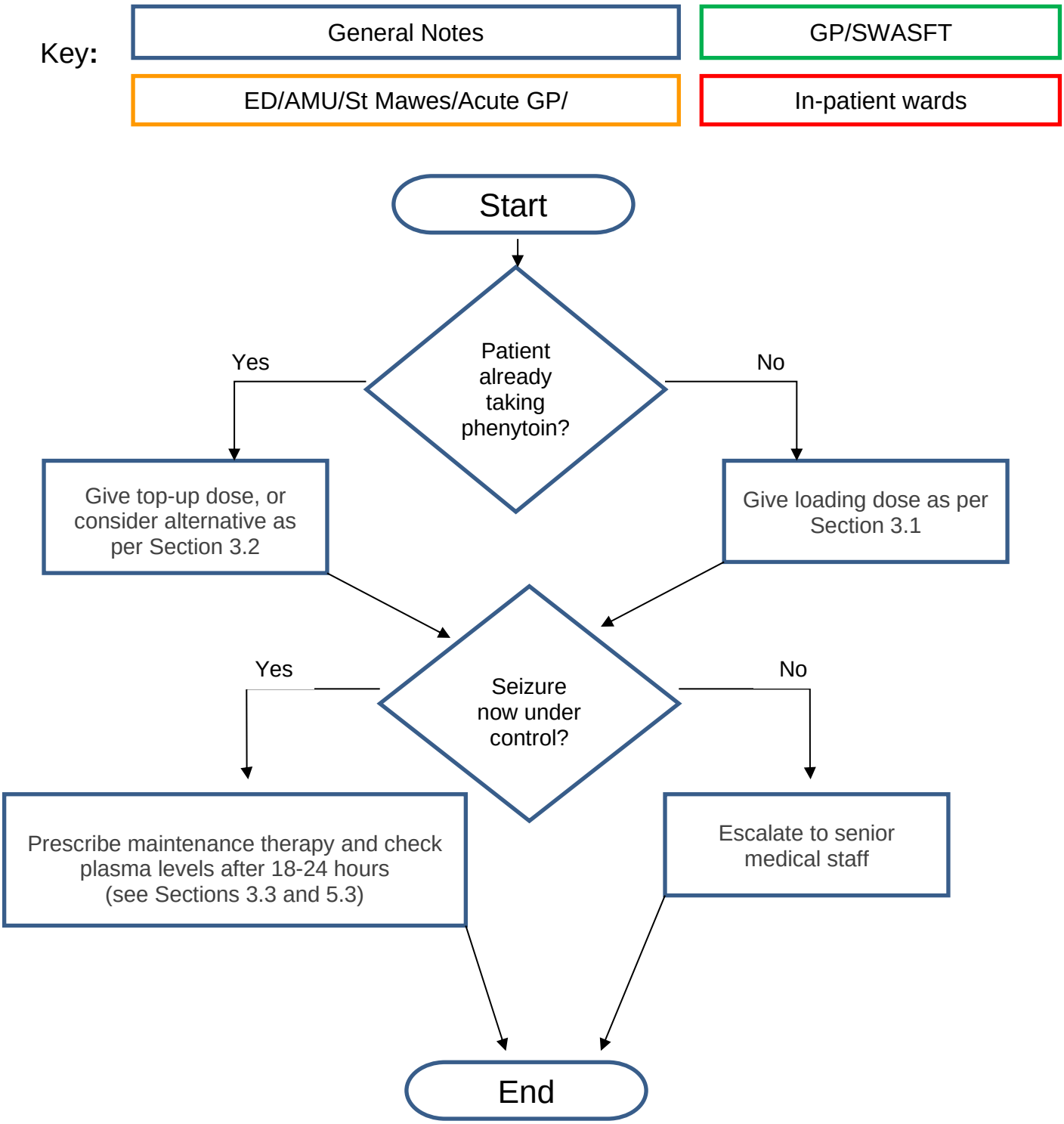
Royal Cornwall Hospitals
NHS Trust

Use of Phenytoin in Epilepsy Clinical Guideline

V3.0

August 2024

Summary


Key:
General Notes
GP/SWASFT
ED/AMU/St Mawes/Acute GP/
In-patient wards
Start
Patient already taking phenytoin?
Yes
No
Give top-up dose, or consider alternative as per Section 3.2
Give loading dose as per Section 3.1
Seizure now under control?
Yes
No
Prescribe maintenance therapy and check plasma levels after 18-24 hours (see Sections 3.3 and 5.3)
Escalate to senior medical staff
End

1. Aim/Purpose of this Guideline

1.1. To provide clinical staff with guidance relating to the management of phenytoin for status epilepticus and follow-on therapy in adults.

1.2. This version supersedes any previous versions of this document.

Data Protection Act 2018 (UK General Data Protection Regulation – GDPR) Legislation.

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Data Protection Act 2018 and UK General Data Protection Regulations 2016/679 is applicable to all staff; this includes those working as contractors and providers of services.

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2. The Guidance

2.1. Phenytoin is one of a number of treatments used in the management of status epilepticus, following which it can be used as maintenance treatment. However, the use of phenytoin is not straightforward; it has a narrow therapeutic index and its use in status epilepticus is further complicated by the requirement for a loading dose.

2.2. When should phenytoin be used for status epilepticus?

Category	Information
Premonitory stage (pre-hospital)	Diazepam 10−20 mg given rectally, repeated once 15 minutes later if status continues to threaten, or midazolam 10 mg given buccally. If seizures continue, treat as below.
Early status **(5 to 15 minutes)**	Lorazepam (intravenous) usually a 4 mg bolus (2mg if <40kg), repeated once after 10−20 minutes; rate not critical. If intravenous route is unavailable, administer lorazepam intramuscularly or give diazepam 10mg-20mg rectally. Give usual anti-epileptic drug (AED) medication if already on treatment. For sustained control or if seizures continue, treat as below.

