NICE National Institute for Health and Care Excellence

Evidence summaries: unlicensed and off-label medicines – Integrated process statement

NICE process and methods
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www.nice.org.uk/process/pmg14

Contents

1 Introduction

This is not the current process. From February 2017, evidence summaries were developed using the evidence summaries: process guide.

1.1 Introduction to integrated process statement

This integrated process statement has been produced to explain how 'Evidence summaries: unlicensed and off-label medicines' (ESUOMs) are developed. It provides an overview of the key process principles and describes all stages of development for ESUOMs. These procedures are designed to ensure that a robust, quality-assured commentary is developed for the NHS in an open, transparent and timely way, with appropriate input from key groups.

1.2 Background to Evidence summaries: unlicensed and off-label medicines

The National Institute for Health and Care Excellence (NICE) provides national guidance and advice to improve health and social care. Further information about NICE and its work is available on the NICE website.

The NICE Medicines and Prescribing Centre provides advice and support for delivering safety, efficiency and effectiveness in the use of medicines. The Medicines and Prescribing Centre is responsible for developing the ESUOMs.

ESUOMs provide a summary of the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, usually when there is no licensed medicine for the condition requiring treatment or no licensed medicines are appropriate for a significant proportion of people requiring treatment. ESUOMs should not be considered to promote the use of unlicensed medicines solely for economic reasons.

ESUOMs provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies. The strengths and weaknesses of the relevant evidence are critically reviewed within each ESUOM. Importantly, **an ESUOM does not constitute formal NICE guidance** and this is clearly

stated on each publication. This information from NICE helps to avoid potential duplication of effort and the need for different NHS organisations to produce similar products for their own local use.

The topics for ESUOMs are selected in collaboration with the existing NICE topic selection programme. Two types of topics are considered:

- An unlicensed medicine; that is, a medicine that does not have a UK marketing authorisation and is not expected to do so in the next 2 years.
- An off-label medicine; that is, a medicine with an existing UK marketing authorisation that is:
  - used outside the terms of its marketing authorisation, for example, by indication, dose, route or patient population and
  - it is not expected that the existing UK marketing authorisation will be extended to cover this use in the next 2 years.

Previous inclusion of an unlicensed or off-label medicine in a NICE clinical guideline is not necessarily a reason for it not to be selected for an ESUOM. ESUOMs do not constitute NICE guidance and do not include recommendations, but they do provide a dedicated summary of the evidence relating to the use of particular medicine in a particular condition within the context of the rest of the NICE guidance. They may include new evidence which has been published since the NICE clinical guideline was last updated. As such, they support local decision-making and implementation of the clinical guideline, and may influence the development of guidance or updates of guidance.

2 Evidence summaries: unlicensed and off-label medicines

2.1 Aims

The aim of 'Evidence summaries: unlicensed and off-label medicines' (ESUOMs) is to provide information about an unlicensed or off-label medicine that is being considered for use in circumstances where there are no clinically appropriate licensed alternatives. The ESUOM helps inform decision-making by clinicians and patients and supports the construction and updating of local formularies.

2.2 Key audiences

ESUOMs are produced for:

- clinicians, to inform their decision-making
- patients and the public, to inform their decision-making
- local decision-making groups involved in commissioning, policy development, or individual funding requests (IFRs), for example, within a Clinical Commissioning Group (CCG) or NHS Trust.

2.3 Key activities

The key activities involved in the production of each ESUOM are:

- identifying, prioritising and selecting the topic
- summarising the published evidence
- critically reviewing the strengths and weaknesses of the evidence
- placing the evidence in the context of the wider evidence base for the management of the condition for which the unlicensed or off-label use is being considered, particularly NICE guidance, if available

- highlighting any potential implications for local decision-making or clinical practice
- producing information for the public for each ESUOM
- identifying any new evidence relevant to published ESUOMs through scanning the literature, reviewing and, if necessary, updating or withdrawing an ESUOM.

