POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

PASS INFORMATION

TITLE	Qualitative Study – Barriers and Facilitators Assessment of adherence to the Risk Minimisation Measures (RMMs), specifically Pregnancy Prevention Programme (PPP) for Women of Childbearing Potential Using Oral Retinoids (acitretin, alitretinoin, and isotretinoin)
PROTOCOL VERSION IDENTIFIER	Version 3.0
DATE OF LAST VERSION OF PROTOCOL	September 26, 2024
HMA-EMA CATALOGUE NUMBER	Study not yet registered
ACTIVE SUBSTANCE	Oral retinoids: • Acitretin: D05BB02 • Alitretinoin: D11AH04 • Isotretinoin: D10BA01
PRODUCT REFERENCE	Information is detailed in the cover letter's Annex.
PROCEDURE NUMBER	PT-H-xxxx-WS-069
MARKETING AUTHORISATION HOLDER(S) (MAH)	The joint initiative involves several companies via a consortium (a full list of all MAHs is provided in Annex 2. 2CARE4GENERICS, ALFASIGMA ESPAÑA, ALMIRALL, AUROBINDO, AXXON, BAILLEUL, BAUSCH HEALTH COMPANIES, CHEPLAPHARM, DERMAPHARM, ENNOGEN, ESPECIALIDADES FARMACÉUTICAS CENTRUM, S.A. EXPANSCIENCE, FIDIA, GALENPHARMA, GAP, GSK, HEXAL AG, IASIS PHARMA, INDUSTRIAL FARMACÉUTICA CANTABRIA, S.A., ISDIN, MEDINFAR, MYLAN PHARMACEUTICALS LIMITED, ORIFARM, PELPHARMA, PHARMATHEN, PIERRE FABRE, ROCHE, SMB, STADA, SUN PHARMA, TARGET, and TEVA
JOINT PASS	Yes
RESEARCH QUESTION	In Europe, what are the barriers and reasons for low adherence to the oral retinoid therapy PPP measures from the perspectives of

	(i) healthcare professionals (HCPs) who prescribe or dispense oral retinoid therapy to women of childbearing potential (WCBP), (ii) WCBP who recently used or are currently using oral retinoid therapy, (iii) parents, guardians or caregivers of adolescent WCBP who recently used or are currently using oral retinoid therapy?
COUNTRY(-IES) OF STUDY	France, Germany, Poland, and Spain
AUTHORS	[redacted]IQVIA Real World Evidence Solutions On behalf of the oral retinoids consortium

MARKETING AUTHORISATION HOLDER(S)

MARKETING AUTHORISATION HOLDER(S)	This section provides contact details of the companies involved in the oral retinoid consortium (all MAHs contact details are provided in Annex 2).
MAH CONTACT PERSON	[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
EC	Ethics Committee
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
DHPC	Direct Healthcare Professional Communication
DUS	Drug Utilisation Study
GDPR	General Data Protection Regulation
GVP	Good Pharmacovigilance Practice
HCPs	Healthcare professionals
HMA	Heads of Medicines Agencies
IRB	Institutional Review Board
ICMJE	International Committee of Medical Journal Editors
PASS	Post-Authorisation Safety Studies
PCS	Patient Centered Solutions
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
PV	Pharmacovigilance
RMMs	Risk Minimisation Measures
RMS	Reference Member State
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
WCBP	Women of Childbearing Potential

1. Title

Qualitative Study – Barriers and Facilitators Assessment of adherence to the Risk Minimisation Measures (RMMs), specifically Pregnancy Prevention Programme (PPP) for Women of Childbearing Potential Using Oral Retinoids (acitretin, alitretinoin, and isotretinoin)

2. Marketing Authorisation Holders

MARKETING AUTHORISATION HOLDER(S)	This section provides contact details of the companies involved in the consortium (all marketing authorisation holders' (MAHs) contact details are provided in Annex 2.
MAH CONTACT PERSON	[redacted]

3. Responsible Parties

Responsible Party	**Name and Affiliation**
Consortium	Oral retinoids consortium of MAH (see Annex 2 for the list of MAHs)
Sponsors	All MAHs involved in the oral retinoids consortium
MAH responsible for submissions to health authority	[redacted]
Contracting vendor	IQVIA Real World Evidence Solutions (RWES) [redacted]
Principal Scientist	[redacted]
IQVIA project team	[redacted]

MAHs involved in the oral retinoids consortium:

2CARE4GENERICS, ALFASIGMA ESPAÑA, ALMIRALL, AUROBINDO, AXXON, BAILLEUL, BAUSCH HEALTH COMPANIES, CHEPLAPHARM, DERMAPHARM, ENNOGEN, ESPECIALIDADES FARMACÉUTICAS CENTRUM, S.A. EXPANSCIENCE, FIDIA, GALENPHARMA, GAP, GSK, HEXAL AG, IASIS PHARMA, INDUSTRIAL FARMACÉUTICA CANTABRIA, S.A., ISDIN, MEDINFAR, MYLAN PHARMACEUTICALS LIMITED, ORIFARM, PELPHARMA, PHARMATHEN, PIERRE FABRE, ROCHE, SMB, STADA, SUN PHARMA, TARGET, and TEVA

SIGNATURE PAGE

Reviewed and approved by:

4. Abstract

Full Study Title: Qualitative Study – Barriers and Facilitators Assessment of adherence to the Risk Minimisation Measures (RMMs), specifically Pregnancy Prevention Programme (PPP) for Women of Childbearing Potential Using Oral Retinoids (acitretin, alitretinoin, and isotretinoin)

Protocol version 3.0 dated 16 December 2024

Rationale and background:

Retinoic acid analogues, known as retinoids, are prescribed for various skin disorders, but their use poses teratogenic risks, leading to strict Pregnancy Prevention Programme (PPP) since 2003. Despite understanding these risks, cases of pregnancy while using oral retinoid therapies still occur. Therefore, patients' and Healthcare Practitioners (HCPs)' adherence to Risk Minimization Measures (RMMs) is still of concern. The Pharmacovigilance Risk Assessment Committee (PRAC) raised concerns in 2016, triggering a review of oral and topical retinoids' benefit-risk profiles which led to an Article 31 referral and RMM update. In 2018, the European Medicines Agency (EMA) mandated updated PPP measures for acitretin, alitretinoin, and isotretinoin, including pregnancy tests, contraception, an acknowledgment form, and patient reminder cards. A subsequent evaluation, prompted by the Article 31 referral and RMM update, revealed inconsistencies in adherence behaviour. Of 477 surveyed HCPs, 93.4% were aware, but only 69.4% adhered to PPP. Among 116 Women of Childbearing Potential (WCBP) surveyed, despite high awareness (94.0%), only 77.8% adhered to PPP.

Based on results from the drug utilisation study (DUS)/survey study, the PRAC has requested marketing authorisation holders' (MAHs) to conduct a qualitative study to investigate adherence to PPP issues despite high awareness of the measures. The PRAC's request for a qualitative study stem from a recognition of the persistent issue of poor adherence to the PPP, despite high levels of awareness among healthcare professionals and WCBP as shown in the DUS/survey study. The committee seeks a deeper understanding of the underlying factors contributing to this low compliance to inform more effective interventions. By imposing a qualitative study, the PRAC aims to explore the nuanced barriers and drivers of adherence behaviour beyond mere awareness. This qualitative study allows for a comprehensive assessment of the socio-cultural, psychological, and systemic factors influencing adherence to PPPs.

This study, categorized as a Category 3 PASS, aims to utilize an implementation science framework, specifically aligning with the PRECEDE-PROCEED Model. By adopting the PRECEDE-PROCEED framework, the study seeks to support targeted interventions and improve PPP implementation in real-world clinical settings, addressing the persistent gaps in adherence to PPP measures while WCBP using oral retinoid therapies.

Research question and objectives:

Research question: In Europe, what are the barriers and reasons for low adherence to the oral retinoid therapy PPP measures from the perspectives of (i) healthcare professionals (HCPs) who prescribe or dispense oral retinoid therapy to women of childbearing potential (WCBP), (ii) WCBP who recently used or are currently using oral retinoid therapy, (iii) parents, guardians, or caregivers of adolescent WCBP who recently used or are currently using an oral retinoid therapy?

Objectives:

The overarching objectives for all three populations of this study are the following:

P1. To describe the understanding of oral retinoid therapy PPP measures
P2. To describe the perception of oral retinoid therapy PPP measures
P3. To identify barriers and potential facilitators influencing adherence to oral retinoid therapy PPP measures

Study design:

This is a non-interventional qualitative cross-sectional study, using qualitative interviews conducted in multiple European countries (France, Germany, Poland, and Spain).

The interview procedure involves providing background information, obtaining consent, confirming consent and audio-recording permission. Interviews will be conducted via web-enabled audio conference platform using semi-structured guides. The interview process allows iterative adjustments based on ongoing reviews and participant feedback.

Population

The study target population includes HCPs who prescribe or educate on oral retinoids PPP measures, WCBP taking or having taken oral retinoid therapies, or parents of adolescents WCBP taking or having taken oral retinoid therapies.

The inclusion criteria for HCPs include being a medical specialist (dermatologists, paediatricians, and/or general practitioners) or an allied HCP (pharmacists and/or nurses, if applicable per country) who dispensed and/or educated WCBP on oral retinoid therapy PPP measures) at least once in the last 6 months in France, Germany, Spain or Poland.

The inclusion criteria for WCBP include being aged 18-49 and currently or recently (in the past 6 months) using any oral retinoid therapies in France, Germany, Spain, or Poland.

The inclusion criteria for parents, guardians, or caregivers, the primary inclusion criterion is being a parent, caregiver, or guardian of an adolescent WCBP aged 13-17 currently or recently (in the last 6 months) using oral retinoids (except alitretinoin) in France, Germany, Spain, or Poland.

Recruitment channels include clinician referral, patient advocacy groups, social media outreach, and IQVIA's in-house physician and patient panels.

Variables and Data sources:

This study will collect primary data through 60-minute semi-structured interviews with WCBP who recently used or are currently using oral retinoid therapy; parents, guardians, or caregivers of adolescent WCBP who recently used or are currently using oral retinoid therapy, and HCPs who prescribe, dispense, or educate on oral retinoid therapy PPP. Although conversations will be summarised by themes and topics, pre-identified variables can be modified as per topics discussed and cannot be prepopulated in advance, as is usual for qualitative research.

This study will involve up to two IQVIA moderators per country who have been trained and approved as moderators and on the framework and objectives of this study. The moderators will use a semi-structured interview guide to ensure that consistency in the structure of the interviews is maintained and that all relevant topics are covered.

The web-enabled audio conference semi-structured interviews are planned to be conducted in France, Germany, Poland, and Spain. Deidentified verbatim transcripts will be produced and translated into English. The verbatim transcripts will constitute the data and variable source for qualitative analyses.

Study Size:

The study population will include a sample, per country, of:

- 30 HCPs including 20 oral retinoid therapy prescribers (dermatologists, paediatricians, or general practitioners) and 10 dispensers and/or educators (pharmacists and/or nurses, if applicable in the targeted country about oral retinoid therapy PPP measures);
- 25 to 28 WCBP aged 18-49 per country, who currently or recently (in the past 6 months) used oral retinoid therapy, aiming with a distribution to represent:
    - 15 WCBP aged 18-49 using isotretinoin (n=60 across all countries),
    - 5 WCBP* aged 18-49 using acitretin (n=20 across all countries), and
    - 5-8 WCBP* aged 18-49 using alitretinoin in France, Germany, and Spain (n=20 across all countries);
- 10 parents, guardians, or caregivers of adolescent WCBP aged 13-17 currently or recently (in the past 6 months) used oral retinoid therapies, excluding alitretinoin.

** Given the low prescription rates for these two retinoid treatments, the feasibility of identifying WCBP may be challenging. The following hierarchal steps and sampling boosting method will be followed to achieve the sample population, and is described in detail in Appendix 2:*

1. *Identify WCBP aged 18-49 using alitretinoin or acitretin (target 5 WCBP per country for acitretin and 5-8 WCBP in France, Germany, or Spain for alitretinoin);*
2. *If samples of WCBP per country cannot be enrolled, country-specific targets may be varied to account for an overall sample of 20 WCBP globally (representation per country included, while aiming to identify at least 5 WCBP using alitretinoin aged 35-49 globally);*
3. *Additional mitigation strategies that could be implemented includes targeting WCBP using alitretinoin or acitretin in the last 2 years or targeting an additional European country. This includes asking HCPs to provide information about this qualitative study to eligible WCBP for self-referral;*
4. *Identify WCBP aged 35-49 using isotretinoin with vignette descriptions of PPP measures for isotretinoin and/or acitretin;*
5. *Identify WCBP aged 18-49 using isotretinoin with vignette descriptions of PPP measures for isotretinoin and/or acitretin.*

Data Analysis:

The data analysis for this study will adhere to a Qualitative Analysis Plan (Annex 4. Qualitative Analysis Plan). Sociodemographic and clinical variables characterizing participants will be summarized. Continuous variables will be summarized with mean,

standard deviation, minimum, and maximum values. Categorical variables will be described in total numbers and percentages per category.

The qualitative data analysis will employ thematic analysis methods using a qualitative analysis software (MAXQDA 2022). The analysis will be guided by the PRECEDE-PROCEED implementation science framework, which is divided into PRECEDE and PROCEED phases, and aids in systematically assessing various aspects of the study topic. Participants' experiences with oral retinoids PPP measures will be categorized using both deductive and inductive coding approaches.

Deductive coding involves applying findings from other phases of the research to the coding framework, adapted from a standardized dictionary of terms. Inductive coding derives codes from emerging concepts during analysis, contributing to thematic analysis. Inter-coder agreement will be regularly assessed, and dual coding on 20% of the sample will ensure consistency. Code saturation, achieved at the moment where the codebook stabilizes and new codes or code's nomenclatures become increasingly rare as interviews are conducted, will be assessed after each interview by comparing the codes and code's definitions (e.g., reasons for not adhering to PPP measures, preferred methods of communication) used and elicited during each interview, following analysis of the coding performed in MAXQDA 2022, to determine the sufficiency of interviews in capturing participants' experiences. The concept saturation approach will be detailed in the Qualitative Analysis Plan to ensure rigor and validity in the study.

An interim analysis will be conducted when approximately 50% of the total planned interviews have been completed (analysis and reporting planned between October to December 2025). The planned interim analysis is described in detail in the Qualitative Analysis Plan (Annex 4. Qualitative Analysis Plan). The interim analysis will seek to evaluate whether the study sample sizes are adequate for reaching code saturation among participants recruited from each of the four study countries (France, Germany, Poland and Spain) and between the three oral retinoid molecules (isotretinoin, acitretin, and alitretinoin) used by adult WCBP and two oral retinoid molecules used by adolescent WCBP (isotretinoin and acitretin). A decision to expand recruitment to potential additional regions of Europe and/or increasing samples for specific oral retinoids will be taken based on the interim analyses' findings.

Participants will be asked to rank the top five most important barriers and challenges to adhering to PPP measures according to their experience which will serve as basis to assess cross-country and region similarities and/or differences and to assess whether the study sample is representing the various barriers and challenges to adhering to PPP measures reported, which are theorized to be influenced by the geographical location of participants within Europe. In addition, triangulation with existing literature identified following a

narrative review of barriers to adhering to PPP measures highlighted by adult WCBP and parents, guardians or legal caregivers of adolescent WCBP in the Nordic/northern European regions will be compared with the interim analysis' findings. Depending on the findings, the recruitment strategy may be revisited to include samples representative of other European regions (e.g. Nordic countries).

Milestones

The planned dates for key study milestones are:

Milestone	**Planned date**
Member State/RMS approval	October 2024 to March 2025
Registration to the EMA-HMA	March-April 2025
Ethics Committee approval	March to June 2025
Start of data collection	May to August 2025
Interim Report	October to December 2025[4]
Member state and RMS review/approval	January to February 2026
End of data collection	April to July 2026
Final report of study results	November 2026 to April 2027

[4] Please see section 9.2.3.2 for additional detail.

5. Amendments and Updates

Substantial protocol amendments will be submitted to the Ethics Committee (EC) and regulatory authorities following local regulatory requirements.

Approval must be obtained from regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g., change in contact information).

Substantial protocol amendments/updates after the start of data collection: none (original protocol submission).

6. Milestones

Milestone	**Planned date**
Member state and RMS approval	October 2024 to March 2025
Registration to the EMA-HMA Catalogues	March-April 2025
Ethics Committee Approval	March to June 2025
Start of data collection	May to August 2025
Interim analysis and report	October to December 2025
Member state and RMS review/approval	January to February 2026
End of data collection	April to July 2026
Final report of study results	November 2026 to April 2027

7. Background and Rationale

Retinoic acid analogues, collectively known as retinoids, are available in both topical and oral forms. They are prescribed for various therapeutic indications, including the treatment of severe acne (such as nodular or conglobate acne), hand eczema or psoriasis resistant to treatment with potent corticosteroids, and other hyperkeratotic and parakeratotic skin disorders, as well as keratotic genodermatoses. However, retinoid therapy is associated with teratogenicity, making it contraindicated for pregnant women or those planning a pregnancy. Strict prescription guidelines and Pregnancy Prevention Programme (PPP) have been in place since 2003 to mitigate risks, but cases of exposure during pregnancy persist.

Available evidence suggests that there is generally a good understanding of the teratogenic risk associated with retinoid therapy, yet Risk Minimization Measures (RMMs) are not always followed as recommended. One study, published by Bertels et al. (2022), suggested that this low adherence to RMMs is mainly due to poor implementation of pregnancy testing (1). A second study suggests that reserving isotretinoin prescribing to specialists may improve adherence to PPP (2).

In January 2016, the Pharmacovigilance Risk Assessment Committee (PRAC) raised concerns about the PPP's effectiveness, leading to a further assessment. In July 2016, the United Kingdom initiated an Article 31 referral, prompting the PRAC to review the benefit-risk profile of oral and topical retinoids. In March 2018, the European Medicines Agency (EMA) completed its review of retinoid therapies and confirmed that an update of measures for pregnancy prevention is needed. Based on the EMA's communication from 21 June 2018 EMA/261767/2018 pregnancy prevention programme (PPP) update for acitretin, alitretinoin and isotretinoin, the following measures are recommended:

- pregnancy tests before, during and after stopping treatment;
- the need to use effective contraception before, during, and after treatment;
- educational material, specifically
    - prescriber's checklist to be used by HCPs to record the discussion of risks with the patient. A copy should be provided to the patient;
    - an 'acknowledgement form' to confirm that appropriate advice has been given to patients;
    - a 'patient reminder card' stating that the medicine must not be used during pregnancy and including information about pregnancy testing and the need to use effective contraception.

- Pharmacist's checklist to be as a reminder document to dispensing pharmacists if applicable in the Member State.

