Commission on Human Medicines

Report of The Commission on Human Medicines Isotretinoin Implementation Advisory Expert Working Group

Independent report

31 October 2023

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Foreword

The Commission on Human Medicines (CHM) and its Isotretinoin Expert Working Group (IEWG) published their independent report in April 2023. A number of recommendations were made with the aim of improving the safety of isotretinoin for the treatment of acne. The CHM recognised that implementation would require changes in organisational structures, regulatory advice, and clinical care and therefore set up a multi-disciplinary Isotretinoin Implementation Advisory Expert Working Group (IIAEWG), to advise on the best way to implement the recommendations. The IIAEWG was tasked with reporting to the CHM with their suggestions.

This report of the IIAEWG is aimed at all stakeholders involved in the use of isotretinoin, including patients, parents, healthcare professionals, healthcare organisations/providers and regulatory authorities.

The principles adopted by the group were to address the concerns of the report of the Commission on Human Medicines Isotretinoin Expert Working Group (CHM IEWG) in a way which would enable ongoing access for patients requiring isotretinoin, in as safe a way as possible. The group was keen that changes to current practice should be practical to implement without undue barriers relating to access, logistics, patient fears about possible side effects, or cost. The group recognised their role was to advise the CHM on how to safely and effectively implement the advice of the CHM, rather than comment on the recommendations themselves. The group also recognised it was important to try and mitigate against future safety issues that could arise over the next few years due to the changing healthcare environment, including:

- increased decision making and prescribing by non-medical healthcare professionals.
- increased use of technology in healthcare enabling a move towards remote consultations.
- increasing availability of private and cosmetic healthcare providers.

During the initial meetings and preparation for the report it became apparent that there is current variation in practice and lack of clarity around several aspects of isotretinoin prescribing which is potentially impacting on safety. This includes variation in:

- patient information provided by primary care to the specialist.
- the type/qualification of specialists who are assessing patients and initiating isotretinoin and the healthcare setting in which they are seen.
- quantity and quality of counselling provided prior to initiation of isotretinoin.

- monitoring practices for identification and management of possible side effects.
- enrolment into the Pregnancy Prevention Programme and use of an ‘opt out form’ for some people with childbearing potential.

The group felt that it was important to address these issues in addition to those directly addressed in the CHM IEWG report. This is because clarity was considered to be essential to reduce unwanted variation in safety practice.

The group recognises that it will take time for any changes to be embedded into practice. It strongly recommends that the MHRA continues to work with stakeholders, including professional organisations representing dermatologists, GPs, and dermatology nurses; Marketing Authorisation Holders and patient groups or representatives to progress implementation and address any issues that may arise.

The recommendations of the IIAEWG were endorsed by the CHM in July 2023 and are presented in this report.

1. Introduction

1.1. Background to this guidance

In September 2019, the Commission on Human Medicines (CHM) reconvened the Isotretinoin Expert Working Group (IEWG) to consider whether further regulatory action was required following concerns raised by patients and other stakeholders about the risks of psychiatric (mental health) side effects and sexual side effects associated with the use of isotretinoin for the treatment of acne.

The CHM and its IEWG published their report in April 2023 and recommended new measures to strengthen the safety of isotretinoin treatment. These recommendations have been extracted from the CHM IEWG report and highlighted below for reference:

Regulatory action

Changes to product information

'Given the concerns about the lack of robust evidence to support the accuracy of current frequency estimates for psychiatric side effects in the product information, current information on the frequency of psychiatric side effects (depression, depression aggravated, suicide, suicidal attempt and suicidal ideation) in the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) should be changed to 'not known'. Careful consideration must be given to how these risks are explained to patients and supported by educational materials.

Warnings about the potential for the sexual side effects (erectile dysfunction, vulvovaginal dryness, reduced libido, orgasm difficulties and genital hypoaesthesia) to continue long-term, after treatment with isotretinoin has been stopped should be added to the SmPC and PIL.

Although the data is limited, it is considered that there is sufficient evidence to justify adding orgasm difficulties and genital hypoaesthesia as possible side effects in the SmPC and PIL.'

Counselling, information provision and monitoring

Psychiatric side effects

'The SmPC and PIL should be updated to state that patients, and where applicable parents or carers, must be counselled about the risk of possible psychiatric side effects with isotretinoin prior to prescription of isotretinoin, and ideally prior to any referral that might include consideration of isotretinoin treatment.

The SmPC and PIL should be updated to state that patient's mental health status should be assessed prior to prescription of isotretinoin and regularly during treatment for developing or worsening psychiatric disorders.

To support consistent implementation of the regulatory change further work involving professional bodies and health system organisations will be required to determine appropriate tools (e.g. questionnaires) to assess mental health status; periodicity of monitoring and clinical pathways to manage patients with severe or ongoing psychiatric disorders during or after treatment with isotretinoin.'

Sexual disorders

'The SmPC and PIL should be updated to state that patients, and where applicable parents or carers, must be counselled about the possible risk of sexual dysfunction with isotretinoin prior to the prescribing decision, and ideally prior to any referral that might include consideration of isotretinoin treatment. The age and maturity of the patient should be taken into account in considering the most appropriate counselling approach, including giving the option to discuss without parents or carers present.

To support consistent implementation of the regulatory change further work involving professional bodies and health system organisations will be required to determine appropriate tools (e.g. age-appropriate questionnaires) to assess sexual function; periodicity of monitoring and clinical pathways to manage patients with sexual dysfunction during or after treatment with isotretinoin.'

Information for patients

'Information in a range of formats should be developed to provide accessible, plain language information to patients under consideration for isotretinoin treatment, and where appropriate their parents or carers, taking account of the recommendations on psychiatric and sexual side effects above. This information should include:

- reference to the possibility of side effects continuing after treatment has stopped.
- information on the self-management of common side effects such as skin dryness.
- a process for facilitating discussion, understanding and acknowledgement of the possible risks of treatment'.

Patients and their parents/carers should have adequate time between initial counselling and subsequent prescription to reflect on the information about isotretinoin and ask questions before prescription of isotretinoin.'

Acknowledgement of risk form

‘Patients and parents/carers should receive full information about the possible risks as well as the benefits of treatment in order to be able to make an informed decision about their treatment. There is currently an acknowledgement of risk form for female patients. It was recommended that this form is expanded to cover all potential risks and used for all patients. Stakeholders, including patients, parents/carers and healthcare professionals, should be involved in the development of the form to ensure it meets requirements.’

Isotretinoin use in adolescents

‘More data are needed on the use of isotretinoin in adolescents under 18 years of age, including any long-term effects in adulthood and recommended longitudinal studies would be of benefit.

Adolescents under 18 years of age should be treated by a healthcare professional with appropriate expertise in treating children and young people, ideally in a setting that is able to support the appropriate counselling of patients and parents or carers for the above risks and with an identified appropriate care pathway if side effects occur.

There should be greater oversight of isotretinoin treatment in those under 18 years, including agreement by two healthcare professionals that isotretinoin is the most appropriate treatment option before it is prescribed and that patients and their families have been adequately informed about the potential risks.’

Roles and responsibilities of healthcare professionals

‘The potential for General Practitioner with an Extended Role (GPwERs) to independently prescribe isotretinoin for adult patients should be explored with the appropriate professional bodies and reflected in clinical guidance. There should be clear communication from dermatology services to general practice that a patient has started treatment with isotretinoin. Emphasis is placed on clear communications notifying all involved healthcare professionals of any problems experienced by the patient.’

Further research

‘More research is needed on the side effects associated with isotretinoin, including their frequency, the biological mechanisms underlying their occurrence, the identification of any relevant biomarkers and genetic factors.

