.3)	*P* = 0.001
	Pegfilgrastim (*n* = 180): 6 (3.3)	
	Hospitalization due to fever	
	Daily G-CSF (*n* = 211): 9 (4.3)	
	Pegfilgrastim (*n* = 180): 7 (3.9)	
	Hospitalization due to pancytopenia	
	Daily G-CSF (*n* = 211): 6 (2.8)	
	Pegfilgrastim (*n* = 180): 2 (1.1)	
	Hospitalization due to other hematologic toxicities	
	Daily G-CSF (*n* = 211): 6 (2.8)	
	Pegfilgrastim (*n* = 180): 2 (1.1)	
Almenar *et al*., 2009 [20]	**Hospitalization due to FN, *n* (%) [95% CI]**	Patients who were treated with pegfilgrastim appeared to have a numerically lower incidence of FN than those who received daily G-CSF; however, due to the descriptive nature of the analysis in this study, a conclusion of the significance cannot be made
	Daily G-CSF (*n* = 111): 22 (19.8) [13.4–28.3]	
	Pegfilgrastim (*n* = 75): 7 (9.3) [4.3–18.3]	
Brito *et al*., 2012 [21]; Brito *et al* 2016 [22]	**Hospitalization, No. hospitalizations/No. cycles with FN, %**	No statistical analysis reported
	Reference filgrastim (*n* = 147): 20/27 (74)	
	Biosimilar filgrastim (*n* = 134): 19/28 (68)	
	Pegfilgrastim (*n* = 139): 14/17 (82)	
	Duration of hospitalization, median (range), days	
	Reference filgrastim (*n* = 147): 5 (1–17)	
	Biosimilar filgrastim (*n* = 134): 4 (1–10)	
	Pegfilgrastim (*n* = 761): 4 (1–8)	
Heaney *et al*., 2009 [25]	**Outcome, No. of events (incidence rate) [95% CI]**	Study did not directly compare filgrastim with pegfilgrastim
	Hospitalization due to FN	
	Filgrastim (*n* = 990): 7 (0.08) [0.03–0.17]	
	Pegfilgrastim (*n* = 982): 9 (0.06) [0.03–0.11]	
	Hospitalization due to infection	

Reference	Hospitalization outcome	Summary statistics reported
	Filgrastim (*n* = 990): 22 (0.26) [0.15–0.37]	
	Pegfilgrastim (*n* = 982): 37 (0.24) [0.16–0.31]	
Henk *et al*., 2013 [26]	**Database analysis 1 (HIRD)**	
	Neutropenia-related hospitalization	Filgrastim vs pegfilgrastim, OR (95% CI) 1.78 (1.28–2.48)
	Filgrastim (*n* = 1669 cycles)	
	Pegfilgrastim (*n*=28,189 cycles)	
	All-cause hospitalization	Filgrastim vs pegfilgrastim, OR (95% CI) 1.57 (1.25–1.97)
	Filgrastim (*n* = 1669 cycles)	
	Pegfilgrastim (*n* = 28,189 cycles)	
	Database analysis 2 (OptumInsight)	
	Neutropenia-related hospitalization	Filgrastim vs pegfilgrastim, OR (95% CI) 2.36 (1.82–3.06)
	Filgrastim (*n* = 1351 cycles)	
	Pegfilgrastim (*n* = 22,649 cycles)	
	All-cause hospitalization	Filgrastim vs pegfilgrastim, OR (95% CI) 1.95 (1.60–2.38)
	Filgrastim (*n* = 1351 cycles)	
	Pegfilgrastim (*n* = 22,649 cycles)	
		Analysis of both the databases showed that filgrastim prophylaxis had a higher risk of neutropenia-related hospitalization and all-cause hospitalization vs pegfilgrastim
Marina *et al*., 2009 [34]	**Hospitalization due to FN**	No differences in FN hospitalization between filgrastim vs pegfilgrastim
	Filgrastim (*n* = NR)	
	Pegfilgrastim (*n* = NR)	
Mazo *et al*., 2009 [36]	**Hospitalization due to feverish neutropenic episodes, *n***	No significant differences between filgrastim and pegfilgrastim were observed
	Filgrastim (*n* = NR): 2	
	Pegfilgrastim (*n* = NR): 3	
Naeim *et al*., 2010 [38]	**Outcome, mean per cycle**	
	Total hospitalization incidents	Filgrastim vs pegfilgrastim, $P < 0.001$
	Filgrastim (*n* = 852 cycles): 0.13	
	Pegfilgrastim (*n* = 12,218 cycles): 0.06	
	Total ambulatory visits	Filgrastim vs pegfilgrastim, $P < 0.001$
	Filgrastim (*n* = 852 cycles): 8.6	
	Pegfilgrastim (*n* = 12,218 cycles): 5.5	
	Total emergency room visits	

