Guidelines for the Prevention and Treatment of Chemotherapy Induced Nausea and Vomiting

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Applies to: Salford Royal Care Organisation
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1. **What is this policy about?**

1.1 This guideline advises on the prevention and treatment of chemotherapy induced nausea and vomiting in Haematology Oncology patients.

If you have any concerns about the content of this document please contact the author or advise the Document Control Administrator.

2. **Where will this document be used?**

2.1 Clinical staff, including doctors, pharmacists and nurses, with responsibility for prescribing, dispensing or administering chemotherapy to patients.

2.3.1 This policy must be read in conjunction with the Trust Medicines Policy.

2.3.2 This document applies to adult patients only.

3. **Why is this document important?**

3.1 The safe prescribing and administration of anti-emetics is the responsibility of medical, nursing and pharmacy staff. Chemotherapy Induced Nausea and Vomiting (CINV) pose a significant clinical problem and there is difficulty in managing it effectively. Little is understood but it is recognised that uncontrolled nausea affects quality of life and impacts on cancer treatment. CINV can have a profound impact on the cancer treatment experience impairing social, physical and emotional functioning, negatively affecting quality of life (Decker et al, 2006; Glaus et al, 2004; Martin et al, 2003).

3.2 The safe administration of all anti-emetic drugs is the responsibility of medical, nursing and pharmacy staff. Care must be taken to protect patients from receiving the incorrect drug, dosage, or route of administration. If anti-emetic drug treatment is indicated the drug is chosen according to the aetiology of nausea and vomiting.

4. **What is new in this version?**

4.1 Addition of aprepitant and Akynzeo as additional options for acute and delayed chemotherapy induced nausea and vomiting.

5. **Guideline**

5.1 **Pattern and risk factors for CINV**

5.1.1 Nausea and vomiting are biological defence mechanisms that it is estimated would affect up to 50-60% of patients receiving chemotherapy if left untreated. Chemotherapy can cause several clinically distinct forms of emesis. The difference is important, as specific
management strategies are deployed based on the differing pathophysiologic processes and inciting events of each form.

5.1.2 There are four types of nausea and vomiting linked to chemotherapy treatment each with different aetiologies:

- Acute nausea and vomiting – onset 12 –24 hours post chemotherapy
- Delayed nausea and vomiting onset – more than 24 hours post chemotherapy.
- Anticipatory nausea and vomiting – a form of ‘Classical Pavlovian Conditioning’ in which patients become ‘conditioned’ to associate specific stimuli such as sights, sounds and smells with the chemotherapy experience.
- Refractory nausea and vomiting – symptoms remain uncontrolled despite preventative anti-emetic therapy.

5.1.3 There are certain characteristics that can indicate whether a patient will be more or less predisposed to developing chemotherapy induced nausea and vomiting. These include:

- Age – the younger the patient the more likely they are to develop chemotherapy induced nausea and vomiting, even when using the same chemotherapeutic agents. In addition, younger patients are more prone to the dystonic reactions associated with the dopamine - blocking agents used to prevent or treat chemotherapy induced emesis.
- Gender – The prevalence of CINV is higher in women, especially if they have a history of pregnancy related emesis.
- Motion sickness – Patients with a history of motion sickness have an increased risk.
- History of heavy alcohol use – patients with a history of high alcohol intake experience less chemotherapy related emesis, particularly with highly emetogenic agents such as cisplatin.
- Concomitant radiation treatment and previous exposure to chemotherapy - increase the risk
- Non-chemotherapy related causes of emesis - should be considered in this client group. These include bowel obstruction, renal insufficiency, brain metastases and other medicines such as narcotic analgesia.

5.2 Hesketh classification of emetogenic potential

5.2.1 For the purposes of these guidelines chemotherapy medicines have been grouped using 5 levels of emetogenic treatment including the levels of emetogenic potential (Table 1). The Hesketh classification is both practical and easy to use, and has been utilised by many reputable centres as a framework for the development of anti-emetic guidelines. It considers important treatment variables such as dose and route of administration and
proposes an algorithm to predict the emetogenesis of combination chemotherapy regimens (Diagram 1).

5.2.2 However, it can only be utilised for patients receiving standard chemotherapy treatment. It cannot be used to determine the emetogenic potential of high-dose chemotherapy regimens for the mobilisation of peripheral blood stem cells or autologous bone marrow transplant procedures. Physicians should continue to be guided by the recommended anti-emesis treatment contained in current high dose treatment protocols.

5.2.3 The algorithm presented in Diagram 1 – Recommendations for the Prevention and Treatment of Nausea and Vomiting related to Cancer Chemotherapy is a suggested guideline and is not fully comprehensive. These recommendations are intended to be practical, cost effective and where possible evidence based.