More data are needed on the use of isotretinoin in adolescents under 18 years of age, including the study of any potential long-term effects in adulthood and suggested longitudinal studies would be of benefit.

An isotretinoin drug registry should be developed to:

- gather further information on psychiatric events and sexual dysfunction with isotretinoin including the nature and magnitude of risks associated with isotretinoin, risk factors, natural progression of events, vulnerable age groups and the complex relationship between psychiatric events and sexual disorders.

- facilitate identification of adverse events which are currently not listed in the product information, the frequency of side effects and gather information and understanding on side effects which continue long term as well as the onset of adverse events after isotretinoin treatment has stopped.

Applied research should be conducted to evaluate the impact of the new risk minimisation measures.’

1.2. Scope of the advice and terms of reference

The CHM IEWG had noted that stakeholders, including both patients and HCPs, should be involved in the development and implementation of the recommendations in the report in order to aid successful implementation given the significant changes to risk minimisation materials, clinical practice, and monitoring tools.

The CHM formed an Isotretinoin Implementation Advisory Expert Working Group (IIAEWG), composed of experts and representatives of healthcare organisations, to advise on the implementation of these recommendations.

The IIAEWG met on 10 March 2023, 31 March 2023 and 12 May 2023.

‘The terms of reference of the Isotretinoin Implementation Advisory Expert Working Group (IIAEWG) were finalised and adopted by the IIEAWG at its second meeting on 31 March 2023, as follows:

To inform the Commission on Human Medicines on:

- pathways and strategies for implementing the recommendations in the Isotretinoin Expert Working Group Report.
- communication and education: the development of communication and educational materials to support and record informed prescribing decisions.
- monitoring compliance: plans for measurement of compliance and impact with the recommendations.
- advice and recommendations on future research and a registry.’

1.3. Membership

Membership of the IIAEWG included those with expertise in dermatology, general practice, paediatrics, psychiatry (including child and adolescent psychiatry), psychology, nursing, and pharmacy. In addition, there was a lay member. The Chair was a consultant dermatologist. All members declared their interests and adhered to the MHRA conflict of interest policy.

Observers to the meetings were invited from the National Institute for Health and Care Excellence (NICE), Care Quality Commission (CQC), General Medical Council (GMC), NHS England and representatives from Scotland, Wales and Northern Ireland.

The IIAEWG fully recognised the importance of the patients’ voice and supported the involvement of stakeholders who would be able to provide invaluable input into the patient guidance and materials.

2. Pathways and strategies for implementing the recommendations in the Isotretinoin Expert Working Group Report

2.1. Isotretinoin prescribing

The therapeutic indications for isotretinoin stated in the Summary of Product Characteristics (SmPC) are:

> ‘Severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.’

The SmPC also states that:

> ‘Isotretinoin should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.’

In the UK this was historically interpreted to mean isotretinoin should be prescribed by, or under the supervision of, a consultant dermatologist. As healthcare services have evolved and new healthcare professional (HCP) roles have developed, a wider group of HCPs are prescribing isotretinoin. Prescribing occurs in secondary care, community services and the private sector (with boundaries between secondary and community care now often overlapping), and there is significant variability in practice across the UK.

The CHM IEWG report made two separate recommendations concerning isotretinoin prescribing and HCPs:

‘There should be greater oversight of isotretinoin treatment in those under 18 years, including agreement by two healthcare professionals that isotretinoin is the most appropriate treatment option before it is prescribed and that patients and their families have been adequately informed about the potential risks.’

‘The potential for GPwERs to independently prescribe isotretinoin for adult patients should be explored with the appropriate professional bodies and reflected in clinical guidance. There should be clear communication from dermatology services to general practice that a patient has started treatment with isotretinoin. Emphasis is placed on clear communications notifying all involved healthcare professionals of any problems experienced by the patient.’

The IIAEWG therefore sought to define and advise on:

- which HCPs would be suitable prescribers for isotretinoin both in adults and adolescents (under 18 years old).
- the role of the Lead Prescriber, who makes the decision to initiate isotretinoin.
- the role of the Second Approved Named HCP, for adolescents under 18 years old, who agrees that isotretinoin is the most appropriate treatment option.

The CHM IIAEWG recommendations outlined in this report also formalise some existing prescribing practices and endeavour to reduce variation in practice, ensuring that appropriate prescribing is in place.

2.1.1. Lead Prescriber

The Lead Prescriber is the HCP making the decision to initiate isotretinoin treatment. They should assess the patient face-to-face. The Lead Prescriber must have expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.

The Lead Prescriber should be one of the following clinicians:

i. Consultant Dermatologist.

ii. Associate Specialist Dermatologist.

iii. Nationally accredited General Practitioner with an Extended Role (GPwER)[1] working within a Consultant Dermatologist agreed pathway.

iv. General Practitioners with a Special Interest (GpwSI) who are currently prescribing isotretinoin within a Consultant Dermatologist agreed pathway. GpwSI must have been signed off locally prior to the introduction of GPwER accreditation. (GpwSI have been replaced with GPwER).

[1] Link to accreditation: https://www.bad.org.uk/education-training/gps/become-a-gpwer-in-dermatology/

v. Junior doctor or Specialty doctor with evidence of competency in isotretinoin initiation[2] working under the supervision of the clinicians listed above (i, ii, iii).

vi. Band 8a or above Dermatology Clinical Nurse Specialist or Dermatology Nurse Consultant working within a Consultant Dermatologist agreed and supervised pathway. Nurses working in the private sector should have equivalent levels of qualifications and experience.

vii. Band 8a or above Dermatology Pharmacist or Dermatology Consultant Pharmacist working within a Consultant Dermatologist agreed and supervised pathway. Pharmacists working in the private sector should have equivalent levels of qualifications and experience.

viii. For adolescents under 18 years old, a Consultant Paediatrician (with specialist accreditation in dermatology and working within a Consultant Dermatologist agreed pathway) may also initiate isotretinoin.

ix. For adolescents under 18 years old, Consultant Paediatricians who were signed off locally prior to the introduction of specialist accreditation in Dermatology for Paediatricians and are already prescribing isotretinoin (within a Consultant Dermatologist agreed pathway). This pathway does not exist going forwards.

2.1.2. Second Approved Named HCP in adolescents under 18 years old

The key role of the Second Approved Named HCP is to agree, independently, that isotretinoin is the most appropriate treatment option for that patient. The patient must have a severe form of acne for which other standard treatments have been sufficiently tried and were ineffective. The Second Approved Named HCP does not require highly specialised skills in isotretinoin prescribing (in contrast to the Lead Prescriber). However, the second prescriber should have experience in the management of people with acne, be an independent prescriber, and understand that they have a shared responsibility for the treatment decision.

The IIAEWG considered which group of HCPs would have the most appropriate skills to fulfil this role, noting that the General Practitioner (GP) or other primary care clinician would be in a position to have a full understanding of the patient's medical history.

[2] Work-place based assessments should be used to evidence competency in isotretinoin initiation e.g. Mini-Clinical Evaluation Exercise (Mini-CEX) and Case-based Discussion (CbD). It is the responsibility of consultants to ensure the trainees are competent.