Reference	Hospitalization outcome	Summary statistics reported
	Filgrastim (*n* = 852 cycles): 0.11	
	Pegfilgrastim (*n* = 12,218 cycles): 0.11	
	Neutropenia-related hospitalization incidents	Filgrastim vs pegfilgrastim, *P* < 0.01
	Filgrastim (*n* = 852 cycles): 0.02	
	Pegfilgrastim (*n* = 12,218 cycles): 0.01	
	Neutropenia-related ambulatory visits	Filgrastim vs pegfilgrastim, *P* < 0.001
	Filgrastim (*n* = 852 cycles): 1.5	
	Pegfilgrastim (*n* = 12,218 cycles): 0.36	
	Neutropenia-related emergency room visits	
	Filgrastim (*n* = 852 cycles): 0	
	Pegfilgrastim (*n* = 12,218 cycles): 0	
		Filgrastim vs pegfilgrastim, risk of neutropenia-related hospitalization, OR (95% CI) 0.33 (0.19–0.58)
		Filgrastim vs pegfilgrastim, risk of all-cause hospitalization, OR (95% CI) 0.56 (0.43–0.72)
Naeim *et al*., 2013 [39]	**Outcome, *n* (%)**	
	Total hospitalization incidents	Pegfilgrastim vs filgrastim, OR (95% CI) 0.50 (0.35–0.72)
	Filgrastim (*n* = 373 cycles): 38 (10.2)	
	Pegfilgrastim (*n* = 11,683 cycles): 582 (5.0)	
	Hospitalization due to neutropenia	Pegfilgrastim vs filgrastim, hospitalization due to neutropenia, narrow definition: OR (95% CI) 0.43 (0.16–1.13); broad definition: OR (95% CI) 0.38 (0.24–0.59)
	Filgrastim (*n* = 373 cycles): 5 (1.34)	
	Pegfilgrastim (*n* = 11,683 cycles): 68 (0.58)	
Salar *et al*., 2009 [41]	**Duration of hospitalization due to FN, mean (SD) days**	No statistics reported
	Filgrastim (*n* = NR): 12.4 (11.1)	
	Pegfilgrastim (*n* = NR): 5.9 (5.8)	
Tan *et al*., 2011 [44]	**Hospitalization due to neutropenia, *n* (%)**	Filgrastim vs pegfilgrastim, *P* = 0.001
	Filgrastim (*n* = 231 cycles): 8 (3.5)	
	Pegfilgrastim (*n* = 4636 cycles): 51 (1.1)	
von Minckwitz *et al*., 2008 [45]	**Outcome, *n* (%)**	
	Total hospitalization incidents	Daily G-CSF vs pegfilgrastim, *P* < 0.01
	Daily G-CSF (*n* = 2400 cycles): 76 (3)	
	Pegfilgrastim (*n* = 1930 cycles): 36 (2)	

Reference	Hospitalization outcome	Summary statistics reported
	Pegfilgrastim plus ciprofloxacin (*n* = 1890 cycles): 39 (2)	
	Ciprofloxacin alone (*n* = 1478 cycles): 92 (6)	
	Hospitalization due to FN	
	Daily G-CSF (*n* = 2400 cycles): 19 (1)	
	Pegfilgrastim (*n* = 1930 cycles): 6 (<1)	
	Pegfilgrastim plus ciprofloxacin (*n* = 1890 cycles): 7 (<1)	
	Ciprofloxacin alone (*n* = 1478 cycles): 21 (1)	
	Hospitalization due to neutropenia	Daily G-CSF vs pegfilgrastim + ciprofloxacin,
	Daily G-CSF (*n* = 2400 cycles): 30 (1)	*P* < 0.01
	Pegfilgrastim (*n* = 1930 cycles): 11 (1)	
	Pegfilgrastim plus ciprofloxacin (*n* = 1890 cycles): 9 (<1)	
	Ciprofloxacin alone (*n* = 1478 cycles): 44 (3)	
	Hospitalization due to infection	
	Daily G-CSF (*n* = 2400 cycles): 15 (1)	
	Pegfilgrastim (*n* = 1930 cycles): 10 (1)	
	Pegfilgrastim plus ciprofloxacin (*n* = 1890 cycles): 10 (1)	
	Ciprofloxacin alone (*n* = 1478 cycles): 12 (1)	
Wetten *et al*., 2015 [47]		
	Outcome (Individual data not reported)	Prophylactic daily G-CSF vs prophylactic
	Risk of FN-related hospitalizations ("narrow" definition)	pegfilgrastim, adjusted OR (95% CI) 2.19 (1.41–3.39), *P* < 0.001
	Risk of FN-related hospitalization ("broad" definition)	Prophylactic daily G-CSF vs prophylactic pegfilgrastim, adjusted OR (95% CI) 1.63 (1.11–2.40), *P* = 0.01
Weycker *et al*., 2009 [48]	**Outcome, %**	
	Risk of neutropenia-related hospitalization ("narrow" definition[a])	Filgrastim vs pegfilgrastim, unadjusted OR
	Filgrastim (*n* = 2704): 1.4	(95% CI) 1.53 (1.07–2.17), *P* = 0.019;
	Pegfilgrastim (*n* = 18,361): 0.9	adjusted OR (95% CI) 1.61 (1.06–2.44), *P* =
	Sargramostim (*n* = 495): 3.0	0.026
	Risk of neutropenia-related hospitalization ("broad" definition[a])	Filgrastim vs pegfilgrastim, unadjusted OR
	Filgrastim (*n* = 2704): 3.3	(95% CI) 1.32 (1.05–1.66), *p* = 0.020;
	Pegfilgrastim (*n* = 18,361): 2.5	adjusted OR (95% CI) 1.39 (1.05–1.83), *P* =