3 Who is involved in producing Evidence summaries: unlicensed and off-label medicines?

3.1 The Medicines and Prescribing Centre

The Medicines and Prescribing Centre is part of NICE's Centre for Clinical Practice (CCP). The Medicines and Prescribing Centre consists of a programme director, associate directors and clinical, technical, project and administrative staff. For 'Evidence summaries: unlicensed and off-label medicines' (ESUOMs), senior members of the medicines evidence and medicines education teams within the Medicines Prescribing Centre are responsible for:

- developing and reviewing processes and methods for producing ESUOMs
- identifying potential topics for ESUOMs in collaboration with the NICE topic selection team
- developing and preparing ESUOMs for publication in line with the agreed process and standards
- identifying external specialist commentators to help ensure the content is relevant and useful
- providing quality assurance of the content of ESUOMs
- ensuring timelines and quality assurance standards are followed
- reviewing and updating content of published ESUOMs, when required.

3.2 The NICE Public Involvement Programme

The Public Involvement Programme (PIP) provides NICE with advice on involving patients, carers and members of the public. The role of the PIP team in the ESUOM programme is to provide editorial input into the information for the public as well as helping to identify expert patients, or commentators from patient organisations or groups[1], to input into the

topic selection and content of the information for the public.

3.3 Other NICE teams

In addition to the PIP, the Medicines and Prescribing Centre works closely with members of other NICE teams to develop ESUOMs. These include:

- Topic Selection, to assist in topic identification and prioritisation
- Technology Appraisals, to ensure that there is no conflict or overlap with published, planned or proposed NICE technology appraisals
- Clinical Guidelines, to suggest topics for prioritisation and ensure that there is synergy with published or planned NICE clinical guidelines, including the review and updating of NICE clinical guidelines
- Communications, to carry out an editorial review, then to publish and promote the final versions
- Guidance Information Services, to assist at the topic selection stage with checking the topics against the exclusion criteria.

3.4 Unlicensed and Off-label Medicines (UOM) Prioritisation Panel

The UOM Prioritisation Panel has a standing membership, which advises NICE on topics that should be prioritised for development as an ESUOM. Members of the panel include lay members, representatives from the Association of the British Pharmaceutical Industry (ABPI), Royal College of Paediatrics and Child Health (RCPCH), and NHS secondary and tertiary care pharmacists. The membership of the panel and UOM Prioritisation Panel minutes are published on the NICE website.

3.5 External specialist commentators

The specialist commentator(s) are identified to review draft ESUOMs before publication. They are practitioners who have significant expertise in the therapeutic area for which the unlicensed or off-label medicine is to be used. Their role is to clarify any issues about the reviewed evidence and the practical implications of the information contained in the

ESUOM. Suggestions for appropriate external specialist commentators come from existing NICE networks, national professional organisations and NICE Medicines and Prescribing Associates (see section 3.8).

3.6 Manufacturers

When a topic is selected for the ESUOM programme, NICE informs the manufacturer[2] of the medicine of its intention to produce an evidence summary and the expected time frame for production. NICE invites them to provide relevant information to support the production of the evidence summary.

The manufacturer is also invited to comment on a draft of the evidence summary, and provides comments within an agreed time frame. The manufacturer has the opportunity to comment on matters of factual accuracy, and respond to any specific questions from NICE about the information they submitted to inform the development of the ESUOM.

3.7 The Medicines and Healthcare products Regulatory Agency (MHRA)

The NICE Medicines and Prescribing Centre contacts the MHRA (or the European Medicines Agency [EMA], as appropriate) to ask for any evidence on the topic held on file that is not confidential. It is invited to comment on a draft of the ESUOM within an agreed time frame. The role of the MHRA or EMA is to comment on regulatory and safety issues within the topic covered by the ESUOM.

3.8 The NICE Medicines and Prescribing Associates programme

NICE Medicines and Prescribing Associates are a network of health professionals for whom influencing medicines and prescribing strategy in the NHS is a significant part of their job. They work within their own NHS organisation, health board or service and in their wider local health economy to support high-quality, cost-effective prescribing and medicines optimisation. Details of current Associates are published on the NICE website. NICE Medicines and Prescribing Associates assist with the identification of topics (see section 4.1), and help to identify external specialist commentators.

3.9 Conflicts of interest

NICE staff, members of the UOM Prioritisation Panel, NICE Medicines and Prescribing Associates and specialist commentators are required to comply with the NICE code of conduct on conflicts of interest. For more information about how NICE deals with conflicts of interest, please see A code of practice for declaring and dealing with conflicts of interest.