The second approved named HCP (for adolescents under 18 years old) who agrees isotretinoin is the appropriate treatment should be one of the following:

i. Any of the HCPs who are eligible to be a Lead Prescriber. However, one HCP cannot act in both roles. Two different HCPs are required.

ii. The primary care clinician making the referral to a specialist. This may be a GP, Advanced Nurse Practitioner (ANP), Advanced Clinical Practitioner (ACP) or future equivalents. Note that the referring clinician cannot automatically be assumed to act as the second named HCP. They must agree to act in this role and indicate this explicitly.

iii. Non-medical prescribers (such as a Band 6 or above Dermatology Nurse Specialist or Pharmacist with appropriate dermatology expertise, skills and training) experienced in prescribing isotretinoin, working within a Consultant Dermatologist or GPwER agreed pathway.

iv. A Multidisciplinary Team (MDT), which should consist of at least one HCP eligible to be a Lead Prescriber and at least one clinician eligible to be a second named HCP. The MDT lead clinician should not be the same person as the Lead Prescriber for the patient.

The details of the Second Approved Named HCP (including job title and place of work) should be documented on the Acknowledgement of Risk Form. If the MDT is acting as Second Approved Named HCP then the date of the MDT and name of the lead MDT clinician must be documented. Agreement by the referring primary care HCP to be named as the second approved named HCP can be communicated either on the Acne Primary Care Referral Proforma, explicitly in a referral letter, or through further direct communication between the primary care HCP and Lead Prescriber.

The means by which the Second Approved Named HCP can independently assess the patient will depend on individual circumstances and prescribers. Options include:

1. In-person (face-to-face) assessment.

2. Remote assessment by telephone (with images) or video consultation.

3. Review of patient history and examination findings in a MDT meeting (with images). If the Lead Prescriber is present at the MDT then images may not be required.

In circumstances where a HCP who is approached to be the Second Approved Named HCP does not agree with the decision to treat with isotretinoin, there should be effort made to reach a mutual decision. This should involve the patient. Note that the agreement that

isotretinoin is an appropriate treatment by two HCPs is distinct and separate to the process of consent primarily involving the patient and Lead Prescriber.

Both the Lead Prescriber and the Second Approved Named HCP should have access to the advice of an experienced colleague or specialist dermatology MDT to discuss any challenging cases or issues.

2.1.3. Continuation and monitoring of isotretinoin treatment

The Follow-up Prescriber who monitors the patients and continues to prescribe isotretinoin may be the Lead Prescriber who initiates treatment. They may also be a non-medical prescriber (such as a Band 6 or above Dermatology Nurse Specialist or Pharmacist with appropriate dermatology expertise, skills and training) experienced in prescribing isotretinoin, working within a Consultant Dermatologist or GPwER agreed pathway.

2.1.4. Community pharmacies

Community Pharmacists, with appropriate skills and training, can dispense isotretinoin, and some are already doing so. All pharmacists dispensing isotretinoin need to be fully aware of the requirements for dispensing isotretinoin. There should be training or professional educational information and materials available for Dispensing Pharmacists in the community and hospital settings. The British Association of Dermatologists (BAD) and British Dermatological Nursing Group (BDNG) have produced a new training video specifically for pharmacists.

2.1.5. Summary table of HCPs involved in isotretinoin prescribing

	HCP role	Lead Prescriber Over 18s	Lead Prescriber Under 18	Second approved named HCP in under 18s *This must be a different HCP to the Lead Prescriber*	Follow-up Prescriber
1	Consultant Dermatologist	✓	✓	✓	✓
2	Associate Specialist Dermatologist	✓	✓	✓	✓
3	Nationally accredited General Practitioner with an Extended Role (GPwER) working within a Consultant Dermatologist agreed pathway.	✓	✓	✓	✓
4	General Practitioners with a Special Interest (GPwSI) who are currently prescribing isotretinoin within a Consultant Dermatologist agreed pathway. GPwSI must have been signed off locally prior to the introduction of GPwER accreditation. (GPwSI have been replaced with GPwER).	✓	✓	✓	✓
5	Junior doctor or Specialty doctor with evidence of competency in isotretinoin initiation working under the supervision of the clinicians listed above.	✓	✓	✓	✓
6	Band 8a or above Dermatology Clinical Nurse Specialist or Dermatology Nurse Consultant working within a Consultant Dermatologist agreed and supervised pathway. Nurses working in the private sector should have equivalent levels of qualifications and experience.	✓	✓	✓	✓
7	Band 8a or above Dermatology Pharmacist or Dermatology Consultant Pharmacist working within a Consultant Dermatologist agreed and supervised pathway. Pharmacists working in the private sector should have equivalent levels of qualifications and experience.	✓	✓	✓	✓
8	Consultant Paediatrician (with specialist accreditation in dermatology and working within a Consultant Dermatologist agreed pathway) may also initiate isotretinoin.		✓	✓	✓ Only in patients under 18 years of age
9	Consultant Paediatricians who were signed off locally prior to the introduction of specialist accreditation in Dermatology for Paediatricians and are already prescribing isotretinoin (within a Consultant Dermatologist agreed pathway). This pathway does not exist going forwards.		✓	✓	✓ Only in patients under 18 years of age
10	The primary care clinician making the referral to a specialist. This may be a GP, Advanced Nurse Practitioner (ANP), or Advanced Clinical Practitioner (ACP) or future equivalents.			✓	
11	Non-medical prescribers (such as a Band 6 or above Dermatology Nurse Specialist or Pharmacist with appropriate dermatology expertise, skills and training) experienced in prescribing isotretinoin, working within a Consultant Dermatologist or GPwER agreed pathway.			✓	✓
12	A Multidisciplinary Team (MDT), which should consist of at least one HCP eligible to be a Lead Prescriber and at least one clinician eligible to be a second named HCP. The MDT lead clinician should not be the same person as the Lead Prescriber for the patient.			✓	

2.2. Mental health framework

The CHM IEWG report made the following recommendation:

> 'To support consistent implementation of the regulatory change further work involving professional bodies and health system organisations will be required to determine appropriate tools (e.g. questionnaires) to assess mental health status; periodicity of monitoring and clinical pathways to manage patients with severe or ongoing psychiatric disorders during or after treatment with isotretinoin.'

The CHM IIAEWG therefore developed a framework for mental health to aid assessment and monitoring of patients prescribed isotretinoin.

2.2.1. Information provision and counselling

Patients, and where appropriate, parents/carers, must be counselled about the possible risk of psychiatric adverse events with isotretinoin in order for them to be able to make an informed decision about their treatment. This should be balanced with discussion of potential psychological benefits of managing problematic acne. The age and maturity of the patient should be taken into account in considering the most appropriate counselling approach, including giving the option to discuss without parents/carers present.

Ideally, some aspect of information provision should occur at the time of referral (usually from primary care), noting that the final decision on whether to prescribe will be made by the specialist. Information may be given through sharing or signposting to patient educational materials, including the Isotretinoin Patient Guide or the Oral Isotretinoin Guide for Young People. Giving information at the time of referral will create the opportunity for patients and their parents or carers to reflect on the information about isotretinoin and ask questions before isotretinoin is prescribed. Information materials can be used to facilitate discussion and should be available for the patient to take with them or access at home.

Further information for primary care clinicians may be available on local referral management platforms to help with management and referral decisions. The British Association of Dermatologists (BAD) have developed an Acne Referral Guidance for Primary Care, which can be adapted for local use.

When the patient is seen by the specialist, they should check that the patient has read the relevant patient information. If not, it must be given to the patient and the patient must have the chance to consider it prior to completion of the Acknowledgment of Risk Form. The Acknowledgement of Risk Form records that patients and parents or carers have received information about possible mental health risks associated with isotretinoin.

If isotretinoin is prescribed, the patient should also be asked to read the Patient Information Leaflet (PIL) that is dispensed with the isotretinoin tablets, which covers all the important information about isotretinoin including information about mental health.

2.2.2. Assessment

All patients should have an assessment of their mental health before starting treatment with isotretinoin. Mental health monitoring should continue at follow-up appointments during treatment.

