Pegylated granulocyte colony stimulating factor versus non-pegylated granulocyte colony stimulating factor for peripheral stem cell mobilization

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To compare the efficacy and safety of pegylated G-CSF with non-pegylated G-CSF for peripheral blood stem cell mobilization.
BACKGROUND

Description of the condition

The first allogenic non-identical twin bone marrow transplantation was done in 1956 by Dr. E. Donnall Thomas (Thomas 1957). However, it failed owing to graft rejection. The first successful bone marrow transplantation was done in 1958 by Dr. Georges Mathe in four physicists who had radiation exposure during a nuclear reactor accident in Yugoslavia in 1958 (Ilic 2011). Since then, there have been many advances in the field of stem cell transplantation. Traditionally, bone marrow has been the source of hematopoietic stem cells. However, the process of harvesting hematopoietic stem cells from the bone marrow results in unwanted general anesthetic risk, short-term physical morbidity and impaired quality of life of the donors (Bredeson 2004). Hence, other source of hematopoietic stem cells, such as the peripheral blood stem cells, is warranted (Siddiq 2009).

In humans under normal conditions, there is a constant quantity of hematopoietic stem cells that are able to escape from the large pool of hematopoietic stem cells in the bone marrow into the circulatory system (Cronkite 1997; Goodman 1962). However, this quantity of circulating hematopoietic stem cells (the peripheral blood stem cells) is too small to enable meaningful collection for the purpose of hematopoietic stem cell transplantation (HSCT).

Various methods have been used to increase the quantity of peripheral blood stem cells by mobilizing the hematopoietic stem cells from bone marrow. The most widely used methods are chemotherapy or colony stimulating factor or a combination of both. Stem cell mobilization using chemotherapy such as cyclophosphamide has been demonstrated to increase the quantity of peripheral blood stem cells by four times (Richman 1976), whereas granulocyte macrophage colony stimulating factor alone increased the peripheral blood stem cells by 18 times (Socinski 1988). Chemotherapy plus granulocyte macrophage colony stimulating factor was able to increase the quantity of peripheral blood stem cells up to 60 times (Socinski 1988). Another colony stimulating factor, granulocyte colony stimulating factor (G-CSF), alone or with chemotherapy was reported to increase the peripheral blood stem cells count by 58 times (Sheridan 1992) and 194 times (Hohaus 1993), respectively. Besides increasing the quantity of peripheral blood stem cells, G-CSF decreases the rates of infection in patients receiving cancer chemotherapy or those undergoing stem cell transplantation (Sung 2007). The peripheral blood stem cells have emerged as another source of hematopoietic stem cells and the term 'bone marrow transplantation' was hence changed to 'hematopoietic stem cell transplantation'.

G-CSF is an endogenous glycosylated hormone. Human G-CSF was first purified in 1985 (Nomura 1986; Welte 1985) following the purification of the G-CSF from rat in 1983 (Nicola 1983). Its cloning and characterization occurred at around the same time (Nagata 1986a; Souza 1986). It is a glycoprotein with a molecular weight of about 19 kDa. Its polypeptide production is controlled by a single locus gene located on chromosome 17q21-22. The core protein comprises 177 or 174 amino acids plus 33 amino acid signal sequences that are removed from the secreted form. There are two different core deoxyribonucleic acids (DNAs) that encode polypeptides of 177 amino acids (G-CSFa) and 174 amino acids (G-CSFb) owing to alternative splicing (Nagata 1986b). The amino acid sequences of these two G-CSF polypeptides are identical, except that G-CSFa has the insertion of three amino acids (Val-Ser-Glu) between Leu-35 and Val-36. These 177 or 174 amino acids are α-glycosylated at residue threonine 133. For therapeutic applications, the recombinant form of human G-CSF is available, which includes filgrastim, lenograstim, nartograstim, pegfilgrastim and pegnartogastim.

