SWL Integrated Care System

Safe Use of Valproate Policy

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1.0 Introduction

This policy provides advice and guidance for healthcare professionals to ensure the safe prescribing and dispensing of valproate for all patients across SWL. The policy must be used in conjunction with local standard operating procedures, organisational policies and the Medicines and Healthcare products Regulatory Agency (MHRA) Healthcare Professional Guide.

'Valproate' is used to mean oral sodium valproate, valproic acid and valproate semi sodium. **Intravenous valproate may still be used in status epilepticus, where the immediate priority is preservation of life. Initiation of intravenous valproate must not be delayed due to signatory issues and /or patient counselling. These should be addressed if, and when transferring the patient to oral valproate and / or when the patient has recovered.**

Valproate is a medication that is licensed to treat all forms of epilepsy and mental health disorders such as bipolar disorder. It can also be used as migraine prophylaxis; however, this is an unlicensed indication. For dosing guidance refer to the current British National Formulary (BNF).

Generic sodium valproate, valproate semi sodium and valproic acid are active ingredients licensed under several brand names such as Epilim®, Depakote® Convulex® and Episenta®. This is not an exhaustive list of all of the brands available. Further information on the various brands available can be obtained from the BNF or the Electronic Medicines Compendium.

This standardised SWL Policy ensures that all healthcare professionals employed by all provider organisations in SWL will operate to the same standard: they must abide by their employer's policy including when working on other sites such as in psychiatric liaison services.

The MHRA has issued new safety and educational materials (see appendix 1) for patients and healthcare professionals.

2.0 Regulatory requirements

The Commission on Human Medicines (CHM) and the MHRA implemented in Patient Safety Alert NatPSA/2023/013/MHRA Dec 2023 has advised that:

- Valproate **must not** be started in new male or female patients younger than 55 years, unless two specialists 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. This includes patients who have taken valproate in the past but are not prescribed it currently.
- Where possible, existing patients should be switched to another treatment option unless two specialists independently consider and document that there is no other effective or tolerated treatment, or the risks do not apply.
- All women and girls of childbearing age **currently** taking valproate will need a second opinion signature at their **next** annual specialist review if valproate is to continue. This will be documented on the female valproate Risk Acknowledgement Form (RAF), which is to be completed annually whilst there is a risk of pregnancy.
- After the first completion of the female valproate RAF and review by a second independent specialist, subsequent annual reviews for female patients can be conducted by one specialist unless the patient's situation changes.
- All male patients who are **newly** prescribed valproate will need a second opinion signature if valproate is to be initiated. This will be documented on the male valproate RAF. On-going reviews for male patients newly prescribed valproate are not required.
- Inform existing male patients (of any age) who may father children of the potential risks associated with valproate at their next regular treatment review. This counselling should be given irrespective of the indication for valproate and also after administration of intravenous valproate.

3.0 Risks of valproate

There is an inherent risk of catastrophic relapse with precipitous discontinuation of valproate in patients for whom it is effective, and this must be balanced against the teratogenic risk. **Patients should not stop taking valproate, even if pregnancy is suspected, without advice from their specialist.**

Valproate use in women poses a significant risk of foetal harm. There may also be some risks with respect to men, so valproate should be avoided, other than in very exceptional circumstances. Prior to initiation of valproate, the risk: benefit ratio must be evaluated, and risks mitigated where possible.

3.1 Female patients (those assigned female at birth)

Taking valproate during pregnancy can cause serious birth defects. For women in the general population, around 2 to 3 babies in every 100 will have a birth defect. For women who take valproate while pregnant, around 11 babies in every 100 will have a birth defect.

Birth defects may result in disabilities which may be severe and/or permanent. These may include:

- Spina bifida
- Face and skull malformations – including ‘cleft lip’ and ‘cleft palate.’
- Malformations of the limbs, heart, kidney, urinary tract, and sexual organs.
- Eye malformations in association with other birth defects
- Hearing problems or deafness.

In women who take valproate whilst pregnant up to 30 to 40 children in every 100 may have problems with development, for example:

- Being late in learning to walk and talk.
- Lower intelligence than other children of the same age.
- Poor speech and language skills.
- Memory problems.

Children of mothers who take valproate during pregnancy are at an increased risk of having autism and related disorders and are at increased risk of developing Attention Deficit Hyperactivity Disorder, this is known as Foetal Valproate Syndrome (FVS).

3.2 Male patients (those assigned male at birth)

A retrospective observational study has indicated a possible association between valproate use by men around the time of conception and an increased risk of neurodevelopmental disorders in their children.

Valproate can potentially cause

- Male infertility (may be reversible after treatment is stopped or the dose is reduced for some patients).
- Toxic effects on the testes (testicles) of animals. The relevance to human testicular development, particularly in the paediatric population, is unknown.

4.0 Pregnancy Prevention Programme (PPP, also known as 'PREVENT')

The MHRA states that the conditions of the PPP must be fulfilled for **all** female patients of childbearing potential.

The requirements of PPP are as follows:

1. Continuous use of highly effective contraception
    a. Pregnancy must be excluded, by means of negative serum pregnancy test, before the first prescription is issued.
    b. Arrangements for highly effective contraception (see section 5.0) must be in place, and documented as such, before the first prescription is issued.
2. An annual review by a specialist.
3. Annual completion of the female valproate RAF by two independent specialist(s).

Shared decision making is key, and the prescriber must discuss the risks of valproate use in pregnancy with the patient before treatment is initiated. This is to allow the patient to make an informed choice on their treatment and use of contraception. The patient's capacity to consent to treatment as well as if any support is required from carers and / or family members must also be documented

clearly in the patients' medical notes. Section 6.0 has further information around mental capacity.

Note that in some instances, the absence of risk may change (e.g., the patient is pre-menarche, developmental delay). Although the PPP does not apply to these patients, their treatment with valproate must be reviewed regularly, typically annually in adolescence and also on transition to adult services, and the absence of risk reassessed.

The only exemption to PPP is when the specialist prescriber considers that there is **permanently** no possible risk of pregnancy (e.g., post-menopausal (1 year after last menstrual period) or post hysterectomy). At initiation, the specialist must complete the female valproate RAF (front page and step 1 only) once at initiation, highlighting the permanent absence of pregnancy risk. This should also be clearly documented in any notes and correspondence with an indefinite date of expiry. The patient will not require any further annual review by the specialist.

4.1 Unlicensed prescribing of valproate

Use of valproate in female patients of childbearing potential under 55 years is **contraindicated** and subsequently considered **unlicensed,** unless

- Two specialists independently consider and document that there is no other effective or tolerated treatment. If there is only one signature by a specialist then this is still considered unlicensed use), *and*
- All conditions of the PPP are fulfilled. If the patient makes an informed choice not to use contraception, then this is still considered unlicensed use.

4.2 Patients who do not meet all criteria of the PPP

All female patients of childbearing potential who are **newly initiated** (after 31st January 2024) on unlicensed valproate require a Shared Care Agreement (SCA) to be in place. Prescribing arrangements for female patients of child bearing potential who are taking unlicensed valproate before this date remain unchanged.

In other organisations such as acute trusts, 'unlicensed' prescribing of valproate will be considered 'non-formulary' and warrants an application to the Drug and Therapeutics Committee for approval. Individuals must abide by their employer's policy including when working on other sites such as in psychiatric liaison services.

Where a decision is made by the hospital specialist to initiate valproate in a female patient who is not enrolled onto the PPP (unlicensed use), then the reason/s for doing so must be clearly documented:

- By the specialist signatories completing the female valproate RAF
- In the patients' medical notes

4.3 Potential scenarios

The benefits and risks of prescribing unlicensed valproate in the potential scenarios mentioned below must be carefully considered.

4.3.1 Patients who do not engage with services or PPP.

It is acknowledged that in some cases it may not be possible and / or patients may choose not to engage with the requirements of the PPP. Patients who choose not to engage with services may do so for various reasons including due to fears that valproate will be stopped or switched without their input. Patient choice must be respected. The specialist must inform the patient and / or carers of the risks of not engaging with the PPP as well as the risks of taking valproate in pregnancy. It is important to safeguard both the patient and the prescriber.

Where valproate is contraindicated, discontinuing treatment may prevent avoidable harm from potential pregnancy in the future. However, stopping treatment could cause the patients' condition to worsen; this is particularly concerning in patients with some specific (or unclassified) types of epilepsy, especially those at higher risk of sudden unexpected death in epilepsy (SUDEP).

The decision of whether to continue unlicensed valproate must be balanced carefully with the individual circumstances of the patient and patients should be reassured that their thoughts and opinions are pivotal to their management plan.

The GP must be copied into any correspondence from the specialist to the patient. See section 12.2.2 for further information.

4.3.2 Patients who do not wish to comply with the contraception criteria.

It is important to note that some female patients may make an informed decision **not** to use highly effective contraception, despite having capacity and being informed of the risks in pregnancy.

It is crucial that the reason/s along with the outcome is documented clearly in the female RAF by the specialist and communicated to the GP. Any conversations relating to the latter should also be documented in the patient's medical record. Providing this is done as outlined in this policy, and fully documented, primary care prescribing should continue

4.3.3 Patients who have childbearing potential with severe intellectual or physical disability and have mental capacity

A patient who has mental capacity should be involved in all discussions regarding valproate and the risks of valproate use in pregnancy. Assumptions about the likelihood of sexual intercourse should not be made and it is important for a careful evaluation to take place with the patient, the patients' carer and key healthcare professionals assessing if there is a risk / absence of risk of pregnancy and if the patient has capacity to consent to receive contraception *as well as* valproate.

It may be distressing for patients and their families to require regular reviews to discuss pregnancy risk and contraception therefore it is important that all conversations on this matter are documented clearly in the female valproate RAF and in the patients' medical notes.

4.3.4 Patients who have childbearing potential with or without severe intellectual or physical disability and lack mental capacity

Prior to initiating valproate, the specialist should evaluate the patient and decide, after discussion with the patient/carer, if there is a risk of pregnancy.

Where the specialist considers that there is a risk of pregnancy then a decision will need to be made by the specialist which is in the patient's best interest. Each case will need to be assessed individually, and it may be appropriate to consider carrying out risk assessments, best interest decision meetings, peer reviews and / or consultation with multidisciplinary team to facilitate decision making. As well as this

other teams such as safeguarding and sexual health teams may need to be made aware and have an input into the decision-making process. See section 6.0 for further information.

It is important to communicate outcomes with patient and / or carer and ensure clear documentation in the patients' medical record and on the female valproate RAF.

4.3.5 Patients who do not attend appointments with the specialist

Female patients are required to attend an annual review with a specialist. If the patient does not attend the annual review, the specialist should inform the GP and offer the patient another appointment.

If the patient does not attend a 2nd appointment, the specialist should write to the patient (copying in the patients GP) with key information and offer another opportunity to attend.