Reference	Hospitalization outcome	Summary statistics reported
	Sargramostim (*n* = 495): 5.5	0.023
	Risk of all-cause hospitalization	Filgrastim vs pegfilgrastim, unadjusted OR (95% CI) 1.29 (1.09–1.52), *P* = 0.003; adjusted OR (95% CI) 1.34 (1.09–1.65), *P* = 0.006
	Filgrastim (*n* = 2704): 6.6	
	Pegfilgrastim (*n* = 18,361): 5.2	
	Sargramostim (*n* = 495): 10.3	
Weycker *et al*., 2012 [49]	**Outcome, *n* (%)**	
	Risk of neutropenia-related hospitalization (narrow definition[a])	Filgrastim vs pegfilgrastim, OR (95% CI) 1.93 (1.63–2.28), *P* < 0.001
	Filgrastim (*n* = 8286 cycles): 170 (2.1)	
	Pegfilgrastim (*n* = 67,247 cycles): 723 (1.1)	
	Sargramostim (*n* = 1736 cycles): 44 (2.5)	
	Risk of neutropenia-related hospitalization (broad definition[a])	Filgrastim vs pegfilgrastim, OR (95% CI) 1.53 (1.35–1.72), *P* < 0.001
	Filgrastim (*n* = 8286 cycles): 328 (4.0)	
	Pegfilgrastim (*n* = 67,247 cycles): 1768 (2.6)	
	Sargramostim (*n* = 1736 cycles): 88 (5.1)	
	Risk of all-cause hospitalization	Filgrastim vs pegfilgrastim, OR (95% CI) 1.55 (1.42–1.69), *P* < 0.001
	Filgrastim (*n* = 8286 cycles): 658 (7.9)	
	Pegfilgrastim (*n* = 67,247 cycles): 3,553 (5.3)	
	Sargramostim (*n* = 1736 cycles): 167 (9.6)	

AE adverse event, *CI* confidence interval, *FN* febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor, *HIRD* HealthCare Integrated Research Database, *ICD-9-CM* The International Classification of Diseases, Ninth Revision, Clinical Modification, *non-RCT* nonrandomized controlled trial, *NR* not reported, *OR* odds ratio, *RCT* randomized controlled trial

[a] The incidence of hospitalization for neutropenic complications was assessed using 2 alternative criteria: a ‘‘narrow’’ definition was admission to hospital with a principal or secondary diagnosis of neutropenia (ICD-9-CM 288.0), a ”broad” definition was admission to hospital with a principal or secondary diagnosis of neutropenia, fever (ICD-9-CM 780.6) or infection

Supplementary Appendix Table S10 Short- vs long-acting G-CSFs for the reduction of chemotherapy-induced FN: Summary of chemotherapy dose reductions or delays