Initial mental health assessment

The initial mental health assessment should always be carried out in person. This should cover current and past mental health problems, impact of the skin condition on mental health and quality of life, family psychiatric history and the aspects of the mental state examination, as appropriate. Patients should be assessed for symptoms of depression, mood disturbance, psychosis, aggression, self-harm and suicidal ideation.

An objective mental health Patient Reported Outcome Measure (PROM) should be completed by the patient prior to prescribing isotretinoin. PROMs should not be used in isolation and do not replace clinical assessment. There are no validated screening tools or questionnaires for assessment of mental health in the context of prescribing isotretinoin for acne. Research is under way but, in the interim, the following questionnaires (PROMs) or combination of PROMs may be used:

- Patient Health Questionnaire (PHQ)-9[3] in combination with General Anxiety Disorder 7-item (GAD-7)[4] or Generalized Anxiety Disorder 2-item (GAD-2).[5]
- Hospital Anxiety and Depression Scale (HADS).[6]
- Mood and Feelings Questionnaire.[7]

There is a version of the PHQ-9 modified for Adolescents (PHQ-A) which may be the most appropriate in this age group. These PROMs are available in a variety of languages.

[3] Kroenke K, Spitzer R L, Williams J B. The PHQ-9: validity of a brief depression severity measure. Journal of General Internal Medicine. 2001;16(9): 606-613.
[4] A brief measure for assessing generalized anxiety disorder: the GAD-7. Spitzer RL, Kroenke K, Williams JBW, Löwe B. Arch Intern Med. 2006;166:1092-1097.
[5] Kroenke K, Spitzer RL, Williams JB, et al. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med. 2007;146:317-25.
[6] Zigmond AS, Snaith RP: The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983;67:361–70.
[7] Angold, A., Costello, E. J., Messer, S. C., Pickles, A., Winder, F., & Silver, D. The development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. International Journal of Methods in Psychiatric Research. 1995;5:237-249.

Consideration of the impact of acne on the person should be part of initial assessment. The patient should be asked about acne-related concerns and behaviour. The British Society for Paediatric and Adolescent Dermatology (BSPAD) questionnaire 'You and Your Skin' may be useful as a history-taking aid for adolescents. A quality of life PROM may be used to enhance the assessment. There are a number of acne-specific quality of life PROMs but none are widely accepted due to concerns about content validity and time taken to complete. The Cardiff Acne Disability Index (CADI)[8] is a short 5-item questionnaire which can be completed in approximately 1 minute, and may be considered. The Assessment of Psychological and Social Effects of Acne (APSEA)[9] is undergoing some changes and further validation. It may be helpful in the future as it specifically addresses appearance related concerns. The following generic PROMs may also be used:

- Dermatology Life Quality Index (DLQI).[10]
- Teenager's Quality of Life Index (TQoL).[11]
- Children's Dermatology Quality of Life index (CDLQI).[12] This is suitable for children and adolescents (up to 16 years old).

The mental health assessment should be used to consider whether there are significant mental health concerns prior to isotretinoin treatment and whether isotretinoin is an appropriate treatment. If the prescriber has concerns about the patient's mental health, or feels unable to assess risk, further expert help (such as specialist psychiatry input) should be sought.

Monitoring mental health at follow-up appointments during isotretinoin treatment

Where possible, the patient should be reviewed by the same HCP at each follow-up appointment to aid monitoring and continuity. Patients should discuss with the Lead Prescriber if there are concerns.

The initial follow-up appointment should be conducted face-to-face approximately 1 month after initiation of treatment. The patient should be asked about symptoms of depression and concerns about mood changes, including any thoughts of self-harm or suicide. Baseline PROMs should be repeated at least once within the first 3 months of treatment and more

[8] Motley RJ, Finlay AY. Practical use of a disability index in the routine management of acne. Clinical and Experimental Dermatology.1992;17:1-3.
[9] Layton A. Psychological assessment of skin disease. Interfaces Dermatol 1994;1:9–11
[10] Finlay, A. Y. and Khan, G. K. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clinical and Experimental Dermatology.1994;19(3):210-216.
[11] Basra MKA, Salek MS, Fenech D, Finlay AY. Conceptualization, development and validation of T-QoL© (Teenagers' Quality of Life): a patient-focused measure to assess quality of life of adolescents with skin diseases. British Journal of Dermatology. 2018;178:161-175
[12] Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): Initial validation and practical use. British Journal of Dermatology. 1995; 132: 942-949.

frequently if concerns are raised. The frequency and mode (face-to-face or remote) of further follow-up appointments will depend on mental health concerns identified, if any, as well as other factors (Pregnancy Prevention Programme, other side effects, dosing, patient preference, and hospital systems).

Patients should be given the opportunity to discuss their mental health concerns at every follow-up appointment and advised to report new concerns between appointments. A side effects patient questionnaire for patients to complete before clinic appointments, either online or in the waiting room, may be helpful. An example questionnaire (Isotretinoin Side-effects Patient Questionnaire) has been developed by the BAD, which can be adapted for local services. An Isotretinoin Follow-up Proforma has also been developed by the BAD to aid clinicians and help standardise monitoring at follow up appointments. This can also be adapted locally. Stopping isotretinoin and referral to mental health services should be considered at any time by any HCP if there are concerns about a patient's mental health.

2.2.3. Communication

The referrer (generally the primary care clinician) should provide details of all current and previous mental health problems, and any relevant social and family history to the specialist, ideally using the Acne Primary Care Referral Proforma, which can be adapted for local service platforms. If the referrer has conducted an assessment of mental health, this should also be documented and communicated to the specialist HCP.

The specialist HCP should communicate their assessment with the GP and other relevant HCPs. The BSPAD guidelines[13] recommend communication with relevant health, education, and social services when psychological concerns arise in adolescents with skin disease, with due consideration of safeguarding and consent, ensuring the GP is included in all correspondence.

Patients, and if appropriate their family, friends or carers, should be informed of what they should do if they develop any changes in their mental health or mood. This should include who they should contact, how they should do this, and when it would be appropriate to stop isotretinoin.

2.2.4. Pathways for managing mental health problems

If problems are identified, consideration should be given to stopping isotretinoin. Patients should be signposted to support, and referral to mental health services should be considered. All HCPs involved in the treatment should be copied into all correspondence.

[13] McPherson T, Ravenscroft J, Ali R et al., on behalf of British Society of Paediatric and Adolescent Dermatology (BSPAD) mental health consensus recommendation development group (CRDG), British Society for Paediatric and Adolescent Dermatology assessment and support of mental health in children and young people with skin conditions: a multidisciplinary expert consensus statement and recommendations. British Journal of Dermatology. 2023;189(4):459–466.

Information regarding crisis support should be given to all patients at the time of initiation of isotretinoin and indicated on the Acknowledgement of Risk Form. The GP should remain a key partner in the care of the patient, regardless of whether they are directly managing the mental health problem.

If mental health side effects are suspected to be associated with isotretinoin therapy, this should be reported via the Yellow Card scheme.

2.3. Sexual function framework

The CHM IEWG report made the following recommendation:

> 'To support consistent implementation of the regulatory change further work involving professional bodies and health system organisations will be required to determine appropriate tools (e.g. age-appropriate questionnaires) to assess sexual function; periodicity of monitoring and clinical pathways to manage patients with sexual dysfunction during or after treatment with isotretinoin.'

