

Dear Colleague

## GUIDANCE ON THE IMPLEMENTATION OF THE ULTRA-ORPHAN PATHWAY

### Introduction

I am writing to share with you guidance documents to support the implementation of the new ultra-orphan pathway. This guidance is intended to provide information to Health Boards, clinicians, pharmacists, patient groups and pharmaceutical companies on the approach to the new assessment of ultra-orphan medicines.

### Overview

The Scottish Government announced the introduction of a new pathway in the Scottish Medicine Consortium (SMC) process for ultra-orphan medicines in June 2018 with a phased implementation period: phase one commenced in October 2018, with the rest of the pathway due to be implemented by the end of April 2019.

An ultra-orphan condition affects around 1 in 50,000 people and that is approximately 100 people in Scottish population terms.

Under this new pathway, medicines which are validated by the SMC as ultra-orphan under a revised definition, with specific qualifying criteria, can be made available through the NHS in Scotland for a period of up to three years. The SMC will then review the evidence after three years and make a final decision on its routine use in NHS Scotland.

It is expected that between eight to ten medicines a year will qualify for the new ultra-orphan pathway. However, pharmaceutical companies still have the option to make a submission through the standard SMC health technology assessment process.

### Guidance

Attached to this letter are two guidance documents.

Attached at **ANNEX A** is general guidance on the process, outlining each stage of the ultra-orphan pathway. **ANNEX B** offers guidance about the specific process in relation to the data collection and evidence generation phase of the new pathway.

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### Addresses

#### For information

Chief Executives, NHS  
Boards  
Medical Directors, NHS  
Boards  
Directors of Pharmacy,  
NHS Boards  
Directors of Finance, NHS  
Boards

Chairs, NHS Boards  
Directors of Public Health,  
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In parallel, updated Patient Access Scheme (PAS) guidance is being published by National Services Scotland to reflect that companies must offer a PAS to enable an ultra-orphan medicine to be available through the pathway. The updated PAS guidance also reflects the recent changes brought in by the UK Voluntary Scheme for Branded Medicines Pricing and Access Scheme (VPAS) 2019.

These arrangements for an ultra-orphan pathway supplement general guidance about the availability of newly licensed medicines (as described in QEL 17(2010), SGHD/CMO (2011)3 and SGHD/CMO (2012) 1). The Scottish Government keeps these items of guidance under review and will consider the issue of a general update to take into account the number of developments since 2012.

Yours sincerely

A handwritten signature in cursive script that reads "Rose Marie Parr".

Dr Rose Marie Parr  
**Chief Pharmaceutical Officer**

## A Guide to the Ultra-Orphan Pathway

This guidance is intended to provide information to Health Boards, clinicians, pharmacists, patient groups and pharmaceutical companies on the new approach to the assessment of ultra-orphan medicines which was introduced in Scotland in October 2018, with applications for new medicines available from April 2019.

The changes mean if the medicine meets the new definition of an ultra-orphan medicine and undergoes a full assessment of its clinical and cost-effectiveness by the Scottish Medicine Consortium (SMC), then it will be available on the NHS for up to three years while further evidence on its effectiveness is generated. The SMC will then review the evidence after three years and make a final decision on its routine use in NHS Scotland

To enable an ultra-orphan medicine to be available through the pathway, there are four conditions that must be met. They are that a pharmaceutical company:

- has the medicine validated as an ultra-orphan according to the SMC definition;
- makes a full submission to the SMC for the initial assessment stage that meets SMC requirements for assessment under the ultra-orphan process;
- offers a Patient Access Scheme (PAS) that complies with the standard terms and conditions considered acceptable by the Patient Access Scheme Assessment Group (PASAG); and
- supports the data collection arrangements that meets the evidence generation requirements for assessment under the ultra-orphan pathway.

The new pathway comprises of four key stages:

1. **Validation** – the medicine must be validated as an ultra-orphan medicine by the SMC under a new definition which includes set criteria;
2. **Initial SMC Assessment** - a full submission (along with a PAS) must be made by the pharmaceutical company to the SMC to allow an initial assessment of the clinical and cost effectiveness of the medicine;
3. **Evidence Generation** - the pharmaceutical company must undertake to collect data in order to generate evidence over a period of up to three years to increase the SMC's confidence in the clinical and cost-effectiveness of the ultra-orphan medicine at time of reassessment; and
4. **Reassessment** – a full update of the submission offered at stage 2 should be made to the SMC by the company following the three year data collection period. The SMC will make a decision as to whether the medicine is to be accepted for general use in NHS Scotland.