Reference	Incidence of dose reduction or delay	Summary statistics reported
RCT		
Bozzoli *et al*., 2015 [1]	**Median dose intensity, %** Filgrastim (*n* = 24): 87.5 Pegfilgrastim (*n* = 27): 89.4 **Significant reduction to a dose intensity <80%, *n* (%)** Filgrastim (*n* = 24): 5 (20.8) Pegfilgrastim (*n* = 27): 7 (26.9)	Filgrastim vs pegfilgrastim, *P* = 0.9
Green *et al*., 2003 [4]	**Dose reduction** Filgrastim (*n* = 75) Pegfilgrastim (*n* = 77)	Total chemotherapy dose administered in each group was similar, with ~5% of patients having >25% dose reduction in any cycle
Grigg *et al*., 2003 [5]	**Full dose of chemotherapy delivered, %** Filgrastim (*n* = 59 cycles): 94 Pegfilgrastim, 60 μg/kg (*n* = 68 cycles): 96 Pegfilgrastim, 100 μg/kg (*n* = 62 cycles): 100	In cycles 2–6, 8 patients developed a delay in the start of chemotherapy of >3 days; no delays were related to neutropenia
Lopez *et al*., 2005 [6]	**>75% of the planned dose delivered, %** Filgrastim (*n* = 145 cycles): 100 Pegfilgrastim (*n* = 188 cycles): 97 **Chemotherapy delivered on time, %** Filgrastim (*n* = 145 cycles): 94 Pegfilgrastim (*n* = 188 cycles): 96 **Planned doses of chemotherapy delivered on time, % (95% CI)** Filgrastim (*n* = 26): 81 (61–93) Pegfilgrastim (*n* = 32): 69 (50–84) **Dose delays, *n* (%)** Filgrastim (*n* = 145 cycles): 7 (5) Pegfilgrastim (*n* = 188 cycles): 0 (0)	Pegfilgrastim is safe and well tolerated, having a safety profile similar to that of daily filgrastim in this patient population
Non-RCT		
Almenar Cubells *et al*., 2013 [19]	**Dose delay, *n* (%)** Daily G-CSF (*n* = 211): 111 (54.7) Pegfilgrastim (*n* = 180): 70 (41.7)	Daily G-CSF vs pegfilgrastim, *P* = 0.013

Reference	Incidence of dose reduction or delay	Summary statistics reported
	Dose reduction, *n* (%)	Daily G-CSF vs pegfilgrastim, *P* = 0.116
	Daily G-CSF (*n* = 211): 78 (38.4)	
	Pegfilgrastim (*n* = 180): 53 (31.6)	
	Chemotherapy dose intensity <85%, *n* (%)	Daily G-CSF vs pegfilgrastim, *P* = 0.030
	Daily G-CSF (*n* = 211): 82 (39.4)	
	Pegfilgrastim (*n* = 180): 52 (28.9)	
Almenar *et al*., 2009 [20]	**Dose reduction, *n* (%) [95% CI]**	
	Daily G-CSF (*n* = 111): 23 (20.7) [14.2–29.2]	
	Pegfilgrastim (*n* = 75): 11 (14.7) [8.2–24.6]	
	Dose reduction due to neutropenia, *n* (%) [95% CI]	Patients who were treated with pegfilgrastim appeared to have a numerically lower incidence of dose reduction due to neutropenia, than those who received daily G-CSF; however, due to the descriptive nature of the analysis in this study, a conclusion of the significance cannot be made
	Daily G-CSF (*n* = 111): 23 (20.7) [14.1–29.2]	
	Pegfilgrastim (*n* = 75): 5 (6.7) [2.5–15.0]	
	Dose delay, *n* (%) [95% CI]	
	Daily G-CSF (*n* = 111): 51 (46.0) [36.0–55.0]	
	Pegfilgrastim (*n* = 75): 33 (44.0) [33.0–55.0]	
Brito *et al*., 2012 [21]; Brito *et al* 2016 [22]	**Dose reduction due to FN, *n* (%)**	Not reported
	Reference filgrastim (*n* = 147): 1 (1)	
	Biosimilar filgrastim (*n* = 134): 1 (1)	
	Pegfilgrastim (*n* = 139): 1 (1)	
	Dose delay due to FN, *n* (%)	
	Reference filgrastim (*n* = 833 cycles): 11 (1)	
	Biosimilar filgrastim (*n* = 761 cycles): 16 (2)	
	Pegfilgrastim (*n* = 761 cycles): 4 (0.5)	
	Early termination due to FN, *n* (%)	
	Reference filgrastim (*n* = 833 cycles): 3 (2)	
	Biosimilar filgrastim (*n* = 761 cycles): 1 (1)	
	Pegfilgrastim (*n* = 761 cycles): 6 (4)	
Chan *et al*., 2011 [23]	**Dose reduction, *n* (%)**	
	First cycle	Filgrastim vs pegfilgrastim, *P* = 0.45
	Filgrastim (*n* = 81): 4 (4.9)	
	Pegfilgrastim (*n* = 123): 4 (3.3)	