The PPP measures address the issues of effective contraceptive use, pregnancy testing, and rigorous monitoring of the treating physician (i.e., dermatologist, paediatrician, or general practitioners in some countries after first prescription). The difference between the implemented PPP before and after the implementation of the updated RMMs is relatively small (see Table 1). The PPP measures are similar in the countries of interest for this study.

The updated RMMs include updated educational material, patient reminder cards and pictogram on the outer package in some countries, and in addition, the redistribution of direct healthcare professional communication (DHPC). Differences in the set of implemented tools may exist between countries due to the requirements of local authorities.

Table 1. Measures of the PPP before and after the newly implemented, updated Risk Minimisation Measures (RMMs)

Active substance	PPP	Contraception			Pregnancy test			Prescriber's checklist	Acknowledgement form	Patient reminder card	Days' supply/Length of prescription
		Before	During	After	Before	During	After	Before	Before	Before	
Acitretin	Old[1]	Yes	Yes	3yrs	Yes	Monthly	3yrs	Yes	Yes	Yes	Limited to 30d
	New[2]	1mo	Yes	3yrs	Yes	Ideally monthly	3yrs	Yes	Yes	Yes	Ideally limited to 30d
Alitretinoin	Old[1]	1mo	Yes	1mo	Yes	Ideally monthly	5wks	Yes	Yes	Yes	Limited to 30d
	New[2]	1mo	Yes	1mo	Yes	Ideally monthly	1mo	Yes	Yes	Yes	Ideally limited to 30d
Isotretinoin	Old[1]	1mo	Yes	1mo	Yes	Ideally monthly	5wks	Yes	Yes	Yes	Limited to 30d
	New[2]	1mo	Yes	1mo	Yes	Ideally monthly	1mo	Yes	Yes	Yes	Ideally limited to 30d

1 Summary of product characteristics for acitretin, alitretinoin, and isotretinoin in countries of interest (i.e., France, Germany, Poland, and Spain); for the time period 2012-2017
2 Annex to the Amendments to relevant sections of the Product Information from 22 March 2018

In response to the Article 31 referral and subsequent update of Risk Management Measures (RMMs), the PRAC mandated an evaluation of RMM effectiveness. Two Post-Authorisation Safety Studies (PASS) were conducted, focusing on patient and prescriber awareness, as well as adherence to the PPP. A Category 3 PASS survey assessed healthcare professionals' (HCPs) and patients'/caregivers' awareness, knowledge, and adherence to the PPP.

Survey results revealed discrepancies in self-reported behaviour across several domains, indicating that both WCBP and HCPs sometimes deviate from PPP measures despite their knowledge. Out of 477 surveyed HCPs, 93.4% were aware, 93.3% had access to the Summary of Product Characteristics (SmPC)/patient information leaflet, and 91.6% had read these materials. However, only 69.4% adhered to PPP measures.

Among 116 participating WCBP/caregivers, over 90% engaged in discussions with their HCPs regarding pregnancy risks associated with oral retinoids. Despite high awareness (94.0%) of pregnancy risks under retinoid therapy and high acknowledgement (88.1%) of the harm to an unborn baby, only 77.8% were deemed adherent to PPP measures. Based on the results from this DUS/survey study, the PRAC has requested MAHs to also conduct a qualitative study to investigate adherence to PPP issues despite high awareness of the measures.

Improving adherence to PPP measures requires a deeper understanding of the factors influencing adherence to oral retinoid therapies. Although existing RMMs and PPP guidelines are useful, there are gaps between knowledge and behaviour and in their implementation. Therefore, a more detailed assessment of the implementation process, along with the associated barriers and facilitators, is needed to enhance their effectiveness. Previously reported barriers to contraceptive adherence among WCBP include contraceptive options, access to medication, social influence, lack of habit, insufficient knowledge, and necessity concerns balance (3–5). A case study of WCBP who failed to comply with the PPP suggested young teenagers have poor understanding of birth control methods resulting in their improper use (i.e., using contraception on an irregular basis or not using both a barrier and hormonal method) (6). PPP measures were not followed and while patients were aware of teratogenic risk of their medication, they do not recall being advised to use two modes of contraception or being advised of the PPP, and most did not sign the consent form (6).

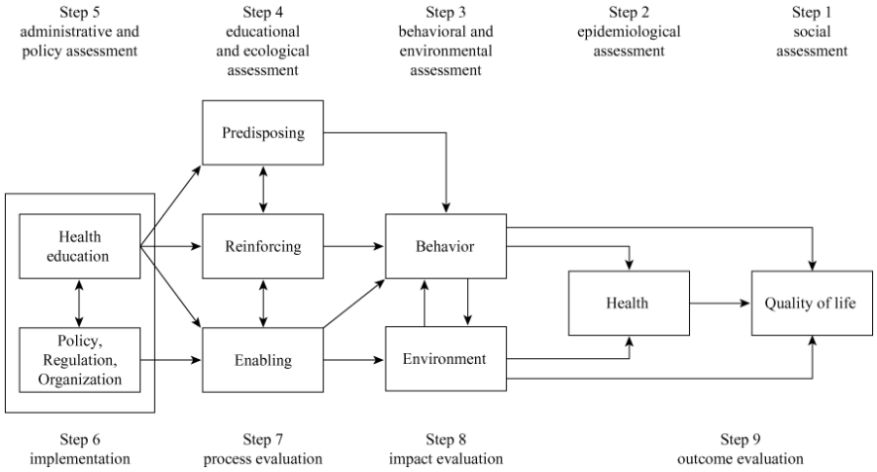
An analysis of barriers to following guideline recommendations among physicians suggest the most perceived barriers to be lack of agreement with the recommendations, organisational and time constraints due to clinical responsibilities, lack of knowledge, and guideline factors including complex, unclear, or ambiguous recommendations (7–9).

Implementation science, a multidisciplinary field that focuses on bridging the gap between research findings and their effective integration into routine clinical practice (10), can help

understand the barriers and the facilitators for poor adherence to PPP. The goal of implementation science is to describe and/or guide the process of translating research into practice (i.e., "implementation practice") rather than to predict or analyse what factors influence implementation outcomes (i.e., "implementation research") (11). In simpler terms, the field of implementation science seeks to close the gap between what we know and what we do (often referred to as the know-do gap) by identifying and addressing the barriers that slow or halt the uptake of proven health interventions and evidence-based practices.

Several theoretical frameworks have been developed to guide different aspects of the implementation of best evidence-based interventions in routine practice. Nilsen (2015) summarized the implementation sciences theoretical frameworks into five categories: 1) process models, 2) determinants frameworks, 3) classic theories, 4) implementation theories, and 5) evaluation frameworks (11). One of the comprehensive evaluation frameworks is the PRECEDE-PROCEED (Predisposing, Reinforcing and Enabling Constructs in Educational Diagnosis and Evaluation-Policy, Regulatory, and Organizational Constructs in Educational and Environmental Development) which allows assessing needs for designing, implementing, and evaluating health programs to meet those needs (12). This framework classifies implementation aspects of a health program that should be considered to design or improve a successful implementation strategy. The PRECEDE-PROCEED Framework (shown in Figure 1 below), provides a structured and comprehensive analysis for assessing potential successes and pitfalls of in the planning or implementation of a public health program (11). It provides a theoretical framework that organizes factors at both personal and various social-ecological levels. (13). Through this systematic approach, the goal is to contribute meaningful data that can inform targeted interventions and RMM planning, enhancing the implementation of effective oral retinoids PPP measures in routine clinical settings.

Figure 1. The PRECEDE–PROCEED Framework for Health Promotion Program (12)



8. Research Question and Objectives

In Europe, what are the barriers and reasons for low adherence to the oral retinoid therapy PPP measures from the perspectives of (i) healthcare professionals (HCPs) who prescribe or dispense oral retinoid therapy to women of childbearing potential (WCBP), (ii) WCBP who recently used or are currently using oral retinoid therapy, (iii) parents, guardians, or caregivers of adolescent WCBP who recently used or are currently using an oral retinoid therapy?

8.1 Global Objectives:

The overarching global objectives for all three populations of this study are the following:

P1. To describe the understanding of oral retinoid therapy PPP measures
P2. To describe the perception of oral retinoid therapy PPP measures
P3. To identify barriers and potential facilitators influencing adherence to oral retinoid therapy PPP measures

8.2 Specific objectives for Healthcare Professionals (HCPs) who prescribe or dispense oral retinoid therapy

The specific objectives for HCPs who prescribe or dispense oral retinoid therapy are the following:

O1. To describe HCPs' understanding of the oral retinoid therapy PPP measures.

- To understand the extent to which HCPs are aware of the oral retinoid therapy PPP measures including use of effective contraception and mandated regular interval repeated pregnancy testing, before, during, and after oral retinoid therapy treatment;
- To describe the content and the format of communication given to WCBP (adult or adolescent) and parents of adolescent WCBP about the oral retinoid therapy PPP measures at the time of prescription, dispensing, and termination (if applicable) of oral retinoid therapy (e.g., educational material given, in which format, reminders given, pregnancy testing communication given, etc);
- To describe the aspects or the oral retinoid therapy PPP measures that are challenging and not challenging in understanding for HCPs;

- For pharmacists (or any other relevant dispenser of oral retinoid therapy per local practice), to identify what barriers and facilitators in explaining the patient card to WCBPs and ensure its content is well understood;
- To describe the understanding, from the HCPs perspective, of measures to take if a WCBP (adult or adolescent) is planning or becomes pregnant.

O2. To describe the perception of oral retinoid therapy PPP measures by HCPs.

- To describe HCPs' perceptions of the oral retinoid therapy PPP measures, from their perspective and the WCBP's perspectives;
- To describe the HCPs' perceptions of their role in WCBP adhering to PPP measures;
- To explore HCPs' opinions on existing measures to communicate or enhance adherence to current oral retinoid therapy PPP measures;
- To describe HCPs' perceptions of the parents' opinion of the suitability of PPP measures to be applied in adolescent WCBP.

O3. To identify barriers and potential facilitators influencing adherence to oral retinoid therapy PPP measures.

- To describe the extent to which HCPs perceive WCBP (adult or adolescent) adhere to the type and frequency of oral retinoid therapy PPP measures, per oral retinoid therapy type including use of effective contraception and mandated regular interval repeated pregnancy testing;
- To describe the challenges HCPs perceive in adhering to oral retinoid therapy PPP measures based on WCBP personal and environmental characteristics, organizational characteristics, communications and coordination with other HCPs, and oral retinoid therapy intervention characteristics;
- To describe the transparency HCPs believe adolescent WCBP have with their parents in being sexually active and whether different clinical encounters strategies are implemented to ensure adherence to PPP measures (e.g., individual clinical encounter, etc);
- To understand whether HCPs perceive WCBP (adult or adolescent) may be hesitant to discuss and review some or all aspects of oral retinoid therapy PPP measures with their HCPs;

- To identify the preferred ways for HCPs to communicate information on oral retinoid therapy PPP measures per WCBP type;
    - May include reactions on currently implemented measures in their specific country of residence (e.g., France: use of videos or QR codes)
- To identify currently implemented and potential more effective ways to communicate oral retinoid therapy PPP needs to other HCPs involved in the WCBP's care;
- To identify potential ways to improve the dissemination of PPP information around oral retinoid therapies to WCBP and other HCPs;
- To identify potential ways to improve adherence to PPP measures for oral retinoid therapies in WCBP and HCPs;
- To describe the HCPs experiences of a WCBP becoming pregnant or being pregnant while on oral retinoid therapy, the aspects of the PPP measures that were either not understood or not possible to implement, and potential solutions for prevention in the future.

8.3 Specific objectives for WCBP who recently used or are currently using oral retinoid therapy

The specific objectives for WCBPs who recently used or are currently using oral retinoid therapy are the following:

In WCBP aged 18 to 49 years of age currently or recently using oral retinoid therapy:

O1. To describe the understanding of oral retinoid therapy PPP measures.

- To understand the extent to which WCBP are aware of the oral retinoid therapy PPP measures, including use of effective contraception and mandated regular interval repeated pregnancy testing, (ideally monthly), before, during, and after oral retinoid therapy treatment (including 1 month to 3 years post-treatment when applicable);
- To describe the content and the format of communication received about PPP measures by their HCPs at the time of prescription, dispensing and termination (if applicable) of oral retinoid therapy (e.g., types of HCPs involved, educational material received in paper or digital format, reminders received, pregnancy testing communication received, etc);
- To describe the aspects or the oral retinoid therapy PPP measures that are challenging and not challenging to understand;

- To describe the understanding of WCBP of measures to take when intending to or becoming pregnant.

O2. To describe the perceptions of oral retinoid therapy PPP measures.

- To assess WCBP perceptions of the oral retinoid therapy PPP measures;
- To describe WCBP perceptions of their role in adhering to PPP measures;
- To explore WCBP opinions on existing measures to communicate or enhance adherence to current oral retinoid therapy PPP measures.

O3. To identify barriers and potential facilitators influencing adherence to oral retinoid therapy PPP measures.

- To describe the extent to which WCBP adhere to the type and frequency of oral retinoid therapy PPP measures including use of effective contraception and mandated regular interval repeated pregnancy testing;
- To describe the challenges in understanding and adhering to oral retinoid therapy PPP measures based on personal characteristics, experiences with HCPs, oral retinoid therapy intervention characteristics, and person's environmental characteristics;
- To understand whether WCBP are hesitant to discuss and review some or all aspects of oral retinoid therapy PPP measures with their HCPs;
- To identify the preferred ways for WCBP to access and/or receive the information on the oral retinoid therapy PPP measures;
    - May include reactions on currently implemented measures in their specific country of residence (e.g., France: use of videos or QR codes)
- To identify potential ways to improve the dissemination of PPP information around oral retinoid therapies;
- To identify potential ways to improve adherence to the oral retinoid therapy PPP measures;
- If WCBP have become pregnant or are pregnant while on oral retinoid therapy, describe what aspects of the PPP measures were not possible to adhere.

8.4 Specific objectives for Parents, guardians, or caregivers of adolescent WCBP who recently used or are currently using oral retinoid therapy

The specific objectives for parents, guardians, or caregivers of adolescent WCBP who recently used or are currently using oral retinoid therapy are the following:

O1. To describe parents' understanding of oral retinoid therapy PPP measures.

- To understand the extent to which parents are aware of the PPP measures associated with oral retinoids, including use of effective contraception and mandated regular interval repeated pregnancy testing, before, during, and after oral retinoid therapy treatment;
- To describe the content and the format of communication received by parents about PPP measures by their child´s HCPs at the time of prescription, dispensing, and termination (if applicable) of oral retinoid therapy (e.g., types of HCPs involved, educational material received in paper or digital format, reminders received, pregnancy testing communication received, etc);
- To describe the aspects or the oral retinoid therapy PPP measures that are challenging and not challenging for parents to understand;
- To describe the understanding, from the parents' perspective, of measures to take if their adolescent WCBP becomes pregnant.

O2. To describe the perceptions of oral retinoid therapy PPP measures by parents.

- To assess parents' and their adolescent's perceptions of the oral retinoid therapy PPP measures;
- To describe the parent and their adolescent's perceptions of their role in adhering to PPP measures;
- To explore parents' opinions on existing measures to communicate or enhance adherence to current oral retinoid therapy PPP measures;
- To describe the parents' perception of the suitability of PPP measures to be applied in adolescent WCBP.

O3. To identify barriers and potential facilitators influencing adherence to oral retinoid therapy PPP measures.

- To describe the extent to which parents perceive their adolescent WCBP adheres to the type and frequency of oral retinoid therapy PPP measures including use of

effective contraception and mandated regular interval repeated pregnancy testing;

- To describe the challenges in adhering to oral retinoid therapy PPP measures based on personal characteristics, experiences with HCPs, oral retinoid therapy intervention characteristics, and person's environmental characteristics;
- To describe the transparency between parents and their adolescent WCBP in communicating if they are sexually active and needing to adhere to PPP measures;
- To understand whether parents or their adolescent WCBP are hesitant to discuss and review some or all aspects of oral retinoid therapy PPP measures with their HCPs;
- To identify the preferred ways for parents and their adolescent WCBP to access and/or receive the information on the oral retinoid therapy PPP measures;
    - May include reactions on currently implemented measures in their specific country of residence (e.g., France: use of videos or QR codes)
- To identify potential ways to improve the dissemination of PPP information around oral retinoid therapies;
- To identify potential ways to improve adherence to PPP measures for the use of oral retinoid therapies;
- If their adolescent WCBP has become pregnant or is pregnant while on oral retinoid therapy, describe what aspects of the PPP measures were not possible to implement, from the parent's perspective.

9. Research Methods

9.1 Study design

This is a non-interventional qualitative cross-sectional study that will be conducted in multiple European countries (i.e., France, Germany, Poland, and Spain). The data will be collected using qualitative interviews.

9.1.1 Sample Size and Inclusion/Exclusion Criteria

Qualitative studies do not involve power estimates for sample size, as they rely on establishing saturation to determine when data collection is complete. Saturation in this study will be defined by the achievement of "code saturation" (14). Previous studies involving the assessment of code saturation observed that approximately 9 interviews were sufficient to achieve saturation (14). Sample size recommendations are based on this evidence, while also considering the various subgroups of interest involved in the study and

the anticipated diversity of experiences to be comprehensively captured. Additional information about the adequacy of the sample size and the saturation approach considered for this study is provided in section 1.1.1.1 and further detailed in the Qualitative Analysis Plan, which can be accessed in Annex 4. Qualitative Analysis Plan.

Included oral retinoid therapies in this study are acitretin, isotretinoin and alitretinoin.
The target population will include a sample of

- HCPs who prescribe or dispense oral retinoid therapy;
- WCBP who currently or recently used oral retinoid therapy, and;
- Parents of adolescent WCBP who currently or recently used oral retinoid therapy (except alitretinoin).

9.1.1.1 Inclusion / Exclusion Criteria for HCPs Prescribing/Dispensing Oral Retinoid Therapy

A combination of different HCPs including medical specialists who prescribe oral retinoid therapy (n=20) and allied HCPs who dispense and/or educate WCBP about PPP measures whilst using oral retinoid therapy (n=10) in each of the study countries (France, Germany, Poland, and Spain) will be included if they meet the following inclusion criteria:

9.1.1.1.1.1 Inclusion Criteria for HCPs Prescribing/Dispensing or Informing on Oral Retinoid Therapy

HCPs will be included in this study if they meet the following criteria:

- Being a licensed medical specialist in one of the study countries who has prescribed oral retinoid therapies to WCBP (e.g., dermatologists, paediatricians, and/or general practitioners) at least once in the last 6 months (n=20 per country);
- Being a registered pharmacist in one of the study countries who dispensed oral retinoid therapy to WCBP at least once in the past 6 months (n=5 to 10 per country);
- Being a registered nurse providing education on PPP measures for oral retinoid therapies to WCBP, if applicable in the target country, at least once in the past 6 months (Poland, Spain, and France only (15); n= up to 5 for France, Poland, and Spain, not applicable for Germany);
- Willing to consent to participate in this study.

