Regional Drug and Therapeutics Centre

New Drug Evaluations Process Manual

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NHS

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1. Introduction

This document describes in detail the policies, principles and processes by which New Drug Evaluations (NDEs) are produced. These procedures are designed to ensure that high-quality evidence-based publications are produced in a timely way, with appropriate input from all stakeholder groups. The same essential procedures, transparency and values apply to all RDTC publications.

2. Background

The Regional Drug and Therapeutics Centre (RDTC) was established in 1991 as a collaboration between Newcastle University and the Northern Regional Health Authority. In 1994, NHS boundary changes allowed the centre to increase its activities to cover the Northern and Yorkshire Region. Since the abolition of Regional Health Authorities in 1996, the Centre has been managed as a partnership with Primary Care Organisations and other stakeholders.

The RDTC is a non-commercial, not-for-profit NHS organisation hosted by the Newcastle Upon Tyne Hospitals NHS Trust, which is responsible for employing all of the staff. The RDTC delivers a broad range of services relating to prescribing and the use of medicines, prevention of adverse drug reactions, management of poisoning, and the appropriate use of medicines during pregnancy, which include:

- Prescribing Analysis and Support Services
- Regional Medicines Information Service
- Regional Yellow Card Centre Northern and Yorkshire
- National Poisons Information Service (NPIS)
- The UK Teratology Information Service (UKTIS)

The unique blend of services and proactive support provided by the RDTC allows knowledge and expertise to be shared across stakeholders reducing duplication of effort and facilitating best and equitable use of limited resources.

Further information about the RDTC and its work is available at www.rdtc.nhs.uk.

3. The Prescribing Analysis and Support Unit

The provision of high-quality, timely information and expert advice remains essential to the commissioning and delivery of safe, clinically excellent and cost-effective healthcare. The Prescribing Analysis and Support Unit (PASU) are commissioned to provide strategic prescribing support services to Clinical Commissioning Groups, other primary care organisations, and NHS Hospital Trusts in the North of England.

The PASU delivers a broad range of services relating to prescribing and the use of medicines. This encompasses primary care prescribing analysis, supporting local decision making groups, conducting high-quality critical appraisals of recently-licensed or existing drugs on the UK market and by providing expert training.

The support provided by the unit in prescribing and medicines optimisation aims to help primary care organisation address some of the challenges associated with the medicines optimisation agenda such as high deprivation and high disease prevalence, and manage the impact that this has on the prescribing budget. In addition the unique blend of services and proactive support provided by the unit allows specialist knowledge and expertise to be shared across stakeholders reducing duplication of effort and facilitating best and equitable use of limited resources.

3.2 Funding

The RDTC is a non-commercial, not-for-profit NHS organisation, commissioned and funded by a mix of different organisations such as Public Health England, NHS England, MHRA and Clinical Commissioning Groups. The PASU are entirely independent of the pharmaceutical industry and do not receive any funding from them.

The RDTC maintains a policy of transparency with respect to its funding sources. An annual financial summary is openly published in the RDTC annual report which is freely available to both Commissioners and the Public on the RDTC website.

The work of the PASU is solely funded by Clinical Commissioning Groups (CCGs) from across the North of England and the services commissioned are outlined in a Service Level Agreement (SLA) which is broadly similar for each region. This agreement is currently a three year rolling agreement with an annual review. Staff working within the PASU are wholly and editorially independent from all funding sources and are employed by the Newcastle Upon Tyne Hospitals NHS Trust which hosts the RDTC service.

4. Publications Working Group

National recommendations state that localities should have access to staff with the specialist skills in evidence synthesis and critical appraisal if they are to review and make decisions on the use of medicines. Commissioning the RDTC to provide this support enables commissioners to access specialist expertise without duplicating job roles or positions in each locality. Shared working arrangements across staff employed by the RDTC afford economies of scale to commissioners of the service. In addition working collaboratively across regions allows the centre to facilitate sharing of best practice and aims to support reduction in variations.

The Publications Working Group (PWG) within the PASU is responsible for producing a range of high-quality evidence-based publications and supporting materials to promote the safe, effective and economical use of medicines in the NHS. The PWG has over 20 years of experience in providing evidence-based publications and support to NHS organisations and healthcare professionals. In line with the ever changing environment of the modern NHS and the varying needs of stakeholders, the range of publications and supporting materials has evolved considerably over this time to ensure that outputs continue to remain fit for purpose. These include:

- New Drug Evaluations
- Medicines in Practice
- Evaluation Reports
- Safer Medication Use
- Academic Detailing Aids and Comparison Tables
- Monthly Horizon Scanning Reports

In addition, the PWG produces specialised appraisal reports for various bodies such as the Northern Treatment Advisory Group (NTAG), North of England Commissioning Support (NECS) unit and the Greater Manchester Medicines Management Group (GMMMG). The group also provides support for local and regional Area Prescribing Committees, New Drugs and Formulary groups and Drug and Therapeutics Committees.

Nationally the group has acted as the Evidence Review Group for the clinical efficacy section on several National Institute for Health and Care Excellence (NICE) Single Technology Appraisals (STA), and is currently undertaking evidence reviews for NHS England Specialised Services to support development of its clinical commissioning policies. The PWG is a key contributor to the production of Prescribing Outlook - an UKMi National Horizon Scanning document to assist NHS commissioners in planning, implementing and budgeting for new medicines.

4.1 Composition of the PWG

The PWG is a multidisciplinary team consisting of clinicians, pharmacists, information scientists and administrative and support staff (box 1). The PWG meets at least once every month, although individuals from the group will meet more frequently.

Box 1. Membership of the Publications Working Group.