If there is still no response, the specialist should contact GP and to discuss how best to proceed for the individual patient. The patient should be informed of any decisions which are made, and an effort made to contact and speak to the patient directly.

Any correspondence from the specialist, decisions made relating to valproate and conversations with the patient should be recorded in the patient's medical record.

5.0 Contraception

Female patients of childbearing potential who are prescribed valproate must use highly effective contraception without interruption during the entire duration of treatment with valproate.

At least one effective method of contraception, preferably a highly effective user independent form or two complementary forms of contraception including a barrier method should be used.

Highly effective contraceptive options have less than 1% failure rate and are user-independent, these include:

1. Long-acting reversible contraception (LARC), such as:
    a. Copper intrauterine device (Cu-IUD)
    b. Levonorgestrel releasing intrauterine system (LNG-IUS)

    c. Progestogen only implant (IMP) (effectiveness of the IMP is reduced if taking any enzyme inducing medicines)
2. Female sterilisation

Complementary forms of contraception have a failure rate more than 1% and are user dependent methods, these include:

- Combined Oral Contraceptives (COC)
- Progestogen-Only contraceptive Pill (POP)
- Depot Medroxyprogesterone Acetate (DMPA) injections
- Fertility awareness-based methods

Failure rates with DPMA injections are due to repeat injections being missed or administered late; if there are regular documented administrations, this may be deemed a highly effective form of contraception.

The aide-memoire table produced by the MHRA is a useful tool for clinicians to compare various forms of contraception.

Patients can access Contraception Choices which provides information about the various forms of contraception available. A Contraception Choices Tool is also available allowing patients to make an informed decision.

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

Individual circumstances should be evaluated in each case when choosing the contraception method with the patient, involving the patient in the discussion to support her engagement and compliance with the chosen measures. Even if she has amenorrhea, she must follow all the advice on effective contraception.

Advise the patient to share information with their specialist and GP regarding contraception, especially if this is not obtained from the GP practice. Similarly, if contraception is stopped, removed, or changed or if the patient is planning to become pregnant the GP and specialist must be informed.

5.1 Perimenopause and menopause

The Faculty of Sexual Health and Reproduction (FSRH) has guidance on menopause and perimenopause. Perimenopause is the transition phase preceding menopause and ending 1 year after the last menstrual period (LMP). Contraception is required in women who are experiencing perimenopause until menopause has been confirmed. Once confirmed, the GP practice should add the diagnosis and SNOMED code to the patients record and inform the specialist who will need to update the female valproate RAF.

5.2 Contraceptive services available across SWL

The specialist who initiates valproate must ensure that the patient is referred / signposted to a contraceptive service prior to valproate being started. Details of local contraceptive services available are listed in appendix 2. Individual Trusts may have their own processes for referring patients initiated on valproate to local contraceptive services.

The Contraception Choices website also provides information for patients on where the nearest sexual health clinics are located.

5.3 Gynaecologists/obstetricians, midwives, and nurses

Patients should not stop taking valproate, even if pregnancy is suspected, without advice from their specialist.

Any of the above groups of healthcare professionals may encounter patients who are prescribed valproate. If a female patient presents on valproate, it is important to:

- Provide counselling on suitable/recommended methods of contraception and pregnancy planning.
- Provide information about the risks of using valproate during pregnancy and what to do if a patient thinks that they may be pregnant.
- When a patient consults for pregnancy, urgently refer the patient to their specialist and also inform the GP practice.
- Encourage the patient to communicate with their specialist and GP regarding insertion / removal of contraception.
- Remind the patient when the contraceptive device is due for renewal.

6.0 Mental capacity

The Mental Capacity Act 2005 is relevant to individuals over 16 years who have (or appear to have) difficulty making informed decisions about their care and / or treatment. For children and young people under 16 Gillick competency is required.

To assess an individual's capacity, the reference guide to consent for examination or treatment provides useful information around mental capacity in both adults and young people.

All healthcare professionals involved in the prescribing, monitoring and / or supplying valproate may encounter patients who require a Mental Capacity Assessment and should therefore be aware of this.

If the person lacks capacity to make an informed decision to consent to treatment with valproate or the use of highly effective / complementary forms of contraception, then a best interests decision making meeting may be required prior to initiating valproate.

Information on valproate, including the risks as well as the use of contraception should be provided to the patient in a format that they can understand. This information should also be provided to the patient's parents/carer/responsible person where appropriate. The educational resource to help clinicians discuss sex / sexual health / pregnancy prevention with those that have autism and / or a learning disability and are taking valproate is available as well as a valproate review appointment letter to invite people with a learning disability for a consultation about their medication and the PPP. The following London MCA Resource Pack provides useful information such as Capacity Guide for clinicians and other useful resources.

In exceptional circumstances, valproate may be initiated in certain scenarios (e.g. in patients who lack capacity with / without learning or physical disabilities which prevents them from becoming pregnant). In this case as the requirements of the PPP are not being met, this would be constituted as unlicensed prescribing (see section 4.1 for further information).

In the above circumstances, details of any discussions must be recorded clearly in the valproate RAF and in the patient's medical record. It is important to communicate

any assessments relating to mental capacity and their outcomes with the patients GP when transferring prescribing responsibilities (see section 12.0).

7.0 Prescribing valproate

There are various decision support tools available for patients which can be used alongside the consultation with the specialist. Bipolar disorder: is valproate the right treatment for me? and Is valproate the right epilepsy treatment for me?

The support tool contains useful information for patients which explain the risks of valproate use in pregnancy, use flow diagrams to help patients make decisions about their medicines, signpost to other useful resources and highlight pictorially which methods of contraception are more effective.

Female patients over 55 years who are not of childbearing potential may start valproate without need for a specialist independent review.

7.1 For new patients assigned female at birth (women and young girls) of childbearing potential

Valproate must not be started in females younger than 55 years, unless:

a) Two specialists independently consider and document that there is no other effective tolerated treatment, or
b) There are compelling reasons that the reproductive risks do not apply (see section 4.0 for further information).

If a female patient is of childbearing potential and two specialists agree that valproate is an appropriate treatment, ensure the following measures are in place:

- The PPP must be in place. This is designed to ensure patients are fully aware of the risks of valproate and the need to avoid becoming pregnant during treatment.
- Complete the female valproate RAF with the patient.
- If the patient does not meet all criteria as outlined in the PPP, then valproate use is unlicensed which requires the specialist to complete a SCA (see section 4.1 for further information).
- Three copies of the RAF form are needed. One for the patient's medical record,' one for the patient's GP and one for the patient.

- A copy of the Patient guide must be given to the patient or carer. It is good practice to document that this has been done in the medical record.
- The female patient must be reviewed by the specialist annually, and a RAF completed at each review.
- At menarche, the patient should be referred to the specialist for completion of a new ARAF.

7.2 For existing patients assigned female at birth (women and young girls) of childbearing potential

Females of childbearing potential currently taking valproate must have the PPP in place. At the next annual specialist review;

- Two specialists must independently consider and document that there is no other effective and tolerated treatment. This is only required once.
- A female valproate RAF must be completed if valproate is to be continued.

The GP practice may wish to put a risk stratification process in place (e.g. audit, EMIS searches etc) to prioritise which female patients of childbearing potential, currently prescribed valproate needs to be reviewed by the GP practice and/or specialist as a priority. Existing female patients on valproate must be provided with a copy of the Patient guide.

See section 12.2.1 for information on referring / re-referring patients to specialist services.

7.3 For new patients assigned male at birth

Valproate must not be started in males, unless:

- Two specialists independently consider and document that there is no other effective or tolerated treatment, and the risk of infertility or potential risk of testicular toxicity are not applicable. **OR**
- If a new male patient has a permanent (e.g., confirmed vasectomy, infertility due to other causes) reason that the above reproductive risks do not apply, then the countersigning specialist is not required The specialist should record

the reason in the relevant section of male valproate RAF and in their medical notes.

If two independent specialists agree that valproate is an appropriate treatment, ensure the following measures are in place:

- Discuss the risks of valproate with the patient and consider together how it affects the patient's individual circumstances. This discussion should be documented in the patients' medical record.
- The male valproate RAF must be completed with the patient before prescribing. Subsequent annual reviews for male patients newly prescribed valproate are not currently mandated.
- Three copies of the RAF form are needed. One for the patient's medical record one for the patient and one for the patient's GP.
- A copy of the Patient guide must be given to the patient or carer. It is good practice to document that this has been done in the medical record.

7.4 For existing patients assigned male at birth

Only male patients initiated on valproate after 31st January 2024 will have a male valproate RAF.

The MHRA has issued the following guidance, valproate use in men, for existing male patients on valproate. Healthcare professionals must discuss the current information available and provide the following advice:

- Inform male patients (of any age) who may father children of the possible risk at initiation of valproate or at their next regular treatment review. This counselling should be given irrespective of the indication for valproate and after use of intravenous valproate.

- As a precaution, it is recommended that male patients use effective contraception (condoms, plus contraception used by the female sexual partner) throughout the valproate treatment period and for 3 months after stopping valproate, to allow for one completed sperm cycle not exposed to valproate.

- At the next regular treatment review, discuss with men on oral valproate treatment whether they are planning a family in the next year and if they are, refer to a specialist to discuss alternative treatment options.
- If a female patient reports they are pregnant or planning a pregnancy with a man on valproate (including those undergoing IVF), refer for prenatal counselling.
- Advise men not to donate sperm during valproate treatment and for 3 months after stopping valproate.

The visual risk communication diagram may be used to explain the above risks and a copy of the advice for male patients must be provided to the patient. Clinicians may also find Appendix 3: Paternal Risk of Valproate Exposure: Questions and Answers for General Practice useful to read.

The GP practice may wish to put a risk stratification process in place (e.g. audit, EMIS searches etc) to identify and prioritise male patients currently prescribed valproate who would benefit from a review with the GP practice or referral to their specialist e.g. male patients who are planning a family within the next year.

Any conversations with the patient and or carers should be documented in the patients' medical records and any new patient referred to a specialist for diagnosis and to initiate treatment where appropriate.

8.0 Prescribing valproate in children

Treatment with valproate must be reviewed regularly, typically annually in adolescence and on transition to adult services, and the absence of risk reassessed.

If a patient with a disability in childhood has been discharged from specialist services and the GP has any doubt as to whether the original signature and / or original decision documented on the RAF still applies, then the patient should be referred to specialist services.

It is good practice to document any discussions with the patient and / or responsible person in the patients' medical record at both the annual specialist review and with the GP.

8.1 Children assigned female at birth

Female children receiving valproate who have not yet reached menarche **do not** need to fulfil the conditions of the PPP, but they and their responsible person (parent/carers) need to be aware of the importance of the risks relating to exposure to valproate during pregnancy.

Where appropriate it is important to remind the patient's responsible person to contact their GP once the patient using valproate experiences their first period (menarche). The GP will then need to refer the patient back to the specialist, indicating the reason for referral i.e. menarche.