9.1.1.1.2 Exclusion Criteria for HCPs Prescribing/Dispensing Oral Retinoid Therapy

HCPs will be excluded from this study if meeting the following criteria:

- Being an inactive and retired HCP / allied HCP at the time of the interviews;
- Having a conflict of interest with the study (i.e., being employed by regulatory bodies, and/or pharmaceutical companies).

9.1.1.2 Inclusion/Exclusion Criteria for WCBP (aged 18-49) and Parents, Guardians, or Caregivers of Adolescent WCBP

9.1.1.2.1 Inclusion Criteria for WCBP (aged 18-49) and Parents, Guardians, or Caregivers of Adolescent WCBP

As shown in Table 2 below, between 25-28 WCBP and 10 parents, guardians or caregivers of adolescent WCBP per country (France, Germany, Poland, and Spain) will be targeted, if meeting the following inclusion criteria described below:

For isotretinoin (n=15 per country, 60 WCBP across all countries):

- Being female sex aged 18 to 49;
- Currently or recently (within the last 6 months) using isotretinoin;
- Willing/consent to participate in this study.

For acitretin (n=5 per country, 20 WCBP across all countries):

- Being female sex aged 18 to 49;
- Currently or recently (within the last 6 months) using acitretin*;
- Willing/consent to participate in this study.

For alitretinoin (n=5-8 from France, Germany, and Spain, 0 from Poland, 20 WCBP across all countries):

- Being female sex aged 18 to 49;
- Currently or recently (within the last 6 months) using alitretinoin*;
- Willing/consent to participate in this study.

Parent, guardians, or legal caregivers of Adolescent WCBP (n=10 per country)

- Parent, guardian or legal caregiver of adolescent WCBP aged 13 to 17 who are currently or recently (within the last 6 months) using isotretinoin or acitretin;
- Willing/consent to participate in this study.

Table 2. Target WCBP Samples across oral retinoid medication and country

Target country	Target WCBP samples to be recruited*			
	Isotretinoin	Alitretinoin (Min/Max)	Acitretin	Total (Min/Max)
France	15	5 - 8	5	25-28*

Germany	15	5 - 8	5	25-28*
Poland**	15	N/A**	5	20
Spain	15	5 - 8	5	25-28*
Total	**60**	**20**	**20**	**100**

*Note that this is a target number which may change depend on success of recruitment at local level. Country-specific targets may vary to account for the alitretinoin variability per country, but the overall sample will be of 100 WCBP globally.

Table 2 does not include n=10 parents, guardians, or caregivers of adolescent WCBP from each country.

**N/A: Not Applicable. Alitretinoin does not hold marketing authorisation in Poland. Thus, efforts will be made to recruit patients across France, Germany and Spain (between 5 and 8 per country), to ensure methodological robustness in interpreting results. A total of 20 WCBP taking or recently have taken alitretinoin will be recruited across all countries.

** Given the low prescription rates for these two retinoid treatments, the feasibility of identifying WCBP may be challenging. The following hierarchal steps and sample boosting will be followed to achieve the sample population, and is described in detail in Appendix 2:*

1. *Identify WCBP aged 18-49 using alitretinoin or acitretin (target 5 WCBP per country for acitretin and 5-8 WCBP in France, Germany, or Spain for alitretinoin);*
2. *If samples of WCBP per country cannot be enrolled, country-specific targets may be varied to account for an overall sample of 20 WCBP globally (representation per country included, while aiming to identify at least 5 WCBP using alitretinoin aged 35-49 globally);*
3. *Additional mitigation strategies that could be implemented includes targeting WCBP using alitretinoin or acitretin in the last 2 years or targeting an additional European country. This includes asking HCPs to provide information about this qualitative study to eligible WCBP for self-referral;*
4. *Identify WCBP aged 35-49 using isotretinoin with vignette descriptions of PPP measures for isotretinoin and/or acitretin;*
5. *Identify WCBP aged 18-49 using isotretinoin with vignette descriptions of PPP measures for isotretinoin and/or acitretin.*

9.1.1.2.2 Exclusion Criteria WCBP (aged 18-49) and Parents, Guardians, or legal Caregivers of Adolescent WCBP

WCBP will be excluded from this study if they meet any of the following criteria:

- WCBP does not have childbearing potential during the treatment course for oral retinoids (please see list of potential causes for losing childbearing potential in Appendix 1. List of potential causes for infertility in women);
- Unable to understand or comply to the study procedures, including the interview.

9.1.2 Recruitment and Study Enrolment

Recruitment will start after completing Heads of Medicines Agencies (HMA)-EMA catalogue registration following Ethics Committee approval.

9.1.2.1 Recruitment and Study Enrolment for HCPs

HCPs will be identified using IQVIA's proprietary HCP panel, OneKey. HCPs who have previously consented to be invited to participate in interviews and survey studies will be contacted by email or by telephone.

HCPs will be invited to participate in the study via an email newsletter, which will contain a link to confirm eligibility. If contacted by phone, the study background and objectives, the contact information for any questions, and the study procedures (eligibility criteria, study flyer, and interview content) will be summarized to HCPs. HCPs who agree will be sent an eligibility link by email. If the link confirming eligibility is not completed, the HCPs will be sent a reminder by email 3 times. An HCP will be considered unreachable if they have been contacted 3 times without response.

Once screened, eligible HCPs will be sent a link to an online informed consent and if they agree to participate, preferred interview times will be registered. A confirmation email with the date and time of the interview will be sent back to secure the interview.

The recruitment in each stratum (HCP specialty/country) will be closely monitored and the time required to recruit every five HCPs will be registered to understand whether recruitment is progressing according to the pre-defined study timelines. The recruitment in each stratum will be stopped when the target number is reached.

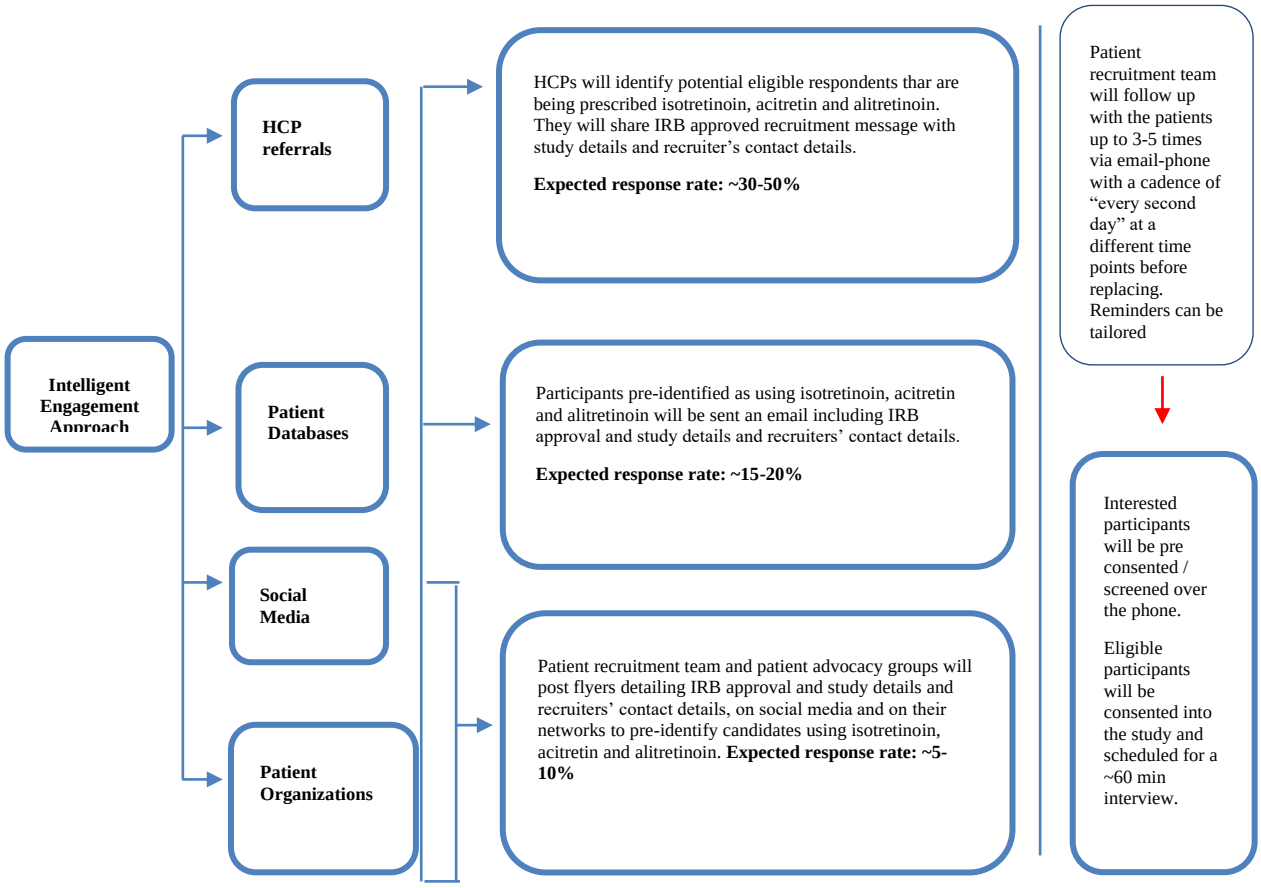
9.1.2.2 Recruitment and Study Enrolment for WCBP and Parents, Guardians, or legal Caregivers of Adolescent WCBP

WCBP and parents of adolescent WCBP will be identified via the following channels:

- IQVIA in-house Direct-to-Patient Recruitment channel
- Recruitment via HCP referral

Using its in-house recruitment service, IQVIA can locate potential participants through diverse avenues (primarily HCP and patient databases, along with social media and Patient Organizations), thus offering access to the study for prospective patients who are currently using Oral Retinoids from various sourcing channels, described in Figure 2.

Figure 2. Recruitment sources and strategy for WCBP (aged 18-49) and parents, guardians, or caregivers of adolescent WCBP



Additional recruitment and sample boosting stepwise approaches for the identification of WCBP (aged 18-49) using oral retinoids are described in Appendix 2. Stepwise identification and sample boosting approach.

9.1.2.2.1 Recruitment via HCPs Referral

Within IQVIA's network of preferred sites, HCPs will be approached by the recruitment team, who will provide them with recruitment flyers and/or email newsletters to disseminate to eligible participants. HCPs will examine the screener information and disseminate it to eligible WCBP or parents of WCBP. HCPs will encourage these potential participants to reach out directly to the recruitment team for further screening and consent procedures, as well as for any inquiries about the study. WCBP or parents of WCBP eligible to the study will receive a link to an online informed consent form, and upon agreement to participate, they will be able to select preferred interview times.

HCPs assisting in this process will receive remuneration in accordance with the fair market value for their time spent on recruitment activities.

9.1.2.2.2 Direct-to-Patient Recruitment (Patient Databases)

IQVIA's in-house Direct-to-Patient recruitment channel, *Global Perspectives*, will engage in identifying WCBP and parents, guardians, or caregivers of adolescent WCBP. IQVIA's *Global Perspectives* will reach out to potential participants through their extensive databases of patients and caregivers, as well as via social media, connections with local patient associations, and direct conversations with clinicians.

IQVIA's Global Perspectives will publicize the study through email newsletters, recruitment flyers, and/or social media posts (template for outreach available in Annex 5. Outreach template for adult WCBP, parents or guardians of adolescent WCBP and HCPs). The outreach materials will provide a link to an online study screener (Annex 6. Example of screeners which will be used). Eligible individuals will be directed to an online informed consent form (Annex 7. Examples of the informed consent forms used). Alternatively, verbal screening via telephone may occur before obtaining both verbal and electronic consent.

Proof of eligibility for study inclusion criteria will be required from participants. This might entail a physician's confirmation of treatment, a photo of the current prescription for oral retinoids, or a photo of their oral retinoid medication package. Upon qualifying and consenting to participate, IQVIA's *Global Perspectives* will record the participant's contact details - including name, address, email, and phone number - in a private patient portal respecting General Data Protection Regulation (GDPR) and will coordinate an interview with IQVIA's Patient Centered Endpoints Research team.

Recruitment across each demographic stratum will be closely monitored and the time required to recruit every five participants will be registered to understand whether recruitment is progressing according to the pre-defined study timelines. Recruitment will halt once the target number of participants is reached.

Should the initial recruitment strategies prove insufficient, a mitigation plan will be put into action to guarantee successful recruitment outcomes, as described in section 9.1.1.2.1.

9.2 Interview Procedure

Interviews will be scheduled based on a confirmed date and time once their eligibility and informed consent are confirmed. Participants with a scheduled interview will receive an online link prior to the interview including an online conference link and telephone number to join the interview on the date and time of the scheduled interview.

At the beginning of the interview, a trained moderator from the IQVIA team will:

- Verify consent verbally,
- Provide background information about the study,
- Provide the opportunity for participants to ask any questions concerning the study,
- Will obtain permission to audio-record the interview and subsequently to be transcribed, coded, analysed, and interpreted leading to a final written report of aggregated results,
- If applicable, will ask for permission if a second IQVIA team member may listen to the interview for training/quality assurance and/or notetaking purposes,
- Will inform the participants about the honorarium for their participation in the study.

One-on-one interviews will be conducted via web-enabled audio conference, which will be accessible via the internet and/or local telephone number, as preferred by the participating respondent. Semi-structured interview discussion guides will be used to support the interviews and content of the interview expected. Discussion guides will utilize a combination of open-ended questions to capture participants' responses in their own words and in-depth follow-up probing questions to encourage elaboration and clarification when necessary. The interview guides will not be pilot tested with external participants as this would preclude them from further participating in the study. See section 9.2.1 for a description of the IQVIA moderator qualification process and the use of mock interviews to facilitate familiarity with the discussion guide and the conduct of the interviews.

Interviews will be conducted in waves of approximately n=5 interviews per wave (and per country). This approach allows for iteration of the discussion guide questions and process as needed, especially after the first several interviews are completed or if local adaptations of the questions or probes are needed. As the remaining interviews are conducted, the interview team will regroup to discuss the interviews on an ongoing basis. In addition, the project team will review the interview data in between waves to determine whether any modifications to the interview questions are needed. When necessary, the interview questions will be modified to improve clarity and to be tested in the following wave(s) of interviews.

Once the interview is complete, the participants will be compensated for their time per fair market value, if allowed per country regulations.

9.2.1 Moderator Training and Quality Assurance

To ensure consistency, this study will involve up to two IQVIA moderators per country who have been internally approved as moderator and have been trained on the study characteristics. The moderators will use a semi-structured interview guide to ensure that consistency in the structure of the interviews is maintained and that all relevant topics are

covered. A topics list will be provided to moderators to assist with the coverage of relevant topics during the course of the interview, however the moderators will base the approach to the discussion largely by the use of open-ended questions.

In order to maintain the quality and consistency of interviews, safeguard a positive experience for respondents, and achieve the project objectives, all moderators will have completed IQVIA's rigorous Patient Centered Solutions (PCS) qualitative moderator training program. The steps associated with moderator training and qualification include:

- **Experience**: Demonstration of the appropriate amount of prior, relevant moderating experience (i.e., moderation of 20+ concept elicitation, in-trial, and cognitive debriefing interviews independently across 3+ therapeutic areas)
- **General training**: Completion of all established, pre-set generalized training modules and readings, including modules related to Qualitative Research Methods for Collecting and Analyzing Patient Experience Data, and Moderating Sensitive Interviews; additionally, moderators are expected to be familiar with FDA, EMA, ISPOR, and other industry guidance on conducting qualitative research
- **Study-specific training**: Receipt of study-specific training and support materials provided by senior members of the project team to orient moderators to the objectives and nuances of the project and the use of its discussion guides. Before conducting interviews with participants, approved moderators will review the content of each discussion guide and participate in mock interview sessions with members of the IQVIA qualitative research team. The purpose of these mock interview sessions is to gain familiarity with the interview guide and the objectives of the interviews, to test the flow of the questions, to find any problematic, slow, or awkward topics or questions that may be leading or contribute to social desirability bias, and to test the general timing of the interview. Any questions regarding the content will be discussed with the IQVIA research team.
- **Approval and Qualification**: Evaluation and approval by the IQVIA Principal Investigator and project leadership; moderators are qualified if all prior steps have been completed
- **Monitoring**: Periodic assessment of moderation proficiency by the IQVIA Principal Investigator and project leadership.

All interviews will be audio-recorded, transcribed verbatim, and deidentified by a third-party transcription agency for qualitative analysis and subsequent quality control analysis. Transcriptions of the interviews that are conducted in different languages will be translated to English by a third-party agency or IQVIA's in house translation services. and the quality of the translation will follow IQVIA's standardized translation quality process where all translations are confirmed by the IQVIA translations team.

9.2.2 Variables and Data Analysis Framework

Data analysis will follow the guidance outlined in a separate Qualitative Analysis Plan (Annex 4. Qualitative Analysis Plan).

9.2.2.1 Quantitative Data and Analyses

Participants will be characterized by variables including:

- Age,
- Educational level of HCPs, WCBP, and parents of WCBP;
- Country,
- Condition for using oral retinoid therapy,
- Time since initiation of oral retinoid therapy,
- Frequency of oral retinoid therapy use,
- Frequency of adherence to PPP measures,
- HCPs involved in prescribing , dispensing, or informing of oral retinoid therapy
- PPP measures and frequency of information received,
- Past participation in an oral retinoid therapy PPP study.

HCPs prescribing/dispensing oral retinoid therapy will also be characterized by variables including:

- Year of graduation from medical training,
- Country,
- Medical specialty,
- Years in practice,
- Clinical setting characteristics,
- Conditions for which prescribe/dispense oral retinoid therapies,
- Years prescribing, dispensing, or educating oral retinoid therapies,
- Frequency of prescribing, dispensing, or educating on oral retinoid therapies,
- Frequency of PPP measures,
- Past participation in an oral retinoid therapy PPP study.

Continuous variables will be summarized by mean, standard deviation, minimum, and maximum. Categorical variables will be described as the totals and percentage per category.

9.2.2.2 Qualitative Data and Analyses

Qualitative data analysis will be done using a qualitative analysis software (e.g., MAXQDA 2022) and will be guided by the PRECEDE-PROCEED implementation science model. This model has two main phases and four internal phases as shown in Table 3. The PRECEDE or evaluative phase, provides a framework for systematically assessing the social, epidemiological, educational ecological, administrative and policy aspects of the topic studied. On the other hand, the PROCEED or intervention phase, used in this study

for describing the barriers and the facilitators for poor adherence to existing PPP measures, recognizes the need to move beyond traditional educational approaches to those that facilitate policy regulation along with improved environmental and organizational resources and services.