5.2.4 When determining an appropriate anti-emetic regimen it is important to assess each patient individually as the degree of emesis they experience after chemotherapy will vary widely. Specific patient characteristics are known to enhance or diminish the risk of developing treatment-induced emesis are discussed in section 3.
## Table 1
Hesketh classification of individual chemotherapy agents’ emetic potential

<table>
<thead>
<tr>
<th>Level</th>
<th>Frequency of emesis</th>
<th>Agents</th>
<th>Dose / Route Considerations (IV or indicate otherwise)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;10%</td>
<td>Bleomycin, Busulphan, Chlorambucil, Cladribine, Fludarabine, Hydroxycarbamide, Melphalan, Mercaptopurine, Methotrexate, Thioguanine, Vinblastine, Vincristine</td>
<td>PO, PO, PO, PO, &lt;50mg/m2</td>
</tr>
<tr>
<td>2</td>
<td>10-30%</td>
<td>Amsacrine, Azacitidine, Bortezomib, Doxorubicin, Etoposide, High Dose Methotrexate</td>
<td>sc, All doses IV or PO 50-250mg/m²</td>
</tr>
<tr>
<td>3</td>
<td>30-60%</td>
<td>Asparaginase, Cyclophosphamide, Doxorubicin, Epirubicin, Idarubicin, Ifosphamide, Lomustine, Methotrexate, Mitoxantrone</td>
<td>PO, &lt;750mg/m², 20-60mg/m², &lt;90mg/m², PO, 250 -1000mg/m², 15mg/m²</td>
</tr>
<tr>
<td>4</td>
<td>60-90%</td>
<td>Carmustine, Cisplatin, Cyclophosphamide, Cytarabine, Daunorubicin, Doxorubicin, Methotrexate, Procarbazine</td>
<td>&lt; 250mg/m², &lt; 50mg/m², 750mg - 1500mg/m², &lt; 1gm/m², &gt; 60mg/m², &gt;1gm/m², PO</td>
</tr>
<tr>
<td>5</td>
<td>&gt;90%</td>
<td>Bendamustine, Carmustine, Cisplatin, Cyclophosphamide, Dacarbazine</td>
<td>&gt;250mg/m², &gt;50mg/m², &gt;1500mg/m²</td>
</tr>
</tbody>
</table>
Diagram 1: Recommendations for the Prevention and Treatment of Nausea and Vomiting Related to Cancer Chemotherapy

1. Prevention of Acute Chemotherapy Induced Nausea & Vomiting for first 24 hours
   - No routine preventative agents required
   - Cyclizine 50mg po 30min pre chemo and / or dexamethasone 8mg po iv 30min pre chemo 1,3

2. Prevention of Delayed Chemotherapy Induced Nausea & Vomiting (post 24 hours)
   - No routine preventative agents
   - Ondansetron 8mg bd po for 48 hours post last dose of chemotherapy

3. Treatment (breakthrough or rescue) of Nausea & Vomiting following failure of Primary Prevention
   - Dosage:
     - Dexamethasone 4mg po bd or 8mg po od x 3 days, only if not on steroids.
     - May add Anti-emetic or Akyroiz - see additional information
   - Domperidone 10mg po 30min pre meals and at bedtime x 4-5 days

Footnotes:
1. May add to any regimen lorazepam 0.5-1mg SL (or po) pre chemo for anxiety related nausea.
2. For all patients on chemotherapy, irrespective of Hesketh levels, treatment for breakthrough or rescue nausea and vomiting, used on a PRN basis, should be prescribed. The sequential use of these agents is supported only by clinical experience.
3. Oral route is preferred. may use iv route when patient cannot retain oral dosage form.

* Determine Hesketh level first
5.3 Prevention of acute CINV

5.3.1 CINV is classified as acute if it occurs within a few minutes or up to 24 hours post chemotherapy administration. Generally the intensity of acute onset emesis peaks after 5-6 hours, with the exception of the commonly used agent Cyclophosphamide; this may cause a more delayed acute emetic response that begins 8-10 hours post administration.

5.3.2 The most important thing to remember about the management of acute chemotherapy induced emesis is that prevention is better than cure. The administration of effective anti-emetic medicines prior to chemotherapy can significantly reduce the incidence of severe acute emesis, but it is very difficult to control once it is established. The problems of delayed, anticipatory and refractory vomiting can be ameliorated if acute emesis is prevented or minimised.