Reference	Incidence of dose reduction or delay	Summary statistics reported
	All cycles	Filgrastim vs pegfilgrastim, *P* = 1.00
	Filgrastim (*n* = 81): 8 (9.9)	
	Pegfilgrastim (*n* = 123): 13 (10.6)	
	Dose delay, *n* (%)	
	First cycle	Filgrastim vs pegfilgrastim, *P* = 0.25
	Filgrastim (*n* = 81): 7 (8.6)	
	Pegfilgrastim (*n* = 123): 7 (5.7)	
	All cycles	Filgrastim vs pegfilgrastim, *P* = 0.71
	Filgrastim (*n* = 81): 14 (16.0)	
	Pegfilgrastim (*n* = 123): 23 (18.7)	
Kourlaba *et al*., 2015 [28]	**Dose reduction, % (95% CI)**	Filgrastim vs pegfilgrastim, *P* < 0.001
	Filgrastim (*n* = 529): 18.5 (15.3–22.1)	
	Pegfilgrastim (*n* = 529): 10.8 (8.3–13.7)	
	Dose delay >2 days, % (95% CI)	Filgrastim vs pegfilgrastim, *P* < 0.001
	Filgrastim (*n* = 529): 42.0 (37.7–46.3)	
	Pegfilgrastim (*n* = 529): 27.6 (23.8–31.6)	
Leonard *et al*., 2009 [30]; Leonard *et al*., 2015 [31]	**Relative dose intensity of ≥85%, %**	No statistics reported (study was not designed to test any differences in outcome between short- vs long-acting G-CSFs)
	Filgrastim (*n* = 129): 69.5	
	Pegfilgrastim (*n* = 75): 84.9	
Leung *et al*., 2015 [33]	**Dose reduction, cycle 2, *n***	Filgrastim vs pegfilgrastim, *P* = 0.17
	Filgrastim (*n* = 48): 8	
	Pegfilgrastim (*n* = 94): 8	
	Dose delay, cycle 2, *n*	Filgrastim vs pegfilgrastim, *P* = 0.5
	Filgrastim (*n* = 48): 5	
	Pegfilgrastim (*n* = 94): 7	
	Dose delay due to neutropenia, cycle 2, *n* (%)	Filgrastim vs pegfilgrastim, *P* = 0.12
	Filgrastim (*n* = 48): 2 (4)	
	Pegfilgrastim (*n* = 94): 0 (0)	
Salar *et al*., 2009 [41]	**Received full dose on schedule, %**	No statistics reported
	Daily G-CSF (*n* = NR): 61.2	

Reference	Incidence of dose reduction or delay	Summary statistics reported
	Pegfilgrastim (*n* = NR): 72.1	
Skarlos *et al*., 2009 [43]	**Dose reductions, *n* (%)**	*P* = 1.00
	Daily G-CSF (*n* = 107): 25 (23)	
	Pegfilgrastim (*n* = 107): 25 (23)	
	Dose delays >2 days, *n* (%)	*P* = 0.65
	Daily G-CSF (*n* = 107): 65 (61)	
	Pegfilgrastim (*n* = 107): 61 (57)	
von Minckwitz *et al*., 2008 [45]	**Dose reduction, %**	Chemotherapy dose reductions were similar in all 4 cohorts
	Daily G-CSF (*n* = 2400 cycles): 2–3	
	Pegfilgrastim (*n* = 1930 cycles): 2–3	
	Pegfilgrastim + ciprofloxacin (*n* = 1890 cycles): 2–3	
	Ciprofloxacin alone (*n* = 1478 cycles): 2–3	

CI confidence interval, *FN* febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor, *non-RCT* non-randomized controlled trial, *RCT* randomized controlled trial