Table 3. Eight Phases of the PRECEDE–PROCEED Model

PRECEDE	Predisposing	Phase 1: Social assessment
	Reinforcing	Phase 2: Epidemiological assessment
	Enabling Constructs in Educational Diagnosis	Phase 3: Educational and ecological assessment
	Evaluation	Phase 4: Administrative and policy assessment and intervention alignment
PROCEED	Policy	Phase 5: Implementation
	Regulatory	Phase 6: Process evaluation
	Organizational Constructs in Educational and Environmental Development	Phase 7: Impact evaluation
		Phase 8: Outcome evaluation

The phases of the PRECEDE-PROCEED framework were used to develop moderating guides per respondents that align with the study objective and are included in Annex 8. Semi-structured discussion guides.

The topics discussed align per respondent group, but also to the specific study objectives per respondent shown in sections 8.2 to 8.4 of the current protocol. Grouping of barriers and facilitators across countries and specific oral retinoids in HCPs, WCBP, and parents/caregivers of teenage WCBP will support suggestions for future targeted actions to improve adherence to PPPs.

9.2.2.2.1 Topics to be interviewed with HCPs prescribing or dispensing/educating about PPP to WCBP using oral retinoid therapies

summarises the phases of the moderating guides aligned with the phased of the PRECEDE-PROCEED framework as well as key topics to interview that are related to HCP experiences with oral retinoid therapy PPP measures.

Table 4. Interview topics for HCPs Who Prescribe or Dispense/Educate Oral Retinoid Therapies

Discussion Guide sections	Phases of the PRECEDE-PROCEED	Specific objectives covered	Specific questions discussed
Participant background	Phase 1: Social assessment	• N/A	• Oral retinoid HCP is most familiar with • Number of WCBP using oral retinoids they see in a month
HCP's social assessment of healthcare professionals' knowledge of PPP measures and their relevancy for WCBP	Phase 1: Social assessment	• To understand the extent to which HCPs are aware of the oral retinoid therapy PPP measures including use of effective contraception and mandated regular interval repeated pregnancy testing, before, during, and after oral retinoid therapy treatment • To describe the understanding, from the HCPs perspective, of measures to take if a WCBP (adult or adolescent) is planning or becomes pregnant	• Overall level of knowledge and awareness of PPP measures for prescribed/dispensed oral retinoid treatment • Perception of WCBP's health literacy, self-efficacy, and locus of control of health care management influencing PPP adherence for oral retinoids • Overall level of knowledge and awareness of actions to take when WCBP intends to or becomes pregnant while using oral retinoid therapy • Perception of oral retinoid therapy PPP measures (from their perspective, and from the perspectives of WCBP as per their own experiences) • Details on how HCPs assess if WCBP are able to understand the information about PPP measures received and how confident HCPs are about WCBP's ability to understand • Perceived role in adherence of PPP measures
Epidemiological assessment of healthcare professionals' thoughts about factors influencing PPP adherence,	Phase 2: Epidemiological assessment	• To describe the aspects of the oral retinoid therapy PPP measures that are challenging and not challenging in understanding for HCPs	• Current adherence to PPP measures when prescribing/dispensing oral retinoid therapy

including local, systemic and administrative and policy related barriers/facilitators	Phase 4: Administrative and policy assessment and intervention alignment Phase 8: Outcome evaluation	• To describe HCPs' perceptions of oral retinoid therapy PPP measures, from their perspective and the WCBP's perspectives • To describe the extent to which HCPs perceive WCBP (adult or adolescent) adhere to the type and frequency of oral retinoid therapy PPP measures, per oral retinoid therapy type including use of effective contraception and mandated regular interval repeated pregnancy testing • To describe the challenges HCPs perceive in adhering to oral retinoid therapy PPP measures based on WCBP personal and environmental characteristics, organizational characteristics, communications and coordination with other HCPs, and oral retinoid therapy intervention characteristics • To describe the transparency HCPs believe adolescent WCBP have with their parents in being sexually active and whether different clinical encounters strategies are implemented to ensure adherence to PPP measures (e.g., individual clinical encounter, etc) • To describe the HCPs experiences of a WCBP becoming pregnant or being pregnant while on oral retinoid therapy, the aspects of the PPP measures that were either not understood or not possible to implement, and potential solutions for prevention in the future	• Perceptions from HCPs of WCBP behavioural factors leading to low adherence to PPP measures when prescribing/dispensing oral retinoid therapy • Perception from HCPs of WCBP behavioural factors enabling to high adherence to PPP measures when prescribing/dispensing oral retinoid therapy • Intent to abide by PPP measures • HCPs perception of parents' sense of appropriateness, need to abide to PPP measures • HCPs perceptions of transparency about adolescent WCBP's sexually active status and how it influences adherence to PPP measures • Environmental factors (i.e., clinical setting, organizational factors) leading to low adherence to PPP measures when prescribing/dispensing oral retinoid therapy • Modifiable risk factors to adherence to PPP measures (from HCP, organizational, and WCBP´s perspectives) • Local policies and resources for PPP measures • Systemic factors influencing implementation of PPP measures • Systemic barriers to implementation of PPP measures • Current adherence to PPP measures when using oral retinoid therapy • Challenges in adhering to oral retinoid therapy PPP measures based on personal characteristics, experiences with WCBP, oral retinoid therapy intervention characteristics, and person's environmental characteristics

Assessment of information provided to WCBP and opinion about HCPs role of educating them	Phase 3: Educational and ecological assessment	• To describe the content and the format of communication given to WCBP (adult or adolescent) and parents of adolescent WCBP about the oral retinoid therapy PPP measures at the time of prescription, dispensing, and termination (if applicable) of oral retinoid therapy (e.g., educational material given, in which format, reminders given, pregnancy testing communication given, etc.) • To describe the HCPs' perceptions of their role in WCBP adhering to PPP measures • To describe HCPs' perceptions of the parents' opinion of the suitability of PPP measures to be applied in adolescent WCBP	• Details of communication given to WCBP about oral retinoid therapy PPP measures (e.g., types of HCPs involved, content) • Frequency of communication given to WCBP about oral retinoid therapy PPP measures • Reaction to communication received from WCBP/parents • Aspects of communication given about PPP measures unclear to the HCP or from HCPs' perspectives to WCBP/their parents • Hesitance from WCBP to discuss and review some or all aspects of oral retinoid therapy PPP measures with HCPs from HCPs' perspectives • Aspects of communication given about PPP measures promoting low adherence to oral retinoid therapy PPP • Format of communication given about PPP measures promoting high adherence to oral retinoid therapy PPP
Thoughts about implementation of PPP communication measures, thoughts about their value, impact/outcomes and evaluation of benefit	Phase 5: Implementation Phase 6: Process evaluation Phase 7: Impact evaluation	• To identify the preferred ways for HCPs to communicate information on oral retinoid therapy PPP measures per WCBP type • To explore HCPs' opinions on existing measures to communicate or enhance adherence to current oral retinoid therapy PPP measures • To identify currently implemented and potential more effective ways to communicate oral retinoid therapy PPP needs to other HCPs involved in the WCBP's care; • For pharmacists (or any other relevant dispenser of oral retinoid therapy per local practice), to identify what barriers and	• Format of communication given to WCBP about oral retinoid therapy PPP measures (e.g., educational material received in paper or digital format, or QR code, video) • Preferred ways to access and/or give the information on the oral retinoid therapy PPP measures • Adherence to the type and frequency of oral retinoid therapy PPP measures from HCPs and WCBP perspectives • If WCBP have become pregnant or are pregnant while on oral retinoid therapy, aspects of the PPP measures that were not possible to implement (and estimated frequency of pregnancy whilst on oral retinoids) • Current communication/coordination processes between HCPs and action taken for adherence of PPP measures throughout continuity of care • Opinions on existing measures to communicate or enhance adherence to current oral retinoid therapy PPP measures

		facilitators in explaining the patient card to WCBP and ensure its content is well understood • To identify potential ways to improve the dissemination of PPP information around oral retinoid therapies to WCBP and other HCPs; • To identify potential ways to improve adherence to PPP measures for oral retinoid therapies in WCBP and HCPs	• Potential ways to improve the dissemination of PPP information around oral retinoid therapies • Potential ways to improve adherence to PPP measures for the use of oral retinoid therapies • Potential ways to improve communication or coordination of PPP measures for oral retinoid therapies between HCPs throughout continuum of care • Reactions on currently implemented measures at the country level (e.g., France: use of videos or QR codes)

9.2.2.2.2 Topics to be interviewed with WCBP and parents of adolescents who are using or have recently used oral retinoid therapies

Table 5 summarises the phases of the PRECEDE-PROCEDE framework that will answer key study objectives aligned with WCBP experiences with oral retinoid therapy.

Table 5. Interview Topics for WCBP and Parents of Adolescents Who Currently or Recently Used Oral Retinoid Therapies

Discussion Guide sections	Phases of the PRECEDE-PROCEED	Specific objectives covered	Specific questions discussed

For adult women: Participant background **For parents and adolescent WCBP:** Parent or guardian/Adolescent background	Phase 1: Social assessment	○ **N/A**	• History of use of oral retinoids
For adult women: Social assessment of the participant's perception and knowledge about PPP measures **For parents and adolescent WCBP:** Social assessment of the parent's or guardian's perception and knowledge about PPP measures	Phase 1: Social assessment	• **For adult women:** ○ To understand the extent to which WCBP are aware of the oral retinoid therapy PPP measures, including use of effective contraception and mandated regular interval repeated pregnancy testing, (ideally monthly), before, during, and after oral retinoid therapy treatment (including 1 month to 3 years post-treatment when applicable) ○ To describe the understanding of WCBP of measures to take when intending to or becoming pregnant • **For parents and adolescent WCBP:** ○ To understand the extent to which parents are aware of the PPP measures associated with oral retinoids, including use of effective contraception and mandated regular interval	• Overall level of knowledge and awareness of actions to take when intending to or becoming pregnant while using oral retinoid therapy Perception of oral retinoid therapy PPP measures

		repeated pregnancy testing, before, during, and after oral retinoid therapy treatment ○ To describe the understanding, from the parents' perspective, of measures to take if their adolescent WCBP becomes pregnant	
For adult women: Epidemiological assessment of participant's willingness to follow PPP measures and thoughts about their adequacy **For parents and adolescent WCBP:** Epidemiological assessment of adolescent of childbearing age (and parents or guardians) willingness to follow PPP measures and thoughts about their adequacy	Phase 2: Epidemiological assessment Phase 4: Administrative and policy assessment and intervention alignment Phase 8: Outcome evaluation	• **For adult women:** ○ To describe the aspects or the oral retinoid therapy PPP measures that are challenging and not challenging to understand ○ To assess WCBP perceptions of the oral retinoid therapy PPP measures ○ To describe WCBP's perceptions of their role in adhering to PPP measures ○ To describe the extent to which WCBP adhere to the type and frequency of oral retinoid therapy PPP measures including use of effective contraception and mandated regular interval repeated pregnancy testing ○ To describe the challenges in understanding and adhering to oral retinoid therapy PPP measures based on personal	• Current adherence to PPP measures when using oral retinoid therapy • Behavioural factors leading to low adherence to PPP measures when using oral retinoid therapy • Behavioural factors enabling to high adherence to PPP measures when using oral retinoid therapy • Intent to abide to PPP measures • For parents: appropriateness, need to abide to PPP measures • Environmental factors (i.e., living situation, access to healthcare, etc.) leading to low adherence to PPP measures when using oral retinoid therapy • Modifiable risk factors to adherence to PPP measures • Local policies and resources for PPP measures • Systemic factors influencing implementation of PPP measures • Systemic barriers to implementation of PPP measures • Current adherence to PPP measures when using oral retinoid therapy • Challenges in adhering to oral retinoid therapy PPP measures based on personal characteristics, experiences with HCPs, oral retinoid therapy intervention characteristics, and person's environmental characteristics • Hesitance to discuss and review some or all aspects of oral retinoid therapy PPP measures with HCPs

		characteristics, experiences with HCPs, oral retinoid therapy intervention characteristics, and person's environmental characteristics ○ To understand whether WCBP are hesitant to discuss and review some or all aspects of oral retinoid therapy PPP measures with their HCPs ○ If WCBP have become pregnant or are pregnant while on oral retinoid therapy, describe what aspects of the PPP measures were not possible to implement • **For parents and adolescent WCBP:** ○ To describe the aspects or the oral retinoid therapy PPP measures that are challenging and not challenging for parents to understand ○ To assess parents' and their adolescent's perceptions of the oral retinoid therapy PPP measures ○ To describe the parent and their adolescent's perceptions of their role in adhering to PPP measures ○ To describe the parents' perception of the suitability of	• Perceived role in adherence of PPP measures • Perceived confidence in their ability to follow the PPP measures as they were explained • For parents: Transparency about adolescent WCBP's sexually active status • If pregnant whilst on oral therapy treatment, aspect of PPP measure challenging to adhere to

		PPP measures to be applied in adolescent WCBP ○ To describe the extent to which parents perceive their adolescent WCBP adheres to the type and frequency of oral retinoid therapy PPP measures including use of effective contraception and mandated regular interval repeated pregnancy testing ○ To describe the challenges in adhering to oral retinoid therapy PPP measures based on personal characteristics, experiences with HCPs, oral retinoid therapy intervention characteristics, and person's environmental characteristics ○ To describe the transparency between parents and their adolescent WCBP in communicating if they are sexually active and needing to adhere to PPP measures ○ To understand whether parents or their adolescent WCBP are hesitant to discuss and review some or all aspects of oral retinoid therapy PPP measures with their HCPs ○ If their adolescent WCBP has become pregnant or is pregnant	

		while on oral retinoid therapy, describe what aspects of the PPP measures were not possible to implement, from the parent's perspective	

For adult women: Educational assessment of participant's perceptions of information received related to PPP measures
 	
For parents and adolescent WCBP: Educational assessment of parent's or guardian's and their adolescent's perceptions of information received related to PPP measures
	Phase 3: Educational and ecological assessment	• **For adult women:**
		  ○ To describe the content and the format of communication received about PPP measures by their HCPs at the time of prescription, dispensing, and termination (if applicable) of oral retinoid therapy (e.g., types of HCPs involved, educational material received in paper or digital format, reminders received, pregnancy testing communication received, etc.)
		• **For parents and adolescent WCBP:**
		  ○ To describe the content and the format of communication received by parents about PPP measures by their child´s HCPs at the time of prescription, dispensing, and termination (if applicable) of oral retinoid therapy (e.g., types of HCPs involved, educational material received in paper or digital format, reminders received, pregnancy testing communication received, etc.)
			• Details of communication received about PPP measures by their HCPs when they were prescribed/dispensed oral retinoid therapy (e.g., types of HCPs involved, content)
			• Frequency of communication received about PPP measures by their HCPs when they were prescribed/dispensed oral retinoid therapy
			• Format of communication received about PPP measures by their HCPs when they were prescribed/dispensed oral retinoid therapy (e.g., educational material received in paper or digital format, or QR code, video)
			• Preferred ways to access and/or receive the information on the oral retinoid therapy PPP measures
			• Reaction to communication received
			• Aspects of communication received about PPP measures unclear to the participants
			• Format of communication received about PPP measures unclear to the participants
			• Aspects of communication received about PPP measures promoting high adherence to oral retinoid therapy PPP
			• Aspects of communication received about PPP measures promoting low adherence to oral retinoid therapy PPP
			• Format of communication received about PPP measures promoting high adherence to oral retinoid therapy PPP
			• Format of communication received about PPP measures promoting low adherence to oral retinoid therapy PPP

For adult women: Participants' thoughts about implementation of PPP measures, thoughts about their value and evaluation of benefit
For parents and adolescent WCBP: Parent's or guardian's and their adolescent's thoughts about implementation of PPP measures, thoughts about their value and evaluation of benefit
	Phase 5: Implementation
	Phase 6: Process evaluation
	Phase 7: Impact evaluation
		• **For adult women:**
		  ○ To identify the preferred ways for WCBP to access and/or receive the information on the oral retinoid therapy PPP measures
		  ○ To identify potential ways to improve the dissemination of PPP information around oral retinoid therapies
		  ○ To identify potential ways to improve adherence to PPP measures for the use of oral retinoid therapies
		• **For parents and adolescent WCBP:**
		  ○ To identify the preferred ways for parents and their adolescent WCBP to access and/or receive the information on the oral retinoid therapy PPP measures
		  ○ To identify potential ways to improve the dissemination of PPP information around oral retinoid therapies
		  ○ To identify potential ways to improve adherence to PPP measures for the use of oral retinoid therapies
			• Adherence to the type and frequency of oral retinoid therapy PPP measures
			• If WCBP have become pregnant or are pregnant while on oral retinoid therapy, describe what aspects of the PPP measures were not possible to implement
			• Opinions on existing measures to communicate or enhance adherence to current oral retinoid therapy PPP measures
			• Potential ways to improve the dissemination of PPP information around oral retinoid therapies
			• Potential ways to improve adherence to PPP measures for the use of oral retinoid therapies
			• Reactions on currently implemented measures at the country level (e.g., France: use of videos or QR codes)

9.2.3 Interim and Final Qualitative Analyses

The goal of coding these data is to facilitate the identification of concepts regarding the understanding of and adherence to PPP measures that are most important and relevant to participants who use oral retinoid therapy. The coding process identifies and categorizes WCBP and HCP's expressions into concepts of relevance aligned with the established coding frame. Coders will review each transcript to identify text that includes concept expression data and tag selected text with individual codes.

The codes will be organized using overall categorization following the PRECEDE–PROCEED model phases which are established at the beginning of the coding process and refined/expanded during coding using a standardized dictionary of terms.

Both deductive and inductive approaches will be used.

The deductive coding approach allows researchers to apply findings from other phases of the research to the coding framework, based on the topics included in the discussion guide. The deductive coding framework will be developed using the standardized dictionary of terms which will then be adapted to the project as needed. This standardized dictionary is continually updated to reflect the most recent research conducted across all PCS projects and ensures consistency in qualitative data analysis.

On the other hand, inductive coding is a technique whereby codes are derived from the data as concepts and ideas naturally emerge during coding. This combined approach helps to ensure the coding structure necessary for the content analysis of this type of qualitative data. Further, it provides an opportunity to thematically analyse new concepts and ideas as they emerge spontaneously from the data.

Inter-coder agreement will be regularly assessed throughout the coding process and dual coding will take place on a 20% sample of transcripts, with any revised or new codes retroactively applied to already coded transcripts. In addition, code saturation will be assessed after each interview by comparing the codes and code's definitions (e.g., reasons for not adhering to PPP measures, preferred methods of communication) used and elicited during each interview, following analysis of the coding performed in MAXQDA 2022, to evaluate whether the number of interviews conducted is sufficient to comprehensively characterize the participants' experiences with PPP measures.

9.2.3.1 Code Saturation and Code Meaning

Saturation refers to the point in qualitative research where new data collection or analysis ceases to yield additional insights or information, indicating that the exploration of the research topic has reached a point of completeness (16). It signifies that researchers have thoroughly explored and understood the key concepts and themes related to their study. At this stage, the redundancy of information becomes apparent, and further data collection may not contribute substantially to the richness or depth of the findings.