5.3.3 For chemotherapy agents with mildly emetogenic potentials (Hesketh level 2), the use of cyclizine (and/or dexamethasone if steroids are not part of the chemotherapy regimen) as acute prophylactic anti-emetic therapy is often sufficient. Effective control of emesis induced by agents with moderate or highly emetogenic potentials (Hesketh levels 3-5); the addition of a 5HT₃ receptor antagonist is recommended. The 5HT₃ receptor available in this Trust is ondansetron.

5.3.4 Please note that a recent directive from the MHRA www.mhra.gov.uk limits the maximum IV dose to 16mgs infused over at least 15 minutes (8mg limit if patient over 75) to reduce the risk of QT interval prolongation and cardiac arrhythmias. However the data demonstrates that the oral route is equally as efficacious and this is the preferred route when used in Haemato-oncology in this Trust. If patients are vomiting then ondansetron melts should be considered. If clinically IV is considered the most effective route then not more than 8mgs should be administered infused over at least 15 minutes and a prior ECG should be considered in the at risk group. The concomitant use of steroids enhances the efficacy of the anti-emetic regimen.

5.3.5 Persistent nausea and vomiting which fails to respond to the above interventions may be treated using aprepitant or Akynzeo®.

5.3.6 Aprepitant is licensed in moderately emetogenic and highly emetogenic chemotherapy for preventing acute and delayed CINV. Aprepitant is a selective high affinity antagonist at human substance P neurokinin (NK1) receptors. It is used in combination with ondansetron and dexamethasone. Patients should receive 125mg aprepitant orally 1 hour prior to chemotherapy on day 1, then 80mg in the morning on day 2 and 3 respectively. Patients should receive ondansetron as normal (8mg twice daily). Dexamethasone needs to be prescribed according to potential emetogenicity of the regimen the patient is due to have: for moderately emetogenic regimens, dexamethasone is 12mg in the morning on day 1. For highly emetogenic chemotherapy, patient should have 12mg in the morning on day 1, then 8mg in the morning on day 2, 3 and 4 respectively.

5.3.7 Aprepitant commonly causes headache, loss of appetite, constipation, fatigue and raised LFTs.

5.3.8 Aprepitant has significant interactions, most notably with drugs metabolised via the CYP3A4 pathway. Aprepitant reduces the effectiveness of the combined oral

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contraceptive pill. Additional barrier contraceptive precautions need to be used if aprepitant is prescribed to a patient reliant on the combined oral contraceptive pill.

5.3.9 See the Summary of Characteristics for full prescribing advice.

5.3.10 Akynzeo® is a single dose combined anti-emetic, licensed for use in preventing acute and delayed chemotherapy induced nausea and vomiting. It is formulated as a single capsule containing 0.5mg palonosetron and 300mg netupitant. Palonosetron is a 5HT3 antagonist and netupitant is a selective antagonist of human substance P/neurokinin 1 (NK1) receptors. Suggested dexamethasone dosing is dependent on likely emetogenicity of chemotherapy (see table above). Patients receiving a regimen that is known to be highly emetogenic should receive dexamethasone 12mg in the morning on day 1, followed by 8mg in the morning on day 2, 3 and 4 respectively.

5.4 Prevention of delayed chemotherapy induced nausea and vomiting

5.4.1 CINV is classified as delayed if it occurs more than 24hrs after the administration of chemotherapy and is very common following the administration of cisplatin, cyclophosphamide or doxorubicin. Cisplatin related emesis reaches its maximum intensity 48 to 72hrs post administration and can last for up to 6-7 days.

5.4.2 As with acute emesis prevention is better than cure, the approaches include:

- Continuing ondansetron for 48hrs post treatment, after which the 5HT3 receptor antagonists become much less effective.
- add in dexamethasone 4mgs orally bd or 8mg IV daily (only if the patient is not already taking steroids as part of their chemotherapy regimen) for 2-5 days
- and/or domperidone 10mg orally tds.

5.4.3 Dexamethasone and domperidone have been shown to be effective for the prophylaxis of delayed onset of nausea and vomiting.

5.4.4 Please note that domperidone is a dopamine antagonist, and dopamine antagonists are associated with extrapyramidal side effects such as dystonic movements, sedation and oculogyric crisis. However, as domperidone does not cross the blood brain barrier, extrapyramidal side effects are rare. In the rare circumstances that they do occur they reverse spontaneously and completely when treatment is stopped. Epidemiological studies have also demonstrated a possibility that domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. The risk appears to be greater in patients older then 60yrs and at a daily dose of more than 30mgs. Use of domperidone combined with other drugs that prolong the QTc interval requires that caution be exercised in patients who have existing prolongation of cardiac conduction intervals (particularly QTc), patients with significant electrolyte disturbance or an underlying cardiac disease such as congestive heart failure.