Established status (failed to respond 15 to 30 minutes after onset)	Note: With the exception of contra-indications phenytoin is the second choice from the 3 second line options of levetiracetam, phenytoin and sodium valproate in the current "Management of Convulsive Status Epilepticus in Hospital Clinical Guideline". Phenytoin infusion - see Section 3.1 for loading doses. If the patient is already taking phenytoin, see Section 3.2. Phenobarbital bolus of 10–15 mg/kg at a rate of 100 mg/minute. N.B. For potential use in Critical Care only due to the risk of respiratory failure, especially if benzodiazepines have been previously administered.
Refractory status	General anaesthesia

2.3. Phenytoin dosing

Use the red supplementary drug chart for an IV prescription.
Sample prescription – example 70kg patient:

EPMA Supplementary intravenous therapy prescription sheet

All infusions, infusion fluids, blood and plasma must also be prescribed in EPMA

Date	Infusion solution	Name and dose of additive	Infusion volume	Duration of infusion	Infusion rate	Proposed start time	Prescriber signature	Infusion bag batch no	Time actually started	Given by / Checked by	Time finished	Pharmacy use
1/4/2014	Sodium Chloride 0.9%	Phenytoin 1250mg	250mL	35 minutes			Doctor (bleep)					

EPMA Form available from Unit 4: CHA 3179

2.4. IV loading dose

2.4.1. Phenytoin is the second choice of the second line treatment options in status epilepticus (levetiracetam first choice and sodium valproate third choice). However, re-consider its use if phenytoin levels will not be able to be carried out as set out in the therapeutic monitoring in 8.3.

2.4.2. For phenytoin-naïve patients, loading doses can be calculated as follows:

Weight (kg)	Dose (mg/mL)
40-49	750mg in 100mL
50-64	1000mg in 100mL
65-78	1250mg in 250mL
78-92	1500mg in 250mL
>92	1750mg in 250mL

Table 2: Banded phenytoin loading doses.