This guidance outlines each stage of the pathway, including the PAS requirements. A diagrammatic illustration of the process can be found at the end of this guidance document.

## **Stage 1: Validation** (around 8 weeks)

In the first instance, a medicine must be validated by the SMC as an ultra-orphan medicine under revised criteria. All criteria listed below should be met:

1. the condition has a prevalence of 1 in 50,000 or less in Scotland,
2. the medicine has a European Medicines Agency (EMA) orphan designation for the condition and this is maintained at time of marketing authorisation,
3. the condition is chronic and severely disabling; and
4. the condition requires highly specialised management.

A company can apply for validation by completing the SMC ultra-orphan proforma (which can be found at the following link - <https://www.scottishmedicines.org.uk/how-we-decide/revised-process-ultra-orphan-medicines-for-extremely-rare-conditions/>).

Companies are encouraged to engage with the SMC at the earliest opportunity for validation, and ideally prior to receiving a positive opinion from the EMA's Committee for Human Medicinal Products (CHMP).

The SMC will review the application and will confirm whether or not the medicine has been validated as ultra-orphan within around eight weeks. Confirmation that the medicine is validated for the ultra-orphan pathway is required before the company can make a full submission for SMC initial assessment.

The SMC will contact companies with the outcome of the validation process and, in the case of disagreement, there will be an opportunity for the company to appeal. The outcome of the ultra-orphan validation is shared with Health Boards in confidence.

## **Stage 2: Initial SMC Assessment** (around 18 weeks)

Once a company has been informed that the medicine has been validated as an ultra-orphan and if they have received a positive opinion from the EMA's CHMP, they can then make a full submission (which must include a PAS) to the SMC for an initial assessment of the clinical and cost effectiveness of the medicine. This assessment will highlight uncertainties within the available evidence-base and will help to inform the data collection and evidence generation stage of the ultra-orphan pathway.

Companies should complete the New Product Assessment Form (NPAF) for Ultra-Orphan Medicines (which can be found at <https://www.scottishmedicines.org.uk/how-we-decide/revised-process-ultra-orphan-medicines-for-extremely-rare-conditions/>)

It will take around 14 weeks from submission to the SMC formally meeting to consider the medicine. During the assessment, the SMC will use a broad framework to assess the ultra-orphan medicine, taking into account the following:

- nature of the condition;
- impact of the medicine;
- value for money;
- impact of the technology beyond direct health benefits and on specialist services; and
- costs to the NHS and Personal Services.

Patient Group submissions will inform the initial assessment report. A Patient and Clinician Engagement (PACE) meeting will not take place at the initial assessment stage but it will form part of the SMC's reassessment stage.

The SMC will publish its initial assessment report within standard timelines.

Further guidance and information on completing the NPAF for ultra-orphan medicines and making a full submission to the SMC can be found on the *Making a submission* section of the SMC website: <https://www.scottishmedicines.org.uk/making-a-submission/>

### *Patient Access Scheme (PAS)*

Pharmaceutical companies must offer a PAS to enable an ultra-orphan medicine to be available through the pathway. The purpose of the PAS is to improve the cost-effectiveness of the medicine and to enable patients to receive access to cost-effective innovative medicines.

Companies are encouraged to offer a fair price in return for the additional flexibility offered by the ultra-orphan assessment approach; giving market access for a period of three years and the further data collection opportunities to address uncertainties in the clinical data.

Pharmaceutical companies should complete either the concise or full PAS application pack, as appropriate. Once completed, the PAS application pack should be submitted

to the SMC Secretariat along with the New Product Assessment Form (NPAF) and associated documents.

The PASAG will review the PAS proposal and will advise the SMC on the feasibility of the proposed scheme for implementation. It operates separately from the SMC to maintain the integrity of the assessment process.

The company has the opportunity to submit a new or revised PAS following the SMC's New Drugs Committee meeting (which comes before the SMC initial assessment meeting).

