University Hospitals of Derby and Burton
NHS Foundation Trust

# TRUST POLICY FOR INITIATION AND REVIEW OF VALPROATE-CONTAINING MEDICINES

| **Reference Number**<br><br>POL-CLIN/4451/24 | **Version:**<br>1.0 | | **Status:**<br>Final | **Author:**<br>James Hooley<br>**Job Title:**<br>UHDB Medication Safety Officer |
|---|---|---|---|---|
| Version / Amendment History | Version | Date | Author | Reason |
| | 1.0 | March 2024 | James Hooley | New Policy in response to new regulatory requirements and National Patient Safety Alert |

**Intended Recipients:**

- Adult and Paediatric Neurology services.
- Pharmacy Business Unit - All clinical pharmacy staff (Pharmacists and Medicines Management Technicians).
- Medical and non-medical prescribers covering all adult and inpatient areas at UHDB (elective and emergency).

**Training and Dissemination:**

- Adult and Paediatric Neurology and Pharmacy: All prescribers and specialists managing epilepsy or seizures to receive and read Policy. Incorporate into induction and updates. Ensure change history and link to new document is cascaded to all during version updates or related SOP changes.
- Pharmacy BU Clinical team: As above.
- Medical and non-medical prescribers outside of epilepsy / seizure management. Receive general communications from Trust safety groups (Medicines Safety Group / Valproate short-life working group) in relation to risk of valproate which highlights the Policy and procedures for reference if / when required

**To be read in conjunction with:**

- Clinical Procedures included in the appendices to this Policy
- Pharmacy SOP 043 - Valproate-containing Medication
- Trust's clinical guidelines for initiation of valproate in an emergency for this age group

**In consultation with and Date:**

UHDB Sodium Valproate Short Life Working Group (set up by Deputy Medical Director - Quality and Safety in response to NatPSA2023 / 013 and including input from adult neurology, paediatric neurology and pharmacy).

UHDB Medication Safety Group, August 2024.

| | |
|---|---|
| **EIRA stage One** Completed Yes<br>stage Two Completed No | |
| **Approving Body and Date Approved** | Trust Delivery Group<br>2 September 2024 |
| **Date of Issue** | August 2024 |
| **Review Date and Frequency** | August 2027 (every 3 years) |
| **Contact for Review** | James Hooley<br>UHDB Medication Safety Officer |
| **Executive Lead Signature** | Executive Chief Medical Officer |

**Contents Page**


| SECTION | | Page Number |
|---|---|---|
| 1. | Introduction | 4 |
| 2. | Purpose and Outcomes | 4 |
| 3. | Key Responsibilities and Duties | 4 |
| 4. | Definitions Used | 6 |
| 5. | Policy | 6 |
| 6. | Monitoring Compliance and Effectiveness | 10 |
| 7. | References and Useful Links | 10 |
| APPENDICIES | | |
| Appendix 1 | SOP 1 Inpatient Admissions (Emergency and Elective): Procedure for FEMALE patients on Valproate-containing Medication | 11 |
| Appendix 2 | SOP 2 - Inpatient initiation (MALE and FEMALE under 55 years): Procedure for initiating Valproate-containing Medication | 12 |
| Appendix 3 | Pharmacy Department SOP: Valproate-containing Medication (document held on QPulse/ Sharepoint) | 13 |

## 1. Introduction

Due to the known significant risk of serious harm to a baby after exposure to valproate in pregnancy, the MHRA introduced new regulatory measures in 2024 for sodium valproate, valproic acid and valproate semisodium (valproate). This follows a comprehensive review of safety data, advice from the Commission on Human Medicines (CHM) and an expert group, and liaison with clinicians and organisations.

Exposure to valproate in pregnancy is associated with physical birth defects in 11% of babies and neurodevelopmental disorders in up to 30-40% of children, which may lead to permanent disability. Since 2018, valproate has been contraindicated in women of childbearing potential unless the Pregnancy Prevention Programme (PPP) is in place.

In 2022, the CHM reviewed the latest data on the safety of valproate. The CHM heard from patients and other representatives on their views about how valproate was being used and how the risks were currently managed. The CHM noted that data from the Medicines and Pregnancy Registry show pregnancies in England continue to be exposed to valproate.