- Clinical Editor (Chair)
- Medical Director/Consultant Physician
- Director of Pharmacy
- Consultant Physician
- Head of Prescribing Support
- Principle Pharmacist (Medicines Management) x 2
- Senior Information Scientist
- Principle Pharmacist Medicines Information (NHSD Lead)
- Principle Pharmacist
- Senior Pharmacist Medicines Information
- Senior Pharmacist
- Lay member

In developing its publications, implementation and support tools, the PWG works in close collaboration with other members of the PASU, including information specialists, data analysts, a statistician and a website/electronic media developer. The PWG also has access to a unique blend of knowledge and expertise provided by other RDTC staff in the fields of pharmacovigilance, teratology and toxicology.

In all instances, members of the PWG and associated staff are required to conduct themselves in accordance with RDTC and NHS polices and procedures.

Prior to publication, the RDTC Senior Management Team must formally approve the content of all PWG publications. The senior management team consists of a Medical Director, a Director of Pharmacy, a Consultant Physician and the Head of the PASU.

In order to promote openness, transparency and impartiality in its business, the PWG requires at least one lay member to be directly involved in the process of developing each NDE. Nevertheless, having lay or patient representatives on the PWG is only one method of public engagement and the PWG continues to explore a variety of methods to reach across to patients and service users.

Lay members are not expected to be expert individuals and require no formal qualifications. However, each lay member must have good communication and team working skills, the ability to be objective, and an understanding of the issues important to patients. They must also have the time to commit to the work of the group in attending meetings, reading papers including summaries of research evidence, and commenting on draft documents. Although their knowledge, skills and experience will vary, lay members have equal status within the group.

The PWG will provide lay members with clear guidance on their roles and responsibilities within the group. The key roles of lay members on the PWG are outlined in box 2.

Box 2. Key roles of lay members of the Publications Working Group.

- Ensuring that the key questions are informed by issues that are important to patients and carers.
- Helping to identify patient-orientated outcomes and relevant terms for the literature search.
- Raising awareness of grey literature which highlights patient issues or concerns.
- Identifying areas where patients' preferences and choices may need to be acknowledged in the document.
- Making sure that the evidence which addresses patients' and carers' concerns is reflected in the evaluation.
- Assisting in identifying relevant individuals to take part in the peer-review process.
- Helping to ensure the evaluations are worded appropriately, avoid unnecessary jargon, and whether any technical terms need to be explained.
- Ensuring that the evaluation and recommendations addresses issues that may be overlooked by health professionals.

As with all professional members of the PWG, lay members are required to comply with the RDTC code of conduct on conflicts of interest (see section 13). In addition, all lay members are asked to complete a confidentiality agreement to ensure that

they do not make the work of the group public. The PWG will not pay Lay members for taking part in the group, but will cover reasonable travel expenses.

4.2 Stakeholder involvement

Stakeholders for NDEs are Area Prescribing Committees, New Drugs and Formulary groups and Drug and Therapeutics Committees. They are also routinely used by General Practitioners, Secondary Care Consultants, Prescribing Advisers, Community/Primary Care Pharmacists and Nurse Prescribers. The PWG maintains an up to date contact list of stakeholder organisations and their members and actively encourages stakeholder involvement in the development, reviewing and quality assurance process of all publications. The lead author of each publication will contact a representative sample of stakeholders and invite them to participate in the publications process, or to nominate a specialist contact to whom a draft copy may be sent for review.

The PWG regularly reviews the format of publications to ensure they continue to meet the needs of all stakeholders. The group values the contribution of stakeholders and encourages comments and suggestions on the style and content of NDEs, and on all aspects of the publications process. Established quality assurance processes monitor feedback from stakeholders and enable a prompt response to any issues which may arise.

4.3 Patient involvement

Patients are not the intended audience for RDTC publications. However, the PWG believes it is essential that the needs, concerns and preferences of patients and their careers are considered from the beginning of the development process. It is essential that the PWG has a comprehensive understanding of the efficacy and safety outcomes that matter directly to patients when drawing conclusions and considering recommendations. The publications process has been developed to specifically incorporate a patient perspective wherever possible. One of the principle measures used to achieve this is to conduct a specific literature search to find relevant information on patients and carers preferences in relation to the topic under consideration. This search will cover both quantitative and qualitative research. The websites and networks of relevant patient support organisations, carer groups and charities are also examined. As the documents are utilised at local decision making groups which may include patient membership; patient views or feedback in particular is encouraged. In addition, as part of the Newcastle Upon Tyne Hospitals NHS Trust, the RDTC has access to the patient involvement forum where specific topics can be taken for patient feedback if necessary. If important gaps are identified in the evidence related to patient's preferences the PWG will consider the targeted use of patient focus groups and social media.

As patients are not the intended audience for RDTC publications, each NDE includes a definitive statement that they are intended for use by healthcare professionals, and that patient information on many topics can be accessed via NHS direct.

4.4 Equality and diversity considerations

The RDTC is committed to promoting equality in healthcare. All RDTC publications and the procedures used to develop them are in accordance with the Newcastle upon Tyne Hospitals NHS Foundation Trusts Equal opportunities and diversity policy.

4.5 Training for professional PWG members

All healthcare professionals within the RDTC receive appropriate induction and undertake structured training packages in medicines information, poisons and teratology, with formal evaluation before unsupervised working.

In addition, all professional members of the PWG are provided with the necessary training to ensure they have the appropriate knowledge and skills to produce high-quality drug evaluations. This may involve specialised in-house training in evidence based medicine, critical appraisal, statistics and medical writing. Ongoing learning is supported by regular CPD sessions, courses and attendance, as appropriate, at national training events and conferences. Regular review and staff development has ensured that outputs continue to remain fit for purpose.