Description of the intervention

The initial form of recombinant human G-CSF has a very short half-life and needs to be administered daily or even twice daily in order to achieve a sustained effective blood concentration. By convention, stem cell mobilization using G-CSF with or without chemotherapy usually requires at least three to five days of daily subcutaneous injections to maximally mobilize the bone marrow stem cells to the peripheral blood. Therefore, a new form of recombinant human G-CSF, pegylated G-CSF, with a longer half-life and higher potency, has been developed to overcome this problem. The pegylated G-CSF, when used in the combination with chemotherapy for peripheral blood stem cell mobilization, is given as a single dose, usually one to two days after the completion of chemotherapy.

The pegylated recombinant human G-CSF currently available in the market is pegfilgrastim (Neulasta®, Amgen Inc. and Peplrex®, Kyowa Hakko Kirin Co. Ltd.) whereas the conventional non-pegylated recombinant human G-CSFs are filgrastim (Neupogen®, Amgen Inc.), lenograstim (Granocyte®, Chugai Pharmaceutical Co. Ltd.) and nartograstim (Neu-Up®, Kyowa Hakko Kirin Co. Ltd.).

Filgrastim (Neupogen®, Amgen Inc.) is a non-glycosylated G-CSF with one additional amino acid, methionine, at its N-terminal compared with human G-CSF. It is derived from Escherichia coli (E. coli) and was the first G-CSF approved for clinical usage in the US in 1991 (Molineux 2004). It is administered at the daily dose of 5 µg/kg to 10 µg/kg until the completion of peripheral blood stem cell collection depending on the type of mobilization. Its elimination is biphasic, with a static phase that correlates with renal excretion, which is the predominant route, and a phase that varies with white cell count owing to neutrophil receptor-mediated endocytosis and degradation. The half-life of filgrastim is about three and a half hours.

Lenograstim (Granocyte®, Chugai Pharmaceutical Co. Ltd.) is an authentic glycosylated G-CSF, derived from Chinese hamster ovary cells. It is given as a daily dose of 5 µg/kg to 10 µg/kg until the completion of peripheral blood stem cell collection depending
on the type of mobilization. Its half-life at steady state is about three to four hours and one to two hours if given subcutaneously and intravenously, respectively. Glycosylated G-CSF is more stable than non-glycosylated G-CSF in terms of temperature, pH and degradation by proteases in vitro. Lenograstim can be transported and stored at room temperature whereas filgrastim needs to be maintained at 4°C. Glycosylated G-CSF is more potent than non-glycosylated G-CSF on a weight for weight basis. Despite the potential benefits of physical, chemistry and bioactivity properties, there are no prospective randomized controlled trials to show superiority of lenograstim in terms of peripheral blood stem cell yield compared to filgrastim in chemotherapy plus G-CSF mobilization (Kopf 2006; Orciuolo 2011), or G-CSF mobilization alone (Ataergin 2008; de Arriba 1997) especially at bioequivalent dose (de Arriba 1997; Orciuolo 2011). The only available randomized controlled trial was G-CSF mobilization in donors, suggesting higher collection potency in males than females, and higher collection yields using lenograstim than filgrastim among male subjects (Fischer 2005).

Nartograstim (Neu-Up®, Kyowa Hakko Kirin Co. Ltd.) is a non-glycosylated mutated recombinant human G-CSF derived from E. coli with five peptide sequences change, which permits radioactive iodine attachment if needed. It is given as a daily dose of 8 µg/kg until the completion of peripheral blood stem cell collection. It was found to have two to four times higher specific activity, and more physicochemical, biologic and pharmacokinetic stability than filgrastim (Okabe 1990). Its half-life is nine hours and one hour if given subcutaneously and intravenously, respectively. It is available commercially in Japan. The available randomized control trial showed no statistical significant of stem cell yield between nartograstim and other G-CSFs (Takemoto 2000).

Pegfilgrastim (Neulasta®, Amgen Inc. and Peglasta®, Kyowa Hakko Kirin Co. Ltd.) is the pegylated form of filgrastim. It is a covalent conjugate between the N-terminal methionyl residue of the 11 grastim and mono-methoxypolyethylene glycol (PEG) with a molecular weight of 39 kDa, in which 20 kDa is attributed to PEG. Because its increased molecular weight prevents it from renal clearance, neutrophil-regulated kinetics become the primary route of clearance (> 99%) and hence the half-life is much longer compared with non-pegylated filgrastim. The half-life of pegfilgrastim ranges from 15 to 80 hours after a subcutaneous injection for a person without neutropenia. For a patient with neutropenia following chemotherapy, the drug level will remain in the therapeutic range initially but starts to drop as the neutrophil count recovers (Fenk 2006; Mey 2007; Zamboni 2003). Hence, pegfilgrastim is usually given as a ‘once-only injection’ and the dose can range from 100 µg/kg to 300 µg/kg depending on local practice. It is usually given at the dose of 6 mg or 12 mg because of the preparation.