If at initiation of valproate, the female child was identified as not being able to meet the eligibility criteria of PPP e.g. due to severe permanent or progressive neuro-disability and / or unable to consent to consensual sex, and this was clearly documented on the female valproate RAF then a discussion with the specialist is needed when the patient reaches menarche and outcome clearly documented in the patient notes. However, if there is any doubt about this, specialist review should be requested.

8.2 Children assigned male at birth

Male children receiving valproate and their responsible person should be made aware of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance.

[1]9.0 The Responsible Specialist

The Responsible Specialist who has made the decision to initiate the patient on valproate must be a consultant, associate specialist, speciality doctor practicing independently, or specialist nurse in the relevant area. Local policies must be adhered too.

Consultants are not required to have a specialist interest in epilepsy and/or the condition for which valproate is prescribed. However, they should be regularly seeing

[1] **This policy will use the term 'Responsible Specialist' rather than the term 'Specialist Prescriber' as mentioned in the MHRA documents.**

people with that condition in a clinical setting, and confident that their knowledge of epilepsy and the relevant condition is up to date:

- For epilepsy, the appropriate specialist is likely to be a neurologist, paediatric neurologist, or a consultant neurologist having expertise in epilepsy, paediatrician with expertise in epilepsy, or in some instances a learning disability psychiatrist (if they are managing the epilepsy).
- For mental health indications, the appropriate specialist is likely to be a psychiatrist.
- For people with both epilepsy and mental health conditions taking valproate, the Responsible Specialists should agree between them which condition is the ‘priority’ need, and which specialist should take primary responsibility.
- Specialist nurses need not be a prescriber, but they must have the knowledge and skills to make the decision and to do so independently.

The following requirements must also be adhered too:

1. At least one signatory on the two signatory forms must be a consultant working within the relevant area of practice
2. Trainees, speciality doctors working under supervision, or GPs cannot act as signatories

10.0 The Countersigning Specialist

Any of the clinicians identified in section 9.0, within the relevant area of practice and / or speciality can be a 2nd signatory. This may vary in different organisations; local policies must be adhered too.

There should not be managerial relationships between the responsible specialist and countersigning signatory (for example, an epilepsy nurse specialist supervised and managed by the responsible consultant).

The following requirements must also be adhered too:

1. At least one signatory on the two signatory forms must be a consultant working within the relevant area of practice
2. Trainees, speciality doctors working under supervision, or GPs cannot act as signatories

11.0 Communication from the secondary to primary care

If valproate is to be prescribed, both the responsible and countersigning specialist must sign the relevant female / male valproate RAF and where appropriate, initiate referral to sexual health services (see section 5.2 for further information).

The responsible specialist must communicate the decision to start valproate to the patient's GP. A copy of the female valproate RAF must be sent to the patients GP as soon as possible after the consultation. If unlicensed valproate is prescribed for a female patient of childbearing potential, then a SCA must also be completed and sent to the patients GP (see section 4.1 for further information) and the reason/s for doing so must be clearly indicated on the RAF.

The specialist must ensure that **all new patients** initiated on valproate receive a **4-week supply** of valproate from secondary care. This will give primary care clinicians

sufficient time to receive and acknowledge paperwork, ask any questions, arrange for the patient to be seen, and put systems in place for on-going prescriptions.

Additionally, if after review by the responsible specialist, valproate is switched to an alternative treatment, this must be communicated to the patients' GP. The GP practice must also communicate this change to the pharmacy which dispenses the patient's medication, to ensure the current repeat medication list is updated.

To ensure smooth transition of care and safe prescribing of valproate, it is important that all information provided in the female / male valproate RAF, including details of any mental capacity assessments (where relevant) to the GP practice from secondary care:

- Is clear and concise
- Has all of the necessary information / fields competed on the forms
- Clearly documents any exemptions to the PPP
- Has the necessary signatories

Once valproate has been initiated and the practice has received confirmation of this via the female / male valproate RAF, the GP continue to prescribe valproate. The patient must be seen in primary care by a healthcare professional in a timely manner following a review by the specialist.

12.0 General Practitioners

The GP practice should arrange to see each female patient after a specialist review and, if on valproate, ensure the patient is complying with the criteria outlined in the PPP.

The practice should also ensure that:

1. The practice has received a valid valproate RAF completed within the previous 12 months.
2. The patient is aware of the recommendations, and is using highly effective contraception, where indicated.

3. There is no change to the patients' circumstances since the RAF was completed that may affect its status (e.g. if the patient has reached menarche).

If unlicensed valproate is prescribed for a female patient of childbearing potential, then the Specialist Prescriber must also complete a SCA. It is important that each GP practice, upon receipt of a female / male valproate RAF and SCA (where applicable), codes the patient correctly via SNOMED (see appendix 4) for the

- Indication for valproate
- ARAF completion
- PPP (where appropriate)
- Contraception (where appropriate)

The GP practice must also

- Have an awareness and an agreement in place of how patients on valproate will be reviewed within the practice.
- Have a process of informing and / or reminding patients of the importance of having an annual review with their specialist (if relevant).
- Discuss contraception with the patient (if relevant).

Any conversations with the patients as well as any reviews by the GP practice must be documented in the patients' medical records. See appendix 1 for a list of resources available to help support discussions.

12.1 Non-medical prescribers

All non-medical prescribers working within the GP practice must:

- Read and familiarise themselves with the updated valproate guidance.
- Ensure valproate is specifically documented as part of the 'scope of practice.'

12.2 Common scenarios which may occur in primary care

Patients should not stop taking valproate, nor GPs refuse to prescribe without specialist advice.

12.2.1 Expired, expiring, or absent 'female valproate RAF'

If the patient has never had a 'female valproate RAF' completed, the GP should acknowledge that prescribing valproate for this patient is unlicensed, however it is in the patients' best interest that the prescription is continued. The GP must refer the patient back to the specialist for a review and completion of a RAF.

If the specialist and / or team who initiated valproate is known and the patient is in the appropriate catchment and / or appropriate age group, the GP can refer the patient back to the same specialist and / or team.

If any of the potential scenarios below apply, then the GP should complete a *new* referral to a local neurology or community mental health team:

- Specialist and / or team who initiated valproate is outside of the SWL ICS
- Patient has relocated from a different area
- Patient has transferred from paediatric to adult services

The patient's GP should continue to prescribe valproate and provide a sufficient quantity of medication to cover the period until the patient is seen by their specialist. All referrals must be clearly documented in the medical notes and the appropriate SNOMED code applied to the patients record.

12.2.2 Patients who do not attend GP appointments and / or reviews

The GP practice is required to review the patient once they have been transferred to primary care following initiation of valproate by the specialist. Alongside this, periodically, the GP practice may request additional reviews with the patient.

If the patient does not attend the appointment, an attempt should be made to contact the patient to offer another appointment. If the patient does not attend multiple appointments and there are concerns around the use of valproate, then the GP practice should liaise with the patients' specialist for advice. The GP and specialist should discuss how best to proceed with the individual patient.

If the patient has an immediate need for valproate, and there is no risk at present (e.g. the patient is not pregnant), prescriptions for a limited duration of valproate should continue until a joint discussion with the specialist has taken place.

The patient should be informed of any decisions which are made, and an effort made to contact and speak to the patient directly. Any correspondence from the specialist, decisions made relating to valproate and conversations with the patient should be recorded in the patient's medical record and copied to the patients GP.

Following joint discussions between the specialist and GP:

- Where a specialist and GP make a joint decision that continuing valproate is in the best interest of the patient, the decision along with the rationale must be clearly documented in both the Trust and primary care medical record for the patient.
- Where a specialist and GP make a joint decision that discontinuation of valproate is in the best interest of the patient, clinicians should make every effort to contact the patient to discuss an ongoing management plan. Again, the decision and rational must be clearly documented in both the Trust and primary care medical record for the patient

12.2.3 Patients who withdraw from/have a change in circumstances since enrolment on the PPP

Patients may wish to withdraw from the PPP or have a change in circumstances (e.g. new hysterectomy) since commencing valproate. If a patient has chosen to withdraw from the PPP but is of child-bearing potential, then a discussion should be had between the specialist and the patient. The female valproate RAF must be updated, and the specialist must inform the GP of this decision.

12.2.4 Patients initiated on valproate from a private provider

Medication initiated by private providers should only be taken on by primary care prescribers once they are satisfied that prescribing is appropriate, responsible and what would be considered for NHS patients for equitable treatment.

Patients should be informed at the point of seeking private healthcare of the possible restrictions and limitations that may arise with requests for ongoing prescriptions from the NHS prescriber. This should be ideally communicated to the patient by the private health care provider. The SWL IMO website, Prescribing – Interface Policy provides further information.

- Primary care providers may wish to make this clear to the patient during consultation to ensure that the patient understands this prior to prescribing and consider including the private prescription patient leaflet on their practice website.
- Patients who have had a private consultation for investigations and diagnosis may transfer to the NHS for any subsequent treatment, but must be treated according to NHS protocols
- Where the drug is not routinely offered as part of NHS services or the patient would not be eligible for the NHS service, there is no obligation to prescribe.

Medications suggested by a private provider which are not aligned with national or local guidance will not be routinely continued by the primary care prescriber; therefore, the private provider should only transfer prescribing if they are able to fulfil all the duties of the 'specialist' in this guidance, including acceptance of referrals for the completion of a RAF.

12.2.5 Pregnancy (suspected and planned) in female patients

It is important to advise female patients to contact their GP / specialist immediately if they suspect there has been a problem with their contraception or suspect that they may be pregnant. If a patient in the above group contacts the practice, **then the GP should advise the patients <u>not</u> to stop valproate.** If the patient is considering continuing with the pregnancy, an urgent referral should be made by the GP to the specialist. The MHRA states that the patient will need to be reviewed without delay, ideally within days, however it is accepted that due to demands on services the patient may not be seen immediately, and in many instances, there will be no clinical indication for urgent review. We recommend the responsible specialist team is informed of any pregnancy. The specialist will advise accordingly on the timing of review and also provide any interim advice.

Alongside the above referral to the specialist, if a joint service is not available between the epilepsy team and prenatal service, then the patient and partner should be referred to a specialist in prenatal medicine for evaluation and counselling regarding exposed pregnancy.

Any conversations with the patient, partner, carers and / or family members must be documented in the patient's medical record.

Female patients planning to become pregnant should be referred to their specialist. The **GP should advise the patient not to stop valproate or contraception unless told to by their specialist**.

12.2.6 Existing female patients who do not meet the criteria outlined in the PPP and are therefore receiving unlicensed valproate in primary care.

Prescribing arrangements for existing female patients of child bearing potential who are receiving valproate in primary care remain as they currently are. Please see section 4.2 for further information.

13.0 Safe dispensing of valproate

The regulatory measures apply to both primary (community) and secondary care (hospital) pharmacies. Community pharmacies should refer to the guidance update from Community Pharmacy England.