Various definitions of saturation may be applicable depending on the qualitative study design, methodologies implemented and objectives (16).

Considering the coding methodology implemented in this study, saturation will be defined by the achievement of "code saturation" (14): this occurs when the codebook has stabilized, indicated by a low percentage or absence (<10% of total codes in the codebook) of new codes or changes to the code's definition.

Additionally, a "code meaning" (14) assessment will also be conducted to explore the dimensions contained within each of the codes of the codebook. "Code meaning" will be monitored by compiling the various individual meanings reported by participants during the interviews attributed to the codes used. In this approach, from the coding of the initial interview, and throughout subsequent interviews, new aspects, dimensions, or nuances of already documented codes will be captured and summarized, according to the participant-reported experiences, thoughts and opinions. The "code saturation" and "code meaning" approaches are further in the Qualitative Analysis Plan (Annex 4. Qualitative Analysis Plan) to present how these will be performed to monitor saturation related to the experiences of participants recruited from different countries and to the experiences of adult WCBP and parents, guardians or legal caregivers of adolescent WCBP using different oral retinoids.

9.2.3.2 Interim Analysis and go/no-go decision

Interim analysis will be conducted after 50% of the total planned interviews have been completed (per country and molecule)[2].

The interim analysis will seek to evaluate whether the study sample sizes are adequate for reaching code saturation among participants recruited from each of the four study countries (France, Germany, Poland and Spain) and between the three oral retinoid molecules (isotretinoin, acitretin, and alitretinoin) used by adult WCBP and two oral retinoid molecules used by adolescent WCBP (isotretinoin and acitretin). A decision to expand recruitment to potential additional regions of Europe and/or increasing samples for specific oral retinoids will be taken based on the interim analysis' findings.

To assess the diversity and representativeness of experiences reported across European countries, the challenges and barriers of adhering to PPP measures highlighted by adult WCBP and parents, guardians or legal caregivers of adolescent WCBP from each of the four study countries (France, Germany, Poland and Spain) will be described and compared between the study sample. Participants will also be asked to rank the top five most important

[2] The interim analysis and reporting is planned to take place between October to December 2025, as described in section 6.

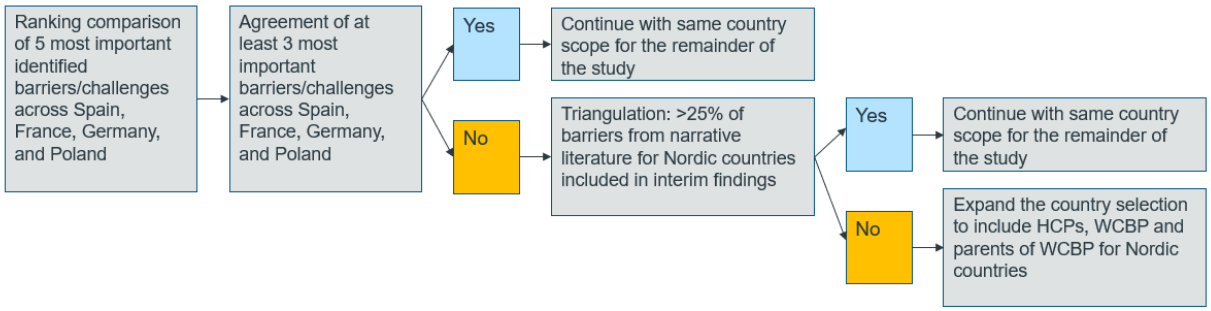
barriers and challenges to adhering to PPP measures according to their experience which will further serve as basis to assess cross-country and region similarities and/or differences.

This ranking will serve as the main basis to assess cross-country and region similarities and/or differences. A comparison of the most important barriers/challenges with a cut-off score of three common barriers will be used to conclude sufficient similarities between geographical scope. That is, if amongst the five most important barriers and challenges identified, at least three are common to the four included study countries (France, Germany, Poland and Spain), it will be concluded that there are similarities that are sufficient amongst the countries included in the scope of the study to prevent the need to add an additional country for the subsequent portion of the study.

If this is not the case, triangulation of the qualitative findings related to barriers/challenges ranked by participants with existing literature (either peer-reviewed or from reports or assessments performed by institutional country agencies) identified following a narrative review of barriers to adhering to PPP measures highlighted by adult WCBP and parents, guardians or legal caregivers of adolescent WCBP in the Nordic/northern European regions will be performed. The triangulation will seek to confirm if the diversity of the qualitative findings collected is able to cover known barriers and challenges to adhering to PPP measures previously identified in northern European countries.

If the most important barriers identified compare across all included countries, no additional country will be included for the subsequent portion of the study. If this is not the case, a recruitment strategy including samples representative from other European regions (e.g. Nordic countries) will need to be considered. Additional details are presented in the Qualitative Analysis Plan (Annex 4. Qualitative Analysis Plan). The decision-making plan for assessing if the study data is representative of the diversity of barriers/challenges reported across European regions, including northern Europe, is presented in **Figure 3**.

Figure 3. Decision flow for conclusions on the representativeness of the diversity of barriers/challenges reported across European regions



Similarly, to assess the consistency of barriers and challenges to adherence between the three oral retinoid molecules (isotretinoin, acitretin, and alitretinoin) used by adult WCBP and two oral retinoid molecules used by adolescent WCBP (isotretinoin and acitretin), code

saturation between molecules will be assessed and compared. The interim analysis will involve the coding of the transcripts and assessment of code saturation and code meaning, as described in section 9.2.3.1. Reviewing the frequency and consistency of codes to determine if new codes continue to emerge or if the existing codes sufficiently capture the data will determine whether additional samples for specific molecules (e.g. acitretin) will need to be increased to achieve code saturation per molecule. Additional details are presented in the Qualitative Analysis Plan (Annex 4. Qualitative Analysis Plan).

The results of the interim analysis will be documented in an interim report, which will include a summary of the data collected to date, an assessment of code saturation, and recommendations for any adjustments to the study protocol. The interim analysis will ensure that the study remains on track to achieve its objectives and that the data collected is robust and comprehensive. The interim analysis report will be shared with the Reference Member State (RMS) for review.

9.3 Data Management

The study will be conducted according to the Standard Operating Procedures (SOPs) of IQVIA's Patient Centered Endpoints, IQVIA's Global Perspectives, and IQVIA's Primary Intelligence's teams. A study database will be created by merging the study screener databases of each country.

Participant responses to the screener will be documented in the screening tracker, while responses to interview questions will be captured through audio recordings. Subsequently, audio files will undergo verbatim transcription and all interview transcripts will be deidentified. Deidentified transcripts in languages other than English will be translated into English, ensuring the removal of any identifiable data before utilization in data analysis. Data will be transferred using MoveIT and a secure data storage platform that is only accessible to assigned study team members, called Elvis.

Transcripts will be systematically generated and quality-controlled by trained transcriptionists. At this stage, any personally identifying data within recorded interviews will be removed. Transcriptions may also be masked, signifying personal-level data where named information is obscured, concealed, or eliminated in alignment with consented research. In cases where portions of the transcript are marked as "inaudible" or "unable to be understood," IQVIA researchers will review the audio files to rectify these sections, maintaining the data integrity of the transcript.

Audio recordings, masked screening tracker, codebook, informed consent forms (ICFs), and transcripts will be securely stored with access controls. Results from the interviews will be summarized in a report, potentially featuring exemplary quotes, with the assurance that no identifiable data will be disclosed.

9.3.1 Storing and Archiving of Data

The MAHs must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, documentation of EC and governmental approval/notification (if required) and study reports.

Records and documents pertaining to the conduct of this study will be retained in an access-controlled file for five years for named data and 15 years for masked data from the end of the study. The length of storage can be modified based on MAH-specific SOPs or storage requirements of relevant national or local health authorities to meet the requirement for document retention, whichever is longer. After that period, the documents may be destroyed, subject to local regulations.

9.4 Protection of Human Subjects

The qualitative study is non-interventional and totally anonymous to the study sponsor. Data collected will remain confidential. Only aggregated data will be analysed and communicated in a report. The study will be conducted in agreement with the regulation (EU) 2016/679 of the European Parliament on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation).

9.4.1 Information on survey participants and informed consent

WCBP, parents of WCBP, and HCPs participating in the qualitative interviews will be informed about the targets of the investigation, the nature of the transmitted data, the intended use of data, recipients of these data, and their right of access and rectification to their personal data, as well as their right of objection to use their data or to IQVIA keeping their data.

IQVIA will ensure that the national and European data protection and ethical requirements are met for WCBP, parents of WCBP, and HCPs. This will be done electronically.

9.4.2 Independent ethics committee/institutional review board

9.4.2.1 Ethical principles, laws and regulations

The qualitative study will follow the regulatory and ethical requirements of each country. The survey will comply with the module VIII of the good pharmacovigilance practices (GVP).

IQVIA will follow the European Pharmaceutical Marketing Research Association (EphMRA) code of conduct guidelines for all countries (EphMRA 2013).

HCPs, WCBP and parents, guardians and caregivers of WCBP participating in the study will also have to consent for data collection and need to be informed about the purpose of the qualitative study and their storage of data. IQVIA will make sure that the national and European data protection and ethical requirements are met for all study participants.

Any substantial protocol revisions will be communicated to the ethics committees for review and approval. A protocol change intended to eliminate an apparent immediate hazard (e.g., mainly discomfort) to participants may be implemented immediately, provided the MAHs and the reviewing IRB are notified within 10 working days.

It is the acknowledged responsibility of the IQVIA project director to provide each participant with full and adequate information using IRB-approved language related to informed consent, including the objective and procedures of the study and the possible risks involved, prior inclusion in the study.

9.4.2.2 Potential risks and discomfort

There are no expected physical risks or impact in regular medical care to participants as a result of involvement in this study.

There may be non-physical risks associated with taking part in this study, such as:

- The risk of accidental disclosure of personally identifiable medical information;
- It is possible that some of the questions asked during the study could make participants feel uncomfortable or embarrassed;
    - As a result, participants will be informed that they may decline to answer any of the questions and can decide to stop participating in the study at any time. They will also be informed that they can ask any questions about the study at any time. Participants will be encouraged to notify the moderator or IQVIA project director if they feel uncomfortable or upset during the interview process.

9.4.2.3 Financial disclosure

Study participants will be offered a compensation for the time spent participating in this qualitative study, if permitted by local regulations. The amount of this compensation will be in line with laws like the European Federation of Pharmaceutical Industries and Associations Disclosure Code, and determined according to the EphMRA recommendations and the Association of Opinion and Behaviour in health field research companies charter, which states:

"When it is necessary to compensate a HCP in return to the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly taken by the HCP for his/her advice or consultation and must be proportional to the time provided. The compensations should be clearly stated prior to the HCPs' participation in the survey. They must be declared to the tax authorities in accordance with applicable laws."

9.4.3 Safety and Adverse Events Reporting

Throughout the course of the study, every effort will be made to remain alert to suspected Adverse events (AEs) by following the Guideline on good pharmacovigilance practices (GVP) Module VI (17). All study personnel will be trained in Special Situations, AE and Serious Adverse Events (SAEs) reporting, using British Healthcare Business Intelligence Association or European Pharmaceutical Market Research Association pharmacovigilance training. As per GVP Module VI, all safety observations made during the conduct of the study, if any, will be summarized in the final study report.

9.4.3.1 Definitions

Day zero: The clock for the submission of a valid adverse event begins as soon as the interview moderator becomes aware of information containing the minimum reporting criteria. This date should be considered day zero (Day 0), marking the first day when an interview moderator becomes aware of an adverse event, regardless of whether the information is received during a weekend or public holiday. Submission timelines are based on calendar days.

Causality: Causality in GVP refers to the likelihood that a drug is responsible for an adverse event. Causality assessment involves evaluating the temporal relationship between drug exposure and the onset of the event, the biological plausibility of the event being caused by the drug, the presence of alternative explanations, any dose-response relationship, consistency with known drug effects, exclusion of other potential causes, and expert judgment.

9.4.3.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

9.4.3.1.2 Serious Adverse Event

A Serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is a medically important event

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

9.4.3.1.3 Special Situations

Specific situations that need to be reported whether or not there is an associated AE.

These include:

- Exposure through a parent, i.e., drug exposure to a foetus in utero (whether the foetus is exposed because the mother took the product during pregnancy or transmission from semen following the father's exposure to the product)
- Use of a medicinal product during pregnancy or breastfeeding
- Reports of overdose, abuse, misuse, medication error (including dispensing errors, accidental exposure, maladministration, etc.)
- Lack of therapeutic efficacy including suspected use of counterfeit/falsified medicines/tampering
- Unapproved, or off-label use of a product i.e., intentional medical use that doesn't comply with the authorised product information (including off-label use in children or the elderly)

- Withdrawal syndrome
- Drug-drug or drug-food interactions
- Suspected transmission of an infectious agent (e.g., transmission of HIV from plasma products)
- Occupational exposure (as a result of one's professional or non-professional occupation)

9.4.3.2 Monitoring and Recording Events / Special Situations

Any event or a special situation listed above experienced by the subject and mentioned during the qualitative interview will be recorded by the moderator, regardless of the severity of the event or its relationship to study treatments. In the instance of an event or a special situation listed above, the moderator will collect the name of the active substance and/or commercial name of the oral retinoid mentioned in the interview, the event or the special situation, and will report to IQVIA's Pharmacovigilance (PV) team right after the end of the interview via the IQVIA's electronic Adverse Event Reporting System. IQVIA's PV team will be responsible for notifying the relevant MAH's PV team within one working day. If no brand name available, it will be sent to all MAHs with active marketing authorization in the corresponding country.

The concerned MAHs will be responsible to classify whether a reported event / situation is an AE or SAE reported and will be able to follow-up directly with the participant who reported the event/situation if the participant agreed to waive their confidentiality for this specific purpose. If the participant did not waive their confidentiality, IQVIA will perform a maximum of two attempts of contact per participant for any required follow-up on safety information. The MAHs will forward the safety reports they will receive to the concerned health authorities according to the applicable regulations.

In addition, participants are reminded to report adverse drug reactions (ADRs) associated with the use of a specific product of the involved MAHs or isotretinoin, alitretinoin or acitretin to the concerned competent authorities, according to national requirements. WCBP and parents, guardians or caregivers of adolescent WCBP are reminded to report ADRs associated with the use of these products to their treating physician. Study respondents will be provided with a CIOMS (Council for International Organizations of Medical Sciences) form as well as instructions on how to report such events.

9.4.3.2.1 Handling in Case of Someone Reports Active Thoughts of Harm

In the event that a participant reports active thoughts of harm to themselves or others, the moderator will provide information about the suicide hotline in their country if applicable. Additionally**,** the participant will be encouraged to consider contacting emergency services or going to the local emergency room. This event will be considered as an adverse event (AE) and will be reported to the respective MAH's Pharmacovigilance team, as specified in

Section 9.4.3.2. If the brand name is not available, the report will be sent to all MAHs with active marketing authorization in the corresponding country.

9.4.3.2.2 Confidentiality

All data collected in this study will be strictly confidential per local, state, federal, and international law. Personnel from the following organizations may examine the research study records: IQVIA, representatives of the Sponsor or its collaborators, and regulatory agencies (e.g., EMA).

The confidentiality of records identifying participants will be maintained in the following manner:

- For all personal data that may be collected by IQVIA, IQVIA will house ICFs and contact information in an access-controlled project folder on its secure server for five years for named data and 15 years for masked data from the end of the study. Trained IQVIA team members will be responsible for collecting and storing these data separately from masked study data.

Study data will be maintained in the following manner:

- IQVIA project team members will assign each consented participant a unique case ID number and retain a record maintaining the link between the case ID and participant contact information. The IQVIA project team and staff involved in recruitment will know the identity of participants.
- Participant responses to study questions (i.e., study data) will be housed in an access-controlled project folder that will not contain any personally identifying information and will be stored separately from participant-identifying information.
- Transcripts will be reviewed before analysis to remove personal identifiers that may have been inadvertently mentioned by the patient during the interview. Transcripts with masked data will be stored with other study data, in access-controlled files on secure IQVIA servers.

Recruiters or site staff, vendors who issue payment, and online form programmers will have access to participant-identifying information; however, they will not have access to participant interview responses. Transcribers will have access to interview responses; however, they will not have access to participant-identifying information.

Study-related records identifying patients will be kept confidential and, to the extent permitted by applicable laws and/or regulations, will not be made publicly available. A Sponsor representative (e.g., monitor or auditor), IRB, and/or other regulatory authorities may also have access to masked study-related records. IQVIA will comply with all state /

local laws as applicable. If any results of the study are published for scientific purposes, participants' identities will remain confidential.

9.4.4 Bias

The study acknowledges several potential sources of bias that could affect the robustness of the findings. Volunteer participation introduces the possibility of selection bias among participants, as those who choose to participate may have a higher awareness of the risks or sensitivities associated with PPP associated with oral retinoid use. To assess and quantify this bias, a thorough comparison of stratification criteria, including country, specialty, and demographic information, may be conducted between participants and non-participants, if possible, through the recruitment channel.

Non-response may be another consideration, particularly for HCPs with email filters or multiple email addresses. To mitigate this, alternate contact methods, such as phone calls, will be employed.

Social desirability bias may also affect qualitative interviews, where participants may provide responses, they perceive as socially acceptable rather than reflecting their true knowledge or behaviour.

The web-based nature of the study screener introduces limitations to invited participants, with each participant receiving a unique link and restricted to one participant. Despite these potential biases, the study employs various strategies to minimize their impact and enhance the reliability and validity of the collected data.

9.4.4.1 Generalizability Limitations Inherent to Qualitative Studies

The recruitment methodologies employed—specifically, direct-to-patient and via HCP referrals—limit participation to individuals who not only have an active email address but are also inclined to express interest through online communication. This subset of the population may not completely embody the diversity and breadth of experiences found in the full spectrum of the targeted population.

Furthermore, this study does not include adolescent WCBP aged 13–17 as participants due to the difficulties associated with obtaining ethical approval for this demographic. Instead, their parents, guardians, or caregivers will be interviewed. While this approach provides valuable insights, it inherently comes with the limitation that these adults may hold different views and perspectives than the adolescents they represent, which could affect the applicability of findings to the actual experiences and needs of the adolescent patients.

Additionally, it is highlighted that acitretin and alitretinoin are not prescribed as commonly as isotretinoin. Yet, it is noted that the former are prescribed more frequently to the older segment of WCBP. As such, to capture a broader range of experiences with these drugs, a specific focus group of older WCBP aged 35 to 49 years has been designated to target the patient population using acitretin and alitretinoin. It is anticipated that this will unveil diverse perceptions of the PPP, although variations are expected among older WCBP with different prescription patterns for acitretin or alitretinoin. These factors must be taken into account when considering the generalizability of the study results across oral retinoids in this study.