The CHM also considered other known risks of valproate, including the risk of impaired male fertility. The CHM considered pre-clinical data on possible transgenerational risks with prenatal exposure, as well as data from studies in juvenile and adult animals suggesting adverse effects on the testes. There is currently limited data available on many of these risks in humans and further studies are planned. However, the CHM noted many patients receiving valproate have other therapeutic options with fewer reproductive potential harms.

The MHRA announced the recommendations of the CHM in December 2022, leading to new regulatory measures from the MHRA which commenced in early 2024.

Valproate is contra-indicated in pregnancy or in females under the age of 55 and of child-bearing potential, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled.

## 2. Purpose and Outcomes

In accordance with MHRA regulations, this Policy will support clinical staff at the Trust to:

- Embed practice and procedures that ensure valproate for men and women under 55 years is only being used if other treatments are ineffective or not tolerated
- Reduce initiation of valproate to only those patients for whom no other therapeutic options are suitable
- Ensure that any use of valproate in women of childbearing potential is in accordance with the Pregnancy Prevention Programme (PPP).

## 3. Key Responsibilities and Duties

**Neurology (seizure) Specialists - Adult and Paediatric**
Responsible for prescribing, including dual specialist agreement for new initiation where necessary in this Policy. Reviewing ALL female patients under 55 taking valproate-containing medicines on an annual basis (complete ARAF) and ensuring they continue to meet requirements of the pregnancy prevention programme.

Annotating all prescriptions for patients under 55 to indicate that two specialists have

authorised initiation. Additionally for females under 55, annotating all prescriptions to confirm that the annual RAF has been completed within 12 months.

**Neurology Service - Clinical leads, service managers and activity coordinators**
Identifying and planning for the clinical resource to meet the identified needs of the population and implementing the new regulatory measures. Maintaining a registry of male and female patients who have been initiated on Valproate within their service. Recalling female patients annually for consultation and completion of an ARAF. Ensuring systems are in place to upload any paper RAF / ARAF forms into digital systems and ensure transfer of information across the interface between primary, secondary and if appropriate tertiary care providers.

**Prescribers (all other non-neurology specialties and general areas)**
Liaising with neurology specialists when considering (and always before initiating) oral valproate for patients under 55 years in accordance with this Policy. Following the Trust's clinical guidelines for initiation of valproate in an emergency for this age group (which may still require neurology authorisation as detailed in clinical guidelines or SOPs). For female patients who present already taking valproate, referring relevant patients to neurology in accordance with this Policy and SOPs within the appendices (e.g. if pregnant, planning / risk of pregnancy or if patient attends with uncontrolled epilepsy).

**Clinical Pharmacists and Medicines Management Technicians.**
Supporting specialist and non-specialist prescribers with all of the above. In accordance with pharmacy SOP (Appendix): Checking an ARAF has been completed within 12 months for all females under 55 years and checking / documenting this so it is included on all prescriptions and orders approved for dispensing. For inpatients, documenting relevant checks (ARAF date, PPP status, patient access to alert cards / books, counselling etc) in the medicines reconciliation records and updating throughout episodes of care to ensure relevant changes are transferred to discharge documentation. Dispensary responsibilities as below.

**Pharmacy staff working in dispensaries**
In accordance with pharmacy SOP (see Appendix): Following legislative requirements to only dispense oral valproate in whole packs (except where patient-specific risk assessment has been undertaken and authorises otherwise). Providing patient resources such as the Patient Guide, Patient Card (females under 55 only) and recommended counselling.

**Medication Safety Officer**
Reviewing and updating this Policy in response to national alerts, regulatory guidance or local incidents. Leading on communications to non-neurology prescribers within the Trust and pharmacy teams outside of the specialist neurology teams.

**Medical Director Office**
Implementing this Policy as part of the response to the National Patient Safety Alert (2023)[1] and establishing an ongoing quality audit strategy to provide assurance to ICB and Patients.