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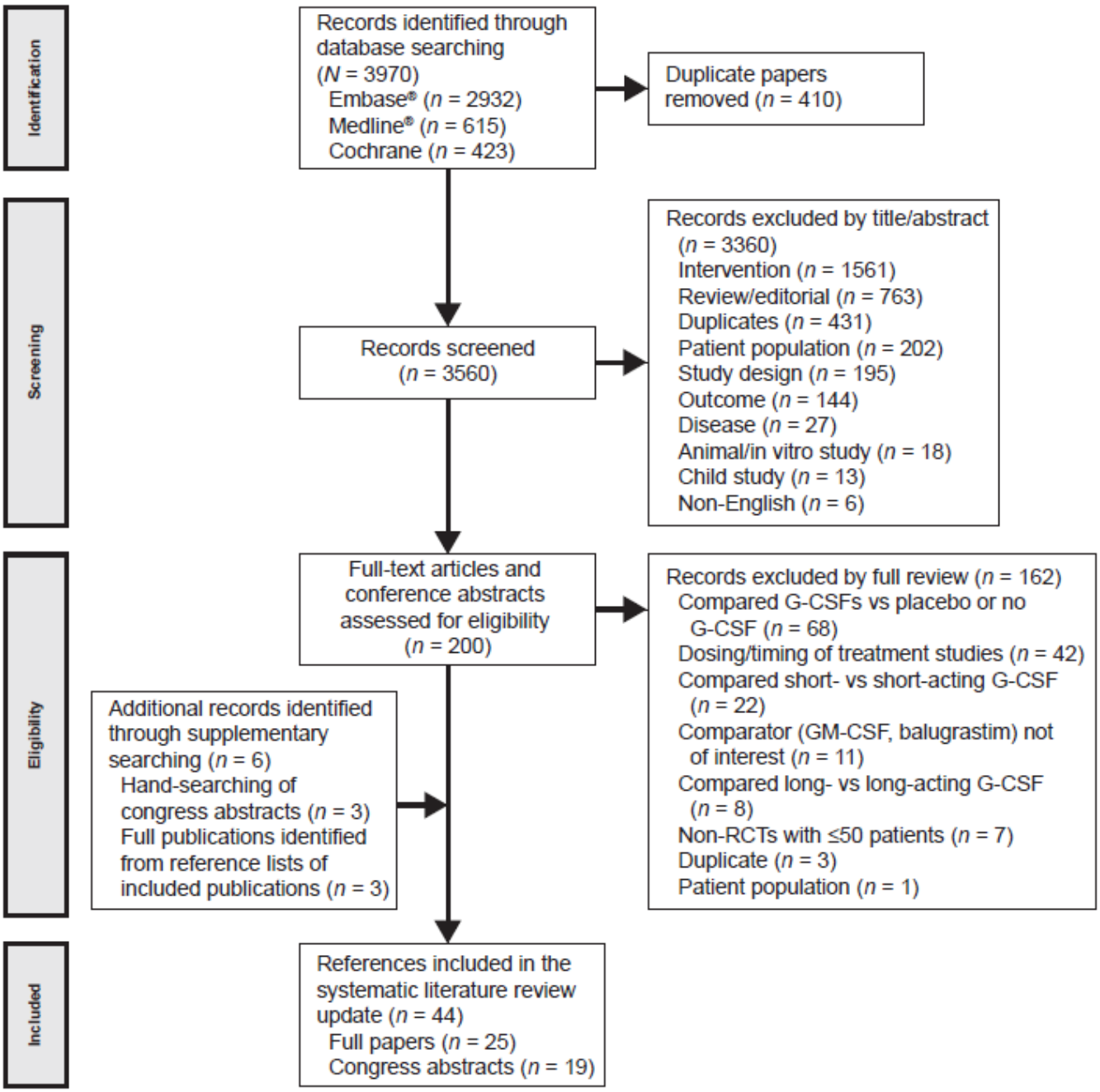