4.6 Training and support for lay members

The PWG will provide lay members with clear guidance on their roles and responsibilities within the group. All lay members will be offered support on a one-to-one basis, and via telephone and e-mail support.

The Clinical Editor will offer tailored training to all lay members of the PWG to help them make an effective contribution to the NDE development process. This will include an introductory session that details how they can contribute to the NDE development process, and focuses on the skills they need to take part in the PWG. Depending upon individual requirements lay members will be offered IT skills and critical appraisal training.

5. New Drug Evaluations

New Drug Evaluations (NDEs) are concise, structured reviews of new drugs recently launched or approved within the NHS that are considered to be primary care orientated and likely to have a significant clinical or financial impact. New indications and new formulations of existing medicines, and drugs that are likely to be initiated in secondary care but transferred to primary care are also evaluated.

NICE underpins the decision making processes regarding the introduction of new medicines within the NHS. However, not all new drugs will be referred to NICE for appraisal and for those interventions that are referred to NICE there may be a significant time lag whilst NICE guidance is being developed. A key role of NDEs is to support primary care organisations to effectively and efficiently manage the introduction of new medicines in the absence of NICE guidance.

NDEs are prepared by a multidisciplinary team based on a review of the best available evidence in accordance with the guiding principles of the Appraisal of Guidelines for REsearch and Evaluation (AGREE) II instrument. Although the AGREE instrument was developed to address the issue of variability in the quality and reporting of clinical practice guidelines, the underlying principles of methodological rigor and transparency are directly applicable to the production of NDEs.

5.1 Aims

In line with current Quality, Innovation, Productivity and Prevention (QIPP) national initiatives NDEs are designed to support quality and efficacy at a local level by guiding primary care organisations in promoting appropriate, effective and efficient prescribing. The aim of each publication is to improve the quality of care for patients by giving a structured appraisal of the best available evidence and thereby aiding commissioners and prescribers alike in making decisions on how healthcare professionals should prescribe new drugs.

5.2 Key audiences

The target audience and stakeholders for NDEs include Area Prescribing Committees, New Drugs and Formulary groups, Drug and Therapeutics Committees, General Practitioners, Secondary Care Consultants, Prescribing Advisers, Community/Primary Care Pharmacists and Nurse Prescribers. The PWG actively encourages stakeholder involvement in the development, reviewing and quality assurance process of all publications. All stakeholders are encouraged to take an active role in suggesting new topics for evaluation. The external peer review process also ensures that the target audience have an opportunity to comment of the proposed place in therapy and identify any potential difficulties for implementation before any recommendations are finalised.

6. Topic identification and selection

The Publications Working Group (PWG) is responsible for selecting topics for NDEs. The horizon scanning activities of the PWG are the primary route for identification of significant new drugs. The group produces Monthly Horizon Scanning Reports detailing newly licensed products, significant license extensions, new and forthcoming NICE guidance, and the determinations and recommendations of other recognised national bodies. These horizon scanning reports are standard agenda items on several Area Prescribing Committees and at multidisciplinary Drug and Therapeutic team meetings. All stakeholders are actively encouraged to comment on the content of NDEs and to suggest new topics for evaluation. Proposals for topics may also be submitted to the PWG through a number of external channels including, but not limited to:

- Local / area group meetings
- Directly from stakeholders
- Intelligence from medicines information related enquiries

All proposed topics for NDEs are discussed by the PWG at one of its monthly publications meetings. In identifying and selecting topics for evaluation the PWG will consider the criteria defined in box 3.

Box 3. PWG criteria for Identification, selection and prioritisation of NDE topics.

- The drug is first-in-class, has a novel mechanism of action or has a major new indication
- The target population is large
- The drug has the potential to provide a significant improvement in disease management
- There are limited alternative treatment options available
- Whether there is significant variation in clinical practice in different areas
- The importance in relation to NHS policy and whether the topic falls within a 'priority area'
- The potential cost-implications are high
- Potentially significant patient and service implications
- There is likely to be considerable clinician, patient and/or media interest

In all instances, topics are considered for an NDE only if a NICE technology appraisal (TA) is not currently in progress, unless an appraisal consultation document (ACD) is unlikely to be published within six months of the drugs approval. In order to avoid duplication of effort and facilitate best and equitable use of limited NHS resources, the Chair of the PWG will liaise with other NHS organisation (e.g. London Medicines Evaluation Network) to ensure that other such reviews are not currently in progress or planned within the expected time frame for production.

In the majority of instances, a process of informal consensus within the PWG is deemed to be sufficient to approve topics for publication. If there are conflicting opinions within the group, the recommendation will be put to a majority vote. If at the time of the meeting there is insufficient information available on which to make a decision, a more detailed scope will be circulated to the group for consideration prior to the next meeting. Once the topic is formally approved, the Chair will confirm the lead author and add the publication to the work plan, along with an estimated publication date.

The Secretary of the PWG takes formal meeting minutes as a permanent and accessible record of business transacted at the monthly PWG meetings. These provide a summary of the discussions which took place, the decisions which were reached, and the actions which are to be taken as a consequence of decisions reached at the meeting. Copies of the agendas, minutes and any supplementary materials are retained by the Chair of the PWG, and made available for inspection upon request.