2.5. Patients already on phenytoin

2.5.1. **If a phenytoin level is known**, single ‘top-up’ doses of 250-750mg for patients already taking phenytoin with sub-therapeutic levels can be calculated using the formula:

phenytoin 'top-up' dose [mg] = (20 - phenytoin level [mg/L]) x 0.7 x weight [kg]

	Body weight			
	50kg	60kg	70kg	80kg
Dose	**Concentration increase**			
250 mg	7 mg/L	6 mg/L	5 mg/L	4.5 mg/L
500 mg	14 mg/L	12 mg/L	10 mg/L	9 mg/L
750 mg	21 mg/L	18 mg/L	15 mg/L	13.5 mg/L

Table 3: Increase in phenytoin concentration with 'top-up' doses (adapted from UKMI).

2.5.2. For example, if the patient weighs 70 kg and has a plasma level of 5 mg/L, a single dose of 750 mg will increase the plasma concentration from 5mg/L to 20mg/L i.e. by 15mg/L.

2.5.3. **When phenytoin levels are not immediately available and other second line treatments (levetiracetam or sodium valproate) have been considered and ruled out:**

Phenytoin levels may take up to an hour to be reported and treatment in status epilepticus should not be delayed. If it is not possible to obtain phenytoin levels in a timely manner, options include:

- Giving half the recommended loading dose until levels are available.
- Limiting loading doses to 500mg.
- Contacting the neurology team.

2.6. Administration:

2.6.1. Before giving, closely inspect the solution for precipitates or discolouration (injection must be clear, but a faint yellow colour is acceptable).

2.6.2. **Do not dilute in a glucose-containing solution. Do not mix with any other fluids or medicines, as precipitation may occur.**

2.6.3. Administer via a **large gauge cannula** through a **0.2micron filter** into a **large vein**, as phenytoin has a high pH and a high osmolality, making it irritating to veins and causing tissue damage if extravasation occurs. Flush the line with sodium chloride 0.9% before and after administration to avoid local venous irritation.

2.7. Loading dose

Dilute in 100-250mL of sodium chloride 0.9% and give over 35 minutes.

2.8. Maintenance and top-up doses

2.8.1. IV phenytoin can be given undiluted by slow injection (preferred) or in a diluted infusion.

2.8.2. Inject via a syringe pump at a rate not exceeding 50 mg/min. In elderly patients, or those with pre-existing cardiac disease, give at a maximum of 25 mg/min.

2.8.3. If dilution is essential, dilute with 50-100mL sodium chloride 0.9% to a final concentration of less than 10 mg/mL and administer via a 0.22-0.5 micron in-line filter.

2.8.4. **Do not dilute with any fluid other than sodium chloride 0.9%.**

2.8.5. **Do not mix with any other drugs.**

2.8.6. **Prepare immediately before administration, and ensure the infusion is completed within 1 hour of preparation.**

2.8.7. For further information, please check Medusa

2.9. Administration via enteral feeding tubes

Administration via enteral feeding tubes is not generally recommended. Contact Medicines Information for further advice if necessary

2.10. Monitoring:

2.10.1. Check LFTs and FBC before initiating.

2.10.2. Continuous ECG and regular blood pressure and respiratory rate monitoring is essential. Reduce rate of administration if bradycardia or hypotension occurs.

2.10.3. Cardiac resuscitation equipment should be available.

2.10.4. Inspect injection site regularly for any signs of irritation or inflammation

2.10.5. Inform medical staff immediately if the following occur:

- Hypotension (marked drop in BP from patient's baseline).
- Arrhythmias.
- Respiratory depression.
- **ANY** pain/erythema at Venflon site, especially tracking along arm.

2.11. Maintenance dose:

2.11.1. Start 18 to 24 hours after the loading dose.

2.11.2. IV or PO – start with 100mg TDS or 300mg OD.

2.11.3. Slow IV injection over 2 minutes or IV infusion using a 0.2micron filter and complete infusion within one hour of preparation.