5.4.5 Aprepitant and Akynzeo are both effective at treating delayed emesis following chemotherapy and may be used if the above interventions have proved ineffective. Dosing is as per their use in acute CINV (See section 5.3 for information)
5.5 Prevention of anticipatory/anxiety related nausea and vomiting

5.5.1 The occurrence of nausea and vomiting before patients receive chemotherapy is a conditioned response, and therefore can only occur following a negative past experience associated with chemotherapy. Benzodiazepines given prior to subsequent chemotherapy can provide some protection from anxiety related nausea and vomiting e.g. lorazepam 0.5-1mg sublingually or orally (sublingual route is unlicensed).

5.6 Treatment of refractory chemotherapy induced nausea and vomiting

5.6.1 Patients for whom nausea and vomiting is uncontrolled despite the administration of preventative anti-emesis treatment should be assessed as to whether it is breakthrough or post anti-emetic emesis. Breakthrough emesis is emesis that occurs despite prophylaxis, and all patients should receive a prescription for medication to treat breakthrough nausea and vomiting (e.g. cyclizine). In the case of breakthrough emesis a reassessment of the preventative anti-emetic medication should be carried out.

5.6.2 If nausea and vomiting persists post completion of anti-emetic therapy then it is classified as refractory. Levomepromazine 6.25mg orally, s/c or IV up to four times a day may be tried; this is an unlicensed use of this drug. The parenteral route might give better symptom control initially then switched to oral.

6. Roles and responsibilities

6.1 Clinical Lead for Chemotherapy, Dr C Barnes, is responsible for advocating compliance with these guidelines.

6.2 All staff are responsible for checking that their activity complies with the recommendations in these guidelines.

7. Monitoring document effectiveness

7.1
- **Key standards:** all patients prescribed chemotherapy will have appropriate anti-emetics prescribed
- **Method(s):** chemotherapy prescriptions will be monitored
- **Team responsible for monitoring:** Chemotherapy Service Group will monitor
- **Frequency of monitoring:** Guideline will be reviewed every three years
- **Process for reviewing results and ensuring improvements in performance:** issues will be discussed through the Chemotherapy Service Group and the Haematology Business Meeting

8. Abbreviations and definitions

8.1 **bd** – twice a day
**CINV** – chemotherapy induced nausea and vomiting

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9. References and Supporting Documents


9.2 Related SRFT/PAT document

Cytotoxic Chemotherapy Policy 200TD(C)46 SRFT
10. Document Control Information

It is the author’s responsibility to ensure that all sections below are completed in relation to this version of the document prior to submission for upload.

<table>
<thead>
<tr>
<th>Nominated Lead author:</th>
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<th>Role - Lead Chemotherapy Nurse</th>
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</thead>
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<td>Lead Author’s Manager:</td>
<td>Name - Debi Lee</td>
<td>Role - Lead Nurse</td>
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<tr>
<td>Applies to:</td>
<td>Please indicate which Care Organisation(s) this document applies to:</td>
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<td>Salford CO</td>
<td>Oldham CO</td>
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<tr>
<td>Document developed in consultation with:</td>
<td>Chemotherapy Service Group including Haematology Consultants, Lead Chemotherapy Pharmacist, Lead Chemotherapy Nurse, Haematology Pharmacist, Haematology CNSs</td>
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<tr>
<td>Keywords/phrases:</td>
<td>Chemotherapy, Nausea and Vomiting, CINV</td>
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<tr>
<td>Communication plan:</td>
<td>This revised guideline will be circulated via the Chemotherapy Service Group. It will be available on the intranet as a resource for medical and nursing staff involved in the management of haematology / oncology patients undergoing treatment with chemotherapy. Haematology Consultants, SpRs, ANP, Pharmacist, CNSs and ward staff will all be notified by e-mail when the revised policy is available on the intranet. These guidelines will be promoted by the Consultant Haematologists, Haematology ANP, Lead Chemotherapy Nurse, Haematology pharmacists and Haematology Clinical Nurse Specialists.</td>
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<tr>
<td>Document review arrangements:</td>
<td>This document will be reviewed by the author, or a nominated person, at least once every three years or earlier should a change in legislation, best practice or other change in circumstance dictate.</td>
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<tr>
<td>Approval:</td>
<td>Medicines Management Group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr Richard Cooper – Chair, Lindsey Harper – Director of Pharmacy Medicines Management Group</td>
<td></td>
</tr>
<tr>
<td>How approved:</td>
<td>Chair’s actions -</td>
<td>Formal Committee decision - Approved</td>
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</tbody>
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### 11. Equality Impact Assessment (EqIA) screening tool

Legislation requires that our documents consider the potential to affect groups differently, and eliminate or minimise this where possible. This process helps to reduce health inequalities by identifying where steps can be taken to ensure the same access, experience and outcomes are achieved across all groups of people. This may require you to do things differently for some groups to reduce any potential differences.