7. Defining the scope

The PWG will hold an internal scoping exercise for each topic formally selected for publication. The scoping document is prepared by the lead author and circulated to all members of the PWG for comment. The purpose of the scoping document is to:

- Confirm the generic name, trade name and pharmaceutical form
- Confirm the pharmaceutical manufacturer and/or UK/EU promotional company
- Clarify the proposed or likely indication and determine the incidence/prevalence to inform an estimation of use
- Establish the licensing and launch plans
- Identify terms for a literature search by defining the:
    - Target population
    - Treatment alternatives (comparators)
    - Outcome(s) of interest
- Gauge the breadth and quality of available evidence
- Identify relevant national guidance and independent reviews
- Outline the key objectives of the evaluation

The time taken to publish a NDE varies according to the scope of the topic, the volume of evidence to be critically appraised, the feedback received during the review process and the competing pressures on the time of members of the PWG.

8. Identifying and selecting the evidence

8.1 Systematic literature review

A systematic literature search is conducted by the lead author to locate the best (highest-quality) available published evidence relating to the efficacy and safety of the medicine under review. The primary literature is identified according to an explicit search strategy, selected according to predefined inclusion and exclusion criteria, and evaluated against consistent methodological standards. Searches should aim to achieve a balance between sensitivity, and precision. Identification of relevant studies is undertaken using a thorough, unbiased search strategy based on the components of the PICO (Population, Intervention, Comparator, and Outcome) format:

Patients - The patients or population to be covered by the literature searches is largely defined by the approved indication for the particular drug that the evaluation will cover. Consideration should be given as to whether any particular ethnic or social groups have specific needs in relation to the topic under review. Exclusion of any specific patient group from the population covered by the search should be identified when defining the scope, and reasons given for their exclusion.

Intervention - Restricted to the named single-agent and/or combination - including generic name, brand name and synonyms.

Comparators - Largely defined by the approved indication. The appropriate comparator will ideally be existing therapies or current best standard of care. However, it is important to explore differences between the new drug and placebo or no treatment in order to identify and evaluate those effects which are truly related to the intervention. Where multiple interventions exist, limiting the types of comparators may not be appropriate or desirable.

Outcomes – Patient-orientated outcomes should be explicitly considered along with more narrowly defined clinically important outcomes. It is particularly important to include any potentially significant safety outcomes with the intervention under review. Such outcome measures might be primary or secondary, short- or long-term.

Depending upon the agent and specifics of the indication, some default options may need to be modified. The preferred search terms are identified during the scoping exercise and the rationale for any exclusion documented. In some instances database limit functions may be used to improve precision. The time period covered by the search will depend on the nature of the topic under consideration. For first-in-class drugs a ten year limit to the search may be appropriate, whereas for established drugs with new indications a longer time frame is necessary.

In order to ensure sufficient coverage of the relevant literature, all searches are undertaken using a variety of bibliographic databases and research registers. For all NDEs it is recommended that MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) are searched, as a minimum. To identify economic data, the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) are searched.

In addition to the primary literature searches, the websites of the Medicines and Healthcare products Regulatory Agency (MHRA), European Medicines Agency (EMA), NICE, Scottish Medicines Consortium (SMC), All Wales Medicines Strategy Group (AWMSG), NHS Clinical Knowledge Summaries (CKS), Scottish Intercollegiate Guidelines Network (SIGN), and the Food and Drug Administration (FDA) are searched for relevant guidance, assessment reports, summary of product characteristics (SPC) and safety reviews.

A broader search for unpublished research 'grey literature' and ongoing trials is also undertaken using relevant clinical trials registries, horizon scanning resources, major conference proceedings, and where available commercial Pharma resources and drug pipeline databases. Cost information is obtained from the current electronic Drug Tariff, or if the product is not listed there, eMIMs, BNF online, or the manufacturer.

Due to resource and time constraints, The PWG does not routinely undertake hand searching of reference lists from primary and review articles as part of the search process. However, such searches may be practical if the relevant articles appear in a limited range of journals or conference proceedings.

8.2 Identifying patient and carer views

A specific search is conducted to find relevant information on patients and carers preferences in relation to the topic under consideration. In the context of this process, patient preferences refers to patients beliefs, expectations, and goals for health, and the factors that individuals consider important in determining the potential benefits, harms and inconveniences of the various treatment options. This search is designed to retrieve both quantitative and qualitative evidence, and is not restricted to specific study designs. It is carried out over the same range of databases and sources as the main literature review, but will also include a detailed examination of the websites and networks of relevant patient support organisations, carer groups and charities. When undertaking these searches it is important to consider how to capture the perspective of 'seldom-heard' or 'socially excluded' patients who are not part of organised groups or who don't have organisations to advocate for them. When important gaps are identified in the evidence related to patient's preferences the PWG will consider the targeted use of patient forums, focus groups and social media.

8.3 Search filters

The literature search should focus on the best (high-quality) available evidence. Existing highly sensitive) methodological search filters may be used to limit large search results or to retrieve specific types of records (e.g. systematic reviews, randomised controlled trials, etc.). Specialised search filters may also be used to identify economic evaluations, and studies on patient issues. These standardised search filters are made up of MeSH and freetext search terms and use advanced search operators. Examples of appropriate search filters can be found on the InterTASC Information Specialists' Sub-Group Search Filter Resource hosted by the CRD (http://www.york.ac.uk/inst/crd/intertasc) and on the SIGN website (http://www.sign.ac.uk).

The search strategy is documented in sufficient detail so that the process for identifying evidence is transparent and reproducible. Details of the core sources, date ranges, date search was conducted, limits and filters used, as well as search terms are made available externally upon request.