2.11.4. Doses should be adjusted carefully according to plasma concentrations at increments **of not more than 25-50mg per day.**

2.11.5. Usual maintenance doses range from 200mg to 500mg per day, preferably taken as a single dose at night.

2.11.6. 100mg phenytoin sodium as injection, tablets or capsules is approximately equal in therapeutic effect to 90mg phenytoin base as suspension (90mg/15ml) or Epanutin Infatabs.

2.12. Renal / hepatic impairment:

2.12.1. Dose as in normal renal function. Monitor closely, as protein binding may be decreased, leading to increased free phenytoin.

2.12.2. 7.2 Dose reductions may be needed in hepatic impairment to avoid toxicity.

2.13. Pharmacokinetic considerations:

2.13.1. Phenytoin is a narrow therapeutic drug - there is little difference between a sub-therapeutic, a therapeutic, and a toxic dose. After initial loading, doses should be guided by plasma levels and the larger clinical picture:

- Therapeutic plasma concentrations tend to reside between 10-20 mg/L, although some patients may be controlled with lower serum levels.
- Toxicity is generally seen with plasma concentrations >20 mg/L.
- Nystagmus, ataxia and diminished mental capacity are seen at 30-40 mg/L.
- Cardiac toxicity may be more related to rapid administration rates, potentially due to transient, high concentrations.

2.13.2. Phenytoin displays capacity-limited metabolism. This means that for a small increase in a therapeutic dose, there can be a large increase in steady state concentrations. Adjustment of phenytoin maintenance doses should be made cautiously, at increments of no more than 25-50mg per day.

2.14. Therapeutic drug monitoring

2.14.1. Trough levels should be taken 18-24 hours after loading, and before the first maintenance dose is given.

2.14.2. Steady state usually occurs 7-10 days after initiation of therapy. Monitor maintenance plasma levels 2 weeks after any dose changes, or following the introduction/withdrawal of a potentially interacting drug.

2.14.3. Do not base treatment on plasma levels alone. Efficacy or toxicity should be determined based on the clinical condition of the patient.

2.14.4. Interpretation of phenytoin levels may be altered in hypoalbuminaemia (especially < 32g/L) as well as uraemia and pregnancy. **Contact Pharmacy or Neurology for further advice in these areas.**

2.15. Drug Interactions

2.15.1. Phenytoin affects and is affected by a large number of drugs. Please see the BNF for a list of common interactions, and/or ask your ward pharmacist for advice.

2.15.2. Phenytoin for intravenous use must not be mixed with other drugs.

2.16. Side effects and monitoring

2.16.1. Serious side-effects include blood dyscrasias and skin disorders such as exfoliative, purpuric or bullous rashes, Lupus erythematosus, Stevens-Johnson syndrome or toxic epidermal necrolysis.

2.16.2. Other side-effects include: nausea/vomiting, constipation, hepatotoxicity, insomnia, transient nervousness, tremor, paraesthesia, dizziness, headache and anorexia.

2.16.3. For a full list, please consult the BNF or relevant SPC.

2.17. Signs of toxicity

2.17.1. Common signs include nystagmus, diplopia, slurred speech and ataxia. Mental confusion, hyperglycaemia and dyskinesias can also occur.

2.17.2. Overdose may result in hypotension, respiratory depression and coma.

2.18. Monitoring requirements

2.18.1. Check liver function tests (LFTs) and full blood count (FBC) before initiating treatment.

2.18.2. Regular blood test monitoring is not recommended as routine, unless problems are suspected. However, FBC, U&Es, LFTs, vitamin D levels and other tests of bone metabolism are recommended every 2-5 years.

2.18.3. Patients should be counselled on how to recognise signs of blood or skin disorders and monitored for signs of suicidal ideation.