Another form of pegylated G-CSF, pegnartograstim (synonym: Ro-25-8315, Kyowa Hakko Kirin Co. Ltd.), is currently available, but solely in Japan and for research purposes only. It is the pegylated form of nartograstim. The pegylation is at the amino terminus and the four lysine residues. The final product is a mixture of one to four PEG molecules attached to each molecule of nartograstim with predominant dipegylated protein (60%). Its half-life is 20 to 30 hours after a subcutaneous injection (van Der Auwera 2001).

In the current review, we will compare the effectiveness of the pegylated G-CSF as an intervention with the conventional non-pegylated G-CSF, namely filgrastim, lenograstim and nartograstim in the peripheral blood stem cell mobilization.

**How the intervention might work**

The twice a day dose of G-CSF (2 x 50 µg/kg) was shown to increase the quantity of peripheral blood stem cell yield as compared to a once daily dose (1 x 10 µg/kg) (Kroger 1999; Kroger 2000; Kroger 2004; Lee 2000). This suggests that a sustainable low level of G-CSF is better than a short pulse-like level of G-CSF to mobilize the peripheral blood stem cells. The pegylated G-CSF has similar tolerability, safety and pharmacologic profile as compared to the conventional G-CSF. Hence, the pegylated form of recombinant human G-CSF, which has a longer bioavailability than the non-pegylated form, might be superior to the non-pegylated form in peripheral blood stem cell mobilization.

The higher cost of pegylated G-CSF compared with non-pegylated G-CSF is always a concern. However, the pegylated G-CSF has been shown to be more cost effective than non-pegylated G-CSF, at least in febrile neutropenia (Eldar-Lissai 2008; Liu 2009; Lyman 2009). In addition, a single injection of pegylated G-CSF is highly preferred by the recipient compared with multiple injections of non-pegylated G-CSF (Tan Sean 2009).

Laboratory research has shown differences in the characteristics of stem cells collected following pegylated G-CSF administration that might promote earlier engraftment and less frequent incidence of graft-versus-host disease (Bruns 2008; Morris 2006; Sarkar 2003). The pegylated G-CSF has similar tolerability, safety and pharmacologic profile as compared to conventional G-CSF.

**Why it is important to do this review**

Different study centers have used different forms of G-CSF intervention in stem cell mobilization based on the local policy, experience and resources available. There is no international consensus on which form of G-CSF intervention (non-pegylated versus pegylated) is better or should be adopted in peripheral blood stem cell mobilization. Since the success of stem cell mobilization is a prerequisite for the success of autologous stem cell transplantation (Cottler-Fox 2003), any potential benefits of pegylated G-CSF compared with the non-pegylated form should be confirmed and translated into clinical practice.
This review will provide clinical evidence for policy makers to decide on the choice of G-CSF to be used in various clinical settings taking into account the cost of the intervention and acceptability by the patients.

**OBJECTIVES**

To compare the efficacy and safety of pegylated G-CSF with non-pegylated G-CSF for peripheral blood stem cell mobilization.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We will include all studies with randomized controlled trial design, evaluating the efficacy and safety of pegylated G-CSF against the non-pegylated G-CSF in peripheral blood stem cell mobilization regardless of the types of G-CSF used. We will exclude quasi-randomized and non-randomized comparative studies as such designs produced unreliable results that may affect the overall result of this review. We will include abstracts and unpublished data only if sufficient information on study design, patient characteristics, interventions and outcomes is available.

**Types of participants**

We will perform separate analyses for allogeneic and autologous stem cell transplantation.

For allogeneic stem cell transplantation, we will include studies with stem cell donors as the participants regardless whether they are unrelated or a sibling match to the stem cell recipient.