9.5 Strengths of the Research Methods

9.5.1 Leveraging the OneKey Database for Comprehensive Insights

This qualitative study takes advantage of the OneKey database, recognized for its continuous updates and proactive maintenance of HCPs information. Rigorous quality controls uphold the reliability of the *OneKey* content, positioning it as a globally comprehensive and up-to-date resource for engaging with a diverse spectrum of HCPs. Utilizing this database minimizes potential bias linked to voluntary participation, employing a systematic contact strategy by reaching out to batches of HCPs up to five times before moving on to others in the lists. This systematic approach proves particularly beneficial in qualitative research, facilitating the capture of a diverse array of perspectives.

9.5.2 Use of Implementation Sciences Supporting the Interview Findings

The qualitative interview semi-structured discussion guide is meticulously crafted using the PRECEDE-PROCEED framework, tailored to the study's objective to capture the most pertinent information. This strategic design ensures that the questions are thoughtfully structured, allowing for a comprehensive exploration of the topics under investigation.

9.5.3 Clarity Checks and Bias Mitigation Measures in Discussion Guide

Prior to commencing the interviews, the discussion guide undergoes thorough testing by Qualitative Researchers and Patient Centered Scientists for clarity, reducing ambiguity and enhancing respondent understanding. Special attention is dedicated to identifying and addressing questions that might inadvertently imply specific answers, especially concerning social desirability bias. These methodological strengths collectively contribute to the reliability and richness of insights garnered in the qualitative study, enhancing the overall quality and validity of the research findings.

10. Protection of Human Subjects

This study is non-interventional, ensuring the anonymity of participants to the study sponsor. All data collected will be treated with the utmost confidentiality, and only

aggregated data will be analysed and communicated in the final report. The study will strictly adhere to the regulations outlined in (EU) 2016/679 of the European Parliament, known as the General Data Protection Regulation (GDPR).

11. Plans for Disseminating and Communicating Study Results

The study will be registered in the EU PAS register (currently the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) e-register of studies) by either the lead MAH of the oral retinoids consortium or IQVIA. Study results will be publicly accessible after the study's conclusion.

11.1 Final Analyses and Reporting

The findings will be documented in a comprehensive qualitative report written in English using an IQVIA template in MS Word format. The final report will undergo validation by the MAHs of the oral retinoids consortium and will be submitted to the EMA by the lead MAH unless an alternative procedure is mandated by the regulations of the participating country. Communication with other drug safety agencies will be coordinated by the lead MAH unless otherwise specified. A synopsis of the study results will also be entered into the ENCePP database (EU PAS register) and the HMA-EMA Catalogues for real-world data sources post-approval by the MAHs of the oral retinoids consortium.

11.2 Publications

Any dissemination of the study results through publications will adhere to the guidelines outlined in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010. The publication process will ensure consistency and adherence to established standards for biomedical journal submissions, reflecting the commitment to transparent and rigorous reporting of the study's outcomes.

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13. APPENDIX

13.1 Appendix 1. List of potential causes for infertility in women

According to the National Health Service in the United Kingdom and the National Institutes of Health in the United States of America, causes of infertility may include, but are not limited, to:

- Polycystic ovary syndrome
- Thyroid problems
- Premature ovarian failure
- Fallopian tube or cervix scarring due to surgery
- Uterine fibroids
- Cervical mucus problems
- Endometriosis
- Pelvic Inflammatory disease
- Primary Ovarian Insufficiency
- Autoimmune disorders, including lupus, Hashimoto's, thyroiditis or rheumatoid arthritis
- Use of some medicines, including non-steroidal anti-inflammatory drugs, chemotherapy, neuroleptic medications, spironolactone
- Sterilisation

13.2 Appendix 2. Stepwise identification and sample boosting approach

To achieve methodological robustness in terms of the assessment of saturation of the insights reported during the interviews, a stepwise mitigation approach was developed for the recruitment and identification of participants using oral retinoids. This approach considers the following channels:

1. IQVIA's in-house Direct-to-Patient Recruitment channel
    a. IQVIA's in-house Direct-to-Patient recruitment channel will assist with identifying WCBP
    b. IQVIA's in-house recruitment channel will help identify WCBP and their parents for a study
    c. Recruitment will be done through various sources such as patient and caregiver databases, social media, local patient associations, and direct clinician contact. The study will be promoted through diverse channels like email newsletters, recruitment flyers, and social media posts
    d. Potential participants will be screened online or verbally via telephone. If eligible, they will be sent a link to an online informed consent
    e. Once a participant qualifies and consents, IQVIA's in-house Direct-to-Patient Recruitment channel will collect their personal information and schedule an interview with IQVIA's Patient Centred Endpoints Research team
    f. As an example for the activation of the next mitigation sample boosting approach, if the team are unable to identify 50% of the minimum alitretinoin sample after the fourth week of recruitment, then the team will move to step 2
2. Extended outreach for HCP-mediated referrals and other sources
    a. As a contingency plan, recruitment through additional HCP referrals may be considered for certain countries
    b. Additional HCPs and clinics will be contacted by IQVIA's in-house Direct-to-Patient Recruitment channel, who will provide them with recruitment materials to help identify potential participants
    c. These HCPs will review screening information and share it with WCBP or their parents who may qualify for the study. Eligible WCBP who express interest in participating and who contact the recruitment team will self-refer to the study and receive a link to an online informed consent form and their preferred interview times will be noted if they agree to participate

   d. The involved HCPs will receive a fixed payment for their time, in line with fair market values; reconsideration of the amount for the fixed payments may be considered[3]. HCPs will not be paid per patient recruited.
   e. Other recruitment channels, including social media and patient advocacy groups may be extended and further considered.
   f. As an example for the activation of the next mitigation sample boosting approach, if the team are unable to identify 50% of the alitretinoin minimum sample by the 16th week of recruitment, the team will move onto step three.
3. Extension of the study's inclusion criteria or extension of study to other market[3]
   a. An extension of the criterion for having used oral retinoids in the last 6 months may be extended to 12 months (or up to 24 months).
   b. Extension of the study to other markets where oral retinoids are marketed may be considered
   c. As an example for the activation of the next mitigation sample boosting approach, if the team are unable to identify 75% of the alitretinoin minimum sample by the 12th week of recruitment, the team will move onto step four.
4. Country re-distribution[3]
   a. Country-specific WCBP samples may be redistributed to the other countries under study, depending on the feasibility of identifying and recruiting patients using alitretinoin.
   b. As an example for the activation of the next mitigation sample boosting approach, if after six months following the start of the recruitment the overall alitretinoin sample is not achieved, the team will implement step five.
5. Clinical vignettes (specific to alitretinoin)
   a. Hypothetical perceptions of the PPP measures for alitretinoin will be explored based on isotretinoin vignette descriptions of PPP measures.
      i. Their hypothetical views on the Pregnancy Prevention Programme (PPP) measures for alitretinoin will then be investigated using scenario-based descriptions of these measures.

14. ANNEX

14.1 Annex 1: List of medicinal products per country

MA Holder Name(s)	Member State	Product Name (in authorisation country)	Active Substance
2care4 Generics ApS	Norway	Isotracin 10 mg myke kapsler	Isotretinoin
2care4 Generics ApS	Norway	Isotracin 20 mg myke kapsler	Isotretinoin
2care4 Generics ApS	Sweden	Isotracin 10 mg mjuka kapslar	Isotretinoin
2care4 Generics ApS	Sweden	Isotracin 20 mg mjuka kapslar	Isotretinoin
2care4 Generics ApS	Denmark	Isotracin, bløde kapsler	Isotretinoin
2care4 Generics ApS	Denmark	Isotracin, bløde kapsler	Isotretinoin
Actavis Group PTC ehf	Denmark	Isotretinoin Actavis	Isotretinoin
Actavis Group PTC ehf	Denmark	Isotretinoin Actavis	Isotretinoin
Actavis Group PTC ehf	Finland	Isotretinoin Actavis 10mg kapseli, pehmeä	Isotretinoin
Actavis Group PTC ehf	Finland	Isotretinoin Actavis 20 mg kapseli, pehmeä	Isotretinoin
Actavis Group PTC ehf	Hungary	Inerta 10 mg lágy kapszula	Isotretinoin
Actavis Group PTC ehf	Hungary	Inerta 20 mg lágy kapszula	Isotretinoin
Actavis Group PTC ehf	Sweden	Isotretinoin Actavis	Isotretinoin
Actavis Group PTC ehf	Sweden	Isotretinoin Actavis	Isotretinoin

Actavis Group PTC ehf	Hungary	Neotigason 10 mg kemény kapszula	Acitretin
Actavis Group PTC ehf	Hungary	Neotigason 25 mg kemény kapszula	Acitretin
Actavis Group PTC ehf	Poland	Neotigason	Acitretin
Actavis Group PTC ehf	Poland	Neotigason	Acitretin
Actavis Group PTC ehf	Sweden	Neotigason	Acitretin
Actavis Group PTC ehf	Sweden	Neotigason	Acitretin
Alfasigma España, S.L.	Spain	MAYESTA 10 MG CÁPSULAS BLANDAS	Isotretinoin
Alfasigma España, S.L.	Spain	MAYESTA 20 MG CÁPSULAS BLANDAS	Isotretinoin
Almirall Hermal GmbH	Czech Republic	Aknenormin (isotretinoin) 10 mg Měkké tobolky	Isotretinoin
Almirall Hermal GmbH	Czech Republic	Aknenormin (isotretinoin) 20 mg Měkké tobolky	Isotretinoin
Almirall Hermal GmbH	Germany	Aknenormin (isotretinoin) 10 mg Weichkapseln	Isotretinoin
Almirall Hermal GmbH	Germany	Aknenormin (isotretinoin) 20 mg Weichkapseln	Isotretinoin
Almirall Hermal GmbH	Poland	Aknenormin (isotretinoin) 10 mg	Isotretinoin
Almirall Hermal GmbH	Poland	Aknenormin (isotretinoin) 20 mg	Isotretinoin
Almirall Hermal GmbH	Slovakia	Aknenormin (isotretinoin) 10 mg mäkké kapsuly	Isotretinoin

Almirall Hermal GmbH	Slovakia	Aknenormin (isotretinoin) 20 mg mäkké kapsuly	Isotretinoin
Aristo Pharma Sp. z o.o.	Poland	Axotret	Isotretinoin
Aristo Pharma Sp. z o.o.	Poland	Axotret	Isotretinoin
Aristo Pharma Sp. z o.o.	Poland	Isotretinoin Aristo	Isotretinoin
Aristo Pharma Sp. z o.o.	Poland	Isotretinoin Aristo	Isotretinoin
Aristo Pharma Sp. z o.o.	Poland	AXOTRET	Isotretinoin
Aristo Pharma Sp. z o.o.	Poland	AXOTRET	Isotretinoin
Arrow Génériques	France	ISOTRETINOINE ACNETRAIT 10 MG, CAPSULE MOLLE	Isotretinoin
Arrow Génériques	France	ISOTRETINOINE ACNETRAIT 20 MG, CAPSULE MOLLE	Isotretinoin
Arrow Génériques	France	ISOTRETINOINE ACNETRAIT 40 MG, CAPSULE MOLLE	Isotretinoin
Arrow Génériques	France	ISOTRETINOINE ACNETRAIT 5 MG, CAPSULE MOLLE	Isotretinoin
Arrow Génériques	France	SORIATANE 10 MG, GÉLULE	Acitretin
Arrow Génériques	France	SORIATANE 25 MG, GÉLULE	Acitretin
Aurobindo Pharma (Italia) S.r.l.	Italy	NEOTIGASON 25 mg capsule rigide	Acitretin
Aurobindo Pharma (Italia) S.r.l.	Italy	NEOTIGASON 10 mg capsule rigide,	Acitretin
Aurobindo Pharma B.V.	Netherlands	Isotretinoine Aurobindo 10mg, capsules	Isotretinoin
Aurobindo Pharma B.V.	Netherlands	Isotretinoine Aurobindo 20mg, capsules	Isotretinoin

Aurobindo Pharma B.V.	Luxembourg	Neotigason 10 mg gélules	Acitretin
Aurobindo Pharma B.V.	Luxembourg	Neotigason 25 mg gélules	Acitretin
Aurobindo Pharma B.V.	Netherlands	Neotigason 10 mg, capsules	Acitretin
Aurobindo Pharma B.V.	Netherlands	Neotigason 25 mg, capsules	Acitretin
Aurobindo Pharma N.V.	Belgium	Neotigason 10 mg harde capsules	Acitretin
Aurobindo Pharma N.V.	Belgium	Neotigason 25 mg harde capsules	Acitretin
Aurovitas Spain, S.A.U.	Spain	Neotigason 10 mg cápsulas duras	Acitretin
Aurovitas Spain, S.A.U.	Spain	Neotigason 25 mg cápsulas duras	Acitretin
BASICS GMBH, DE, LEVERKUSEN	Germany	ISOTRETINOIN BASICS 10 mg Weichkapseln	Isotretinoin
BASICS GMBH, DE, LEVERKUSEN	Germany	ISOTRETINOIN BASICS 20 mg Weichkapseln	Isotretinoin
Bausch Health Ireland Limited	Poland	Izotek	Isotretinoin
Bausch Health Ireland Limited	Poland	Izotek	Isotretinoin
Centrafarm B.V.	Netherlands	Acitretine CF 10 mg, capsules	Acitretin
Centrafarm B.V.	Netherlands	Acitretine CF 25 mg, capsules	Acitretin
Dermapharm AG	Germany	Alitrederm 10 mg Weichkapseln	Alitretinoin
Dermapharm AG	Germany	Alitrederm 30 mg Weichkapseln	Alitretinoin
Dermapharm AG	Germany	Acicutan 10 mg Hartkapseln	Acitretin

Dermapharm AG	Germany	Acicutan 25 mg Hartkapseln	Acitretin
Difa Cooper spa	Denmark	Isotretinoin Difa	Isotretinoin
Difa Cooper spa	Denmark	Isotretinoin Difa	Isotretinoin
Difa Cooper spa	Denmark	Isotretinoin Difa	Isotretinoin
Difa Cooper spa	Denmark	Isotretinoin Difa	Isotretinoin
Difa Cooper spa	Denmark	Isotretinoina Difa Cooper	Isotretinoin
Difa Cooper spa	Italy	Isotretinoina Difa	Isotretinoin
Difa Cooper spa	Italy	Zorias	Acitretin
Difa Cooper spa	Italy	Zorias	Acitretin
Difa Cooper spa	Italy	Isodifa	Isotretinoin
Difa Cooper spa	Italy	Isodifa	Isotretinoin
Difa Cooper spa	Italy	Isodifa	Isotretinoin
Difa Cooper spa	Italy	Isodifa	Isotretinoin
Difa Cooper spa	Italy	Isotretinoina Difa Cooper 10 mg capsule molli	Isotretinoin
Difa Cooper spa	Italy	Isotretinoina Difa Cooper 20 mg capsule molli	Isotretinoin
Difa Cooper spa	Italy	ALITRECARE	Alitretinoin
Difa Cooper spa	Italy	ALITRECARE	Alitretinoin

Especialidades Farmacéuticas Centrum, S.A.	Spain	Flexresan 10 mg cápsulas blandas	Isotretinoin
Especialidades Farmacéuticas Centrum, S.A.	Spain	Flexresan 20 mg cápsulas blandas	Isotretinoin
Eurogenerics N.V./S.A.	Belgium	Isotretinoine EG 10 mg capsules, zacht	Isotretinoin
Eurogenerics N.V./S.A.	Belgium	Isotretinoine EG 20 mg capsules, zacht	Isotretinoin
Eurogenerics N.V./S.A.	Luxembourg	Isotrétinoïne EG 10 mg capsules molles	Isotretinoin
Eurogenerics N.V./S.A.	Luxembourg	Isotrétinoïne EG 20 mg capsules molles	Isotretinoin
Fidia Farmaceutici S.p.A.	Italy	AISOSKIN	Isotretinoin
Fidia Farmaceutici S.p.A.	Italy	AISOSKIN	Isotretinoin
GALENpharma GmbH	Germany	IsoGalen 10 mg Weichkapseln	Isotretinoin
GALENpharma GmbH	Germany	IsoGalen 20 mg Weichkapseln	Isotretinoin
GALENpharma GmbH	Germany	Isogalen 10 mg	Isotretinoin
GALENpharma GmbH	Germany	Isogalen 20 mg	Isotretinoin
GAP S.A.	Austria	Isotretinoin GAP 5 mg Weichkapseln	Isotretinoin
GAP S.A.	Austria	Isotretinoin GAP 10 mg Weichkapseln	Isotretinoin
GAP S.A.	Austria	Isotretinoin GAP 20 mg Weichkapseln	Isotretinoin
GAP S.A.	Austria	Isotretinoin GAP 40 mg Weichkapseln	Isotretinoin

GAP S.A.	Germany	Isotretinoin GAP 10 mg Weichkapseln	Isotretinoin
GAP S.A.	Germany	Isotretinoin GAP 20 mg Weichkapseln	Isotretinoin
GAP S.A.	Ireland	Isotretinoin GAP 10 mg capsule, soft	Isotretinoin
GAP S.A.	Ireland	Isotretinoin GAP 20 mg capsule, soft	Isotretinoin
GAP S.A.	Portugal	Isotretinoina gap 10 mg €	Isotretinoin
GAP S.A.	Portugal	Isotretinoina gap 20 mg	Isotretinoin
GAP S.A.	Greece	REDUCAR	Isotretinoin
GAP S.A.	Greece	REDUCAR	Isotretinoin
Generis Farmacêutica, S.A.	Portugal	Isotretinoína Aurovitas	Isotretinoin
Generis Farmacêutica, S.A.	Portugal	Isotretinoína Aurovitas	Isotretinoin
Generis Farmacêutica, S.A.	Portugal	Isotretinoína Aurovitas	Isotretinoin
Generis Farmacêutica, S.A.	Portugal	Isotretinoína Aurovitas	Isotretinoin
Generis Farmacêutica, S.A.	Portugal	Neotigason	Acitretin
Generis Farmacêutica, S.A.	Portugal	Neotigason	Acitretin
Genus Pharmaceuticals Limited	United Kingdom (Northern Ireland)	Acitretin 10mg Capsules	Acitretin
Genus Pharmaceuticals Limited	United Kingdom (Northern Ireland)	Acitretin 25mg Capsules	Acitretin
GlaxoSmithKline GmbH & Co. KG	Germany	Toctino 10 mg weichkapseln	Alitretinoin
GlaxoSmithKline GmbH & Co. KG	Germany	Toctino 30 mg weichkapseln	Alitretinoin
GlaxoSmithKline oy, fi, espoo	Finland	Toctino 10 mg kapselit, pehmeä	Alitretinoin