The IIAEWG recommendations to CHM regarding a sexual function framework to aid assessment and monitoring of patients prescribed isotretinoin are as follows:

2.3.1. Information provision and counselling

Patients, and where appropriate, parents or carers, must be counselled about the possible risk of sexual function side effects with isotretinoin in order for them to be able to make an informed decision about their treatment. Due to limitations in current knowledge, it is not possible to identify risk factors for changes in sexual function reported to be associated with isotretinoin. The clinician should inform the patient clearly about the limitations of our understanding of the side effects, including their unknown frequencies and that there may be other reasons for sexual function problems. The age and maturity of the patient should be taken into account in considering the most appropriate counselling approach, including giving the option for young people to discuss without parents or carers present.

Ideally, some aspect of information provision should occur at the time of referral (usually from primary care), noting that the final decision on whether to prescribe will be made by the specialist. Information may be given through sharing or signposting to patient educational materials, including the Isotretinoin Patient Guide or the Oral Isotretinoin Guide for Young People.

When the patient is seen by the specialist, they should check that the patient has read the relevant patient information. If not, it must be given to the patient and the patient must have the chance to consider it prior to completion of the Acknowledgment of Risk Form. The

Acknowledgment of Risk Form records acknowledgment by patients (and parents or carers where appropriate) of the possible sexual function side effects associated with isotretinoin.

2.3.2. Assessment

All patients should be asked about sexual concerns before starting treatment with isotretinoin and monitored for the development of new sexual problems during treatment. The opportunity for patients to raise and discuss sexual function concerns should continue at follow-up appointments during treatment.

Initial sexual function assessment

The initial assessment prior to prescription of isotretinoin should always be carried out in person. A non-judgemental listening style will help establish a therapeutic relationship and aid the assessment.

Clinicians should follow guidance on confidentiality and safeguarding when discussing sensitive topics such as sexual function with young people. This should include:

- maintaining professional skills and knowledge through up-to-date safeguarding training and supervision, including knowledge of local safeguarding policies and procedures, and where and how to seek further advice.
- consideration of independent consultation with young people and explaining confidentiality and its limits.
- the use of chaperones.
- provision of age and developmentally appropriate written or web-based information for young people.
- contemporaneous documentation of the consultation.

It is important to enquire about pre-existing sexual function problems in case isotretinoin exacerbates a pre-existing condition. Patients should be asked whether they have any concerns about their sexual function before isotretinoin is prescribed. This may include problems with getting or maintaining an erection, decreased desire for sexual activity (decreased libido), male breast enlargement (gynaecomastia), vulva or vaginal dryness, orgasm difficulties, or altered feeling or sensation in the genitals (hypoaesthesia). If the patient has any concerns, the clinician should go on to ask more detailed questions. The clinician should use clear, non-medical language. The questions should be tailored to age (taking into account the safeguarding concerns outlined above) and biological sex. The impact of acne on the patient's sexual function may be relevant. Discussions about sexual function may be challenging, particularly in young people who are not yet sexually active.

If problems are identified there should be discussion on whether to proceed with isotretinoin treatment and possible referral pathways to an appropriate specialist team (or back to the GP) depending on the issue.

Monitoring sexual function at follow-up appointments during isotretinoin treatment

Where possible, the patient should be seen by the same HCP at each follow-up appointment to aid monitoring and continuity. Patients should be discussed with the Lead Prescriber if there are concerns. Initial follow-up appointments should be face-to-face, approximately 1 month after initiation of treatment.

The frequency and mode (face-to-face or remote) of further follow-up appointments will depend on several factors (Pregnancy Prevention Programme, mental health concerns, other side effects, dosing, patient preference, and hospital systems).

Patients should be given the opportunity to discuss sexual function concerns at every follow-up appointment. This should be age appropriate and follow the same guidance regarding confidentiality and safeguarding as for the initial assessment. Patients should be asked if they have experienced any problems with their sexual function since their last appointment. If the patient expresses concerns, follow up questions should explore problems further and ask about other areas as appropriate including erectile function, vaginal dryness, change in periods, breast tissue development/gynaecomastia, decreased libido, other change in sexual function including genital hypoaesthesia.

A side effects patient questionnaire for patients to complete before clinic appointments, either online or in the waiting room, may be helpful (an example is the Isotretinoin Side-effects Patient Questionnaire which can be adapted locally). This may not be appropriate for young people attending with parents or where online form links may be sent to a parental phone number.

If sexual problems are identified during isotretinoin treatment the HCP should have a discussion with the patient regarding how to manage this, for instance watch and wait approach, dose reduction, stopping isotretinoin, and/or referral (see section 2.3.3. below).

2.3.3. Pathways for managing problems with sexual function

If problems are identified during or after treatment, the HCP should discuss with the patient regarding referral, either back to the GP, or directly to urology (or an andrology subspecialist in larger urology units), sexual health, psychosexual or another appropriate service. There are locally agreed services and systems of which all clinicians involved in isotretinoin treatment need to be aware. Any problems with sexual function suspected to be associated with isotretinoin therapy should be reported via the Yellow Card Scheme.

2.4. Summary of responsibilities in isotretinoin treatment pathway

Referrer (usually GP or primary care HCP)

- Assessment of acne and management as per NICE guideline.
- **Information provision** on acne treatment options including isotretinoin (Isotretinoin Patient Guide or Oral Isotretinoin Guide for Young People).
- **Counselling** (where possible) by referrer regarding benefits and risks of isotretinoin treatment.
- Completion of Acne Primary Care Referral Proforma or other method of referral.
- Referrer to share patient's **current and past medical history** (including mental health history and details of previous treatments for acne) with the specialist.
- In patients under 18, referrer to consider becoming **Second Approved Named HCP**. Agreement to act in this role, confirming isotretinoin as the most appropriate treatment option, must be documented in the referral proforma/letter or directly communicated to the Lead Prescriber.
- Consider checking bloods including fasting serum lipids and liver enzymes.
- Consider contraception for patients with child-bearing potential.

Lead Prescriber (initiation of isotretinoin treatment)

- Assessment of acne and treatment plan as per NICE guideline.
- **Information provision** and **counselling** regarding benefits and risks of isotretinoin treatment (Confirm the patient has read either the Isotretinoin Patient Guide or the Oral Isotretinoin Guide for Young People).
- Complete **Acknowledgment of Risk Form**:
  - Recording the patient's acknowledgment of the risks associated with isotretinoin.
  - **Pregnancy Prevention Programme** (PPP) for patients with childbearing potential.
  - In patients under 18 years old, document details of **Second Approved Named HCP** who agrees that isotretinoin is most appropriate treatment option.
- **Mental health** initial assessment (mental health PROMs to be completed at baseline).
- **Sexual function** initial assessment.
- Check **bloods** (or blood results if already taken by referrer) including fasting serum lipids and liver enzymes.
- Give patient a copy of the Acknowledgment of Risk Form and a Patient Reminder Card.

Follow-up Prescriber (responsible for continuation of treatment and monitoring)

- **Face-to-face** follow-up **approximately 1 month** after initiation and at **least 3 monthly** thereafter
- Remote appointments may be considered in between, to supplement face-to-face follow-up.
- Review **PPP** including contraception and complete pregnancy testing as required.
- Assess response to treatment and manage as per NICE guideline.
- Check for **side effects** (Isotretinoin Side-effects Patient Questionnaire) including:
  - Monitoring **mental health** (follow-up mental health PROM to be completed within first 3 months and subsequently if there are concerns).
  - Monitoring **sexual function**.
- Check **bloods** including fasting serum lipids and liver enzymes (**1 month** after initiation and subsequently at **3 monthly** intervals unless more frequent monitoring is clinically indicated).
- Note that the Lead Prescriber can also be a Follow-up Prescriber (see section 2.1 Isotretinoin prescribing).

3. Communication and education: the development of communication and educational materials to support and record informed prescribing decisions

3.1. Background

It was recommended in the report of the IIAEWG that the following patient materials should be developed. The recommendations are extracted below.