## 4. Definitions Used

| | |
|---|---|
| **Valproate** | Valproate containing medicines encompass those containing active ingredients such as valproic acid, sodium valproate and semi-sodium valproate. Within this Policy the umbrella term of 'valproate' will be used to encompass all the above-named active ingredients. |
| **Male / Female** | Throughout this Policy the term female and male refers to biological sex at birth and not gender. |
| **Pregnancy Prevention Programme (PPP)** | The national programme for valproate pregnancy prevention. This is referred to as 'Prevent' in some publications (summarised in section 5.3.3 of this Policy) |
| **RAF** | Risk Acknowledgement Form. Completion of a RAF is a single process for males under 55 on initiation / first assessment for treatment. |
| **ARAF** | Annual Risk Acknowledgement Form used for female patients. It is a different format to the form used for males, although both may be referred to as RAF. In the case of females it may be referred to as ARAF, as in most cases, they will be reassessed by specialists every 12 months. |

## 5. Policy

5.1. Initiation of Valproate for **patients 55 years and over**

There are no regulatory or legislative restrictions on patients 55 years and over. Prescribing and supply can be undertaken on routine clinical judgment in consultation with the individual patient. National and local clinical guidelines apply alongside general medicines legislation and local Trust-wide medicines Policies.

5.2. Initiation of Valproate for **male and female** patients 0 - 54 years of age

For all patients under 55 years, consider all other suitable therapeutic options before newly prescribing valproate.

5.2.1. Valproate must not be started in new patients **(male or female)** younger than 55 years, unless two specialists (Fig. 1) independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply.[1]

5.2.2. Multidisciplinary Teams (MDTs) may be used to discuss and agree a prescribing decision, with the second signatory being a representative of the MDT who meets the criteria for a specialist signatory.[1,2]

5.2.3. Adult and Paediatric neurology services must maintain a register of approved specialist signatories who can prescribe and / or countersign RAF / ARAF forms.

*Fig 1. The MHRA[2] have published a list of roles that could fulfil the second signatory. These individuals should not be in direct line management of the primary signatory.*

The CHM advised that the second specialist signatory could include the following:

- Consultant adult or paediatric neurologists
- Consultant psychiatrists
- Speciality and associate specialist doctors in psychiatry and neurology
- Speciality doctors in psychiatry
- Paediatrician with special interest in epilepsy
- Paediatrician who regularly manages complex epilepsy or bipolar disorder
- Epilepsy Nurse Consultant
- Specialist Nurses in relevant disciplines

5.2.4. The details of the two signatories and the decision to treat should be recorded in the RAF for all female and male patients under the age of 55.

National templates are available as below:

- Male RAF
- Female ARAF

Completion is a regulatory requirement and not a legal requirement. A wet (pen / ink) signature is therefore not legally required from the two specialists or patient / parent / guardian. However, the form includes fields to facilitate this if being completed in paper format.

The form can be recreated within clinical systems or digital shared care systems as these develop. If digital forms are implemented by clinical specialties, the Trust's Medicines Safety Group should review these as part of the governance process, to ensure the form retains all of the same considerations and data fields as the national RAF / ARAF. Consult the Trust's Medication Safety Officer (Medicines Safety Group chair) to support any transition to digital RAF / ARAF formats.

5.2.5. Confirmation a RAF has been completed (males) and confirmation of ARAF and the date of completion within 12 months (females) must be documented on **all** prescriptions for valproate. E.g. 'ARAF complete DD / MM / YY'

**Note:** The pharmacy will not be able to dispense valproate for outpatients under 55 years without explicit confirmation of RAF / ARAF completion on the prescription (note: recently scanned paper RAF / ARAF are unlikely to be available to the pharmacy on the day of dispensing).

**5.3.** Additional regulations for prescribing in **Females 0 - 54 years**

5.3.1. For patients established on valproate prior to February 2024 and for ongoing continuation of valproate prescribing -

At their next annual specialist review, all females aged 0 - 54 years should be reviewed using an ARAF, which will include the need for a second specialist signature if the patient is to continue with valproate and subsequent annual reviews with one specialist unless the patient's situation changes.[1]

5.3.2. Females of childbearing potential (from menarche to menopause) being treated with valproate medicines must be supported on a Pregnancy Prevention Programme (PPP or *prevent*). These conditions also apply to female patients who are not sexually active unless the prescriber documents compelling reasons to indicate that there is no risk of pregnancy.