The PAS will only become available for implementation if approved by the PASAG and following initial assessment by the SMC.

For more information and guidance, companies may contact the PASAG secretariat ([NSS.NP-PASAG@nhs.net](mailto:NSS.NP-PASAG@nhs.net)).

### *NHS Financial Risk Sharing Scheme*

It is the intention to establish a financial risk-sharing scheme (Health Board pooled funding) for the ultra-orphan pathway. Further information will be provided to Health Boards on this.

### **Stage 3 : Evidence Generation** (up to three years)

Following the SMC initial assessment and its published report, pharmaceutical companies will be required to develop a data collection plan to capture relevant clinical and patient reported outcomes which aim to address as much as possible the uncertainties identified in order to increase the SMC's confidence in the clinical and cost-effectiveness of the medicine at the time of reassessment.

In particular, pharmaceutical companies should:

- undertake to collect data on the ultra-orphan medicine for the duration of its availability through the pathway;
- ensure that the focus of the data collection activity attempts to address the uncertainties within the existing evidence-base, including those highlighted in the initial SMC assessment report;
- draw on any existing data collection activities from other parts of the UK and beyond as part of the overall package of evidence generation;
- seek to collect Patient Reported Outcome Measures (PROMs), where appropriate, and data on the impact beyond direct health benefits and on specialist services; and
- cover all the costs associated with the data collection.

Whilst it is recognised that the data collection plan and evidence generation stage is unlikely to be fully developed until after the SMC's initial assessment report is issued, there will be aspects that can be established in advance. Companies are therefore encouraged to plan the data collection work as soon as possible, and ideally following a positive validation from the SMC.

Companies must submit a short initial report outlining their data collection plan to the Scottish Government (SG) ([medicines.policy@gov.scot](mailto:medicines.policy@gov.scot)) within three months of the publication of the SMC initial assessment report (more time may be granted in exceptional cases). This report will be the evidence that the company has data collection arrangements in place. It should also include a prospective timeline for data collection and a probable date for the updated submission for SMC reassessment. The data collection period will normally be three years, but companies may resubmit earlier if sufficient data is available.

Some companies may welcome external support in the development of their data collection planning, to ensure that the critical weaknesses in data have been accurately reflected and that the plans in place can be expected to address the identified data uncertainties. Work is underway to develop a service from NHS Research Scotland (NRS) which companies will be able to choose to use. Further information on this service and any associated costs will be available as an addendum to the separate guidance document on the evidence generation phase.

Companies will be responsible for determining whether the data being produced during the evidence generation period is adequately measuring and achieving the outcomes identified in their data generation and collection plan, and whether any additional action is required. However, they may use the services of NRS to support them in this.

*Access to NHS Scotland for the three year data collection period*

Once the SMC initial assessment report and agreed PAS are in place and the company submit their short report outlining their data collection plan to the SG, access to the three year data collection period will commence. Health Boards and the company will be notified of the effective start date by the SG.

**Stage 4. Reassessment** (around 22 weeks)



Companies will be expected to submit an updated full submission to the SMC for reassessment of the medicine following the three year data collection and evidence generation stage.

The SMC will review the information presented in the decision-making framework, as before, but will also consider the additional evidence generated during the three year period of availability of the medicine within the ultra-orphan pathway.

As part of its review, the SMC will assess the information the company has provided within its updated ultra-orphan NPAF as well as other sources of evidence, for example clinical experts, patient group submissions and, where relevant, the output from a PACE meeting.

The SMC decision options at reassessment include:

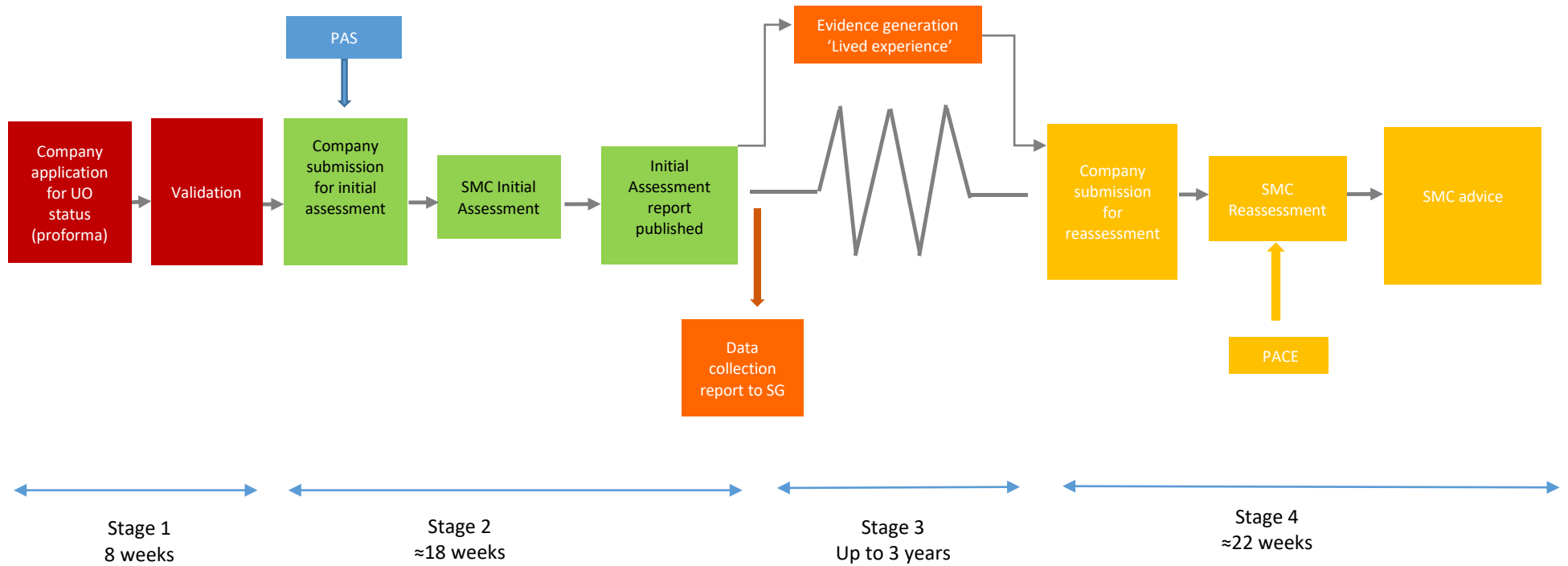
- Accepted for use (where the medicine becomes routinely available in NHS Scotland)
- Accepted for restricted use (where the medicine becomes available in NHS Scotland on a restricted basis); or
- Not recommended (the medicine does not become available in NHS Scotland).

In the event that a medicine is not recommended for routine use at reassessment:

- where the patient continues to derive clinical benefit, the treatment should continue until the patient and clinician consider it appropriate to stop, as per current guidance and best practice;
- all Health Boards have procedures in place to consider requests when a healthcare professional feels that a medicine which is not recommended by SMC, is right for a particular patient; and
- companies will be expected to agree to ensure continuity of supply at the previously agreed PAS price.

# Ultra-Orphan Pathway

UO – ultra-orphan  
PAS – Patient Access Scheme  
SG – Scottish Government  
PACE – Patient and Clinician Engagement meeting



## Guidance on the Evidence Generation Phase of the Pathway for Ultra-Orphan Medicines

### **Purpose**

The purpose of the evidence generation phase of the pathway for ultra-orphan medicines is to collect information about relevant clinical outcomes and patient reported outcomes to address, as much as possible, the uncertainty associated with the ultra-orphan medicine in order to increase the Scottish Medicines Consortium's (SMC) confidence in clinical and cost-effectiveness of treatment at the point of reassessment.

This document offers guidance about the process in relation to the data collection and evidence generation phase of the ultra-orphan pathway.

### **Introduction**

The Scottish Government (SG) announced the introduction of a new pathway for ultra-orphan medicines in June 2018 with a phased implementation period; the validation process commenced in October 2018 and the rest of the pathway from April 2019. To enable an ultra-orphan medicine to be available through the pathway, there are four conditions that must be met. They are that a pharmaceutical company:

- has the medicine validated as an ultra-orphan according to the SMC definition;
- makes a full submission to the SMC for the initial assessment stage that meets SMC requirements for assessment under the ultra-orphan process;
- offers a Patient Access Scheme (PAS) that complies with the standard terms and conditions considered acceptable by the Patient Access Scheme Assessment Group (PASAG); and
- supports the data collection arrangements that meets the evidence generation requirements for assessment under the ultra-orphan pathway.