[1] NICE uses the terms 'patient organisation' and 'patient group' to include patients, carers, and community and other lay organisations, including those representing people from groups protected by equalities legislation.

[2] For some unlicensed or off-label medicines, more than 1 manufacturer may be involved in the development of the drug. On these occasions, all relevant manufacturers based in the UK are contacted for information.

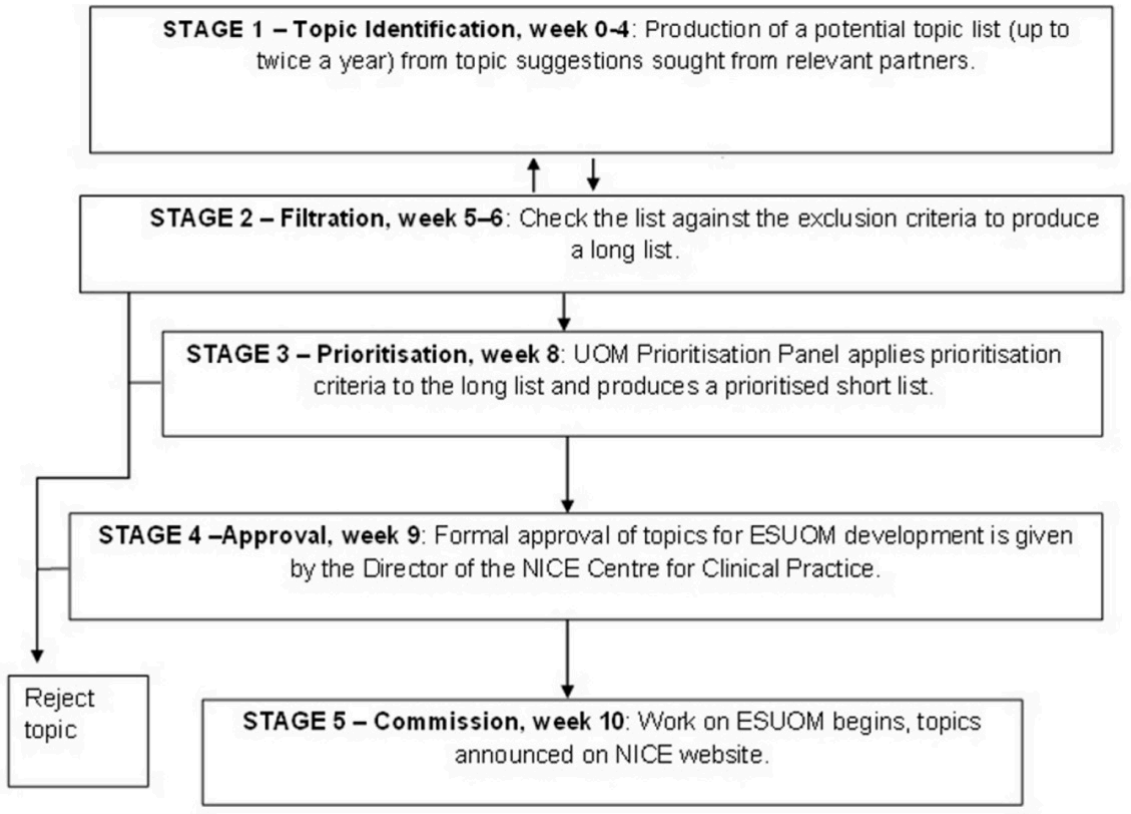
4 Topic identification, prioritisation and selection

4.1 Topic identification and prioritisation

The NICE Medicines and Prescribing Centre is responsible for managing the process of topic identification, prioritisation and selection for 'Evidence summaries: unlicensed and off-label medicines' (ESUOMs). Topics are selected where a demand for information has been identified.

There is no established horizon scanning service to identify potential topics for this work stream. A new approach to gathering this information is therefore required.

Figure 1 The main steps in the process for topic identification, prioritisation and selection for ESUOMs



Stage 1: Identifying potential topics

Partner organisations[3] are approached up to twice a year to suggest potential topics. They are asked to consider the exclusion criteria in box 1 when suggesting topics. These criteria are designed to filter out topics unsuitable for development into an ESUOM and ensure each topic selected will add value. Previous inclusion of an unlicensed or off-label medicine in a NICE clinical guideline is not necessarily an exclusion criterion for its selection for an ESUOM (see section 1.2).