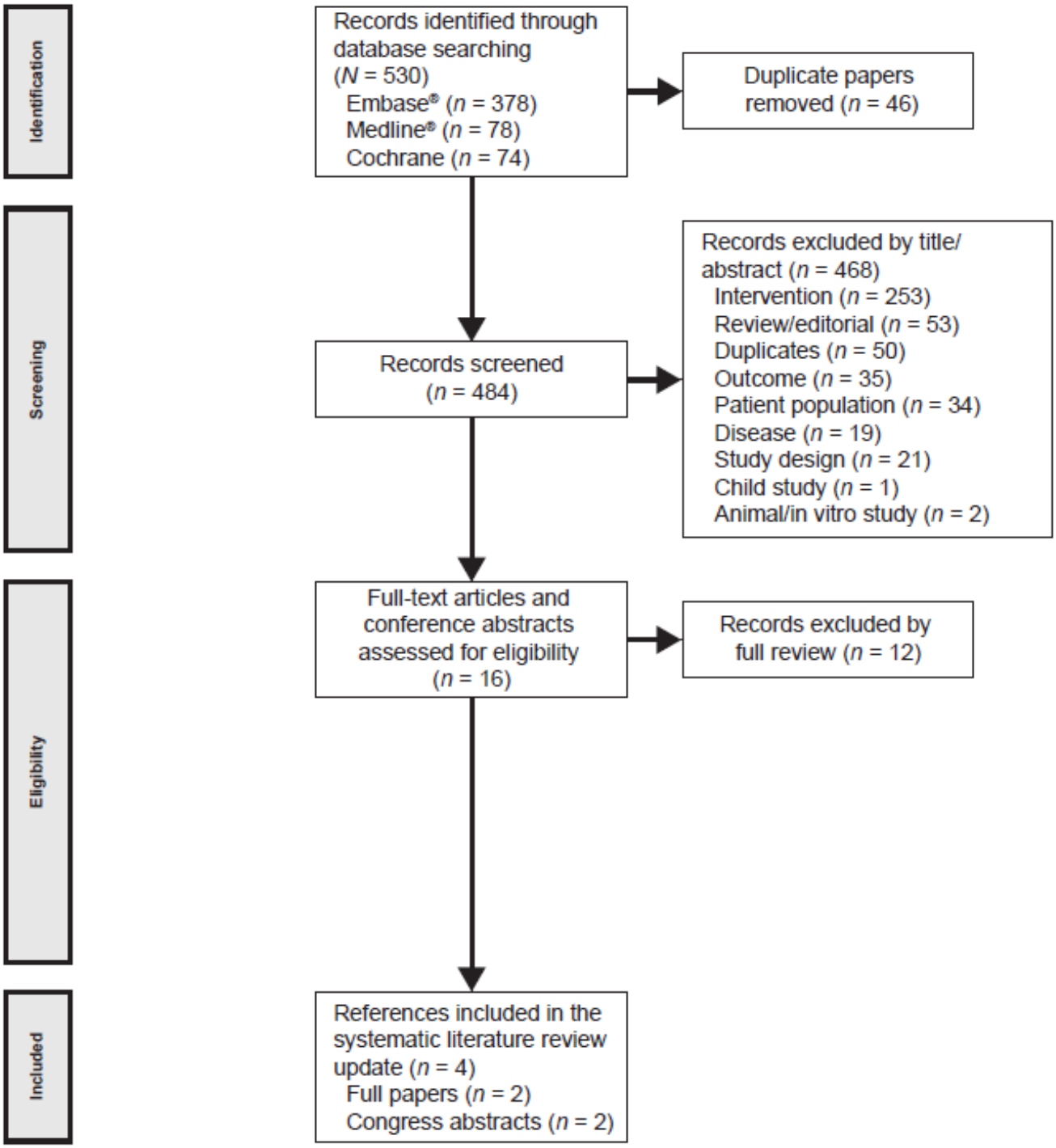
Supplementary Appendix Fig. 1. PRISMA flow diagram