Community Pharmacy England has previously communicated the changes in regulations regarding original pack dispensing and special container status for valproate-containing products.

- The GPhC has also issued guidance around the new regulatory measures.
- A CAS alert has also been issued.

13.1 All patients

- Ensure the patient has received the Patient guide or knows they can access it online using the QR code on the package leaflet.
- Dispense valproate in the original package. If this is not possible for the patient, then a risk assessment must be undertaken.
    - In exceptional circumstances, where a patient needs to receive their medication in different packaging such as a Monitored Dosage System (MDS), **always** provide a copy of the package leaflet, the patient card and add a valproate warning sticker to the outer box.

13.2 Patients assigned female at birth

- Ensure the Patient card is provided every time valproate is dispensed.
- Confirm that the patient has been made aware of the risks in pregnancy.
- Where appropriate, advise the patient to always use effective contraception and to see their GP, to be urgently referred to their specialist, should they be planning a pregnancy or if they think their contraception may have failed.
- Advise the patient even if they think they might be pregnant, **not to stop valproate and to immediately contact their GP for an urgent referral to their specialist.**
- Where appropriate, refer female patients to their GP if they report that they
    - Are not aware of the need for contraception.
    - Are not taking an effective method of contraception and do not know why or have not had a conversation with their specialist or GP about contraception.
    - Have not been seen by their specialist in the past year.

14.0 Providers of inpatient and / or acute care

It is important to note that valproate **must not be stopped** for patients who present in an acute setting even if the criteria for the PPP are not being met.

If a patient, either as an inpatient or an outpatient, is identified as not having had a review by a specialist in the past 12 months or is not on any form of contraception (highly-effective / or complementary) and does not know / understand why, then this should be flagged to the specialist prescriber (if initiated within that organisation).

If the specialist prescriber is not within the same organisation, then the patient's GP must be informed, via communication on the patients discharge letter:

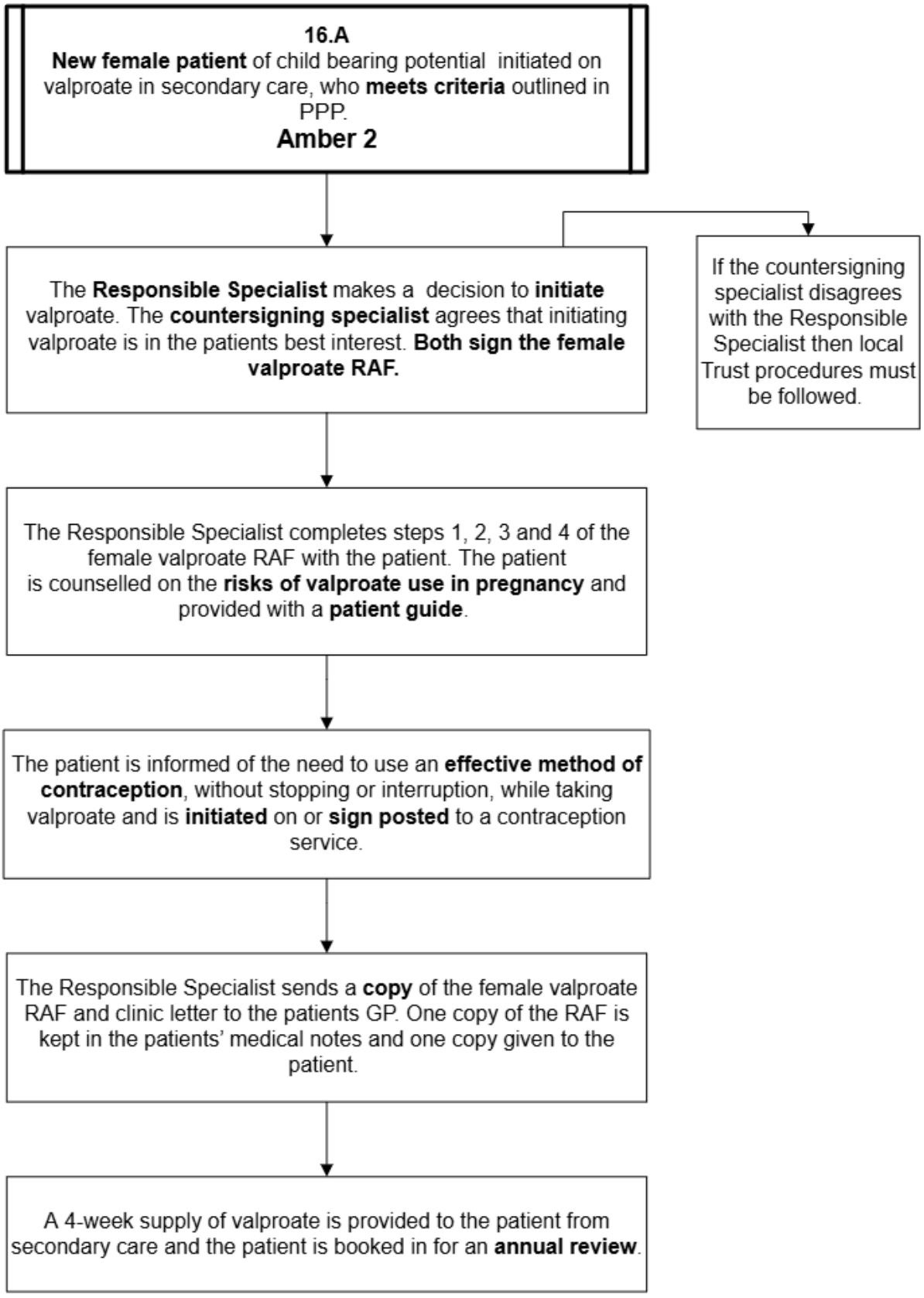
Local policies must be adhered to.