#### 1a) Have you undertaken any consultation/involvement with service users, staff or other groups in relation to this document? If yes, specify what.

Yes
Consulted members of the Chemotherapy Service Group, which includes medical, pharmacy and nursing staff. Policy circulated for comments and readability.

#### 1b) Have any amendments been made as a result? If yes, specify what.

Yes
Changes made to reflect feedback received.

#### 2) Does this policy have the potential to affect any of the groups listed below differently?

Place an X in the appropriate box: Yes, No or Unsure

This may be linked to access, how the process/procedure is experienced, and/or intended outcomes. Prompts for consideration are provided, but are not an exhaustive list.

<table>
<thead>
<tr>
<th>Protected Group</th>
<th>Yes</th>
<th>No</th>
<th>Unsure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (e.g. are specific age groups excluded? Would the same process affect age groups in different ways?)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Sex (e.g. is gender neutral language used in the way the policy or information leaflet is written?)</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Race (e.g. any specific needs identified for certain groups such as dress, diet, individual care needs? Are interpretation and translation services required and do staff know how to book these?)</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Religion &amp; Belief (e.g. Jehovah Witness stance on blood transfusions; dietary needs that may conflict with medication offered.)</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Sexual orientation (e.g. is inclusive language used? Are there different access/prevalence rates?)</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Pregnancy &amp; Maternity (e.g. are procedures suitable for pregnant and/or breastfeeding women?)</td>
<td></td>
<td>X</td>
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</tr>
<tr>
<td>Marital status/civil partnership (e.g. would there be any difference because the individual is/is not married/in a civil partnership?)</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Gender Reassignment (e.g. are there particular tests related to gender? Is confidentiality of the patient or staff member maintained?)</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Human Rights (e.g. does it uphold the principles of Fairness, Respect, Equality, Dignity and Autonomy?)</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Carers (e.g. is sufficient notice built in so can take time off work to attend appointment?)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Socio/economic (e.g. would there be any requirement or expectation that may not be able to be met by those on low or limited income, such as costs incurred?)</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Disability (e.g. are information/questionnaires/consent forms available in different formats upon request? Are waiting areas suitable?) Includes hearing and/or visual impairments, physical disability, neurodevelopmental impairments e.g. autism, mental health conditions, and long term conditions e.g. cancer.</td>
<td></td>
<td>X</td>
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</table>

Are there any adjustments that need to be made to ensure that people with disabilities have the same access to and outcomes | X |  |  |
from the service or employment activities as those without disabilities? (e.g. allow extra time for appointments, allow advocates to be present in the room, having access to visual aids, removing requirement to wait in unsuitable environments, etc.)

3) Where you have identified that there are potential differences, what steps have you taken to mitigate these?
(what action has been taken or will be taken, who is responsible for taking a future action, and when it will be completed by – may include adjustment to wording of policy or leaflet to mitigate)

Patients with learning disabilities may find it more difficult to understand about side effects, medication to manage them and what to do in the event of problems at home.

There may be communication difficulties between staff and patients who don’t speak English or who are deaf.

4) Where you have identified adjustments would need to be made for those with disabilities, what action has been taken?
(what action has been taken or will be taken, who is responsible for taking a future action, and when it will be completed by – may include adjustment to wording of policy or leaflet)

Patients with learning disabilities would be spoken to in language appropriate to their understanding. Best interest meetings are arranged to discuss treatment. Carers are given all medications to be taken by the patient at home and contact numbers given for advice.

Interpreters, usually via Language Line but in person if appropriate, are used to explain to patients who don’t speak English that nausea and vomiting is a side effect of their treatment and the medication they are being given to try and prevent it, how to take medication and what to do in the event of any problems.

For a deaf patient requiring the support of someone to sign, we can also access this through the hospital.

Will this policy require a full impact assessment? No
(a full impact assessment will be required if you are unsure of the potential to affect a group differently, or if you believe there is a potential for it to affect a group differently and do not know how to mitigate against this - Please contact the Inclusion and Equality team for advice on equality@pat.nhs.uk)

Author: Type/sign: Anne Stout Date: 16/07/2018

Sign off from Equality Champion: Date: 30/07/2018