Information for patients

'Information in a range of formats should be developed to provide accessible, plain language information to patients under consideration for isotretinoin treatment, and where appropriate their parents or carers, taking account of the recommendations on psychiatric and sexual side effects above. This information should include:

- reference to the possibility of side effects continuing after treatment has stopped.
- information on the self-management of common side effects such as skin dryness.
- a process for facilitating discussion, understanding and acknowledgement of the possible risks of treatment.

Patients and their parents/carers should have adequate time between initial counselling and subsequent prescription to reflect on the information about isotretinoin and ask questions before prescription of isotretinoin.'

Acknowledgement of risk form

'Patients and parents/carers should receive full information about the possible risks as well as the benefits of treatment in order to be able to make an informed decision about their treatment. There is currently an acknowledgement of risk form for female patients. It was recommended that this form is expanded to cover all potential risks and used for all patients.

Stakeholders, including patients, parents/carers and healthcare professionals, should be involved in the development of the form to ensure it meets requirements.'

The IIAEWG group also advised that a range of resources should be developed for all HCP involved in the isotretinoin pathway and that the pre-existing Pharmacist Checklist should be

amended to reflect the updated Pregnancy Prevention Programme and Acknowledgment of Risk Form.

3.2. New patient and HCP resources

A range of resources has been developed by the IIAEWG and are described below. For the main patient materials, input has also been sought from patients, and parents or carers of patients to ensure that the wording and content is understandable and relevant to those patients who may require isotretinoin and who will be discussing risks with their dermatology specialist.

Summary of new patient and HCP resources

Material	**Produced by:**
Acknowledgement of Risk Form	Marketing Authorisation Holders (MAHs)
Patient Reminder Card	MAHs
Pharmacist Checklist	MAHs
Patient Information Leaflet (PIL)	MAHs
Isotretinoin Patient Guide	British Association of Dermatologist (BAD) – clinical guidance
Oral Isotretinoin Guide for Young People	Medicines for Children Royal College of Paediatrics and Child Health (RCPCH)
Acne Primary Care Referral Proforma	BAD - clinical guidance
Acne Referral Guidance for Primary Care	BAD - clinical guidance
Isotretinoin Follow-up Proforma	BAD - clinical guidance
Isotretinoin Side-effects Patient Questionnaire	BAD - clinical guidance
Training videos	BAD and British Dermatological Nursing Group (BDNG)

3.2.2. Regulatory Risk Minimisation Materials

New compulsory regulatory Risk Minimisation Materials have been produced by the Marketing Authorisation Holders (MAHs). This consists of the new Acknowledgement of Risk Form, Patient Reminder Card and Pharmacist Checklist.

These are all regulatory risk minimisation materials and therefore must be used for all patients.

3.2.2.1. Acknowledgement of Risk Form

An Acknowledgement of Risk Form has been developed which will be compulsory for all patients. The form highlights the possible risks associated with isotretinoin, including possible changes to mental health and sexual function. It is also used to document the involvement of the second approved named HCP for patients under 18 years old. The IIAEWG considered it was important that dermatology team contact details were documented here so that patients knew who to call if they have concerns. Guidance is given on who to contact, including mental health charities, if there is a mental health crisis.

It was highlighted by the IIAEWG that many dermatologists do not use the pre-existing 'Acknowledgement Form for Prescribing Isotretinoin to Female Patients' because it is not appropriate for certain patient groups. Historically, there has been an 'opt-out' form developed by the BAD, but this is not a legally binding document and has potential to be used inappropriately.

The IIAEWG recommended changes to the Pregnancy Prevention Programme section of the Acknowledgement of Risk Form to ensure it is appropriate for all patients with child-bearing potential. This should reduce the current unwarranted variation in practice, and improve both HCP and patient satisfaction, and clinical pathway efficiency, without compromising safety. This includes a change in recommendations for patients on highly effective forms of contraception, who will no longer require monthly pregnancy tests. This is in line with CHM guidance regarding medicines with teratogenic potential.

The new Acknowledgment of Risk Form has been developed to:

- continue to record the patient's acknowledgment of the known risk of harm to unborn babies during pregnancy.
- record acknowledgment of other risks including possible mental health and sexual function side effects.
- continue to record enrolment onto the revised Pregnancy Prevention Programme if the patient has childbearing potential.

- record, in patients under 18 years of age, the agreement of two independent healthcare professionals that isotretinoin is the most appropriate treatment option.

Revised Acknowledgement of Risk Form Pregnancy Prevention Programme section

All patients of child-bearing potential (people who may be able to get pregnant) must be enrolled on to the Pregnancy Prevention Programme.

The key changes to the Pregnancy Prevention Programme section of the Acknowledgment of Risk Form are as follows:

1. The Lead Prescriber is required to assess and document the Pregnancy Prevention Programme (PPP) status of the patient on the Acknowledgement of Risk Form.

2. There are four possible PPP status categories: 'Not applicable', PPP Group A, PPP, Group B, PPP Group C. Patients can only be assigned one category.

3. **'Not applicable'**: the patient has no child-bearing potential and therefore are not part of the Pregnancy Prevention Programme. These are patients who are medically unable to become pregnant (no uterus/ hysterectomy/ oophorectomy/ sterilisation (tubal ligation)/ postmenopausal). Neither contraception nor pregnancy testing are required.

4. **PPP Group A**: the patient and the prescriber agree that there is no expected risk of pregnancy during treatment and for 1 month after treatment and the patient is therefore not required to be on contraception. They will still be enrolled on the Pregnancy Prevention Programme – in other words they must have their pregnancy risk reviewed at every follow-up visit. They are not required to have pregnancy tests as long as the situation remains unchanged. However pregnancy testing may be done at the discretion of the patient or prescriber. Expectation of no risk of pregnancy could include patients in any of the following circumstances:

    - only having sex/sexual intercourse with a person who has no potential to make them pregnant. This must be for the duration of isotretinoin treatment and for 1 month after stopping isotretinoin treatment. Examples include sex with persons of the same-sex, persons who have had a vasectomy with two confirmed tests of being sperm-free, or transgender men.

    - long-term sexual abstinence (no sexual activity) for the duration of isotretinoin treatment and for 1 month after stopping isotretinoin treatment.

5. **PPP Group B**: the patient has been using a non-user dependant, highly effective method of contraception for at least 4 weeks. They do not require pregnancy testing every month but must have pregnancy testing at follow up appointments. Patients should be informed that they may choose to do pregnancy tests monthly at home as no contraceptive is 100% effective.

6. **PPP Group C**: all other patients of childbearing potential who are prescribed isotretinoin. These patients must be advised to use a hormonal contraceptive pill or contraceptive

injection plus a barrier method (in other words, a condom, female condom, vaginal cap). Monthly pregnancy testing is required. The prescription may only be for 30 days and must be dispensed within 7 days.

7. Note that patients in both ‘Not applicable’ and PPP Group A are not required to be on contraception (see Table 2).

8. For patients in ‘Not applicable’, PPP Group A and PPP Group B, once stable on isotretinoin (after the first 1 to 3 months) the prescription may be for longer than 30 days (up to 12 weeks) if no other side effect monitoring required.

9. The PPP status must also be documented on the prescription. This will inform the pharmacist of the pregnancy testing requirements prior to issue of prescription.

10. Patients with child-bearing potential must also complete the relevant part of the Pregnancy Prevention Programme section of the Acknowledgment of Risk Form (see Table 1).