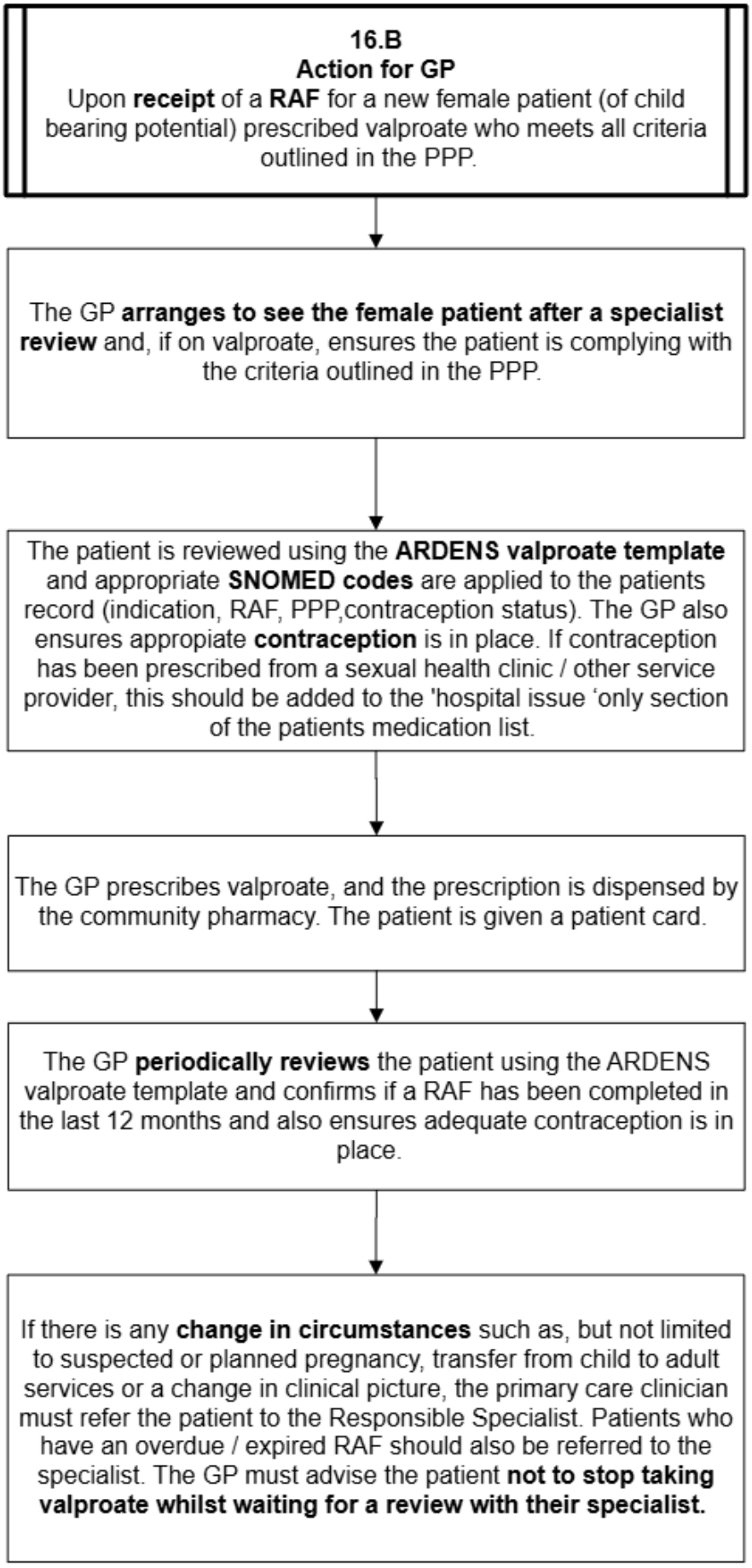
15.0 Monitoring

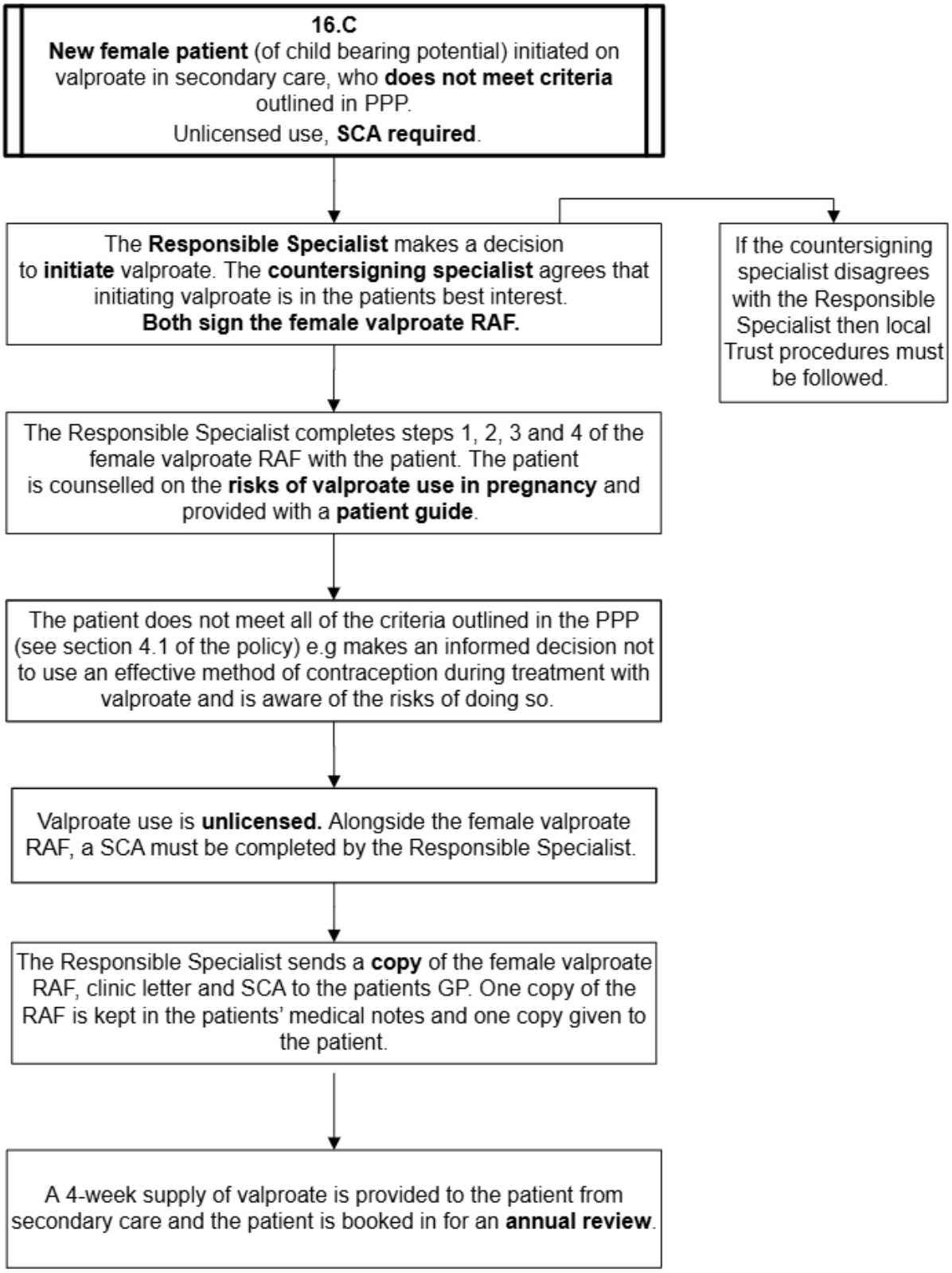
Clinicians are encouraged to audit compliance with the MHRA requirements and this policy annually. Use of SNOMED codes and patient registers will facilitate this.

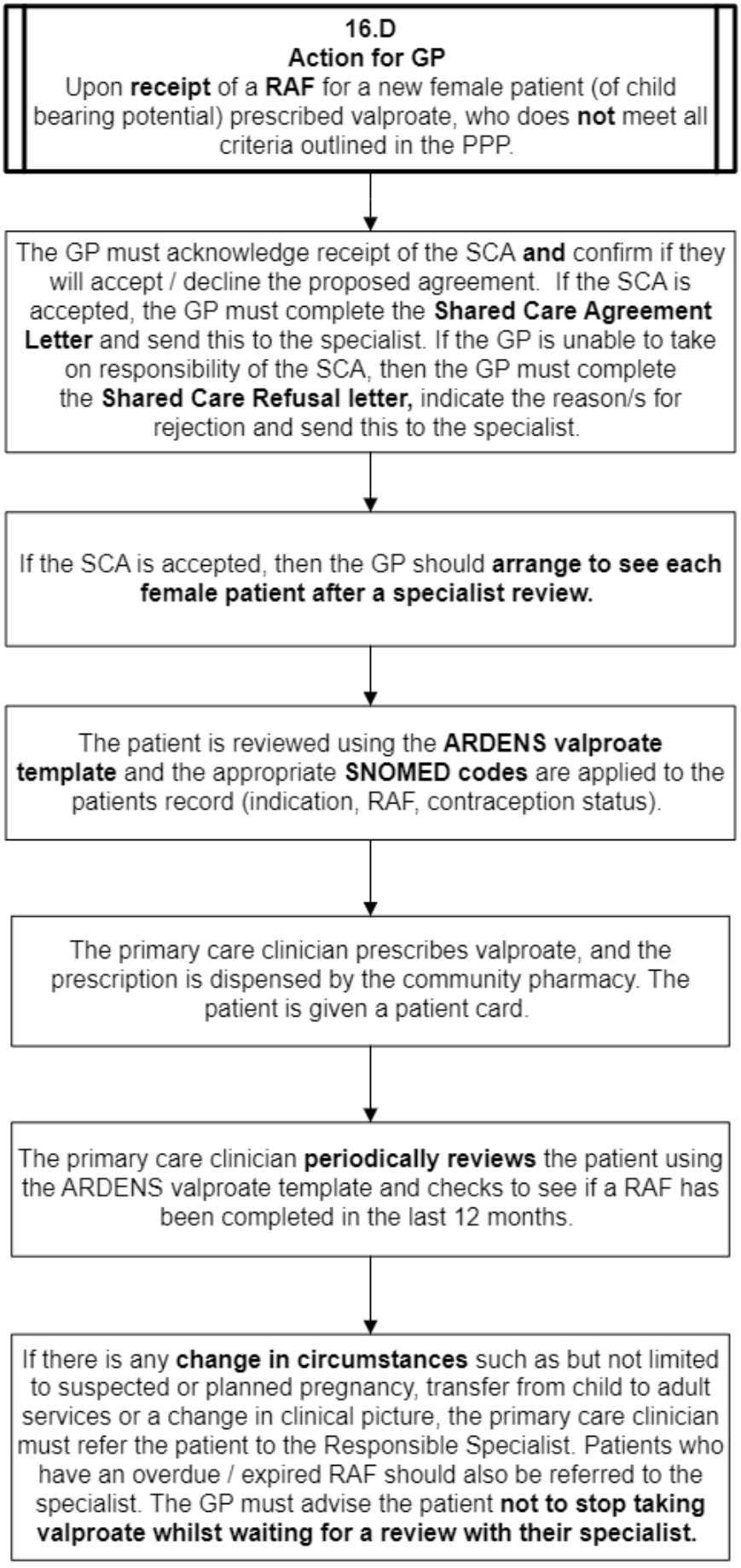
16.0 Best practice pathways for patients prescribed valproate in SWL

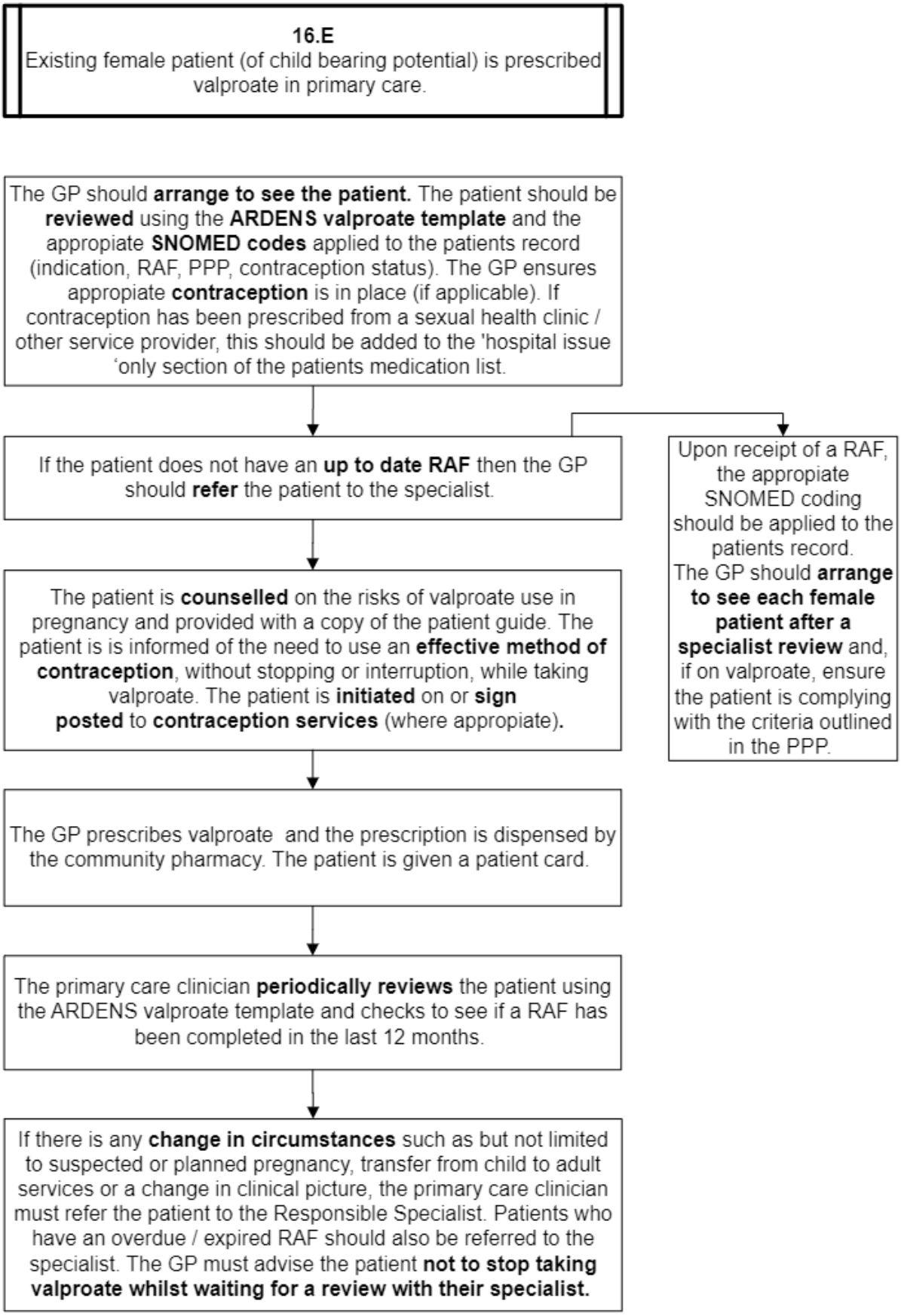
This section summarises key best practice pathways outlined in the policy. It is important to note that the MHRA, under 'actions for healthcare professionals,' the term ‘General Practitioners’ is consistently used. We have aligned the terminology with the Healthcare Professional Guide to ensure uniformity with the MHRA guidance.