The new pathway comprises of four key stages:

1. **Validation** – the medicine must be validated as an ultra-orphan medicine by the SMC under a new definition which includes set criteria;
2. **Initial SMC Assessment** - a full submission (along with a PAS) must be made by the pharmaceutical company to the SMC to allow an initial assessment of the clinical and cost effectiveness of the medicine;
3. **Evidence Generation** - the pharmaceutical company must undertake to collect data in order to generate evidence over a period of up to three years to increase the SMC's confidence in the clinical and cost-effectiveness of the ultra-orphan medicine at time of reassessment; and
4. **Reassessment** – a full update of the submission offered at stage 2 should be made to the SMC by the company following the three year data collection period. The SMC will make a decision as to whether the medicine is to be accepted for general use in NHS Scotland.

In recognition of the uncertainties in the supporting evidence for these medicines, companies must commit to generating evidence by collecting additional data on the effectiveness of the medicine in the specific indication during the three year period of the medicine being available through the pathway. The focus of this activity should be the collection of relevant clinical and patient reported outcomes that would be expected to increase the SMC committee's confidence at the point of re-assessment.

In particular, pharmaceutical companies will:

- undertake to collect data on the ultra-orphan medicine for the duration of its availability through the pathway;
- ensure that the focus of the data collection activity attempts to address the uncertainties within the existing evidence-base, including those highlighted in the initial SMC assessment report;
- draw on any existing data collection activities from other parts of the UK and beyond as part of the overall package of evidence generation;
- seek to collect Patient Reported Outcome Measures (PROMs), where appropriate, and other data on the impact beyond direct health benefits and on specialist health services; and
- cover **all** the costs associated with the data collection, including infrastructure costs such as registry and/or database costs, resourcing costs such as data analyst or input support and PROMs costs.

## **Pre-evidence generation phase**

### Commitment to evidence generation

The commitment from pharmaceutical companies to generate evidence by collecting additional data on the effectiveness of the medicine in the specific indication will be highlighted during early engagement meetings. Evidence of that commitment will take the form of a data collection plan which must be submitted to SG prior to health boards being notified that the medicine is available through the pathway.

### SMC Initial Assessment

Following a positive validation, companies will be required to make a submission to the SMC for an initial assessment of the clinical and cost-effectiveness of the medicine. The SMC will use a broad framework to appraise the medicine which takes account of the nature of the condition, impact of the medicine, value for money, impact beyond direct benefits and on specialist services, and costs to the NHS. Further information is available in the *SMC guidance to submitting companies – supplement for medicines for extremely rare conditions (ultra-orphan medicines)*. (<https://www.scottishmedicines.org.uk/media/4155/guidance-supplement-ultra-orphan.pdf>)

The SMC initial assessment report will highlight uncertainties within the available evidence-base which will help to inform the evidence generation and data collection period of the pathway. The report will be published in normal SMC timelines, within one month of the SMC meeting.

## Health Board notification that the ultra-orphan medicine is available

Once the SMC initial assessment report has been issued and the PAS and data collection conditions of the pathway have been met, Health Boards will be notified by the SG that the ultra-orphan medicine is available for prescribing through the pathway.

### **Evidence generation phase**

The purpose of the evidence generation phase is to collect data to address the uncertainties within the existing evidence-base, including those highlighted in the initial SMC assessment report.

Companies can start to plan the data collection work as soon as possible, ideally following a positive validation. Whilst it is recognised that the evidence generation and data collection plan is unlikely to be fully developed until after the SMC's initial assessment report is issued, there will be aspects that can be established in advance of the plan being finalised. This will be for companies to determine.

### Data Collection Plan

Pharmaceutical companies will need to develop a data collection plan. This will be required as part of the evidence that the data collection condition for entry to the pathway has been met. The plan should seek to describe ongoing clinical and quality of life studies and real world data that can help to address the uncertainties within the existing evidence-base, including those highlighted in the initial SMC assessment report.