8.4 Contacting the manufacturer

When a topic is selected for an NDE, a formal request is sent to the manufacturer of the drug under review inviting them to provide all relevant data to support the production of an evaluation. This may include:

- Details and copies of key published trials relating to the topic under consideration
- Details of any relevant ongoing clinical trials
- Copies of any relevant abstracts or conference proceedings
- Details of proposed licensing and/or marketing plans
- Advanced budgetary notifications, including information on the expected cost
- Details of any post-marketing surveillance and any safety concerns

The manufacturer is also invited to comment on a late-stage draft of the NDE, and provide comments only on factual errors and inaccuracies, and if necessary to respond to any specific questions regarding the information they submitted to inform the evaluation.

The PWG are wholly and editorially independent of the pharmaceutical industry and all staff are required to conduct themselves in accordance with RDTC policy and guidance for interacting and joint working with the Pharmaceutical Industry (available for inspection on request). All data provided by the manufacturers in response to a request for evidence will be considered, but will only be included if it can verified with information obtained from the public domain.

8.5 Inclusion and data extraction process

In order to ensure that the selection process is rigorous and replicable, pre-specified inclusion and exclusion criteria based on the PICO criteria are applied. Studies are selected for inclusion using a standardised two-stage process. In the first stage, the titles and abstracts of all articles are screened to identify those which potentially meet the inclusion criteria. If the relevance of the article is unclear based on the title and abstract,

the full-text version of the paper should be obtained. All papers which potentially meet the inclusion and exclusion criteria and are available in full-text format are included in the second screening stage. It is PWG policy that all authors and others involved in the review should adhere to copyright legislation and the terms of database licensing agreements.

The second stage of the process requires the reviewer to rigorously assess the full manuscripts of potentially relevant citations and decide whether the paper should be included or excluded based on the pre-defined criteria. Any uncertainties are resolved by consensus with a second reviewer, with involvement of an independent third reviewer when necessary. All studies that fail to meet the inclusion criteria will be excluded. No exclusion criteria should be applied to drug safety topics, as all relevant data regarding the topic of interest must be evaluated.

Evidence is prioritised according to the accepted hierarchy of evidence, whereby robust meta-analyses, systematic reviews and randomised controlled trials are taken to be the most authoritative forms of evidence. Where such evidence is lacking for an indication, other study designs will be included; giving preference to those designs which minimise the risk of bias or which are most appropriate to the nature of topic under review.

Data published in the EMA and MHRA regulatory reviews are used to supplement the information included in the evaluation, if this is necessary. Evidence from relevant National and International guidelines will be included were appropriate. Abstracts, conference presentations and unpublished data may be included only if sufficient details are presented to allow a robust critical appraisal of the methodology and results. Non-English language articles will only be considered if there is an acknowledged English translation available. General reviews, commentaries and editorials that interpret the results of published primary studies will not be included in the evaluation, but will be retained for discussion. Animal studies are excluded.

Clinical data provided by the manufacturers in response to a request for evidence will be considered, but will only be included if it can verified with information obtained from the public domain. Confidential budgetary data will not be reported in the final evaluation. Results derived from calculations using confidential data may be included only if back-calculation to the original confidential data is not possible. Any promotional material will not be included in the evaluation, but will be retained for discussion.

To ensure that the process for identifying evidence is transparent and reproducible, the study-selection process is documented with details of the inclusion and exclusion criteria that were applied.

9. Assessing the quality of the evidence

The quality of selected evidence is assessed against consistent methodological standards. Each study is critically appraised for quality using a standardised checklist according to the SIGN methodology. This is a widely recognised and understood methodology which provides a common language for all participants in the NDE development process that can be adapted to suit specific requirements and constraints. The methodological assessment is based on a number of key questions focusing on those aspects of the study design that are likely to have a significant influence on the validity of the results reported and conclusions drawn. These criteria differ between study types and a range of study specific checklists are used to ensure a consistent approach to the assessment process. These checklists were subjected to detailed evaluation to

ensure they meet PWG requirements for a balance between methodological rigour and practicality of use, and are routinely reviewed to take account of any subsequent changes in methodology. Copies of current checklists and accompanying notes on their use are available on the SIGN website http://www.sign.ac.uk/methodology/checklists.html. An example of the checklist used to evaluate controlled trials and systematic reviews and meta-analyses can be found in appendix 1 and 2, respectively. The checklists specific to the type of study being considered are used to facilitate appraisal but are not required to be completed by the authors.

To aid assessment, the data from each study are extracted by the lead author and recorded in evidence summary tables listing the key characteristics of the individual studies. The summary tables provide a basis for comparison and acknowledge any areas of uncertainty and those where there is a lack of quality evidence. The result of this appraisal will determine the level of evidence assigned to the article. Any unpublished data selected for inclusion are subjected to the same quality assessment as published studies.

The evidence assessment process inevitably involves a degree of subjectivity. To minimise potential bias and ensure consistency, quality criteria are applied by the lead author and checked by a second reviewer. Any discrepancies are resolved by consensus, with involvement of an independent third reviewer when necessary. Studies which are considered methodologically unsound are excluded from the review.

9.1 Assigning levels of evidence

Each study meeting the minimum quality criteria is ascribed a level of evidence according to SIGN definitions (table 1). This judgement is made on the basis of an objective assessment of the validity, reliability and applicability of each study.

Table 1. Levels of Evidence (adapted from SIGN)

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

An overall level of evidence is assigned to the evaluation based on the quality of the body evidence and the suitability of that evidence to address the issues under consideration This grading system is intended to demonstrate the overall strength of the evidence available to support any recommendations, and to emphasise that the body of evidence should be considered as a whole.