2.18.4. See Section 2.14 for information on therapeutic drug monitoring, and Section 2.2 for information on monitoring required during intravenous administration.

2.19. Withdrawal

Abrupt withdrawal of phenytoin may precipitate status epilepticus. Doses should be slowly tapered if discontinuation is necessary.

2.20. Other considerations

Check allergy status before prescribing phenytoin. Cross-sensitivity has been reported between phenytoin and carbamazepine.

3. Monitoring compliance and effectiveness

Information Category	Detail of process and methodology for monitoring compliance
Element to be monitored	The prescribing and monitoring of phenytoin in epilepsy.
Lead	Medications Safety Pharmacist
Tool	An audit tool will be developed to monitor compliance. Datix will be used to identify clinical incidents.
Frequency	The policy will be monitored every three years, or sooner as clinical incidents dictate.
Reporting arrangements	The audit results will be reported to the Medication Practice Committee (MPC) and the individual areas audited. Clinical incidents on Datix will be reported to the senior nurse/manager in that area and will also be reported to the Medication Safety Group.
Acting on recommendations and Lead(s)	The MPC will co-ordinate the actions to the audit results. Actions from incident reports will be at a local level and may also resulting broader actions, co-ordinated by the Medication Safety Group.
Change in practice and lessons to be shared	Required changes to practice will be identified and actioned within the time frame specified in the action plan.

4. Equality and Diversity

4.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the Equality Diversity And Inclusion Policy or the Equality and Diversity website.

4.2. Equality Impact Assessment

The Initial Equality Impact Assessment Screening Form is at Appendix 2.

Appendix 1. Governance Information

Information Category	Detailed Information
Document Title:	Use of Phenytoin in Epilepsy Clinical Guideline V3.0
This document replaces (exact title of previous version):	Use of Phenytoin in Epilepsy Clinical Guideline V2.0
Date Issued/Approved:	5 July 2024
Date Valid From:	August 2024
Date Valid To:	August 2027
Directorate / Department responsible (author/owner):	Stephen Chan, Lead Pharmacist for Eldercare, Neurology and Stroke. Jonathan Stewart, Consultant Neurologist.
Contact details:	01872 252598
Brief summary of contents:	Dosing and administration instructions for phenytoin in status epilepticus and ongoing maintenance.
Suggested Keywords:	Phenytoin, Loading Dose, Epilepsy, Status Epilepticus
Target Audience:	**RCHT:** Yes **CFT:** No **CIOS ICB:** No
Executive Director responsible for Policy:	Chief Medical Officer
Approval route for consultation and ratification:	Medication Practice Committee, Neurology
Manager confirming approval processes:	Richard Andrzejuk
Name of Governance Lead confirming consultation and ratification:	Kevin Wright
Links to key external standards:	None
Related Documents:	NHS Improvement (2016), Patient safety alert - Risk of death and severe harm from error with injectable phenytoin.

Information Category	Detailed Information
	NICE (2012), CG137 - Epilepsies: diagnosis and management. UKMI (2016), Q and A 444.1 - How can we minimise the risks to patients when using intravenous phenytoin in status epilepticus (SE)?
Training Need Identified?	No
Publication Location (refer to Policy on Policies – Approvals and Ratification):	Internet and Intranet
Document Library Folder/Sub Folder:	Clinical / Pharmacy

Version Control Table

Date	Version Number	Summary of Changes	Changes Made by
February 2017	V1.0	Initial Issue	Bronwin Staple Lead Pharmacist Medicines Information
November 2020	V2.0	Minor amendments to flow chart to reflect changes in ward names. Minor updates to sections 2 and 3 to reflect changes to trust status epilepticus guidance.	Stephen Chan, Lead Pharmacist for Eldercare, Stroke and neurology
May 2024	V3.0	Amendment to point 2.1 removing reference to recent patient safety alert because it is no longer recent. Minor amendment to table in point 2.2 to reflect phenytoin is the second choice out of the 3 second line options. Amendment to point 2.4 where previously states no preference amongst second line treatment options in status epilepticus to fall in line with current Trust status epilepticus guidelines.	Stephen Chan, Lead Pharmacist for Eldercare, Stroke and neurology

All or part of this document can be released under the Freedom of Information Act 2000.