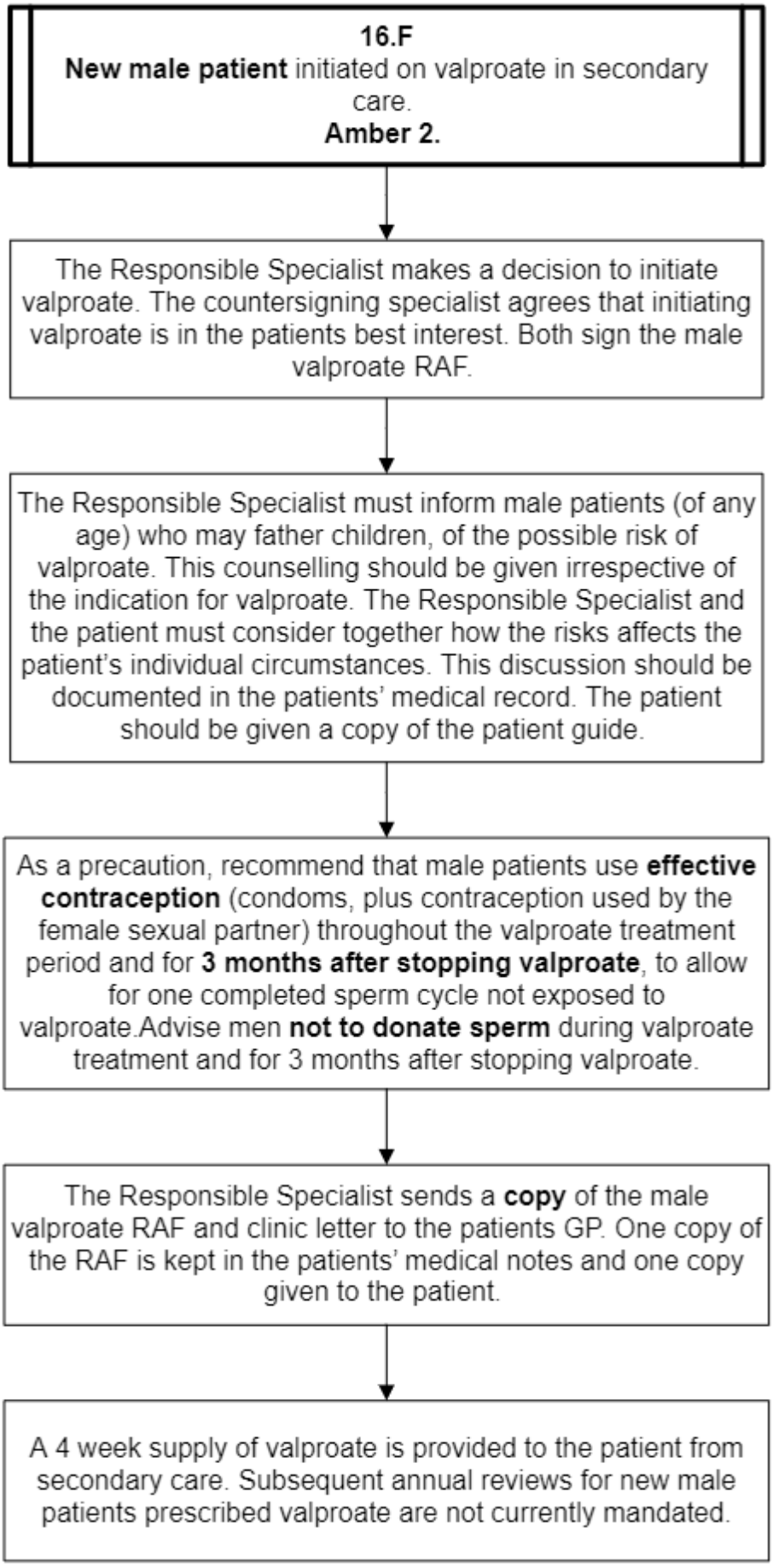

16.A
New female patient of child bearing potential initiated on valproate in secondary care, who meets criteria outlined in PPP.
Amber 2
The Responsible Specialist makes a decision to initiate valproate. The countersigning specialist agrees that initiating valproate is in the patients best interest. Both sign the female valproate RAF.
If the countersigning specialist disagrees with the Responsible Specialist then local Trust procedures must be followed.
The Responsible Specialist completes steps 1, 2, 3 and 4 of the female valproate RAF with the patient. The patient is counselled on the risks of valproate use in pregnancy and provided with a patient guide.
The patient is informed of the need to use an effective method of contraception, without stopping or interruption, while taking valproate and is initiated on or sign posted to a contraception service.
The Responsible Specialist sends a copy of the female valproate RAF and clinic letter to the patients GP. One copy of the RAF is kept in the patients' medical notes and one copy given to the patient.
A 4-week supply of valproate is provided to the patient from secondary care and the patient is booked in for an annual review.

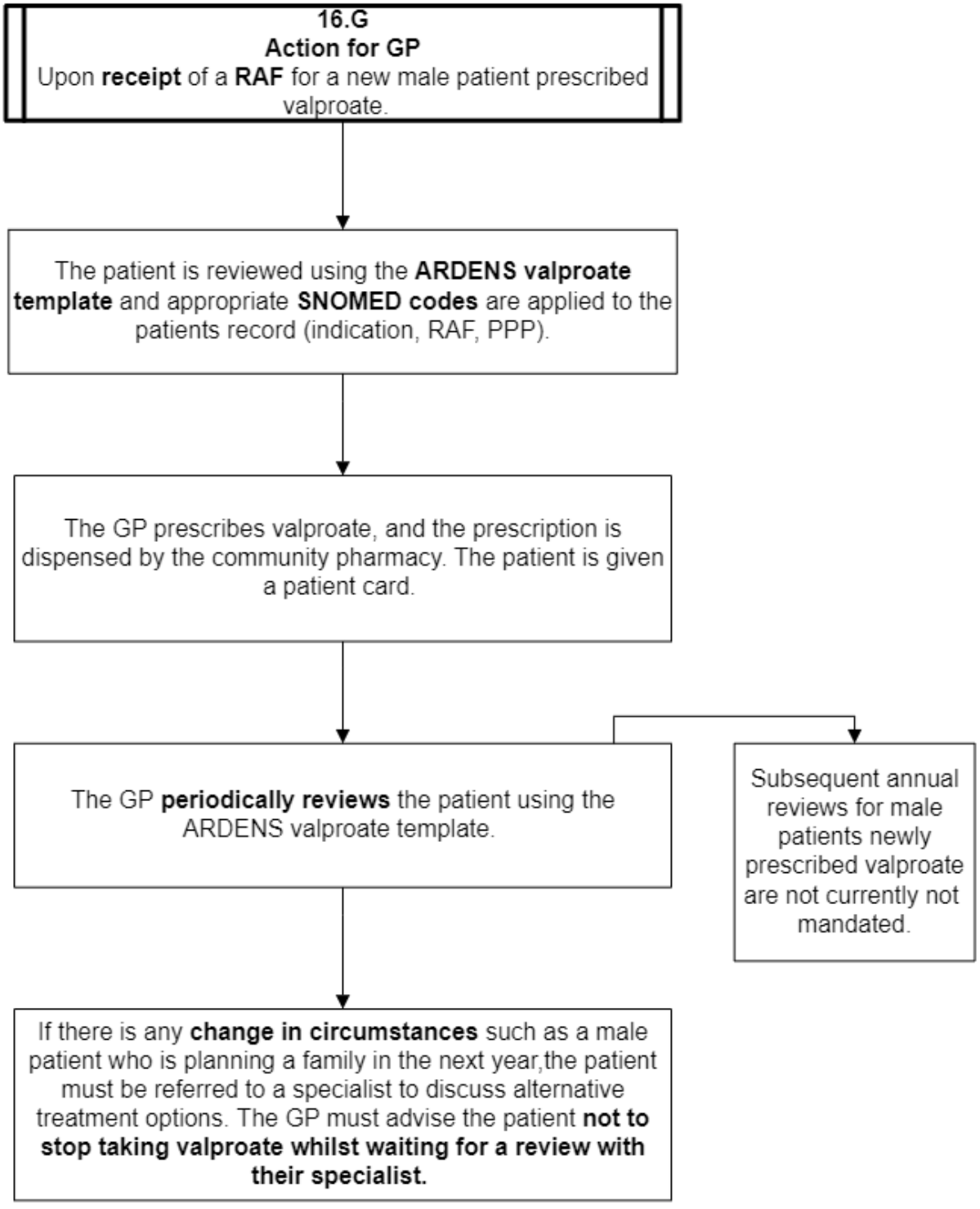

16.B
Action for GP
Upon receipt of a RAF for a new female patient (of child bearing potential) prescribed valproate who meets all criteria outlined in the PPP.
The GP arranges to see the female patient after a specialist review and, if on valproate, ensures the patient is complying with the criteria outlined in the PPP.
The patient is reviewed using the ARDENS valproate template and appropriate SNOMED codes are applied to the patients record (indication, RAF, PPP,contraception status). The GP also ensures appropiate contraception is in place. If contraception has been prescribed from a sexual health clinic / other service provider, this should be added to the 'hospital issue 'only section of the patients medication list.
The GP prescribes valproate, and the prescription is dispensed by the community pharmacy. The patient is given a patient card.
The GP periodically reviews the patient using the ARDENS valproate template and confirms if a RAF has been completed in the last 12 months and also ensures adequate contraception is in place.
If there is any change in circumstances such as, but not limited to suspected or planned pregnancy, transfer from child to adult services or a change in clinical picture, the primary care clinician must refer the patient to the Responsible Specialist. Patients who have an overdue / expired RAF should also be referred to the specialist. The GP must advise the patient not to stop taking valproate whilst waiting for a review with their specialist.