10. Authoring of NDE

This section of the process manual considers the practical issues involved in the presentation of a NDE. The content and presentation of NDEs has evolved following consultation with stakeholders at various stages of development. NDE are concise, structured reviews presented in a clearly defined format using unambiguous language. A well-developed and clearly defined procedural template is used to provide a standardised framework for undertaking NDEs, ensuring that due process is followed in its development. This use of this procedural template enables the author to plan at the outset what type of information will be required and what format this information will take (appendix 3). Each NDE typically considers the following aspects: pharmacology, dosage and administration, efficacy, safety, other treatment options, recommendations on place in therapy, economic impact, comparative cost and references. Additional aspects may be discussed depending upon the topic under consideration.

10.1 Overview

For clarity and consistency of presentation the recommended international non-proprietary name (rINN) is used. The proprietary (brand) name and manufacturer's name are generally only given in parentheses at first mention. The therapeutic class and/or mode of action together with dosage and administration details are given to highlight any potential service implications.

10.2 Efficacy

Clinical effectiveness data are synthesised through a narrative review with tabulation of results where necessary. The focus is on the primary outcome data of key published studies with patient-orientated outcomes specifically included where available. Decisions about whether to consider surrogate outcomes should be informed by available evidence regarding associations between the surrogate and the outcome of interest. If a European Public Assessment Report (EPAR) has been published, it is used to supplement the information included in the evaluation, if this is necessary.

10.3 Safety

Clinical safety data are synthesised through a narrative review detailing the major and most common adverse effects, with an indication of frequency, where possible. The focus is on those adverse effects that are considered by patients or clinicians as the most serious and/or severe and/or troublesome, or likely to lead to withdrawal from treatment. Explicit reference is made to information provided in the SPC (if available), relating to precautions, warnings, clinically important interactions and monitoring requirements, especially where a new drug differs significantly from that of currently available treatments. If an EPAR has been published, it is used to supplement the information included in the evaluation, if this is necessary. However, the content of this section is not intended to be exhaustive and therefore prescribers are expected to consult the respective SPC for full details of adverse effects, administration and monitoring requirements.

10.4 Strengths and limitations of evidence

The potential strengths and limitations of the evidence are critically reviewed in each NDE. Factors highlighted include:

- The reliability of the studies in the body of evidence, focussing on the quantity of evidence available and its methodological quality.
- The consistency of the studies in their conclusions including any conflicting results.
- The applicability of the data to the intended target population, focussing on the relevance of the populations, interventions, comparators or outcomes to the topic under consideration, including use of indirect (surrogate) outcomes.
- Areas where there is uncertainty.

10.5 Other options

To aid systematic decision making the overall pathway of care and the alternative treatments that are available, including use of unlicensed comparators (if appropriate) are summarized along with the recommendations of relevant National Guidelines. Where appropriate, this will include signposting to applicable NICE pathways and quality standards (section 10.5). The preference of each option in the care pathway should be indicated where possible (such as alternative, first-line, second-line). Due to the concise nature of NDEs there is insufficient scope to discuss every treatment option and their relative benefits and harms..

10.6 Cost implications

An important aspect in determining the uptake of new drugs within the NHS is the potential cost-implications. To underline the relative cost of a new drug each NDE includes a cost-chart comparing a range of appropriate drugs for that particular indication. These charts show comparative costs at basic NHS prices and except where indicated otherwise, each shows the cost of one-year of treatment at a standard daily dose. These charts are not intended to be exhaustive. The doses shown are for comparison purposes only and are not intended to imply therapeutic equivalence. Nevertheless, they present a powerful message to prescribers about the wide variation in costs that is often evident within therapeutic classes. If the cost of the new drug is not available at the time of publication the NDE will be updated once pricing information becomes available.

10.7 Place in therapy

Recommendations on the place in therapy of a new drug are produced using a considered judgement process informed by systematic reviews of the best available evidence. Balancing the potential benefits and harms of an intervention are crucial in developing recommendations that are evidence based, but directly applicable to current clinical practice. The lead author must establish what the evidence means in the context of the topic under consideration and where there is sufficient evidence propose what recommendations on the place in therapy can usefully be made to healthcare professionals. For potential recommendation to be implemented effectively, it is essential that the outcomes considered are sufficiently valued by patients for them to be willing to

adhere to the treatment. Therefore, authors must ensure they consider all patient-orientated outcomes, including those for which limited data may be available.

All recommendations should be clear, concise and unambiguous and where possible include a definite statement as to when, or indeed if the new drug should be prescribed, and to whom in relation to existing therapies. Any recommendation should ensure they highlight any potentially significant patient and service implications, along with any uncertainties concerning the proposed recommended place in therapy. Potential financial and organisational barriers to implementation should also be considered especially if it may involve other agencies or professionals across a care pathway. It may also be useful to briefly discuss any change in practice that will be needed for example training programmes or shared care arrangements.

A draft including the proposed recommendation is circulated internally, and the opinion of all PWG members on the place in therapy is sought. In most instances, a process of informal consensus within the PWG is sufficient to formulate recommendations based on the best available evidence. Because the PWG is multidisciplinary, its members will bring with them different beliefs, values and experience. All these perspectives are valued and respected. The role of the Chair is to ensure that each individual has an equal opportunity to present their views and that the discussions are open and constructive. The internal comment process should ensure there is sufficient discussion to allow a range of possible approaches to be considered. If the group cannot come to consensus in a particular area, the recommendation will be put to a majority vote.

The robust external peer review process also ensures that the target audience have an opportunity to comment of the proposed place in therapy and identify any potential difficulties for implementation before any recommendations are finalised. This would also include sending the document to specialist commentators where possible. The PWG will consider all feedback, and if necessary modify the recommendations to address any concerns. Once a recommendation on the place in therapy has been established a final draft is sent to the RDTC senior management/physician team for formal approval of the content.