Box 1 Long list: exclusion criteria

- Use of the unlicensed or off-label medicine instead of licensed alternatives is being proposed solely on economic grounds.
- The topic relates to the use of a licensed medicine for a licensed indication but by an unlicensed delivery route or in a modification to the licensed formulation.
- The topic covers population screening, immunisation or HIV treatment (as these are normally covered by other bodies).
- High-quality, up-to-date reviews are already available from a NICE-accredited source.
- A marketing authorisation for the medicine in this indication is being sought and is expected to be granted within 2 years.

The suggestions from the partner organisations and any other potential topics identified through NICE networks, are compiled to form a list of potential topics.

Stage 2: Filtration: applying the exclusion criteria

The NICE Medicines and Prescribing Centre check the potential list of topics against the exclusion criteria (see box 1). Topics that do not meet the criteria are removed from the list and a long list for prioritisation is created.

Stage 3: Prioritisation: developing the short list

The Unlicensed and Off-label Medicines (UOM) Prioritisation Panel (see section 3.4) meets twice a year to consider the priority for each topic on the long list. They advise NICE on the priority of each topic using the prioritisation criteria in box 2.

Box 2 Short list: prioritisation criteria

- Demand for information: what is the volume of requests from the NHS for information on the topic?
- Clinical impact: what is the potential of the medicine (if effective) to improve significantly the quality of life for the people in whom it might be used?
- Variation in practice: is there large variation in clinical practice, significant divergence of clinical opinion, or reports of difficulty of access to the unlicensed or off-label medicine?
- Need for information: how much uncertainty exists on the risk:benefit balance of the unlicensed or off-label medicine?

The advice from the UOM Prioritisation Panel is considered by NICE and used to produce the short list of topics that NICE intend to develop as ESUOMs.

Stage 4: Approval

The Director of the NICE Centre for Clinical Practice reviews the short list of potential ESUOM topics and gives approval of the topics on which NICE should proceed to develop ESUOMs. Once topics are approved, the manufacturers[4] of the medicines are informed of the intention to produce these ESUOMs and the topics are added to the NICE Forward Planner, as well as being added to the ESUOM page of the Medicines and prescribing section of the NICE website

Stage 5: Development

The NICE Medicines and Prescribing Centre develops an ESUOM for each of the approved topics.

[3] Partner organisations are organisations with a particular interest in the unlicensed and off-label use of medicines. They include professional and patient bodies and trade organisations such as the Royal College of Paediatrics and Child Health, Rare Diseases UK, the Chief Pharmacists Network and the Association of the British Pharmaceutical Industry (ABPI). In addition, the NICE Medicines and Prescribing Associates may also suggest topics. A list of partner organisations is available on the NICE website, but is not intended

to be exhaustive, as we aim to engage with all who can help identify potentially suitable topics.

[4] For some unlicensed or off-label medicines, more than 1 manufacturer may be involved in the development of the drug. On these occasions, all relevant manufacturers based in the UK are contacted for information.

5 Production

5.1 Equality and diversity considerations

'Evidence summaries: unlicensed and off-label medicines' (ESUOMs) are developed in accordance with NICE equality scheme.

5.2 Process and timescales

ESUOMs are not formal NICE guidance and therefore are not subject to the same intensity of process as other NICE products.

Table 1 below shows the key steps in the development of ESUOMs.

Table 1 Key steps for developing an ESUOM with timelines

Key step	Completed by
Topic selected and referred to supplier	Week 0
Scope topic	Week 0
Contact manufacturer and regulator for data	Week 0
Literature search	Week 1
Searching for evidence Sifting and selecting the evidence Appraising and categorising the evidence	Week 2 Week 2 Week 2
Authoring the ESUOM	
Produce initial draft of ESUOM Preliminary technical check of initial draft	Week 5 Week 6
Review of draft ESUOM	