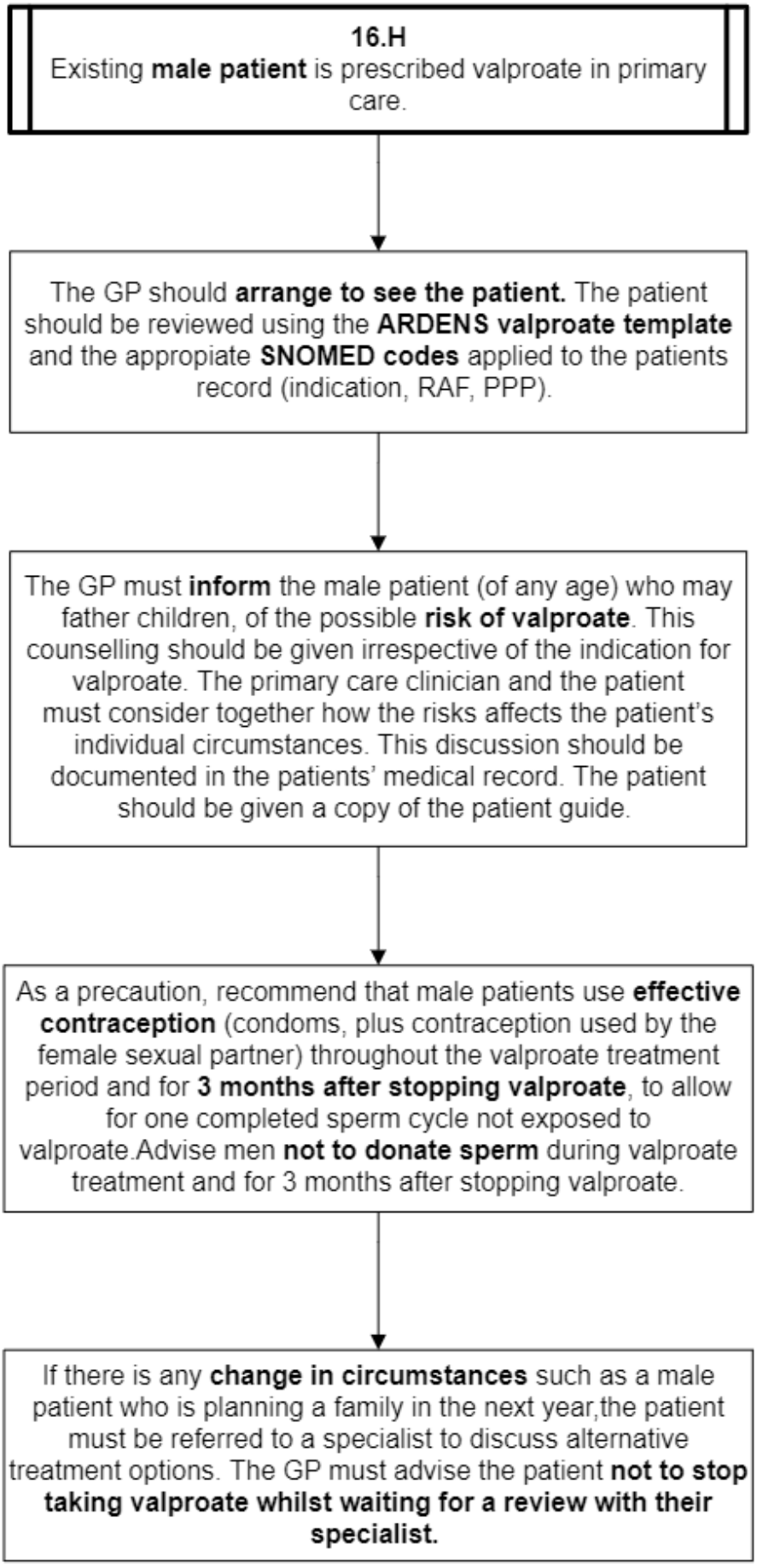

16.C
New female patient (of child bearing potential) initiated on valproate in secondary care, who **does not meet criteria** outlined in PPP.
Unlicensed use, **SCA required**.
The **Responsible Specialist** makes a decision to **initiate** valproate. The **countersigning specialist** agrees that initiating valproate is in the patients best interest. **Both sign the female valproate RAF.**
If the countersigning specialist disagrees with the Responsible Specialist then local Trust procedures must be followed.
The Responsible Specialist completes steps 1, 2, 3 and 4 of the female valproate RAF with the patient. The patient is counselled on the **risks of valproate use in pregnancy** and provided with a **patient guide**.
The patient does not meet all of the criteria outlined in the PPP (see section 4.1 of the policy) e.g makes an informed decision not to use an effective method of contraception during treatment with valproate and is aware of the risks of doing so.
Valproate use is **unlicensed.** Alongside the female valproate RAF, a SCA must be completed by the Responsible Specialist.
The Responsible Specialist sends a **copy** of the female valproate RAF, clinic letter and SCA to the patients GP. One copy of the RAF is kept in the patients' medical notes and one copy given to the patient.
A 4-week supply of valproate is provided to the patient from secondary care and the patient is booked in for an **annual review**.


16.D
Action for GP
Upon receipt of a RAF for a new female patient (of child bearing potential) prescribed valproate, who does not meet all criteria outlined in the PPP.
The GP must acknowledge receipt of the SCA and confirm if they will accept / decline the proposed agreement. If the SCA is accepted, the GP must complete the Shared Care Agreement Letter and send this to the specialist. If the GP is unable to take on responsibility of the SCA, then the GP must complete the Shared Care Refusal letter, indicate the reason/s for rejection and send this to the specialist.
If the SCA is accepted, then the GP should arrange to see each female patient after a specialist review.
The patient is reviewed using the ARDENS valproate template and the appropriate SNOMED codes are applied to the patients record (indication, RAF, contraception status).
The primary care clinician prescribes valproate, and the prescription is dispensed by the community pharmacy. The patient is given a patient card.
The primary care clinician periodically reviews the patient using the ARDENS valproate template and checks to see if a RAF has been completed in the last 12 months.
If there is any change in circumstances such as but not limited to suspected or planned pregnancy, transfer from child to adult services or a change in clinical picture, the primary care clinician must refer the patient to the Responsible Specialist. Patients who have an overdue / expired RAF should also be referred to the specialist. The GP must advise the patient not to stop taking valproate whilst waiting for a review with their specialist.


16.E
Existing female patient (of child bearing potential) is prescribed valproate in primary care.
The GP should arrange to see the patient. The patient should be reviewed using the ARDENS valproate template and the appropiate SNOMED codes applied to the patients record (indication, RAF, PPP, contraception status). The GP ensures appropiate contraception is in place (if applicable). If contraception has been prescribed from a sexual health clinic / other service provider, this should be added to the 'hospital issue 'only section of the patients medication list.
If the patient does not have an up to date RAF then the GP should refer the patient to the specialist.
Upon receipt of a RAF, the appropiate SNOMED coding should be applied to the patients record. The GP should arrange to see each female patient after a specialist review and, if on valproate, ensure the patient is complying with the criteria outlined in the PPP.
The patient is counselled on the risks of valproate use in pregnancy and provided with a copy of the patient guide. The patient is is informed of the need to use an effective method of contraception, without stopping or interruption, while taking valproate. The patient is initiated on or sign posted to contraception services (where appropiate).
The GP prescribes valproate and the prescription is dispensed by the community pharmacy. The patient is given a patient card.
The primary care clinician periodically reviews the patient using the ARDENS valproate template and checks to see if a RAF has been completed in the last 12 months.
If there is any change in circumstances such as but not limited to suspected or planned pregnancy, transfer from child to adult services or a change in clinical picture, the primary care clinician must refer the patient to the Responsible Specialist. Patients who have an overdue / expired RAF should also be referred to the specialist. The GP must advise the patient not to stop taking valproate whilst waiting for a review with their specialist.


16.F
New male patient initiated on valproate in secondary care.
Amber 2.
The Responsible Specialist makes a decision to initiate valproate. The countersigning specialist agrees that initiating valproate is in the patients best interest. Both sign the male valproate RAF.
The Responsible Specialist must inform male patients (of any age) who may father children, of the possible risk of valproate. This counselling should be given irrespective of the indication for valproate. The Responsible Specialist and the patient must consider together how the risks affects the patient's individual circumstances. This discussion should be documented in the patients' medical record. The patient should be given a copy of the patient guide.
As a precaution, recommend that male patients use effective contraception (condoms, plus contraception used by the female sexual partner) throughout the valproate treatment period and for 3 months after stopping valproate, to allow for one completed sperm cycle not exposed to valproate.Advise men not to donate sperm during valproate treatment and for 3 months after stopping valproate.
The Responsible Specialist sends a copy of the male valproate RAF and clinic letter to the patients GP. One copy of the RAF is kept in the patients' medical notes and one copy given to the patient.
A 4 week supply of valproate is provided to the patient from secondary care. Subsequent annual reviews for new male patients prescribed valproate are not currently mandated.


16.G
Action for GP
Upon receipt of a RAF for a new male patient prescribed valproate.
The patient is reviewed using the ARDENS valproate template and appropriate SNOMED codes are applied to the patients record (indication, RAF, PPP).
The GP prescribes valproate, and the prescription is dispensed by the community pharmacy. The patient is given a patient card.
The GP periodically reviews the patient using the ARDENS valproate template.
Subsequent annual reviews for male patients newly prescribed valproate are not currently not mandated.
If there is any change in circumstances such as a male patient who is planning a family in the next year,the patient must be referred to a specialist to discuss alternative treatment options. The GP must advise the patient not to stop taking valproate whilst waiting for a review with their specialist.


16.H
Existing male patient is prescribed valproate in primary care.
The GP should arrange to see the patient. The patient should be reviewed using the ARDENS valproate template and the appropiate SNOMED codes applied to the patients record (indication, RAF, PPP).
The GP must inform the male patient (of any age) who may father children, of the possible risk of valproate. This counselling should be given irrespective of the indication for valproate. The primary care clinician and the patient must consider together how the risks affects the patient's individual circumstances. This discussion should be documented in the patients' medical record. The patient should be given a copy of the patient guide.
As a precaution, recommend that male patients use effective contraception (condoms, plus contraception used by the female sexual partner) throughout the valproate treatment period and for 3 months after stopping valproate, to allow for one completed sperm cycle not exposed to valproate.Advise men not to donate sperm during valproate treatment and for 3 months after stopping valproate.
If there is any change in circumstances such as a male patient who is planning a family in the next year,the patient must be referred to a specialist to discuss alternative treatment options. The GP must advise the patient not to stop taking valproate whilst waiting for a review with their specialist.

Document History

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Review Date: 2 years from approval date or sooner where appropriate.

Complete the 'author' and 'approval date' below. If adding an acknowledgment, - add this below the 'Author' line.

Appendix 1: Resources for all healthcare professionals

All healthcare professionals should review the new measures and updated safety and educational materials available. Some of these are available via the FutureNHS platform which is free to register on.

- Annual Risk Acknowledgement Form for female patients: To support and record the discussion between the patient and specialist prescriber on the risks associated with valproate in pregnancy and to record the decision of the countersigning specialist.
- Advice for male patients on valproate to use contraception: Provides information on the risks of valproate for male patients.
- Easy read valproate: A patient information leaflet translated into 30 languages available for download as PDFs.
- Educational Resource for autism and or LD: To help clinicians discuss sex / sexual health / pregnancy prevention with those that have autism and / or a learning disability and are taking valproate.
- General Practice Responses to Paternal Valproate Risk: Flow chart to support general practice to respond to patients presenting to discuss the risks of neurodevelopmental disorder in children born to men or trans-women who took valproate in the 3 months prior to conception.
- Healthcare Professional Guide: Provides information on the risks of valproate in pregnancy and the risks for male patients, the new conditions for valproate prescribing and key points for patient discussions.
- Male Risk Acknowledgement Form: To support and record the discussion between the patient and specialist prescriber of the risks associated with valproate in males when starting treatment with valproate and to record the decision of the countersigning specialist.
- Patient card: Provides key information for female patients receiving valproate on contraception and pregnancy prevention.
- Patient guide: Provides those taking valproate (or their parent, caregiver, or responsible person) with updated information on the risks of valproate in pregnancy and the risks to male patients and what they need to do.