i Initial screen conducted in August 2015

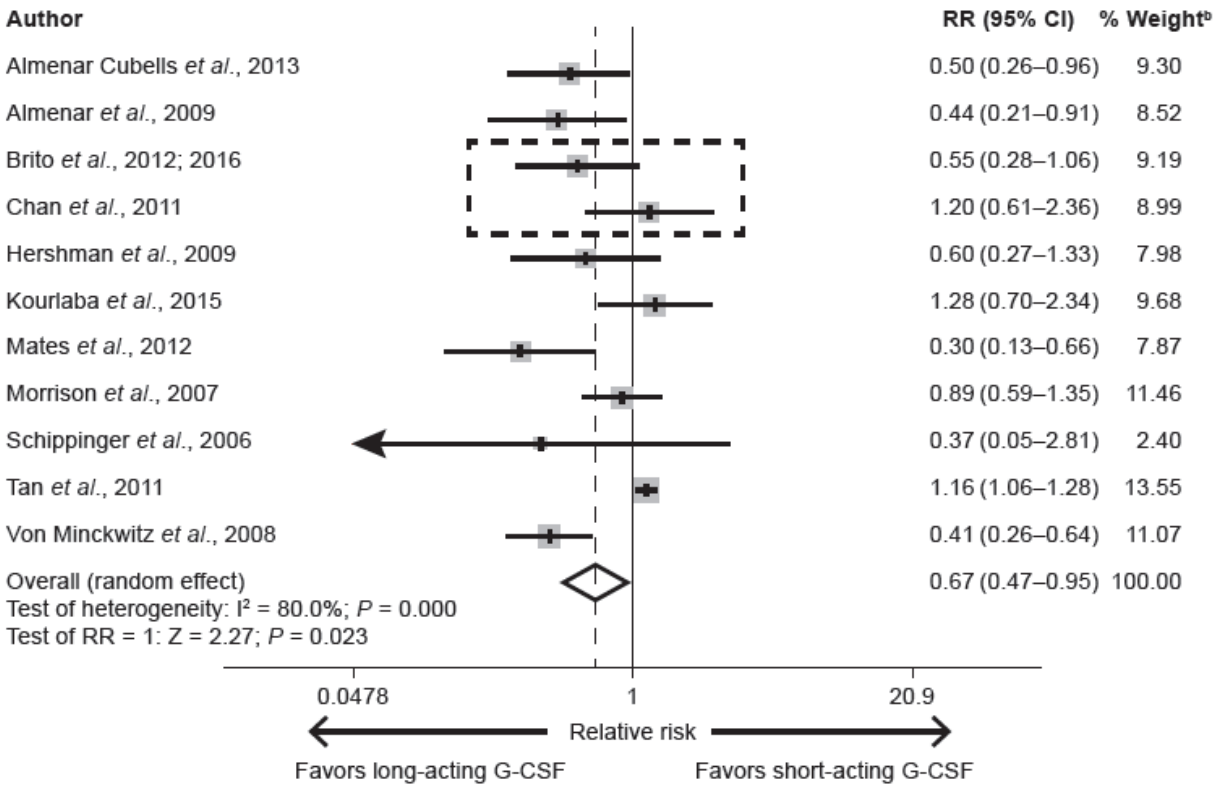


ii Refresher screen conducted in June 2016



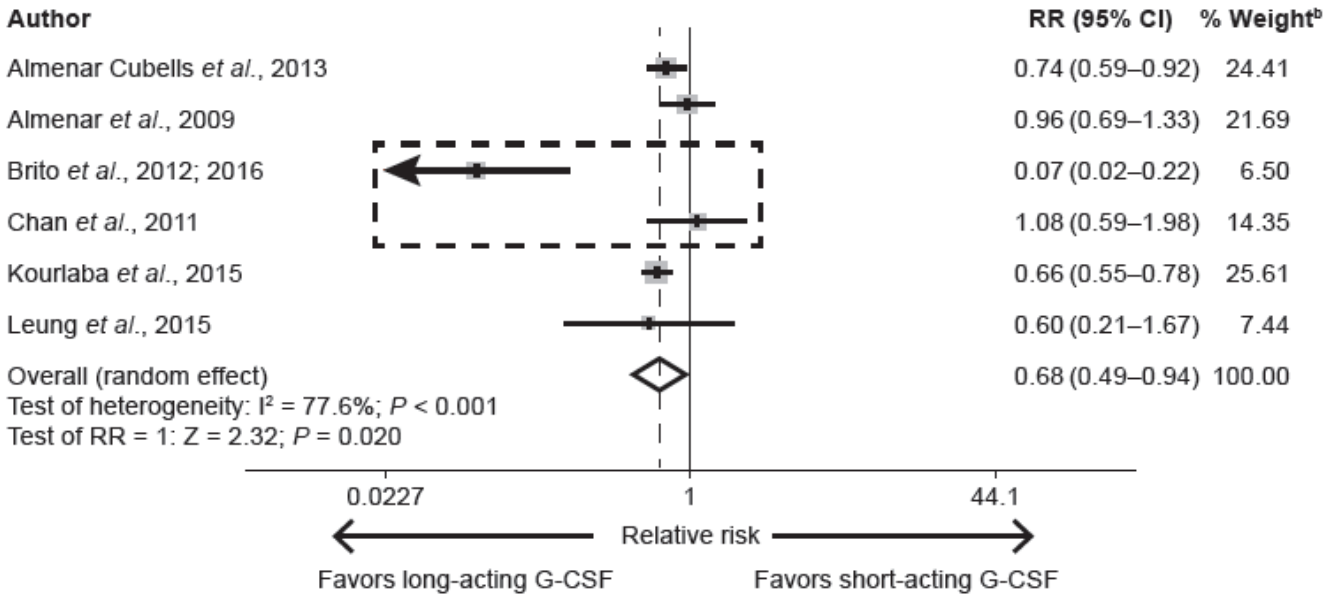
G-CSF granulocyte colony-stimulating factor, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *non-RCT* non-randomized controlled trial.

Supplementary Appendix Fig. 2. Meta-analysis to investigate the effect of short- vs long-acting G-CSFs on the incidence of FN in non-RCTs using a random-effect model.[a]



[a]The dotted square shows studies in which G-CSF administration adhered to label recommendations (≥7 days of treatment). [b]Weights are from random-effect analysis. *CI* confidence interval, *FN* febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor, I^2 chi-squared, *RCT* randomized controlled trial, *RR* relative risk.

Supplementary Appendix Fig. 3. Meta-analysis to investigate the effect of short- vs long-acting G-CSFs on chemotherapy dose delays in non-RCTs using a random-effect model.[a]



[a]The dotted square indicates studies in which G-CSF administration adhered to label recommendations (≥7 days of treatment). [b]Weights are from random-effect analysis. *CI* confidence interval, *G-CSF* granulocyte colony-stimulating factor, I^2 chi-squared, *RCT* randomized controlled trial, *RR* relative risk.