All Policies, Strategies and Operating Procedures, including Business Plans, are to be kept for the lifetime of the organisation plus 6 years.

This document is only valid on the day of printing.

Controlled Document.

This document has been created following the Royal Cornwall Hospitals NHS Trust The Policy on Policies (Development and Management of Knowledge Procedural and Web Documents Policy). It should not be altered in any way without the express permission of the author or their Line Manager.

Appendix 2. Equality Impact Assessment

Section 1: Equality Impact Assessment (EIA) Form

The EIA process allows the Trust to identify where a policy or service may have a negative impact on an individual or particular group of people.

For guidance please refer to the Equality Impact Assessment Policy (available from the document library) or contact the Equality, Diversity, and Inclusion Team rcht.inclusion@nhs.net

Information Category	Detailed Information
Name of the strategy / policy / proposal / service function to be assessed:	Use of Phenytoin in Epilepsy Clinical Guideline V3.0
Directorate and service area:	Pharmacy
Is this a new or existing Policy?	Existing
Name of individual completing EIA (Should be completed by an individual with a good understanding of the Service/Policy):	Stephen Chan, Lead Pharmacist for Eldercare, Stroke and neurology
Contact details:	01872 252587

Information Category	Detailed Information
1. Policy Aim - Who is the Policy aimed at? (The Policy is the Strategy, Policy, Proposal or Service Change to be assessed)	To provide guidance on the dosing and administration of phenytoin in status epilepticus.
2. Policy Objectives	To ensure safe prescribing and use of phenytoin.
3. Policy Intended Outcomes	Use of phenytoin complies with the guidance set out in this document.
4. How will you measure each outcome?	Ongoing audit.
5. Who is intended to benefit from the policy?	Patients receiving phenytoin.
6a. Who did you consult with? (Please select Yes or No for each category)	• Workforce: Yes • Patients/ visitors: No • Local groups/ system partners: No • External organisations: No

Information Category	Detailed Information
	• Other: No
6b. Please list the individuals/groups who have been consulted about this policy.	**Please record specific names of individuals/ groups:** Medications Safety Group. Medicines Information. Neurology.
6c. What was the outcome of the consultation?	Agreed.
6d. Have you used any of the following to assist your assessment?	**National or local statistics, audits, activity reports, process maps, complaints, staff, or patient surveys:** No.

7. The Impact

Following consultation with key groups, has a negative impact been identified for any protected characteristic? Please note that a rationale is required for each one.

Where a negative impact is identified without rationale, the key groups will need to be consulted again.

Protected Characteristic	(Yes or No)	Rationale
Age	No	
Sex (male or female)	No	
Gender reassignment (Transgender, non-binary, gender fluid etc.)	No	
Race	No	
Disability (e.g. physical or cognitive impairment, mental health, long term conditions etc.)	No	
Religion or belief	No	
Marriage and civil partnership	No	
Pregnancy and maternity	No	

Protected Characteristic	(Yes or No)	Rationale
Sexual orientation (e.g. gay, straight, bisexual, lesbian etc.)	No	

A robust rationale must be in place for all protected characteristics. If a negative impact has been identified, please complete section 2. If no negative impact has been identified and if this is not a major service change, you can end the assessment here.

I am confident that section 2 of this EIA does not need completing as there are no highlighted risks of negative impact occurring because of this policy.

Name of person confirming result of initial impact assessment: Stephen Chan, Lead Pharmacist for Eldercare, Stroke and Neurology.

If a negative impact has been identified above OR this is a major service change, you will need to complete section 2 of the EIA form available here:
Section 2. Full Equality Analysis