It is important to note that NDEs are intended to be used as a local decision making aid and DO NOT constitute formal guidance. The ultimate decision regarding the prescribing of a particular treatment will always depend on an individual patient's circumstances and wishes, and the decision to prescribe a treatment remains the clinical judgement of the healthcare professional.

10.8 Referencing

Supporting evidence sections are fully referenced. Bibliographic software (EndNote®), are used to record and manage references. Records can be exported from bibliographic databases and imported automatically into the software using the appropriate import filters. Details of references can also be added manually. By creating a 'library' of references, information can readily be shared by the whole PWG. Linking to word processing packages enables the automatic generation of in-text citations and the production of full reference lists in the standardised PWG output style. References link to freely available full-text articles where possible.

11. External review process

The peer-review process must be transparent, equitable and robust. This requires that all NDEs are reviewed externally by a representative sample of the target audience who are wholly independent of the PWG. The group maintains an up to date contact list of stakeholder organisations and their members including General Practitioners, Secondary Care Consultants, Prescribing Advisers, Community/Primary Care Pharmacists, Nurse Prescribers, and other healthcare professionals. The lead author of each publication will contact a representative sample of these stakeholders and invite them to participate in the publications process, or to nominate a Specialist contact to whom a draft copy may be sent for review. The external reviewers are asked to provide comments on the clarity, validity, applicability and overall usability of the document. Specialist commentators such as General Practitioners or other primary care practitioners with expertise in a relevant therapeutic area may also be asked to provide comments on potentially significant patient and service implications from a primary care perspective.

The manufacturer of the drug under review is also invited to provide comments. The manufacturer is requested to comment only on factual errors and inaccuracies, and if necessary to respond to any specific questions regarding the information they submitted to inform the evaluation.

All draft publications are marked accordingly to prevent unauthorised circulation and any changes to drafts are recorded for audit purposes. Any comments received are considered within the production of a revised draft, and all actions are recorded. A full list of reviewers and their affiliations are made available to stakeholders upon request.

All external reviewers are asked to disclose any potential conflict of interests at the time of submitting their comments. Each reviewer is provided with a declaration of interests form and guidance notes adapted from the RDTC Conflicts of Interest Policy. This provides guidance on what interests (specific or non-specific and financial or non-financial) need to be declared. The PWG endorse a policy of If in doubt, disclose. All completed forms are held in confidence and are available for inspection upon request.

12. Quality control

Quality assurance of the NDE is carried out by the lead author and at least one nominated reference checker. This process involves a detailed check of all content to ensure that all statements are substantiated by an explicit and appropriate source of evidence and that any conclusions accurately reflect the evidence reviewed. A further check for accuracy, clarity, readability, typographical errors, and consistency is undertaken prior to production of the final draft. Once sign-off is received from the Senior Management Team the Clinical editor reviews the NDE and approves the document for publication, ensuring that due process has been followed in its development. All drafts and amendments are retained for audit purposes. Full citations for all the references used in each publication are stored using EndNote®.

The PWG regularly reviews the format of publications to ensure they continue to meet the needs of all stakeholders. The group values the contribution of stakeholders and actively encourages comments and suggestions on the style and content of NDEs, and on all aspects of the publications process. Established quality assurance processes

monitor feedback from stakeholders and enable a prompt response to any issues which may arise.

Several methods for providing feedback are presented to stakeholders accessing the website. Feedback may also be sought via direct contact with users of the service. Techniques employed to date have included user surveys and user group forums. The information received from such exercises is used to guide the future development of publications.

13. Declarations of interest / Conflicts of interest

The RDTC is committed to continuously extending its approach to openness and transparency. Without it, healthcare professionals, the public and the pharmaceutical industry will lack confidence in our work.

All RDTC staff are required to comply with the RDTC code of conduct on conflicts of interest. Given the nature of the centres work, particular care and transparency is necessary in relation to potential interests in the pharmaceutical industry. All members of RDTC staff, including the Medical and Pharmacy Directors, are required to declare all categories of interests on appointment and to complete and sign an annual declaration of interest form. Signed copies of these forms are retained by the RDTC Services Manager and are made available for inspection upon request.

In addition to declaring interests, all staff are required to conduct themselves in accordance with RDTC policy and guidance for interacting and joint working with the Pharmaceutical Industry (available on request). All RDTC staff must also comply with Newcastle Upon Tyne Hospitals NHS Trust's anti-bribery procedures and Standards of Business Conduct policies.

At the start of each PWG meeting all members are asked to declare any potential conflicts of interest that may preclude their involvement in any aspect of the agenda. Any such conflicts of interests are duly recorded in the minutes of the meeting. In accordance with the principles outlined in the RDTC Conflicts of Interest Policy the Chair will determine as to whether or not a declared interest is in conflict with the work of the PWG. Any member with conflicts that could be regarded as prejudicing their contribution to the discussion will be excluded from any further involvement in the related agenda item(s). It is recognised that individuals may have some interaction with the Pharmaceutical Industry, whilst this should be declared; it does not necessarily preclude them from membership of the PWG.

All external reviewers are asked to disclose any potential conflict of interests at the time of submitting their comments. Each reviewer is provided with a declaration of interests form and guidance notes adapted from the RDTC Conflicts of Interest Policy. This provides guidance on what interests (specific or non-specific and financial or non-financial) need to be declared. The PWG endorse a policy of If in doubt, disclose. All completed forms are held in confidence and are available for inspection upon request.