For autologous stem cell transplantation, we will include studies with patients diagnosed with various malignancies and undergoing peripheral blood stem cell mobilization.

No age restriction will be applied. However, analysis will be done separately for pediatric groups if adequate studies are found. No restriction to mobilization for autologous or allogeneic transplantation, specific underlying malignancies, specific mobilizing chemotherapy regimens, or specific G-CSF dosing schedule (i.e. once daily versus twice a day) will be applied. Analysis will be done separately if adequate studies are found for each of the characteristics factors mentioned above.

**Types of interventions**

We will compare pegylated G-CSF with non-pegylated G-CSF used in peripheral blood stem cell mobilization.

**Types of outcome measures**

**Primary outcomes**

Successful mobilization (defined as a CD34+ cell count of at least $2 \times 10^6$/kg of recipient’s body weight (adequate stem cells collection) collected in three or fewer apheresis procedures) (JACIE 1998; Montgomery 2007).

For allogeneic stem cell transplantation, the successful mobilization will be analyzed only in the donors. For autologous stem cell transplantation, this outcome will be analyzed in all patients who underwent stem cell mobilization.

**Secondary outcomes**

We will perform two separate analyses with different sets of secondary outcomes depending on the type of transplantation.

For allogeneic stem cell transplantation, we will analyze the following secondary outcomes:

1. day of engraftment for neutrophils and platelets post transplant in the recipients;
2. incidence of graft rejection and graft-versus-host disease post transplant in the recipients;
3. overall survival in the recipients;
4. disease-free survival in the recipients;
5. progression-free survival in the recipients;
6. adverse events in the donors;
7. quality of life of the recipients;
8. quantity of CD34 cells collected from the donors.

For autologous stem cell transplantation, we will analyze the following secondary outcomes:

1. quantity of CD34 cells collected;
2. day of engraftment for neutrophils and platelets post transplant;
3. overall survival;
4. disease-free survival;
5. progression-free survival;
6. adverse events.

**Search methods for identification of studies**

**Electronic searches**

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, latest issue), MEDLINE (1985 to present) and EMBASE (1985 to present) (Lefebvre 2011). The search strategy for MEDLINE is shown in Appendix 1. This search strategy is adapted for the development of respective search strategy for CENTRAL and EMBASE (see Appendix 2 and Appendix 3). We will also search the MEDLINE® In-Process & Other Non-Indexed Citations (PREM) using the same search
strategy as shown in Appendix 1. No language restrictions will be applied.

Searching other resources
We will search the following conference proceedings from year 2000 to present, if they are not included in CENTRAL:
1. American Society of Clinical Oncology;
2. American Society of Hematology;
3. European Group for Blood and Marrow Transplantation;
4. American Society for Blood and Marrow Transplantation.

Data collection and analysis
Selection of studies
Two review authors will screen the titles and abstracts of the studies identified from the above sources independently based on the eligibility criteria stated above (Higgins 2011a). If the screening process cannot be done satisfactorily from the titles and abstracts alone, the full-text versions of the studies will be retrieved and assessed. The screening for eligibility will be carried out using an eligibility form. The eligibility form will contain the following questions pertaining to the criteria for inclusion of studies in this review:
1. Is the study described as randomized control trial?
2. Is the study comparing pegylated G-CSF against non-pegylated G-CSF?
3. Were the participants undergoing peripheral blood stem cell mobilization?
The study is considered eligible to be included in this review only if it meets all the above criteria. We will contact the first author of the paper for clarification if there is inadequate information in regards to the eligibility. Any disagreement on the eligibility between two review authors will be resolved by discussion. If the disagreement persists, the third review author will be consulted for a final decision. Any duplicate reports will be identified and a final list of eligible studies will be used to obtain the full-text version for quality assessment and data extraction.