It is recognised that some companies may welcome external support in the development of their data collection plan, to ensure that the critical weaknesses in data have been accurately reflected and that the plans in place can be expected to address the identified data uncertainties. Work is underway to develop a service from NHS Research Scotland (NRS) which companies will be able to choose to use. Further information on this service and any associated costs will be available as an addendum to this guidance document.

### *Clinical Data*

The data collection plan should draw on any existing clinical studies or new data collection activities e.g. registries which can be from other parts of the UK and beyond as part of the overall package of evidence generation. There is an expectation that any data from patients being treated in Scotland will be incorporated into appropriate data systems at either a UK or European level.

### *Patient Reported Outcomes and Other Data*

The data collection plan provides the opportunity to collect PROMs and other types of data in the 'real world'. Companies should consider how to capture the patient experience and the impact the medicine has beyond the direct health benefits i.e. other than clinical benefits and adverse effects, and also its impact on specialist health services, as described in the SMC's ultra-orphan framework.

For example, this may include data in relation to:

- opportunities for patients to contribute to society, improve family functioning, continue in employment or education;
- impact on carers' quality of life (e.g. using tools such as the Carer Experience Scale) and ability to work;
- impact of adopting a wider perspective on the cost-effectiveness of the medicine (e.g. incorporating loss of earnings, carer disutility); and
- implications of the introduction of the new medicine on the NHS including staffing, infrastructure and training requirements.

Companies may wish to engage with patients/carers groups, clinicians and other appropriate members of the health and social care team to determine the key questions to be addressed by patients receiving the ultra-orphan medicine. This may take the form of a data collection workshop, focus group or any other appropriate arrangement.

Companies may wish to engage an academic partner when considering the development and collection of any PROMs data.

### Data Governance

Companies will need to ensure that any data collection activities comply with local Health Board governance arrangements.

### Data Collection Report

Companies will be expected to submit a short report outlining their evidence generation and data collection plan to the SG ([medicines.policy@gov.scot](mailto:medicines.policy@gov.scot)).

Companies should consider inclusion of the following information in their report:

- any areas of uncertainty within the available evidence-base specific to the medicine, including those identified during the SMC assessment;
- details of any clinical data sources being used to inform the data collection process;
- details of PROMs and any other real world data that the company intend to collect;
- an explanation of how the data will attempt to address the uncertainties around the medicine for that specific indication;
- information on patient eligibility, such as an estimation of patient numbers during data collection period;
- how the data will be collected and analysed along with anticipated timescales; and
- the details of the academic partner that the company is working with.

In addition, the report should include a prospective timeline for data collection and a probable date for the updated submission for SMC reassessment. The data collection period will normally be three years, but companies may resubmit earlier if sufficient data is available.

Pharmaceutical companies will be expected to submit their initial report to SG within three months of the publication of the SMC initial assessment report. It is envisaged that this should give companies adequate time to finalise their data collection plan in line with the findings in the SMC initial assessment report.

There may be exceptional circumstances where a company requires more time, for example where a medicine requires some service reconfiguration in order for appropriate resources to be in place for the medicine's administration. In these circumstances an effective start date for the three year data collection period can be negotiated with SG.

#### Start of the three year data collection period

The data collection period can start once Health Boards have been notified that the ultra-orphan medicine is available for prescribing through the ultra-orphan pathway. Companies will also be notified of the effective start date.

#### Three year data collection period

Companies will be responsible for determining whether the data being produced is adequately measuring and achieving the outcomes identified in their data generation and collection plan, and whether any additional action is required.

However, they may use the services of NRS to support them in this. The service and any associated costs will be detailed in an addendum to this guidance.

#### Costs

Pharmaceutical companies will be required to cover **all** the costs associated with the evidence generation and data collection period of the pathway.

#### **Post evidence generation Phase**

Pharmaceutical companies will be asked to provide a full update of the submission offered initially to the SMC following the period of evidence generation and data collection. The SMC will then review information provided by the company as well as other sources of evidence e.g. from clinical experts, Patient Groups and, where relevant, the output from a Patient and Clinician Engagement (PACE) meeting, and will make a decision on the routine use of the medicine in the NHS in Scotland.