The only exception to *prevent* is when the specialist prescriber considers that there are reasons to indicate that there is **no** risk of pregnancy.[4] Such reasons can be documented on the ARAF:

- The absence of risk of pregnancy is permanent (e.g., post-menopausal patients or those after hysterectomy)

- The absence of risk may change (e.g., the patient is pre-menarche). Although *prevent* does not apply to these patients, their treatment with valproate must be reviewed regularly and at least annually. Female children receiving valproate who have not yet reached menarche DO NOT need to fulfil the conditions of PPP, but they and their responsible person (parent / caregivers) need to be aware of the importance of the risks relating to exposure to valproate during pregnancy.

Requirements of the PPP

a) Pregnancy must be excluded before initiating treatment
b) Conditions of valproate prescribing in epilepsy and bipolar disorder:

| | Epilepsy | Bipolar Disease |
|---|---|---|
| Female Patients aged under 55 years | Valproate must NOT be prescribed unless:<br>Two specialists independently consider and document that there is no other effective or tolerated treatment.<br>AND<br>The conditions of prevent are fulfilled (as applicable, for female patients of childbearing potential). | |
| In pregnancy | Valproate must NOT be prescribed unless: Two specialists independently consider and document that there is no other effective or tolerated treatment. | Valproate must NOT be prescribed. |

c) Treatment with valproate must be reviewed regularly and at least annually using an ARAF

d) Female patients of childbearing potential who are prescribed valproate must use effective contraception without interruption during the entire duration of treatment with valproate[5]

These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception.

At least one effective method of contraception, preferably a highly effective user independent form such as an intra-uterine device or implant or two complementary forms of contraception including a barrier method should be used.

Even in cases of amenorrhea, patients must follow all the advice on using effective contraception.

5.4. Counselling by Specialists

Full information is available via the national Guide for Healthcare Professionals.[4]

Patients on valproate must be informed to **not** stop taking their treatment without advice from their specialist.

5.5 Further information

**5.5.1 Females:**

Planning pregnancy - Should contact the specialist service (or seek referral via GP) if planning a pregnancy. Continue valproate and effective contraception until advised by the specialist.

Pregnancy - Continue valproate but seek prompt specialist service (or referral via GP) to be seen urgently (within days).[4]

**5.5.2 Females pre-menarche:**
The patient or responsible person must be asked to contact their General Practitioner (GP) once the patient using valproate experiences their first period (menarche). Their GP will refer

the patient back to the specialist.

**5.5.3 Men under 55:**
Additional recommendations are expected later in 2024 in relation to review of men under 55 years of age on valproate. Until these are published, men under 55 on valproate are advised to read the Patient Information Leaflet and should be given the opportunity to discuss concerns with their GP and if required, offered a referral to a specialist to discuss their treatment options.

## 6. Monitoring Compliance and Effectiveness

1) Annual Datix report to check for incidents involving pregnancy whilst taking valproate
Responsibility: Medication Safety Officer / Chair of Medicines Safety Group