Initial draft sent to manufacturers, regulators, specialist commentators, NICE Clinical Guidelines team and NICE Technology Appraisals team for review	Week 6
Initial draft of information for the public sent to NICE Public Involvement Programme	Week 6
Review comments received and produce revised draft	Week 9
Quality assurance of the ESUOM	
Technical check of content by NICE senior adviser	Week 10
Editorial check of content by NICE publishing team/ NICE senior adviser	Week 12
Internal sign off by Medicines and Prescribing Centre Programme Director, Associate Director or Consultant Clinical Adviser	Week 13
Manufacturer invited to check for any remaining factual errors	Week 13
Sign off and publication of the ESUOM	
Guidance Executive sign off	Week 14
Manufacturer informed of date that ESUOM will be published	Week 15
Publication on NICE website	Week 16

5.3 Scoping of individual topics

The Medicines and Prescribing Centre scope each ESUOM topic, supported by the NICE Guidelines Information Services team. The scoping confirms the following:

- Key contacts at the pharmaceutical manufacturer
- Key contacts at the Medicines and Healthcare products Regulatory Agency (MHRA) or European Medicines Agency (EMA), to obtain evidence held on file that is not confidential
- Specialist commentators (through the NICE Medicines and Prescribing Associates and other existing NICE networks, see section 3.8)
- Commentators for the information for the public, in liaison with the NICE Public Involvement Programme (PIP, see section 3.2)

- Terms for a literature search to identify published clinical trial data that reflect the indication for the unlicensed or off-label medicine
- Arrangements for identifying:
  - regulatory status
  - relevant published trials, or other data on the unlicensed or off-label medicine
  - evidence of clinical effectiveness for the unlicensed or off-label medicine in the condition under consideration
  - safety issues, encompassing key adverse drug reactions, precautions and contraindications providing an indication of frequency of the adverse effects if possible
  - incidence and prevalence of the condition, what treatment alternatives exist and an estimate of current drug usage
  - cost of the medicine and the cost of alternative treatment options.

5.4 Contacting the manufacturer and medicines regulator

NICE asks the manufacturer[a] to support the production of the ESUOM by providing any of the following data it holds (within 10 working days):

- Key published clinical trials relating to the indication being reviewed in the ESUOM and information regarding ongoing or recently completed studies.
- The licence status within the European Union or the UK, including whether or not the manufacturer expects to hold a UK marketing authorisation for this medicine in this indication within the next 2 years or is aware that a medicine licensed in the UK for this indication is likely to become available from another manufacturer within 2 years.
- The presentation of the medicine, including brief details of form, strength and pack size (if relevant).
- The usual dose, if known, or best estimate from the available data.

NICE also contacts the MHRA (or EMA, as appropriate) to ask them for any evidence they

hold on file that is not confidential.

Both the manufacturer and the MHRA (or EMA) are sent the timelines for the production of the ESUOM, including the deadlines for receipt of data and the expected dates for comment on a draft of the ESUOM.

5.5 Literature search

5.5.1 Searching for evidence

A literature search is conducted by the NICE Guidelines Information Services team according to the agreed scope and strategy. The search strategy is documented and included in an appendix to the published ESUOM. Quality assurance for the search process is also documented.

The literature search is intended to locate the best (highest quality) available published evidence relating to the efficacy, safety and cost effectiveness of the medicine (recognising that evidence relating to cost effectiveness of unlicensed or off-label medicines is scarce). In addition, explicit reference is made to information in the summary of product characteristics (if one exists) relating to precautions, warnings and undesirable effects and also to published advice from the Medicines and Healthcare products Regulatory Agency (MHRA) (or the European Medicines Agency [EMA] or Food and Drug Administration [FDA] if no there is no relevant MHRA advice). Cost information is obtained from the current Drug Tariff, or if the product is not listed there, the current edition of MIMS, or if the product is not listed there, the manufacturer.

5.5.2 Sifting and selecting the evidence

The final set of search results are sifted using the title and abstract of each article, first applying exclusion and then inclusion criteria. These include the basic criteria as set out below.

First sift

This process removes evidence based on the following exclusion criteria:

- articles of poor relevance against search terms

- publication types that are out of scope:
  - non-English language studies
  - conference abstracts[6]
  - review protocols (for example, Cochrane review protocols)
  - articles if neither the abstract nor full text is freely available online.

Second sift

This sift of evidence includes relevant primary research that addresses the use of the medicine within the defined indication under review. If robust randomised controlled trials or systematic reviews are available, they form the basis of the review. However, given the nature of the work, the best available evidence on which to produce the evidence summary may include evidence other than randomised controlled trials. Evidence that has been excluded from a previous NICE clinical guideline is not normally included.