Data extraction and management
Data extraction will be performed independently by two review authors using a standard form containing a set of required information for this review. The data to be extracted includes the following:
1. general information (title, authors, contact information, country, language and year of publication, sponsors and conflict of interests);
2. trial characteristics (study design, inclusion and exclusion criteria, sample size, randomization procedure, allocation concealment, blinding procedure, presence of incomplete outcome data, presence of selective reporting, assessment of compliance, handling of withdrawals and losses to follow-up, type of analysis, type of apheresis machine, criteria for starting apheresis and presence of other sources of bias);
3. patient’s characteristics (age, gender, status, diagnosis, stage of the disease, type of the chemotherapy for the mobilization received);
4. interventions (type of pegylated and non-pegylated G-CSF, dosage, frequency, timing and duration of intervention);
5. primary outcomes information (mobilization outcome, quantity of CD34+ cells, timing of first apheresis and number of apheresis procedure);
6. secondary outcomes information, if available (post-transplant engraftment or rejection information, overall survival, disease-free survival, G-CSF-related adverse events and toxicity information).
We will contact the corresponding author of the paper to obtain information on any data that is not published or stated in the paper. Any discrepancy of the data extracted will be resolved by consensus between the two review authors. The third review author will be consulted for the final decision if the consensus cannot be achieved.

Assessment of risk of bias in included studies
We will assess the quality of the study using The Cochrane Collaboration’s tool for assessing risk of bias (Higgins 2011b). This will be performed independently by two review authors. The risk of bias will be assessed from the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias. Any disagreement on the ‘Risk of bias’ assessment will be resolved by consensus between the two review authors. If consensus cannot be achieved, the third review author will be consulted for a final decision. We will contact the corresponding author of the paper for further information if we cannot determine the risk of bias from the full text. If the paper does not meet any of the ‘Risk of bias’ criteria or the information on the risk of bias remains unclear, we will perform a sensitivity analysis.

Measures of treatment effect
The measures of treatment effect that will be used in this review are risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes and mean differences (MDs) with 95% CIs for continuous outcomes. For time to event data, we will estimate the log hazard ratio (HR) and standard errors from the results (coefficient, standard errors and P value) of Cox proportional hazards regression models reported in the papers. Then, we will use generic inverse variance method with random-effects model for meta-analysis. The data extraction for the HR from published data will be carried out according to the procedure as specified by Parmar (Parmar 1998) and Tierney (Tierney 2007).
Unit of analysis issues
A unit of analysis error may occur if some of the papers included in this review treat count data as dichotomous data (Deeks 2011). In this situation, we will ensure all information included for data analysis was treated as count data. If we are unable to obtain the relevant count data from the study, we will exclude the study from that particular data analysis. Studies that will be included in our review may have compared the treatment arms in different ways. In this situation, we will include only the relevant pair of comparison for relevant data analysis.

Dealing with missing data
We will contact the corresponding author for any missing data whenever possible. We will impute the missing data with the last observation carried forward or assuming all were of a poorer outcome if we cannot obtain the missing data. We will perform the sensitivity analysis and address the potential impact of the missing data on the findings of this review in the discussion (Higgins 2011c).

Assessment of heterogeneity
We will identify the presence of heterogeneity of treatment effects using forest plots and the Chi² test with a significant level of P value < 0.1. Heterogeneity will be quantified by measuring the inconsistency, I² statistic. We will take 30% < I² < 75% as moderate heterogeneity and I² ≥ 75% as considerable heterogeneity (Deeks 2011). The presence of heterogeneity will be explored by performing subgroup analysis and sensitivity analysis to determine the causes and assessing the robustness of the findings following meta-analysis.

Assessment of reporting biases
The presence of publication bias will be assessed using a funnel plot for each end point investigated. We will proceed with the relevant statistical test for funnel plot asymmetry if there are at least 10 studies available (Sterne 2011).

Data synthesis
Different studies that will be included in this review are likely to differ in the mix of participants and in the implementation of interventions. Hence, we will not assume a common effect size for this review and we will use the random-effects model for meta-analysis (Deeks 2011). Results based on random-effects model will allow generalization to a wider range of populations.

For dichotomous data, RRs will be pooled using the Mantel-Haenszel method. For continuous data, the weight mean difference (WMD) will be calculated if the data were reported using the same scale and standardized mean difference (SMD) will be calculated for the data reported in different scales. Other statistical analyses such as the Chi² test for heterogeneity, calculation of I² statistic, funnel plot and Egger's linear regression test will be carried out where relevant. We will use RevMan 5 (RevMan 2011) and SPSS software for statistical analysis. We will generate a 'Summary of findings' table (Schunemann 2011) using GRADE profiler software.