GlaxoSmithKline oy, fi, espoo	Finland	Toctino 30 mg kapselit, pehmeä	Alitretinoin
GlaxoSmithKline Pharma GmbH.	Austria	Toctino 10 mg weichkapseln	Alitretinoin
GlaxoSmithKline Pharma GmbH.	Austria	Toctino 30 mg weichkapseln	Alitretinoin
GlaxoSmithKline Trading Services Ltd IE	Slovakia	Toctino 10 mg mäkké kapsuly	Alitretinoin
GlaxoSmithKline Trading Services Ltd IE	Slovakia	Toctino 30 mg mäkké kapsuly	Alitretinoin
GlaxoSmithKline Trading Services Ltd IE	Slovenia	Toctino 10 mg mehke kapsule	Alitretinoin
GlaxoSmithKline Trading Services Ltd IE	Slovenia	Toctino 30 mg mehke kapsule	Alitretinoin
GlaxoSmithKline, S.A.	Spain	Toctino 10 mg cápsulas blandas	Alitretinoin
GlaxoSmithKline, S.A.	Spain	Toctino 30 mg cápsulas blandas	Alitretinoin
Hexal AG	Denmark	Pharmiso	Isotretinoin
Hexal AG	Denmark	Pharmiso	Isotretinoin
Hexal AG	Germany	Isotret-HEXAL 10 mg Kapseln	Isotretinoin
Hexal AG	Germany	Isotret-HEXAL 20 mg Kapseln	Isotretinoin
Iasis Pharmaceuticals Hellas ABEE	Cyprus	ISOTROIN 10mg καψάκια μαλακά	Isotretinoin
Iasis Pharmaceuticals Hellas ABEE	Cyprus	ISOTROIN 20mg καψάκια μαλακά	Isotretinoin
Iasis Pharmaceuticals Hellas ABEE	Cyprus	ISOTROIN 40mg καψάκια μαλακά	Isotretinoin
Iasis Pharmaceuticals Hellas ABEE	Cyprus	Isotroin 30mg καψάκια μαλακά	Isotretinoin
Iasis Pharmaceuticals Hellas ABEE	Greece	ISOTROIN 10mg καψάκια μαλακά	Isotretinoin

Iasis Pharmaceuticals Hellas ABEE	Greece	ISOTROIN 20mg καψάκια μαλακά	Isotretinoin
Iasis Pharmaceuticals Hellas ABEE	Greece	ISOTROIN 40mg καψάκια μαλακά	Isotretinoin
Iasis Pharmaceuticals Hellas ABEE	Greece	Isotroin 30mg καψάκια μαλακά	Isotretinoin
IFC Skincare Portugal, Unipessoal Lda.	Portugal	Alitretinoína Cantabria 10 mg cápsulas moles	Alitretinoin
IFC Skincare Portugal, Unipessoal Lda.	Portugal	Alitretinoína Cantabria 30 mg cápsulas moles	Alitretinoin
Industrial Farmacéutica Cantabria, S.A.	Netherlands	Acitretine IFC 10 mg capsules	Acitretin
Industrial Farmacéutica Cantabria, S.A.	Netherlands	Acitretine IFC 25 mg capsules	Acitretin
Industrial Farmacéutica Cantabria, S.A.	Netherlands	Alitretinoïne IFC 10 mg zachte capsules	Alitretinoin
Industrial Farmacéutica Cantabria, S.A.	Netherlands	Alitretinoïne IFC 30 mg zachte capsules	Alitretinoin
Industrial Farmacéutica Cantabria, S.A.	Spain	Acitretina IFC 10 mg cápsulas duras EFG	Acitretin
Industrial Farmacéutica Cantabria, S.A.	Spain	Acitretina IFC 25 mg cápsulas duras EFG	Acitretin
Industrial Farmacéutica Cantabria, S.A.	Spain	Alitretinoína IFC 10 mg cápsulas blandas EFG	Alitretinoin
Industrial Farmacéutica Cantabria, S.A.	Spain	Alitretinoína IFC 30 mg cápsulas blandas EFG	Alitretinoin
Industrial Farmacéutica Cantabria, S.A.	Spain	Dercutane 5 mg cápsulas blandas	Isotretinoin

Industrial Farmacéutica Cantabria, S.A.	Spain	Dercutane 10 mg cápsulas blandas	Isotretinoin
Industrial Farmacéutica Cantabria, S.A.	Spain	Dercutane 20 mg cápsulas blandas	Isotretinoin
Industrial Farmacéutica Cantabria, S.A.	Spain	Dercutane 30 mg cápsulas blandas	Isotretinoin
Industrial Farmacéutica Cantabria, S.A.	Spain	Dercutane 40 mg cápsulas blandas	Isotretinoin
Isdin S.r.l.	Italy	Isdiben	Isotretinoin
Isdin S.r.l.	Italy	Isdiben	Isotretinoin
Isdin S.r.l.	Italy	Isdiben	Isotretinoin
Isdin S.r.l.	Italy	Isdiben	Isotretinoin
ISDIN SA	Spain	Acnisdin 10 mg cápsulas blandas EFG	Isotretinoin
ISDIN SA	Spain	Acnisdin 20 mg cápsulas blandas EFG	Isotretinoin
ISDIN SA	Spain	Acnisdin 40 mg cápsulas blandas	Isotretinoin
ISDIN SA	Spain	Isdiben 10 mg cápsulas blandas EFG	Isotretinoin
ISDIN SA	Spain	Isdiben 20 mg cápsulas blandas EFG	Isotretinoin
ISDIN SA	Spain	Isdiben 40 mg cápsulas blandas	Isotretinoin

Laboratoires Bailleul S.A.	Austria	Isotiorga 10 mg Weichkapseln	Isotretinoin
Laboratoires Bailleul S.A.	Austria	Isotiorga 20 mg Weichkapseln	Isotretinoin
Laboratoires Bailleul S.A.	Austria	Isotiorga 40 mg Weichkapseln	Isotretinoin
Laboratoires Bailleul S.A.	Belgium	Isotiorga 10 mg capsules molles / Isotiorga 10 mg Weichkapseln / Isotiorga 10 mg zachte capsules	Isotretinoin
Laboratoires Bailleul S.A.	Belgium	Isotiorga 20 mg capsules molles / Isotiorga 20 mg Weichkapseln / Isotiorga 20 mg zachte capsules	Isotretinoin
Laboratoires Bailleul S.A.	Czech Republic	Asotiorga	Isotretinoin
Laboratoires Bailleul S.A.	Estonia	Isotiorga	Isotretinoin
Laboratoires Bailleul S.A.	Germany	Isotiorga 10 mg Weichkapseln	Isotretinoin
Laboratoires Bailleul S.A.	Germany	Isotiorga 20 mg Weichkapseln	Isotretinoin
Laboratoires Bailleul S.A.	Greece	Isotretinoin/Bailleul 20 mg καψάκιο, μαλακό	Isotretinoin
Laboratoires Bailleul S.A.	Greece	Isotretinoin/Bailleul 40 mg καψάκιο, μαλακό	Isotretinoin
Laboratoires Bailleul S.A.	Hungary	Isotiorga 20 mg lágy kapszula	Isotretinoin
Laboratoires Bailleul S.A.	Italy	Isotiorga 10 mg capsule molli	Isotretinoin
Laboratoires Bailleul S.A.	Italy	Isotiorga 20 mg capsule molli	Isotretinoin
Laboratoires Bailleul S.A.	Luxembourg	Isotiorga 20 mg capsule molle	Isotretinoin

Laboratoires Bailleul S.A.	Portugal	Isotiorga 10 mg cápsulas moles	Isotretinoin
Laboratoires Bailleul S.A.	Portugal	Isotiorga 20 mg cápsulas moles	Isotretinoin
Laboratoires Bailleul S.A.	Romania	Isotiorga 10 mg capsule moi	Isotretinoin
Laboratoires Bailleul S.A.	Romania	Isotiorga 20 mg capsule moi	Isotretinoin
Laboratoires Bailleul S.A.	Slovakia	Isotiorga 20 mg mäkké kapsuly	Isotretinoin
Laboratoires Bailleul S.A.	Spain	Isotiorga 20 mg cápsulas blandas EFG	Isotretinoin
Laboratoires Bailleul S.A.	Spain	Isotiorga 40 mg cápsulas blandas	Isotretinoin
Laboratoires Bailleul S.A.	France	Contracne 10 mg, capsule molle	Isotretinoin
Laboratoires Bailleul S.A.	France	Contracne 10 mg, capsule molle	Isotretinoin
Laboratoires Bailleul S.A.	France	Contracne 10 mg, capsule molle	Isotretinoin
Laboratoires Bailleul S.A.	France	Contracne 20 mg, capsule molle	Isotretinoin
Laboratoires Bailleul S.A.	France	Contracne 20 mg, capsule molle	Isotretinoin
Laboratoires Bailleul S.A.	France	Contracne 20 mg, capsule molle	Isotretinoin
Laboratoires Bailleul S.A.	France	Contracne 40 mg, capsule molle	Isotretinoin
Laboratoires Bailleul S.A.	France	Contracne 5 mg, capsule molle	Isotretinoin
Laboratoires Bailleul S.A.	France	Contracne 5 mg, capsule molle	Isotretinoin
Laboratoires Expanscience	France	PROCUTA 10 mg, capsule molle	Isotretinoin
Laboratoires Expanscience	France	PROCUTA 20 mg, capsule molle	Isotretinoin

Laboratoires Expanscience	France	PROCUTA 40 mg, capsule molle	Isotretinoin
Laboratoires Expanscience	France	PROCUTA 5 mg, capsule molle	Isotretinoin
Laboratoires SMB S.A	Belgium	ISOSUPRA LIDOSE 16 MG HARTKAPSELN	Isotretinoin
Laboratoires SMB S.A	Belgium	ISOSUPRA LIDOSE 16 MG, CAPSULES, HARD	Isotretinoin
Laboratoires SMB S.A	Belgium	ISOSUPRA LIDOSE 16 MG, GÉLULES	Isotretinoin
Laboratoires SMB S.A	Belgium	ISOSUPRA LIDOSE 8 MG HARTKAPSELN	Isotretinoin
Laboratoires SMB S.A	Belgium	ISOSUPRA LIDOSE 8 MG, CAPSULES, HARD	Isotretinoin
Laboratoires SMB S.A	Belgium	ISOSUPRA LIDOSE 8 MG, GÉLULES	Isotretinoin
Laboratório Medinfar - Produtos Farmacêuticos, S.A.	Portugal	ISOTRETINOÍNA OROTREX, 10 MG, CÁPSULAS MOLES	Isotretinoin
Laboratório Medinfar - Produtos Farmacêuticos, S.A.	Portugal	ISOTRETINOÍNA OROTREX, 10 MG, CÁPSULAS MOLES	Isotretinoin
Laboratório Medinfar - Produtos Farmacêuticos, S.A.	Portugal	ISOTRETINOÍNA OROTREX, 10 MG, CÁPSULAS MOLES	Isotretinoin
Laboratório Medinfar - Produtos Farmacêuticos, S.A.	Portugal	ISOTRETINOÍNA OROTREX, 20 MG, CÁPSULAS MOLES	Isotretinoin
Laboratório Medinfar - Produtos Farmacêuticos, S.A.	Portugal	ISOTRETINOÍNA OROTREX, 20 MG, CÁPSULAS MOLES	Isotretinoin

Laboratório Medinfar - Produtos Farmacêuticos, S.A.	Portugal	ISOTRETINOÍNA OROTREX, 5 MG CÁPSULAS MOLES	Isotretinoin
Laboratório Medinfar - Produtos Farmacêuticos, S.A.	Portugal	ISOTRETINOÍNA OROTREX, 5 MG CÁPSULAS MOLES	Isotretinoin
Q Pharma Kft.	Hungary	Sotret Neo 10 mg lágy kapszula	Isotretinoin
Q Pharma Kft.	Hungary	Sotret Neo 20 mg lágy kapszula	Isotretinoin
Mylan Pharmaceuticals Ltd : IE	Netherlands	Isotretinoïne Capsules [10 mg] [Blister (All)]	Isotretinoin
Mylan Pharmaceuticals Ltd : IE	Netherlands	Isotretinoïne Capsules [20 mg] [Blister (All)]	Isotretinoin
N.V. Roche S.A.	Belgium	Roaccutane 10 mg capsules molles	Isotretinoin
N.V. Roche S.A.	Belgium	Roaccutane 20 mg capsules molles	Isotretinoin
N.V. Roche S.A.	Luxembourg	Roaccutane 10 mg capsules molles	Isotretinoin
N.V. Roche S.A.	Luxembourg	Roaccutane 20 mg capsules molles	Isotretinoin
Orifarm Generics A/S	Denmark	Acitretin Orifarm, 10 mg capsules hard	Acitretin
Orifarm Generics A/S	Denmark	Acitretin Orifarm, 25 mg capsules hard	Acitretin
Orifarm Generics A/S	Denmark	Isotretinoin Orifarm 10 mg capsules, soft	Isotretinoin
Orifarm Generics A/S	Denmark	Isotretinoin Orifarm 20 mg capsules, soft	Isotretinoin
Orifarm Generics A/S	Finland	Acitretin Orifarm, 10 mg capsules hard	Acitretin
Orifarm Generics A/S	Finland	Acitretin Orifarm, 25 mg capsules hard	Acitretin

Orifarm Generics A/S	Finland	Isotretinoin Orifarm 20 mg capsules, soft	Isotretinoin
Orifarm Generics A/S	Norway	Acitretin Orifarm, 10 mg capsules hard	Acitretin
Orifarm Generics A/S	Norway	Acitretin Orifarm, 25 mg capsules hard	Acitretin
Orifarm Generics A/S	Norway	Isotretinoin Orifarm 10 mg capsules, soft	Isotretinoin
Orifarm Generics A/S	Norway	Isotretinoin Orifarm 20 mg capsules, soft	Isotretinoin
Orifarm Generics A/S	RMS: Denmark CMS: SE, NO, FI	Isotretinoin Orifarm 10 mg	Isotretinoin
Orifarm Generics A/S	RMS: Denmark CMS: SE, NO, FI	Isotretinoin Orifarm 20 mg	Isotretinoin
Orifarm Generics A/S	RMS: Denmark CMS: SE, NO, FI,	Acitretin Orifarm 10 mg	Acitretin
Orifarm Generics A/S	Sweden	Acitretin Orifarm, 10 mg capsules hard	Acitretin
Orifarm Generics A/S	Sweden	Acitretin Orifarm, 25 mg capsules hard	Acitretin
Orifarm Generics A/S	Sweden	Isotretinoin Orifarm 10 mg capsules, soft	Isotretinoin
Orifarm Generics A/S	Sweden	Isotretinoin Orifarm 20 mg capsules, soft	Isotretinoin
Pelpharma Handels GmbH	Austria	CISCUTAN 10 MG – KAPSELN	Isotretinoin
Pelpharma Handels GmbH	Austria	CISCUTAN 20 MG – KAPSELN	Isotretinoin
Pelpharma Handels GmbH	Austria	CISCUTAN 30 MG – KAPSELN	Isotretinoin
Pelpharma Handels GmbH	Austria	CISCUTAN 40 MG – KAPSELN	Isotretinoin
Pelpharma Handels GmbH	Austria	CISCUTAN 5 MG – KAPSELN	Isotretinoin

Pelpharma Handels GmbH	Austria	KERACUTAN 10 MG KAPSELN	Acitretin
Pelpharma Handels GmbH	Austria	KERACUTAN 25 MG KAPSELN	Acitretin
Pelpharma Handels GmbH	Austria	Alitretan 10 mg Kapseln	Alitretinoin
Pelpharma Handels GmbH	Austria	Alitretan 30 mg Kapseln	Alitretinoin
Pharmathen Investments Group Limited	Greece	A-cnotren	Isotretinoin
Pharmathen Investments Group Limited	Greece	A-cnotren	Isotretinoin
Pharmathen S.A.	Denmark	Isotretinoin Orion	Isotretinoin
Pharmathen S.A.	Denmark	Isotretinoin Orion	Isotretinoin
Pharmathen S.A.	Finland	Isotretinoin Orion	Isotretinoin
Pierre Fabre Benelux S.A.	Belgium	ISOCURAL 10 mg, soft capsule	Isotretinoin
Pierre Fabre Benelux S.A.	Belgium	ISOCURAL 20 mg, soft capsule	Isotretinoin
Pierre Fabre Benelux S.A.	Belgium	ISOCURAL 40 mg, soft capsule	Isotretinoin
Pierre Fabre Benelux S.A.	Belgium	ISOCURAL 5 mg, soft capsule	Isotretinoin
Pierre Fabre Benelux S.A.	Netherlands	Alizem 10 mg zachte capsules	Alitretinoin
Pierre Fabre Benelux S.A.	Netherlands	Alizem 30 mg zachte capsules	Alitretinoin
Pierre Fabre Iberica SA	Spain	ISOACNE 10 mg, cápsulas blandas	Isotretinoin

Pierre Fabre Iberica SA	Spain	ISOACNE 20 mg, cápsulas blandas	Isotretinoin
Pierre Fabre Iberica SA	Spain	ISOACNE 40 mg, cápsulas blandas	Isotretinoin
Pierre Fabre Iberica SA	Spain	ISOACNE 5 mg, cápsulas blandas	Isotretinoin
Pierre Fabre Italia SpA	Italy	ISORIAC 10 mg, soft capsule	Isotretinoin
Pierre Fabre Italia SpA	Italy	ISORIAC 20 mg, soft capsule	Isotretinoin
Pierre Fabre Medicament	Czech Republic	CURACNÉ 10 mg, měkká tobolka	Isotretinoin
Pierre Fabre Medicament	Czech Republic	CURACNÉ 20 mg, měkká tobolka	Isotretinoin
Pierre Fabre Medicament	Czech Republic	CURACNÉ 40 mg, měkká tobolka	Isotretinoin
Pierre Fabre Medicament	France	CURACNÉ 10 mg, soft capsule	Isotretinoin
Pierre Fabre Medicament	France	CURACNÉ 20 mg, soft capsule	Isotretinoin
Pierre Fabre Medicament	France	CURACNÉ 40 mg, soft capsule	Isotretinoin
Pierre Fabre Medicament	France	CURACNÉ 5 mg, soft capsule	Isotretinoin
Pierre Fabre Medicament	France	ALIZEM 10 mg, capsule molle	Alitretinoin
Pierre Fabre Medicament	France	ALIZEM 30 mg, capsule molle	Alitretinoin
Pierre Fabre Medicament	Poland	CURACNE 10 mg, soft capsule	Isotretinoin
Pierre Fabre Medicament	Poland	CURACNE 20 mg, soft capsule	Isotretinoin
Pierre Fabre Medicament	Poland	CURACNE 40 mg, soft capsule	Isotretinoin
Pierre Fabre Medicament	Poland	CURACNE 5 mg, soft capsule	Isotretinoin