- Pharmacy poster: Provides important actions for pharmacists dispensing valproate to female patients.
- Valproate review appointment letter (editable): A template letter for inviting people with a learning disability for a consultation about their medication and the PPP.
- Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): New safety and educational materials to support regulatory measures in men and women under 55 years of age
- Visual risk communication diagram to be used by a healthcare professional when counselling on the risks: A useful visual representation of the risks of male patients taking valproate in comparison to lamotrigine and levetiracetam.
- Warning stickers: To be added to packaging of medicine in exceptional circumstances where the original pack cannot be dispensed.

Appendix 2: Contraceptive services available across SWL

Place	Name of contraceptive service available	Contact details
Croydon	Croydon Sexual Health Centre	020 8401 3766
Kingston and Richmond	Wolverton Sexual Health	020 8974 9331
Merton and Wandsworth	Patrick Doody Clinic (Merton) Falcon Road (Wandsworth)	Central booking team: 0333 300 2100
Sutton	The Rosehill Clinic	020 8296 3910

Appendix 3: Paternal Risk of Valproate Exposure: Questions and Answers for General Practice

This document aims to answer questions arising following publication of the Drug Safety Update article, Valproate use in men, 5th September 2024, on the risk of Neurodevelopment Disorders (NDD) in children born to men or people who can father children, who have taken valproate in the 3 months before conception (referred to as 'paternal risk').

It was compiled by members of NHS England - Valproate Integrated Quality Programme and has been adapted for use in NHS South West London.

Further advice may be provided by royal collages as consensus emerges. Such advice will supersede this document which is published to stimulate debate.

Q1 Where can I learn more about the paternal risk?

The following links provide further information:

- Valproate use in men: as a precaution, men and their partners should use effective contraception on the Drug Safety Update webpage.
- Valproate: review of safety data and expert advice on management of risks provides detailed background information and can be found in the MHRA's public assessment report.

Q2 When and where will the new supporting materials such as the Risk Acknowledgement Form (RAF) for men, patient card, leaflet, and healthcare professional information be available?

Further information is available at:

- Epilim 200 mg Gastro-resistant tablets - Risk Management Materials. Risk management materials are also available for other brands of valproate on emc.
- Valproate safety measures.
- Advice for male patients on valproate to use contraception.

- Visual risk communication diagram to be used by a healthcare professional when counselling on the risks.

There may be a delay between the publication of the Drug Safety Update (5th Sept 2024) and the availability of the updated supporting materials from the drug manufacturers.

Q3 The MHRA's publication refers to men and males. Do the risks apply to trans-women who retain the capability to generate sperm.

Yes, the risks apply to anyone who can biologically father children. Practices should consider this when searching their systems for at-risk patients as trans-women may not be included in the search results of male patients.

Q4 Is there an age limit for this risk, like there is for women?

No. However, it remains less common for men over the age of 50 to father children.

Q5 How should I prioritise which men and trans-women I should have a conversation with first?

1. Any patients known to the practice to be in IVF treatment or spontaneously declaring their intention to father children. (It is not expected that practices will be able to systematically identify this group, this information may be provided opportunistically by patients).
2. Patients with a learning disability.
3. Trans-women with ability to generate sperm.
4. Patients with sensory disability, language, or communication barriers.
5. Patients with both epilepsy and bipolar disorder.
6. Patients stratified by age, starting with the age group in your community with the highest conception rates.
7. Patients who have had a vasectomy.

Cohorts 2 to 4 are prioritised due to the health inequalities experienced by these groups.

Q6 Do all the men and trans-women who the practice prescribed valproate to need to have a RAF completed.

No. Only men and trans-women who have been initiated on valproate after the 31st of Jan 2024 will have a RAF. This will be completed by the initiating specialist.

Q7 If a man or trans-woman has had a RAF completed in the past, does it need to be repeated annually.

No.

Q8 Does the practice need to have a consultation with all the men or trans-women to whom they prescribe valproate to tell them about the paternal risks.

All men and trans-women currently taking valproate should be informed about the risk. There is a professional responsibility and failure to inform the patients of the risk may leave the prescriber open to a claim or complaint to the regulators.

Practices are able to communicate the risk to patients in any way they feel meets the patient's needs. Electronic messaging is commonplace (example being AccuRx messages) and the practice may consider this appropriate for some or all of their patients.

Practices have suggested a simple signposting message advising that new risks have been found for men and trans-women who take valproate medicines and father children. Include a link to the patient information and a reminder not to stop taking valproate without discussing it with a healthcare professional. It may be possible for the patient to acknowledge receipt of this information electronically. Also See Q12 on SNOMED codes.

Q9 How can I prepare to have a consultation about the paternal risks with a man or trans-woman who is taking valproate.

Patients have said that their satisfaction with a consultation about valproate improves when:

- They have been advised in advance of the subject matter.
- The clinician is well informed about the risk.
- The clinician is confident and comfortable with the discussion.
- The clinician asks what is important for the patient.
- The clinician uses language that the patient finds easy to understand.

Clinicians should understand the information in the Health Professional Guide produced by the drug manufacturers and may consider simulation training with trusted peers before embarking on the consultations.

For pharmacists there is a helpful workshop produced by CPPE (log-in required); "The Hard Conversations". This may help pharmacists prepare for conversations.

A template invite letter and resource to support conversations with people with a learning disability are also available on the FutureNHS platform (log-in required).

Q10 Who, in the practice team, is able to hold a consultation about the paternal risks with a man or trans-woman who is taking valproate?

Any registered healthcare professional, such as GPs, Pharmacists and Nurses who are confident and competent to complete the consultation.

Q11 Now that the paternal risks have been identified, is there a deadline by which time the practice must have informed all the affected patients?

The MHRA has not set a deadline. Commonly practices have suggested that they will see patients at their next scheduled review following their usual procedures for medication review (or other review of long-term conditions).

Q12 How should the practice record and code that the patient has been informed about the paternal risks?

For new male patients, the practice can record the receipt of the RAF using 2078961000000109 |Risk Acknowledgement Form for Male Patients Starting Valproate completed (situation)|

For existing patients, a non-specific SNOMED code is appropriate along with a free text annotation of ‘valproate’ and ‘Risk of Neurodevelopmental Disorder’:

396080005 |Medication side effects education (procedure)|

Q13 Should all the men and trans-women to whom the practice prescribes valproate be referred to a specialist.

There is no requirement to refer patients, as a result of these paternal risks, unless the patient has epilepsy or bipolar disorder and wishes to discuss their treatment options. It is anticipated that discussions about treatment options in epilepsy or bipolar disorder is out-of-scope of practice for majority of primary care clinicians. Practices may wish to use the advice & guidance route before making a referral dependent on local pathways and referral-to-treatment times. Before making a referral, the GP may wish to consider the following with the patient:

- Have other options already been tried? Did they help?
- Are there any barriers to changing medication?

- The severity of the disorder and degree of treatment resistance.
- Current symptomatology.
- Current insight and decision-making capacity.
- Adherence to current medication.

For unlicensed uses of valproate such as migraine, neuropathic pain, and mood stabilisation (other than bipolar disorder), there is less evidence of efficacy and prescribers may wish to consider the justification for continuing therapy.

Q14 What should I do if a sexually active man or trans-woman who understands the risks tells me that they will not use contraception or will not ask their partner(s) to use contraception.

The man or trans-woman's autonomy must be respected. Opportunities should be taken to understand the patient's reasons, dispel any misunderstanding and counsel them on the consequences of their choices whilst offering support to take alternative actions. Clear documentation of the discussion should be made in the notes (see Q12 regarding coding).

Q15 What should I do if a man or trans-woman who is taking valproate says that they are planning to father a child and cannot wait to see a specialist so will stop taking their valproate?

Advise the patient that their epilepsy or bipolar disorder may deteriorate without valproate, or an alternative medication and that deterioration can be fatal.

Discuss that we do not currently know if NDD caused by valproate taken by fathers can be distinguished from baseline incidence, so stopping valproate has no guarantee of a child without NDD.

If valproate is prescribed for conditions other than epilepsy or bipolar disorder, consider supporting the patient's decision to stop with safety-netting.

Q16 What should I do if a man or trans-woman taking valproate expresses concern that their child or children might have been affected.

What should I do if a woman or trans-man expresses concern that their child or children might have been affected by the paternal exposure to valproate.

1. Check if the use of valproate was within 3 months of conception. Data has shown an increased risk of NDD in children of fathers treated with valproate in the 3 months prior to conception is possible. The risks have not been studied when valproate was stopped more than 3 months before conception.
2. Advise them of the relative risks and the uncertainty of the causal nature of valproate. We do not currently know if NDD caused by valproate taken by fathers can be distinguished from baseline incidence.
3. Explain that NDD can take many forms and in some people, this may be diagnosed later in life.
4. Follow local protocols for referral to a specialist for NDD if the parents are concerned and the affected person has displayed signs of a NDD.

Parents can be referred to these groups for more help and advice:

1. INFACT - who provide information, advice, and support to families.
2. Organisation for Anti-Convulsant Syndrome (OACS) - A charity who provide support to all families touched by Fetal Anticonvulsant Syndrome

Q17 If a male/trans-female has had a vasectomy, is counselling on the paternal risk required?

Yes, male vasectomy whilst considered highly effective (>99% as contraceptive), it is not 100% and these patients should still be counselled about these new findings. Vasectomy (Male Sterilisation).

Q18 How can I be part of the national Valproate Integrated Quality Improvement Programme?

Join the collaboration space at Medicines Safety Improvement Programme - FutureNHS Collaboration Platform.

Request invites to group meetings and workshops at

england.medicinessafetyimprovementprogramme@nhs.net.

Appendix 4: SNOMED concept ID coding

Valproate PPP
1129771000000103 | Pregnancy prevention programme started (situation) |
1129801000000100 | Pregnancy prevention programme declined (situation) |
1129791000000104 | Pregnancy prevention programme not needed (situation) |
1129841000000102 | Pregnancy prevention programme discontinued (situation) |
1129831000000106 | Did not attend pregnancy prevention programme (situation) |
1129821000000109 | Pregnancy prevention programme declined by parent (situation) |
1129811000000103 | Pregnancy prevention programme declined by caregiver (situation) |
1960931000006109 | Pregnancy prevention programme form signed by patient |
Valproate RAF
1659031000000103 | Valproate Annual Risk Acknowledgement Form (record artifact) |
1366401000000107 | Valproate Annual Risk Acknowledgement Form completed (situation) |
1366381000000107 | Referral for completion of Valproate Annual Risk Acknowledgement Form (procedure) |
2078951000000106 | Valproate Annual Risk Acknowledgement Form for Female Patients completed (situation) |
2078961000000109 | Risk Acknowledgement Form for Male Patients Starting Valproate completed (situation) |
Other
72531000052105 | Counselling for contraception (procedure) | • Free text valproate as appropriate