Subgroup analysis and investigation of heterogeneity
If sufficient studies are available, we will perform subgroup analysis to investigate for the presence of heterogeneity (Deeks 2011) based on the following factors:
1. age;
2. gender
3. patient’s status (donor or patient with malignancy);
4. diagnosis and stage of the disease;
5. presence of mobilization chemotherapy regimens;
6. type of G-CSF used (filgrastim, lenograstim, or nartograstim).
The test of interaction will be carried out to determine the significant differences between the subgroups.

Sensitivity analysis
The sensitivity analysis will be performed according to the following aspects where relevant:
1. different quality of studies;
2. presence of missing data;
3. presence of heterogeneity;
4. presence of publication bias.

Acknowledgements
We would like to thank Ina Monsef, trials search-coordinator of the Cochrane Haematological Malignancies Group, who has supported us with the development of the trial search strategy and provided us the search results.

We are also grateful to the following persons for their comments and improving the protocol: Céline Fournier (Consumer Editor), Sabine Kluge (Managing Editor) and Andrea Will (Assistant Managing Editor).
Pegylated granulocyte colony stimulating factor versus non-pegylated granulocyte colony stimulating factor for peripheral stem cell mobilization (Protocol)

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## References

### Additional references

**Ataergin 2008**

**Bredeson 2004**


**Bruns 2008**

**Cottler-Fox 2003**

**Cronkite 1997**
Cronkite EP. Response to “Mobilization of peripheral blood ‘stem’ cells: where there is smoke, is there fire?” Yes, there have been many fires, leaving cold coals. *Experimental Hematology* 1997;**25**(3):185–6.

**de Arriba 1997**

**Deeks 2011**

**Eldar-Lissai 2008**

**Fenk 2006**

**Fischer 2005**

**Goodman 1962**

**Higgins 2011a**

**Higgins 2011b**

**Hohaus 1993**

**Ilic 2011**

**JACIE 1998**
mobilization (Protocol)

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Kopf 2006

Kroger 1999

Kroger 2000

Kroger 2004

Lee 2000

Lefebvre 2011

Liu 2009

Lyman 2009

Mey 2007


Morris 2006

Nagata 1986a

Nagata 1986b

Nicola 1983

Nomura 1986

Okabe 1990

Orciuolo 2011

Parmar 1998

RevMan 2011
### Appendix 1. MEDLINE search strategy

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## Appendix 2. CENTRAL search strategy

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#12 (GRANULOCYTE NEAR/3 FACTOR)

#13 (#7 OR #8 OR #9 OR #10 OR #11 OR #12)

#14 (pegfilgrastim* or pegnartograstim* or peglasta*)

#15 (neulastim* or neulasta* or PEG-r*metHuG-CSF)

#16 neupopeg* or neupogem* or MAXY-G34*

#17 (#14 OR #15 OR #16)

#18 (#4 AND (#13 OR #17))

#19 "accession number" near pubmed

#20 (#18 AND NOT #19)

### Appendix 3. EMBASE search strategy

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<tr>
<td>6</td>
<td>(granulocyte*:ab,ti,tt NEXT/1 colony*:ab,ti,tt NEXT/1 stimulating*:ab,ti,tt NEXT/1 factor*:ab,ti,tt) OR G<em>CSF</em>:ab,ti,tt)</td>
</tr>
<tr>
<td>7</td>
<td>#5 and #6</td>
</tr>
<tr>
<td>8</td>
<td>'GRANULOCYTE COLONY-STIMULATING FACTOR':exp OR 'RECOMBINANT GRANULOCYTE COLONY STIMULATING FACTOR':de</td>
</tr>
<tr>
<td>9</td>
<td>(GCSF*:ab,ti,tt OR G-CSF*:ab,ti,tt)</td>
</tr>
<tr>
<td>10</td>
<td>(GRANULOCYTE*:ab,ti,tt NEAR/3 FACTOR*:ab,ti,tt)</td>
</tr>
</tbody>
</table>
### Pegylated granulocyte colony stimulating factor versus non-pegylated granulocyte colony stimulating factor for peripheral stem cell mobilization (Protocol)