Table 1: Acknowledgment of Risk Form Pregnancy Prevention Programme statement to be completed by patient

A - I confirm I do not require contraception because there is no risk of pregnancy during treatment. I do not require pregnancy testing. I will let my prescriber know if my situation changes.
B - I confirm I have been using the contraceptive implant or have had a coil (IUD) or intra-uterine system (IUS) for at least 4 weeks. I agree to pregnancy testing at follow-up appointments. I may choose to do monthly pregnancy tests at home because no contraception is 100% effective. I will let my prescriber know if my situation changes.
C - I confirm I have been using a hormonal contraceptive pill or contraceptive injection plus I agree to use a barrier method (i.e. a condom, femidom, vaginal cap). I agree to pregnancy testing every 30 days during treatment. My prescriptions will be for 30 days. Prescriptions will need to be collected within 7 days.

Table 2: Reasons for not requiring contraception

<u>No child-bearing potential (‘Not applicable')</u> • Medically unable to become pregnant (no uterus/ hysterectomy/oophorectomy, sterilisation or postmenopausal as previously outlined).

<u>Expectation of no risk of pregnancy (PPP Group A)</u>
• Only having sex/sexual intercourse with a person who has no potential to make them pregnant. This must be for the duration of isotretinoin treatment and for 1 month after stopping isotretinoin treatment. Examples include sex with a:
  • person of the same-sex.
  • person who has had a vasectomy with two confirmed tests of being sperm-free.
  • transgender man.
• Long-term sexual abstinence (no sexual activity) for the duration of isotretinoin treatment and for 1 month after stopping isotretinoin treatment.
This should be confirmed at each clinic visit.

3.2.2.2. Patient Reminder Card

A Patient Reminder Card has been developed, which will be compulsory for all patients. It contains essential safety information that patients need to be aware of before and during treatment. The IIAEWG advised that it was important that dermatology team contact details were repeated here as well as details about who to call if you have a mental health crisis. The format is in the form of a card.

3.2.2.3. Pharmacist Checklist

The IEWG also discussed the benefit of supporting materials and training for prescribers and other HCP involved in the isotretinoin pathway. The pre-existing Pharmacist Checklist was updated to align with the revised PPP and Acknowledgement of Risk Form.

3.2.2.4. Patient Information Leaflet

The Patient Information Leaflet (PIL) is another regulatory document, produced by the Marketing Authorisation Holders, to be used by all patients. The PIL has been revised to align with the amendments to the SmPC that were recommended in the CHM IEWG report. The PIL is given to the patient with their medication at the time of dispensing. Electronic copies are also available at MHRA Products.

3.2.3. Supporting resources

A package of additional supporting resources has also been developed by the British Association of Dermatologists, British Dermatology Nursing Group and other stakeholders. These include an Acne Primary Care Referral Proforma, an Isotretinoin Side-effects Patient Questionnaire, and an Isotretinoin Follow-up Proforma. These supporting documents can be adapted to local needs and systems and are intended to be examples or templates to help support clinicians implement the new safety measures.

3.2.3.1. Acne Primary Care Referral Proforma

Following suggestions from the IIAEWG, an Acne Primary Care Referral Proforma was developed as it was noted that information supplied can be variable and a proforma would help ensure consistency. It was agreed that this would help ensure that NICE guideline [NG198] for acne vulgaris management has been followed prior to referral and that the specialist receives all the information they require to help with their prescribing decision. Further information for primary care clinicians can also be made available on local referral management platforms to help with management and referral decisions. The BAD have developed Acne Referral Guidance for Primary Care which can be adapted for local systems.

3.2.3.2. Isotretinoin Side-effects Patient Questionnaire

An Isotretinoin Side-effects Patient Questionnaire (to be completed by patients prior to their appointment). These covers common side effects as well as adverse events involving mental health or sexual function.

3.2.3.3. Isotretinoin Follow-up Proforma

The Isotretinoin Follow-up Proforma (to be used by HCPs at follow-up appointments) includes the key topics to be covered during the appointment, including reviewing PPP requirements and mental health and sexual function.

3.2.3.4. Patient guides (information for patients)

Age-appropriate patient guides have been developed which should be used for all patients. Feedback indicated that patients would prefer the information to be written by clinicians and produced by them. Therefore, the BAD produced the Isotretinoin Patient Guide, with input from the MHRA. This is available, as requested by patients, in either digital format or on paper. In addition, a Medicines for Childrens guide specifically for young people, Oral Isotretinoin Guide for Young People, has been developed by the Royal College of Paediatrics and Child Health. These guides are referred to in the Acknowledgment of Risk Form, which require the patient to confirm they have read the relevant patient information on isotretinoin.

3.2.3.5. Training Videos

The BAD and BDNG have also developed training videos for HCPs to help them implement the new measures into their clinical practice. This includes training specifically for pharmacists who may be new to dispensing isotretinoin, including many community pharmacists.

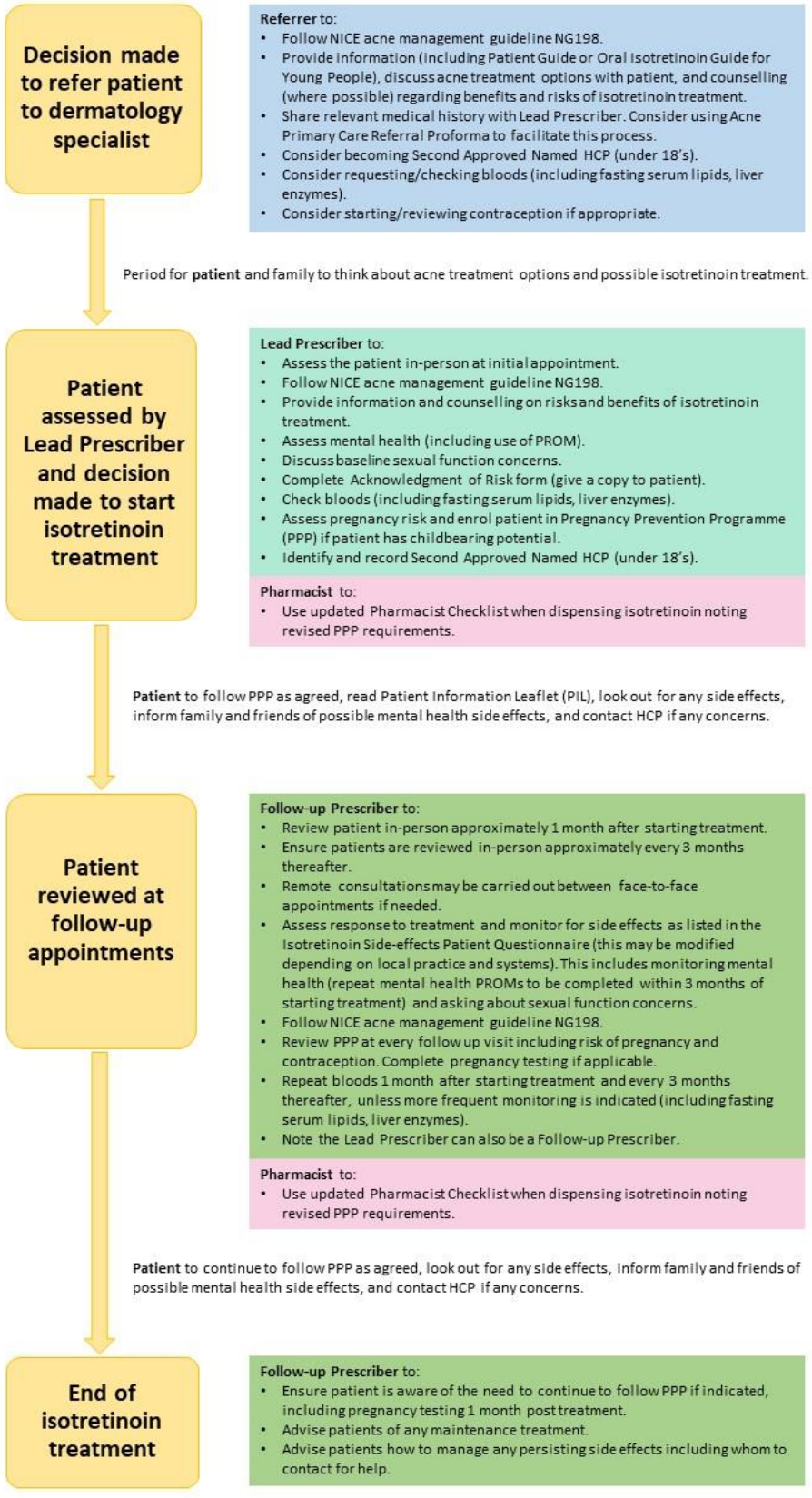
3.2.3.6. Future plans for supporting resources