PUREN Pharma GmbH & CO. KG	Germany	Neotigason 10	Acitretin
PUREN Pharma GmbH & CO. KG	Germany	Neotigason 25	Acitretin
Ratiopharm GmbH	Germany	Isotretinoin-ratiopharm 10 mg Weichkapseln	Isotretinoin
Ratiopharm GmbH	Germany	Isotretinoin-ratiopharm 20 mg Weichkapseln	Isotretinoin
Ratiopharm GmbH	Iceland	Isotretinoin ratiopharm 20 mg mjúkt hylki	Isotretinoin
Roche (Magyarország) Kft	Hungary	Roaccutan 10 mg lágy kapszula	Isotretinoin
Roche (Magyarország) Kft	Hungary	Roaccutan 20 mg lágy kapszula	Isotretinoin
Roche Bulgaria EOOD	Bulgaria	Роакутан 20 mg капсули, меки	Isotretinoin
Roche d.o.o.	Croatia	Roaccutane 10 mg meke kapsule	Isotretinoin
Roche Eesti OÜ	Estonia	Roaccutane 10 mg, pehmekapslid	Isotretinoin
Roche Eesti OÜ	Estonia	Roaccutane 20 mg, pehmekapslid	Isotretinoin
Roche Latvija SIA	Latvia	Roaccutane 10 mg mīkstās kapsulas	Isotretinoin
Roche Latvija SIA	Latvia	Roaccutane 20 mg mīkstās kapsulas	Isotretinoin
Roche Lietuva UAB	Lithuania	Roaccutane 10 mg minkštosios kapsulės	Isotretinoin
Roche Lietuva UAB	Lithuania	Roaccutane 20 mg minkštosios kapsulės	Isotretinoin
Roche Products (Ireland) Ltd	Ireland	Roaccutane 10 mg Soft Capsules	Isotretinoin

Roche Products (Ireland) Ltd	Ireland	Roaccutane 20 mg Soft Capsules	Isotretinoin
Roche Romania SRL	Romania	Roaccutane 10 mg capsule moi	Isotretinoin
Rowex LTD	Ireland	Isotretinoin 10 mg soft capsules	Isotretinoin
Rowex LTD	Ireland	Isotretinoin 20 mg soft capsules	Isotretinoin
Sandoz A/S	Denmark	Isotretinoin Sandoz	Isotretinoin
Sandoz A/S	Denmark	Isotretinoin Sandoz	Isotretinoin
Sandoz A/S	Denmark	Isotretinoin Sandoz	Isotretinoin
Sandoz A/S	Norway	Isotretinoin Sandoz 5 mg kapsel, myk	Isotretinoin
Sandoz A/S	Norway	Isotretinoin Sandoz 10 mg kapsel, myk	Isotretinoin
Sandoz A/S	Norway	Isotretinoin Sandoz 20 mg kapsel, myk	Isotretinoin
Sandoz A/S	Sweden	Isotretinoin Sandoz 5 mg mjuka kapslar	Isotretinoin
Sandoz A/S	Sweden	Isotretinoin Sandoz 10 mg mjuka kapslar	Isotretinoin
Sandoz A/S	Sweden	Isotretinoin Sandoz 20 mg mjuka kapslar	Isotretinoin
Sandoz A/S	Netherlands	Isotretinoïne Sandoz 5 mg, zachte capsules	Isotretinoin
Sandoz A/S	Netherlands	Isotretinoïne Sandoz 10 mg, zachte capsules	Isotretinoin
Sandoz A/S	Netherlands	Isotretinoïne Sandoz 20 mg, zachte capsules	Isotretinoin
Sandoz Pharmaceuticals D.D.	Estonia	Isotretinoin Sandoz	Isotretinoin
Sandoz Pharmaceuticals D.D..	Estonia	Isotretinoin Sandoz	Isotretinoin

Sandoz Pharmaceuticals D.D.	Estonia	Isotretinoin Sandoz	Isotretinoin
Sandoz Pharmaceuticals D.D.	Latvia	Isotretinoin Sandoz 5 mg mīkstās kapsulas	Isotretinoin
Sandoz Pharmaceuticals D.D.	Latvia	Isotretinoin Sandoz 10 mg mīkstās kapsulas	Isotretinoin
Sandoz Pharmaceuticals D.D.	Latvia	Isotretinoin Sandoz 20 mg mīkstās kapsulas	Isotretinoin
Sandoz Pharmaceuticals D.D.	Lithuania	Isotretinoin Sandoz 5 mg minkštosios kapsulės	Isotretinoin
Sandoz Pharmaceuticals D.D.	Lithuania	Isotretinoin Sandoz 10 mg minkštosios kapsulės	Isotretinoin
Sandoz Pharmaceuticals D.D.	Lithuania	Isotretinoin Sandoz 20 mg minkštosios kapsulės	Isotretinoin
Stiefel Laboratories Legacy (Ireland) Ltd	Denmark	TOCTINO	Alitretinoin
Stiefel Laboratories Legacy (Ireland) Ltd	Denmark	TOCTINO	Alitretinoin
Stiefel Laboratories Legacy (Ireland) Ltd	France	TOCTINO 10 MG, CAPSULE MOLLE	Alitretinoin
Stiefel Laboratories Legacy (Ireland) Ltd	France	TOCTINO 30 MG, CAPSULE MOLLE	Alitretinoin
Stiefel Laboratories Legacy (Ireland) Ltd	Italy	TOCTINO	Alitretinoin
Stiefel Laboratories Legacy (Ireland) Ltd	Italy	TOCTINO	Alitretinoin
Stiefel Laboratories Legacy (Ireland) Ltd	Netherlands	TOCTINO 10 MG, CAPSULES, ZACHT	Alitretinoin
Stiefel Laboratories Legacy (Ireland) Ltd	Netherlands	TOCTINO 30 MG, CAPSULES, ZACHT	Alitretinoin
Stiefel Laboratories Legacy (Ireland) Ltd	Norway	TOCTINO 10 MG KAPSLER, MYKE	Alitretinoin

Stiefel Laboratories Legacy (Ireland) Ltd	Norway	TOCTINO 30 MG KAPSLER, MYKE	Alitretinoin
Sun Pharmaceutical Industries Europe B.V.	Netherlands	Isotretinoïne SUN 10 mg, zachte capsules	Isotretinoin
Sun Pharmaceutical Industries Europe B.V.	Netherlands	Isotretinoïne SUN 20 mg, zachte capsules	Isotretinoin
Sun Pharmaceutical Industries Europe B.V.	Spain	Isotretinoína SUN 10 mg cápsulas blandas EFG	Isotretinoin
Sun Pharmaceutical Industries Europe B.V.	Spain	Isotretinoína SUN 20 mg cápsulas blandas EFG	Isotretinoin
Sun Pharmaceutical Industries Europe B.V.	Republic of Ireland	Isotretinoin 10 mg soft capsules	Isotretinoin
Sun Pharmaceutical Industries Europe B.V.	Republic of Ireland	Isotretinoin 20 mg soft capsules	Isotretinoin
Sun-Farm Sp. z.o.o.	Poland	Acitren 10mg kapsulki	Acitretin
Sun-Farm Sp. z.o.o.	Poland	Acitren 25mg kapsulki	Acitretin
Target Pharma Single Member Private LTD	Greece	Tretin soft caps 10mg/cap	Isotretinoin
Target Pharma Single Member Private LTD	Greece	Tretin soft caps 20mg/cap	Isotretinoin
Terapia S.A.	Romania	Sotret 10 mg capsule moi	Isotretinoin
Terapia S.A.	Romania	Sotret 20 mg capsule moi	Isotretinoin
Teva B.V.	Denmark	Acnenor	Isotretinoin
Teva B.V.	Denmark	Acnenor	Isotretinoin
Teva B.V.	Denmark	Isomacne	Isotretinoin
Teva B.V.	Denmark	Isomacne	Isotretinoin
Teva B.V.	Denmark	Isotretinoin Teva	Isotretinoin

Teva B.V.	Denmark	Isotretinoin Teva	Isotretinoin
Teva B.V.	Iceland	Decutan	Isotretinoin
Teva B.V.	Iceland	Decutan	Isotretinoin
Teva B.V.	Slovakia	Isotretinoin Actavis 20 mg	Isotretinoin
Teva B.V.	Slovakia	Neotigason 10 mg	Acitretin
Teva B.V.	Slovakia	Neotigason 25 mg	Acitretin
Teva B.V.	Slovenia	NEOTIGASON ®10 mg trde kapsule	Acitretin
Teva B.V.	Slovenia	NEOTIGASON ® 25 mg trde kapsule	Acitretin
Teva B.V.	Ireland	Neotigason 25 mg capsules	Acitretin
Teva B.V.	Latvia	Neotigason 10 mg cietās kapsulas	Acitretin
Teva B.V.	Lithuania	Neotigason 10 mg kietosios kapsulės	Acitretin
Teva B.V.	Norway	Neotigason	Acitretin
Teva B.V.	Norway	Neotigason	Acitretin

Teva B.V.	Slovakia	Isotretinoin Actavis 10 mg	Isotretinoin
Teva B.V.	Czech Republic	Neotigason	Acitretin
Teva B.V.	Denmark	Neotigason	Acitretin
Teva B.V.	Denmark	Neotigason	Acitretin
Teva B.V.	Estonia	Neotigason	Acitretin
Teva B.V.	Finland	Neotigason 10 mg kapseli, kova	Acitretin
Teva B.V.	Finland	Neotigason 25 mg kapseli, kova	Acitretin
Teva B.V.	Iceland	Neotigason	Acitretin
Teva B.V.	Iceland	Neotigason	Acitretin
Teva B.V.	Ireland	Neotigason 10 mg capsules	Acitretin
Teva B.V.	Croatia	Neotigason 10 mg tvrde kapsule	Acitretin
Teva B.V.	Croatia	Neotigason 25 mg tvrde kapsule	Acitretin
Teva B.V.	Czech Republic	Neotigason	Acitretin
Velit Biopharma srl	Italy	NOIDAK	Isotretinoin
Velit Biopharma srl	Italy	NOIDAK	Isotretinoin

14.2 Annex 2: List of Companies - MAHs that are part of the oral retinoids consortium

	Name	Alias
1	2CARE4GENERICS	2CARE4GENERICS
2	ALFASIGMA ESPAÑA, S.L.	ALFASIGMA ESPAÑA
3	ALMIRALL S.A.	ALMIRALL
4	AUROBINDO	AUROBINDO
5	ARISTO PHARMA SP. Z O.O.	AXXON
6	BAUSCH HEALTH	BAUSCH HEALTH COMPANIES
7	CHEPLAPHARM REGISTRATION GmbH	CHEPLAPHARM
8	DERMAPHARM AG	DERMAPHARM
9	ENNOGEN HEALTHCARE LIMITED	ENNOGEN
10	ESPECIALIDADES FARMACÉUTICAS CENTRUM S.A.	ESPECIALIDADES FARMACÉUTICAS CENTRUM, S.A.
11	F. HOFFMANN-LA ROCHE AG	ROCHE
12	FIDIA FARMACEUTICI S.P.A.	FIDIA
13	GALENPHARMA	GALENPHARMA
14	GAP S.A.	GAP
15	GSK	GLAXOSMITHKLINE
16	HEXAL AG	HEXAL AG
17	IASIS PHARMA	IASIS PHARMA
18	INDUSTRIAL FARMACÉUTICA CANTABRIA, S.A.	INDUSTRIAL FARMACÉUTICA CANTABRIA, S.A.,
19	ISDIN S.A.	ISDIN
20	LABORATOIRES EXPANSCIENCE	EXPANSCIENCE
21	LABORATOIRES BAILLEUL S.A.	BAILLEUL
22	LABORATOIRES SMB S.A.	SMB
23	LABORATÓRIO MEDINFAR	MEDINFAR

24	MYLAN PHARMACEUTICALS LIMITED	MYLAN PHARMACEUTICALS LIMITED
25	ORIFARM	ORIFARM
26	PELPHARMA	PELPHARMA
27	PHARMATHEN SA	PHARMATHEN
28	PIERRE FABRE MEDICAMENT	PIERRE FABRE
29	STADA Arzneimittel AG	STADA
30	SUN PHARMACEUTICAL INDUSTRIES	SUN PHARMA
31	TARGET PHARMA SINGLE MEMBER PRIVATE LTD	TARGET PHARMA SINGLE MEMBER PRIVATE LTD
32	TEVA PHARMACEUTICALS EUROPE B.V.	TEVA

14.3 Annex 3: List of represented MAHs contact details

##	MAH identified as contact for PASS	Represented Affiliates
1	2CARE4GENERICS [redacted]	N/A
2	Alfasigma España, S.L. [redacted]	N/A
3	Almirall, S.A. [redacted]	[redacted]

##	MAH identified as contact for PASS	Represented Affiliates
		[redacted]
4	Laboratoire Arrow [redacted]	P[redacted]

##	MAH identified as contact for PASS	Represented Affiliates
		[redacted]
5	Aristo Pharma Sp. z o.o. [redacted]	N/A
6	Bausch Health Ireland Limited [redacted]	[redacted]
7	Cheplapharm Registration GmbH [redacted]	
8	mibe GmbH Arzneimittel [redacted]	[redacted]

##	MAH identified as contact for PASS	Represented Affiliates
		[redacted]
9	Ennogen Healthcare Limited [redacted]	N/A
10	Especialidades Farmacéuticas Centrum S.A. [redacted]	N/A
11	F. Hoffmann-La Roche AG [redacted]	[redacted]

##	MAH identified as contact for PASS	Represented Affiliates
		[redacted]
12	Fidia Farmaceutici S.p.A.,	N/A

##	MAH identified as contact for PASS	Represented Affiliates
	[redacted]	
13	Galenpharma GmbH [redacted]	N/A
14	GAP S.A. [redacted]	N/A
15	GlaxoSmithKline UK Ltd. [redacted]	[redacted]

##	MAH identified as contact for PASS	Represented Affiliates
		[redacted]
16	Hexal AG [redacted]	[redacted]

##	MAH identified as contact for PASS	Represented Affiliates
	[redacted]	[redacted]
17	Iasis Phrmaceuticals Hellas S.A. [redacted]	N/A
18	Industrial Farmacéutica Cantabria S.A. [redacted]	[redacted]
19	Isdin S.A. [redacted]	[redacted]
20	Laboratoires Expanscience [redacted]	N/A

##	MAH identified as contact for PASS	Represented Affiliates
	[redacted]	
21	Laboratoires Bailleul S.A. [redacted]	N/A
22	Laboratoires SMB S.A. [redacted]	N/A
23	Laboratorio Medinfar Produtos [redacted]	N/A
24	Mylan Pharmaceuticals Limited [redacted]	N/A
25	Orifarm Generics A/S [redacted]	N/A
26	Pelpharma Handels GmbH [redacted]	N/A

##	MAH identified as contact for PASS	Represented Affiliates
27	Pharmathen S.A. [redacted]	[redacted]
28	Pierre Fabre Medicament [redacted]	[redacted]
29	Stada Arzneimittel AG [redacted]	[redacted]

##	MAH identified as contact for PASS	Represented Affiliates
		[redacted]
30	Sun Pharmaceutical Industries Europe B.V. [redacted]	[redacted]
31	Target Pharma Single Member Private Ltd. [redacted]	N/A
32	Teva Pharmaceuticals Europe B.V.	[redacted]

##	MAH identified as contact for PASS	Represented Affiliates
	[redacted]	[redacted]

14.4 Annex 4. Qualitative Analysis Plan

Qualitative Analysis Plan

14.5 Annex 5. Outreach template for adult WCBP, parents or guardians of adolescent WCBP and HCPs

Outreach Letter for HCPs:

Dear <name>,

My name is <name> and I work for IQVIA™, a worldwide healthcare consulting firm. We are currently conducting a research study about pregnancy prevention measures related to using oral retinoids. As part of this study, we are interviewing healthcare professionals who prescribe, dispense or inform women of childbearing potential (WCBP) about oral retinoids and pregnancy prevention, including medical doctors, pharmacists, nurses or midwives.

We would like to invite you to participate in this study. Participation would include a 60-minute interview by audio-conference with one of our team's healthcare research professionals. The interview will focus on your understanding of measures related with the prevention of pregnancies for WCBP taking oral retinoids, your thoughts about the adequacy of these measures and any positive or negative aspects you may highlight from your experience providing care to these WCBP. We would also like to better understand your opinion concerning the factors that may influence WCBP's ability of adhering to these measures, as well as how you present information about these measures to women, and your opinion about the importance of your role in educating them. The interview will be scheduled at a date and time that is convenient for you.

We are offering an honorarium of <€amount> in appreciation for your time and insight.

If you are interested in participating, please access <link to screener> and complete the questionnaire so we can understand if you are able to participate in the study.

Thank you in advance for your time and consideration.

Sincerely,

<Name>

Outreach Letter for adult WCBP:

Dear <name>,

My name is <name> and I work for IQVIA™, a worldwide healthcare consulting firm. We are currently conducting a research study about pregnancy prevention measures related to using oral retinoids. As part of this study, we are interviewing women of childbearing potential who are currently taking oral retinoids or who have taken this medication in the last 6 months.

We would like to invite you to participate in this study. Participation would include a 60-minute interview by audio-conference with one of our team's healthcare research

professionals. The interview will focus on your understanding of measures related with the prevention of pregnancies for women taking oral retinoids, your thoughts about the adequacy of these measures and any positive or negative aspects related to them. We would also like to better understand the factors influencing adherence to these measures. The interview will be scheduled at a date and time that is convenient for you.

We are offering an honorarium of <€amount> in appreciation for your time and insight.

If you are interested in participating, please access <link to screener> and complete the questionnaire so we can understand if you are able to participate in the study.

Thank you in advance for your time and consideration.

Sincerely,

<Name>

Outreach Letter for parents or guardians of adolescent WCBP:

Dear <name>,

My name is <name> and I work for IQVIA™, a worldwide healthcare consulting firm. We are currently conducting a research study about pregnancy prevention measures related to using oral retinoids. As part of this study, we are interviewing parents or guardians of adolescents who are currently taking oral retinoids or who have taken this medication in the last 6 months.

We would like to invite you to participate in this study. Participation would include a 60-minute interview by audio-conference with one of our team's healthcare research professionals. The interview will focus on yours and your adolescent's understanding of measures related with the prevention of pregnancies for women of childbearing potential taking oral retinoids, your thoughts about the adequacy of these measures and any positive or negative aspects related to them. We would also like to better understand your opinion and the opinion of your adolescent concerning the factors that may influence their ability of adhering to these measures. The interview will be scheduled at a date and time that is convenient for you.

We are offering an honorarium of <€amount> in appreciation for your time and insight.

If you are interested in participating, please access <link to screener> and complete the questionnaire so we can understand if you are able to participate in the study.

Thank you in advance for your time and consideration.

Sincerely,

<Name>

14.6 Annex 6. Example of screeners which will be used

Screener for HCPs

Screener for adult WCBP

Screener for parents or guardians of WCBP

14.7 Annex 7. Examples of the informed consent forms used

Informed consent form for HCPs

Informed consent form for adult WCBP

Informed consent form for parent or guardian of adolescent WCBP

14.8 Annex 8. Semi-structured discussion guides

HCP discussion guide

Adult WCBP discussion guide

Parent or guardian of adolescent WCBP discussion guide