The reasons for inclusion and non-inclusion are recorded based on the second sift, as well as a 'long list' of those studies that are excluded from the first sift.

5.5.3 Appraising and categorising the prioritised evidence

The evidence for critical appraisal is prioritised and the reasons for non-inclusion of evidence are recorded. The full text of the prioritised evidence is appraised using an assessment form suitable for the type of evidence.

5.6 Authoring of the ESUOM

The ESUOM is drafted using a standard template, which includes sections relating to the following:

- Key points from the evidence, including:
  - a brief summary of the key points
  - an executive summary of the main sections of the document as detailed below
- Introduction and current guidance

  - general information about the disease or condition, incidence or prevalence and overall survival rate
  - alternative treatment options with links to relevant guidance/evidence
- Product overview
  - information about the drug's action, the product's regulatory status, the course of treatment and cost
- Evidence review
  - a review of the available evidence, with relative strengths and weaknesses of evidence and the evidence selection process
- Context and estimated impact for the NHS
- Relevance to NICE guidance programmes
- References
- Information for the public.

5.7 Review of the draft ESUOM

The draft ESUOM is sent to the identified external specialist reviewers, the manufacturers, the NICE Clinical Guidelines team, the NICE Technology Appraisals team and the drug regulators for review. The draft information for the public is also sent for comment to the NICE PIP team. Any comments received are recorded and considered within the production of the revised draft. Actions and feedback to commentators are also recorded.

5.8 Quality assurance of the ESUOM

Quality assurance of the ESUOM involves a detailed check of all content, to ensure all sections of the document contain statements and conclusions that are fair and balanced. They must accurately reflect the evidence reviewed and be substantiated by an explicit and appropriate source of evidence. A further check for clarity, grammar, spelling and style is carried out, in conjunction with the NICE publishing team. All drafts and any changes to drafts are recorded for audit purposes.

Once sign-off is received from the Medicines and Prescribing Centre Programme Director, Associate Director or Consultant Clinical Adviser, the manufacturer is given the opportunity to review the near-final draft to check for any factual errors (1 working day) and any necessary corrections are made by the Medicines and Prescribing Centre. NICE Guidance Executive reviews the ESUOM, and if appropriate, approves the ESUOM for publication, ensuring that due process has been followed in its development. The manufacturer[5] is informed of the scheduled publication date, and may request an embargoed copy of the ESUOM to be sent to them 24 hours before publication.

5.9 Publication of the ESUOM

The final ESUOM is uploaded and made available online through the Medicines and Prescribing Centre page of the NICE website.

The NICE Communications team develops a communications plan for the ESUOM, together with the Associate Director within the Medicines and Prescribing Centre, and is responsible for disseminating the ESUOM once it has been published.

[5] For some unlicensed or off-label medicines, more than 1 manufacturer may be involved in the development of the drug. On these occasions, all relevant manufacturers based in the UK are contacted for information.

[6] Studies that have been reported only as conference abstracts or otherwise not reported in full are excluded because they cannot be critically appraised. However, the ESUOM may indicate if key clinical trials are ongoing or have been completed but not yet published in full.

[7] For some unlicensed or off-label medicines, more than 1 manufacturer may be involved in the development of the drug. On these occasions, all relevant manufacturers are informed.

6 Review

Every ESUOM states the date of its publication. The literature search (section 5.5) is repeated every 3 years to check if relevant new evidence has been published. In addition, whether or not to update published ESUOMs is considered on a continuing basis by the Medicines and Prescribing Centre at NICE, in the light of its current awareness activities (see Medicines and Prescribing Alerts on the NICE website). Examples of circumstances when an update or withdrawal of an ESUOM might be required include:

- new information or data becoming available that materially affects the efficacy or safety information within the ESUOM
- a marketing authorisation being obtained for the medicine in the stated condition
- NICE publishing a clinical guideline that provides guidance on the use of the medicine in the stated indication.

7 About this integrated process statement

The integrated process statement for 'Evidence summaries: unlicensed and off-label medicines' (ESUOMs) provides a high-level overview of the process for developing ESUOMs and will be supported by the forthcoming NICE guideline manual which explains the processes and methods used to develop and update NICE guidelines. For published ESUOMs, see the NICE website.