The IIAEWG recommended that a decision support tool would be useful for patients to help them decide whether isotretinoin is the right treatment for their acne. This could help them weigh up the benefits versus potential risks of treatment. The unknown frequencies of occurrence of mental health and sexual side effects would be a limiting factor, but some support would still be possible.

The Acne ID trial is comparing the advantages and disadvantages of two different ways of dosing isotretinoin for people with severe acne (low-dose vs. standard-dose isotretinoin). A decision tool is being developed as part of this trial which will help patients choose between the two dosing schedules.

In addition, feedback from patients indicates that a patient video would be helpful to support information provision. An example of an information video for acne was produced by the Spironolactone for Adult Female Acne (SAFA) clinical trial.

4. Isotretinoin treatment pathway



5. Monitoring compliance and recommendations on future research

5.1. Background

It was recommended in the CHM IEWG report that future research was required:

Further research

'More research is needed on the side effects associated with isotretinoin, including their frequency, the biological mechanisms underlying their occurrence, the identification of any relevant biomarkers and genetic factors.

More data are needed on the use of isotretinoin in adolescents under 18 years of age, including the study of any potential long-term effects in adulthood and suggested longitudinal studies would be of benefit.

An isotretinoin drug registry should be developed to:

- gather further information on psychiatric events and sexual dysfunction with isotretinoin including the nature and magnitude of risks associated with isotretinoin, risk factors, natural progression of events, vulnerable age groups and the complex relationship between psychiatric events and sexual disorders.
- facilitate identification of adverse events which are currently not listed in the product information, the frequency of side effects and gather information and understanding on side effects which continue long term as well as the onset of adverse events after isotretinoin treatment has stopped.

Applied research should be conducted to evaluate the impact of the new risk minimisation measures.'

5.2. Monitoring compliance and impact

The IIAEWG recommended an audit of compliance with the new measures, including use of the revised risk minimisation materials, approximately a year after implementation. This can be conducted at a local level. Professional organisations representing dermatologists, GPwER and dermatology nurses may wish to coordinate results and seek more qualitative feedback nationally.

The MHRA will continue to conduct proactive pharmacovigilance including analysing Yellow Card reports for signals related to exposure in pregnancy, mental health and sexual function

and other possible adverse drug reactions. They will also collaborate with health technology providers to explore the potential for digitally collecting data to evaluate compliance.

5.3. Research Proposals

5.3.1. Post-Authorisation Safety Study (PASS)

While a registry was suggested by the IEWG, the IIAEWG advised that a compulsory registry completed by HCPs was disproportionate to the current understanding of risks, impractical to implement and a potential barrier to treatment.

The option to participate in onward safety studies developed by the isotretinoin MAHs should be made available to all patients treated with isotretinoin but should not be a condition for receiving treatment. Development and financing strategy for the studies should be agreed between the MAHs for isotretinoin. The study or studies should consider how best to collect information on sensitive adverse events relating to mental health and sexual function from young patients, especially those under 18 years old. Given the potential sensitivity of the side effects concerned, the IIAEWG advised that information could be better collected/reported directly from patients.

More specifically, the IIAEWG advised the PASS(s) may:

- assess the influence of dosing (cumulative and daily) and duration of treatment on psychiatric and sexual disorders reported in association with isotretinoin, characterising the relationship between these events and isotretinoin, establishing the frequency of their occurrence, their duration, and identifying any risk factors.

- collect data on the compliance with, acceptability to patients, and effectiveness of risk-minimisation measures, including the provision of new educational materials to patients, completion of the Acknowledgement of Risk Form, and monitoring mental and sexual health during treatment.

There is potential for patient reported data for the PASS to be collected digitally (via an app) in partnership or consortium with health technology providers and MAHs. Note that collected data would not be accessible to MAHs. This platform would allow patients to input data directly to the app on their mobile device. This would enable longitudinal data collection and allow temporal analyses of side effects including psychiatric and sexual function problems. The timescale for design and set-up of the system is approximately 12 months.

5.3.2. Clinical trials

The National Institute for Health Research (NIHR) has called for research on whether a smaller dose of isotretinoin could result in a lower risk of side effects while still treating severe acne effectively.

As a result of this call, the NIHR-funded ACNE-ID study is underway to compare the advantages and disadvantages of two different ways of dosing isotretinoin for people with severe acne (low-dose versus standard-dose isotretinoin). Patients will be monitored through this study. Side effects will be monitored including mental health and sexual function, and results will add to the knowledge base. Approval has been granted to obtain patient samples for potential additional research to inform the gaps in knowledge.

Funding applications are in process to study immune responses (cytokine secretion, immune cell functions) along with levels of vitamin B12 and testosterone in patients during isotretinoin treatment. Further biomarker research is being considered subject to further approvals and funding. Data will be made available upon publication.

5.3.3. Acne severity and impact

During the briefings associated with the publication of the IEWG report in April 2023, a question was asked about what acne-severity grading system should be used. It was agreed that this issue would be discussed with the IIAEWG.

The definition of severe acne was discussed. The group advised that there is no common consensus regarding how to assess acne severity. Several grading scales exist but none is widely accepted. The decision as to whether acne is severe is based on a combination of factors including number and extent of lesions, degree and depth of inflammation, duration of acne and response to previous treatment, degree of seborrhoea, presence of scarring and family history of acne. It was noted that mild forms of acne, including acne excoriée, can cause scarring. All grades of acne can have a significant impact on mental health.

The group advised that further research was needed to:

- determine what characterises severe acne.
- establish an acceptable grading system for acne.
- determine the best way to measure the effect of acne on quality of life.
- determine how quality of life and mood are affected by isotretinoin treatment.

5.3.4. British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR) data

It was suggested that information regarding acitretin (a different, longer-acting retinoid for psoriasis which may be used for a long duration) and its association with mental health disorders or sexual dysfunction within BADBIR could be reviewed. This may give some information about class effects of retinoids on mental health/change in sexual function. Note

that BADBIR collects adverse events and serious adverse events in line with their protocol: BAD Biological Interventions for Psoriasis Register (badbir.org).

5.3.5. Model Health System

The Model Health System has been contacted to consider adding ‘number of isotretinoin prescriptions per Integrated Care Board’ to their data. This would allow an estimate of the number of prescriptions per population in secondary care and look for variance in different areas.

6. Next steps

Healthcare professionals should start to introduce the new safety measures as soon as possible for all new patients. The risk minimisation materials will be available to use immediately. BAD have developed an 'Implementation guide to isotretinoin prescribing changes' to provide practical support to clinicians and service managers.

The MHRA will continue to work with all key stakeholders including patients and their families, and professional organisations.