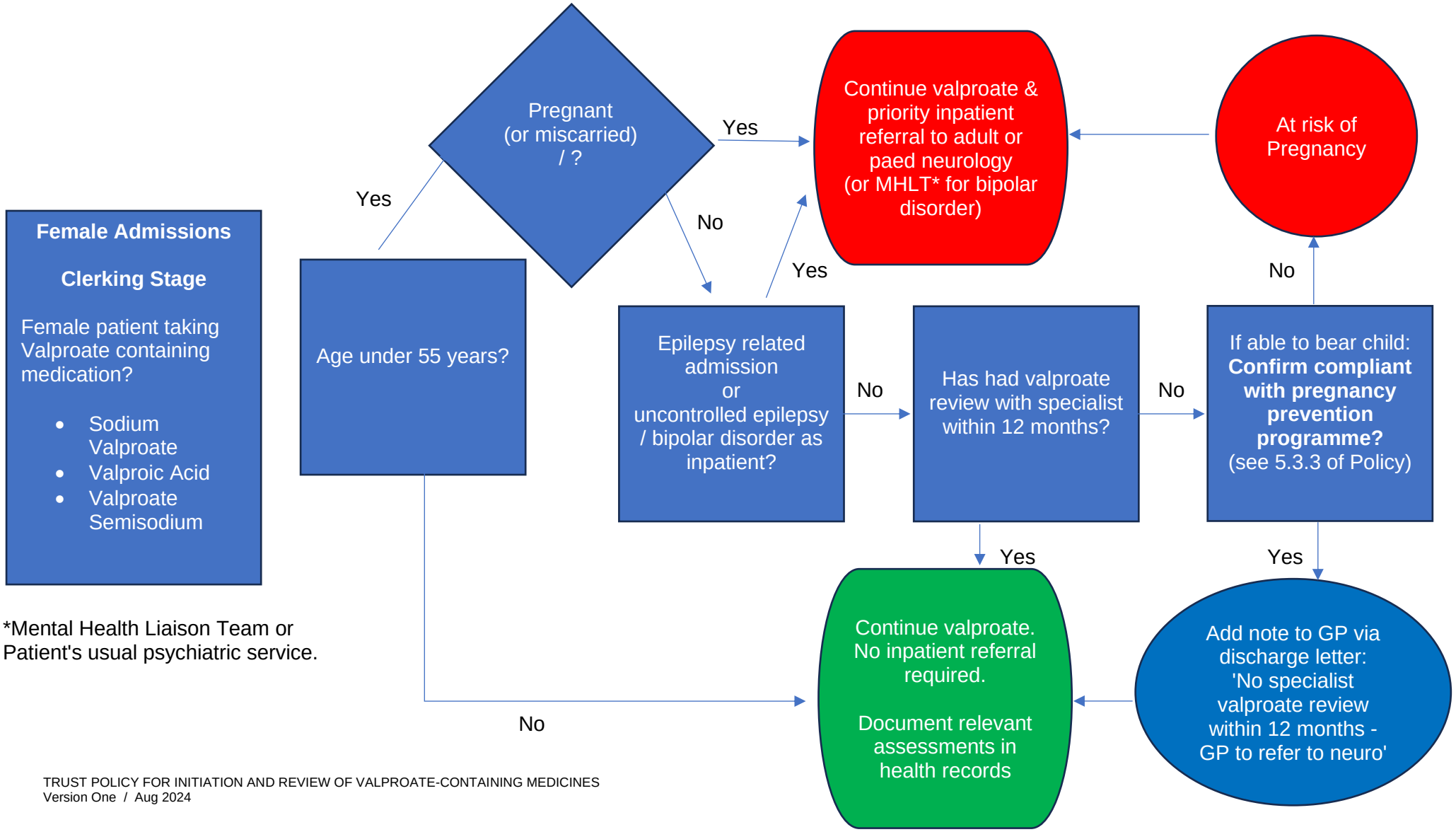
2) Annual audit of compliance with RAF (male) and ARAF (female) by paeds and adult neurology
Responsibility: The Trust's Specialty staff to confirm % patients on local valproate register that have been seen within 12 months. Note: Additional primary-care-coordinated audit results may be shared with provider Trusts for review or response.

## 7. References and Useful Links

1. MHRA. National Patient Safety Alert: Valproate: organisations to prepare for new regulatory measures for oversight of prescribing to new patients and existing female patients (NatPSA / 2023 / 013 / MHRA). November 2023.
2. MHRA. Valproate: review of safety data and expert advice on management of risks (Public Assessment Report). November 2023.
3. Association of British Neurologists. ABN Guidelines for Valproate prescribing in Adult Neurology. November 2023
4. MHRA. Guide for Healthcare professionals: Information on the risks of Valproate use in all patients
5. British Medical Association and Royal Pharmaceutical Society. British National Formulary [Contraception in patients taking medication with teratogenic potential: FSRH (February 2018) and MHRA (March 2019) guidance]. https: / / bnf.nice.org.uk / treatment-summaries / contraceptives-non-hormonal /
6. NICE Clinical Guideline 185 September 2014 Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care
7. S. Sodium Valproate 200mg Gastro-Resistant Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) accessed 09 / 08 / 24
8. Depakote 250mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) accessed 09 / 08 / 24
9. British Paediatric Neurology Association. Prescribing valproate to female patients under 18 years of age. January 2024.