<table>
<thead>
<tr>
<th>Step</th>
<th>Query</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>#7 OR #8 OR #9 OR #10</td>
</tr>
<tr>
<td>12</td>
<td>(pegfilgrastim*:ab,ti,tt OR pegnartogranistim*:ab,ti,tt OR peglasta*:ab,ti,tt)</td>
</tr>
<tr>
<td>13</td>
<td>(neulastim*:ab,ti,tt OR neulasta*:ab,ti,tt OR PEG-r*metHuG-CSF:ab,ti,tt)</td>
</tr>
<tr>
<td>14</td>
<td>(neupopeg*:ab,ti,tt OR neupogem*:ab,ti,tt OR MAXY-G34*:ab,ti,tt)</td>
</tr>
<tr>
<td>15</td>
<td>#12 OR #13 OR #14</td>
</tr>
<tr>
<td>16</td>
<td>(filgrastim*:ab,ti,tt OR lenograstim*:ab,ti,tt OR marogranist*:ab,ti,tt)</td>
</tr>
<tr>
<td>17</td>
<td>(naltoplastim*:ab,ti,tt OR neupogen*:ab,ti,tt OR neu-up*:ab,ti,tt OR topneuter*:ab,ti,tt)</td>
</tr>
<tr>
<td>18</td>
<td>(r-metHuG-CSF:ab,ti,tt OR grastin*:ab,ti,tt OR ngraf*:ab,ti,tt OR shilgast*:ab,ti,tt OR shilgrast*:ab,ti,tt OR grafeel*:ab,ti,tt)</td>
</tr>
<tr>
<td>19</td>
<td>(nartogranist*:ab,ti,tt OR neukine*:ab,ti,tt OR emgrast*:ab,ti,tt OR religrast*:ab,ti,tt OR graslopin*:ab,ti,tt OR nupen*:ab,ti,tt)</td>
</tr>
<tr>
<td>20</td>
<td>#16 OR #17 OR #18 OR #19</td>
</tr>
<tr>
<td>21</td>
<td>#11 OR #15 OR #20</td>
</tr>
<tr>
<td>22</td>
<td>#4 AND #21</td>
</tr>
<tr>
<td>23</td>
<td>(random*:ab,ti,tt OR placebo*:ab,ti,tt OR ((single:ab,ti,tt OR double:ab,ti,tt OR (triple:ab,ti,tt NEXT/1 blind*:ab,ti,tt))</td>
</tr>
<tr>
<td>24</td>
<td>'RETRACTED ARTICLE':de</td>
</tr>
<tr>
<td>25</td>
<td>#23 OR #24</td>
</tr>
<tr>
<td>26</td>
<td>('animal':de OR 'animals':de) NOT ('human':de OR 'humans':de)</td>
</tr>
<tr>
<td>27</td>
<td>('book':it OR 'conference paper':it OR 'editorial':it OR 'letter':it OR 'review':it)</td>
</tr>
<tr>
<td>28</td>
<td>'randomized controlled trial':exp</td>
</tr>
<tr>
<td>29</td>
<td>#27 NOT #28</td>
</tr>
<tr>
<td>30</td>
<td>(random:ab,ti,tt NEXT/1 (sampl*:ab,ti,tt OR digit*:ab,ti,tt OR effect*:ab,ti,tt OR survey*:ab,ti,tt OR regression*:ab,ti,tt))</td>
</tr>
<tr>
<td>31</td>
<td>'randomized controlled trial':exp</td>
</tr>
<tr>
<td>32</td>
<td>#30 NOT #31</td>
</tr>
<tr>
<td>33</td>
<td>#25 NOT (#26 OR #29 OR #31)</td>
</tr>
</tbody>
</table>
**HISTORY**


**CONTRIBUTIONS OF AUTHORS**

The principal author, Jew-Win Kuan, initiated and planned the review. All authors, Jew-Win Kuan, Anselm Ting Su, and Chooi-Fun Leong, were involved in writing the protocol.

**DECLARATIONS OF INTEREST**

None declared.

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**Internal sources**

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**External sources**

- No sources of support supplied