**Appendix 1**

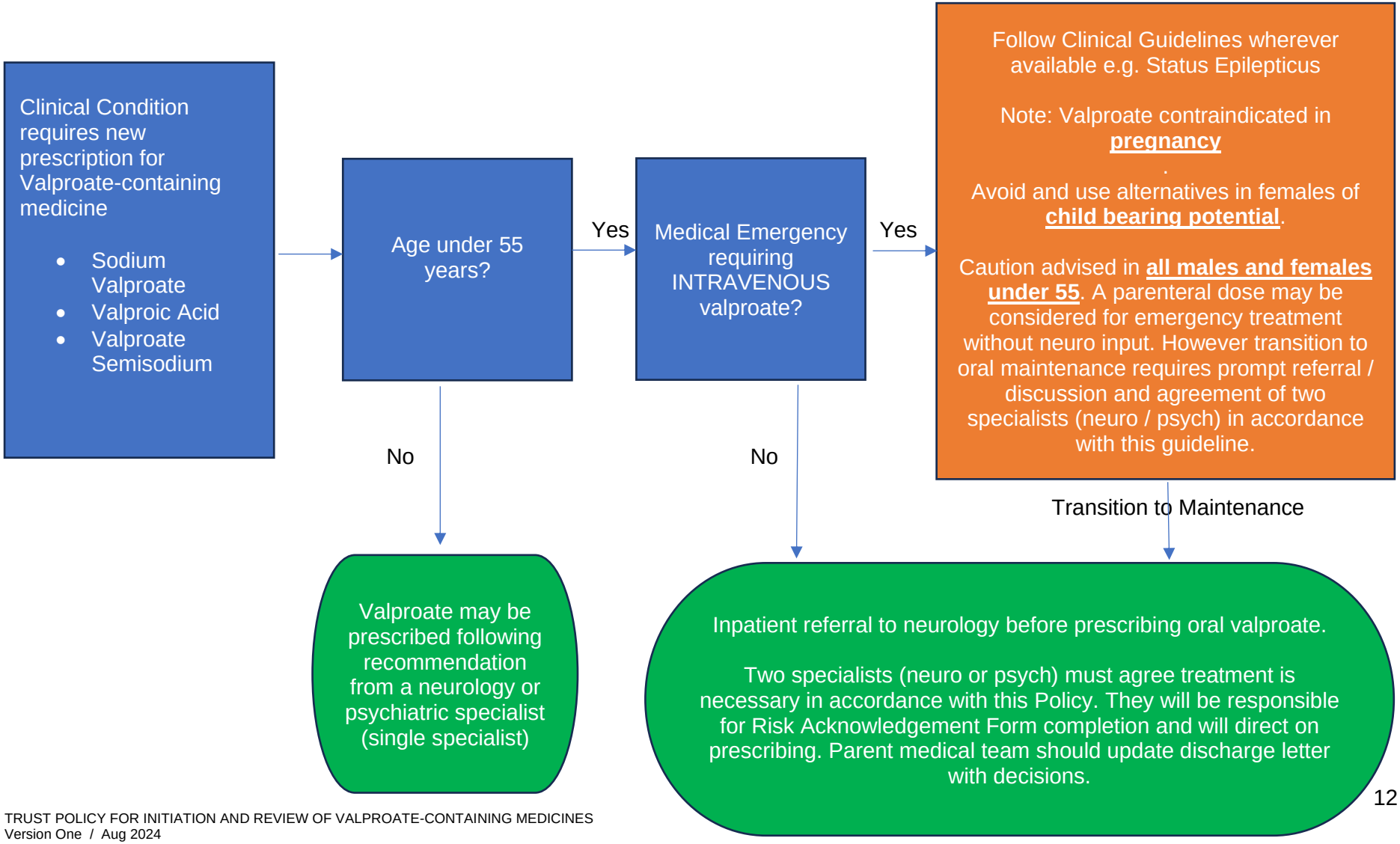
**SOP 1 Inpatient Admissions (Emergency and Elective): Procedure for FEMALE patients on Valproate-containing Medication**




*Mental Health Liaison Team or Patient's usual psychiatric service.

**Appendix 2**

**SOP 2 - Inpatient initiation (MALE and FEMALE under 55 years): Procedure for initiating Valproate-containing Medication**



**Appendix 3**
**Pharmacy Department SOP: Valproate-containing Medication (document held on QPulse/ Sharepoint)**

Please contact Pharmacy team if you require any details of this SOP.