The lead author in consultation with the Clinical Editor has the responsibility for scrutinising declarations of interest submitted by external reviewers. Where the reviewer has a potential conflict to declare, the lead author should liaise with the Clinical Editor who will decide on a case-by-case basis what action should be taken to ensure the integrity of the process and to mitigate the potential for bias. Where there may be a

reasonably perceived conflict of interest or whereby processes are already underway when the perception is raised, the Clinical Editor will be responsible for deciding the impact it may have on the work of the PWG, and what action is necessary.

All declarations of interests are held in confidence by the PWG and are not routinely published. Competing interests are available for inspection upon request, but will not be made public without permission from the individual concerned.

14. Publication and dissemination

The PWG maintains a paperless publishing protocol. Once the Senior Management Team has given final approval ('signed-off') the NDEs are published in electronic format only with a pdf. version made available for download from the RDTC website http://rdtc.nhs.uk/. Access to new publications is restricted to stakeholders only for a period of three months following publication. After three months all NDEs are made publicly available without restriction via the RDTC website or the Specialist Pharmacy Services (SPS) website https://www.sps.nhs.uk/. However, some associated implementation and support materials containing confidential data may remain under password protection to provide security but enable easy access by registered stakeholders.

Stakeholders are notified when a document is published via a number of methods including direct e-mail, RSS feed, and newsletter. All RDTC staff are encouraged to promote awareness of PWG publications and support materials whenever possible.

Copies of the literature searches, evidence tables, references, comments and other relevant materials are held at the RDTC office and can be made available on request. These are kept on file for a period of five years following the publication of the document.

15. Process for reviewing and updating NDEs

Due to the time limited nature of New Drug Evaluations they are published with the expectation that they will not be routinely reviewed or updated. However, the PWG continues to identify new evidence relevant to published NDEs through systematic literature surveillance process ('horizon scanning').

Each month the PWG publishes a comprehensive Monthly Horizon Scanning Report which provides details of new products and changes to licensed indications, summaries of important new evidence (efficacy and safety) for existing drugs, sign-posting to recently published and forthcoming NICE Guidance and Quality Standards, as well as recent decisions of the SMC and AWMSG. The SOP for the Monthly Horizon Scanning Reports is provided as additional evidence.

The PWG have the responsibility for scrutinizing any new data and for identifying factors that may trigger a substantive review of an existing publication. Only in the occurrence of compelling new clinical information that has a significant and direct bearing on the safety of a drug or on the recommended place in therapy will the publication be updated, or in exceptional circumstances withdrawn. Any such updates to the publication will be noted on the RDTC website. If an update is deemed unnecessary the PWG will consider whether to include the new data in the bi-monthly prescribing support newsletter.

If the cost of a new drug is not available at the time of publication the NDE will be updated once confirmed pricing information becomes available. Following publication of a NDE, any agents which are subsequently reviewed by NICE within a Technology Appraisal, are annotated on the website with a (N) after the drug name. Users are referred to the NICE website to access the latest guidance for these agents.

In view of the continued emergence of new evidence, all readers are recommended to re-check the biomedical literature after 18 months beyond the publication date of each NDE. The PWG continues to monitor the uptake and prescribing of new drugs. If there are a number of significant new developments or safety concerns within a therapeutic area covered by one or more NDEs the PWG may consider publishing another document within the publications series (e.g. Medicines in Practice or Safer Medication Use) to support stakeholder medicines optimisation services.

16. Implementation and support tools

The PWG encourages stakeholders to use their networks and influence to encourage implementation of publications at a local level. To aid interpretation and implementation of the publications the PWG and PASU produces a unique blend of additional information and proactive support to reduce duplication of effort across the North of England and to facilitate best and equitable use of limited resources. Some support tools which contain confidential data are available only to registered stakeholders.

Examples of support tools and services include:

- Academic detailing aids (ADAs) - Academic detailing is established as one of the few effective educational methods known to change prescribing behaviour. These concise educational materials aim to support discussions with prescribers on the key prescribing and medicines optimisation messages from NDEs. Practice visit detail aids are provided in Microsoft Word® format to allow addition of local guidance or prescribing data.
- Comparison tables -
- Cost-comparison charts – updated quarterly, these charts illustrate at-a-glance the comparative treatments costs of drugs within therapeutic classes.
- Therapeutic prescribing reports
- Switch savings calculators - updated quarterly, this web based and Excel tool calculates savings that will result from switching one drug or formulation to another with the same / similar therapeutic effect or constituents, respectively.
- Support to formulary and interface groups – this includes provision of evidence base reviews and accompanying decision aids, comparison documents and prescribing data to support individual drug and/or indication RAG status recommendations.
- Medicines information support - as part of the United Kingdom Medicines Information Network (UKMi), the centre provides medicines information support to non-medical prescribers, GPs, pharmacists and doctors working in secondary and tertiary care. All medicines information enquiries received are reviewed monthly to identify any common issues facing those organisations that commission our services. This information is then used to as part of the topics selection process at the PWG publications meetings.

- Monthly Horizon Scanning Reports – These reports provide CCGs with updates on newly licensed products, significant changes to product licenses, summaries of important new evidence (efficacy and safety) for existing drugs, sign-posting to recently published and forthcoming NICE Guidance and Quality Standards, as well as recent decisions of the SMC and AWMSG.
- Prescribing analysis reports - The provision of regular comparative prescribing reports and data analysis to stakeholder organisations allows CCGs to tackle variation in prescribing patterns and promotes best practice across regions. The comparative prescribing reports present prescribing data in a manner which enables the reader to readily identify areas of prescribing which may warrant further attention. Information is included within the reports to aid users in their interpretation of variations in prescribing such as national, regional and local guidance, safety alerts, products entering or leaving the market and significant product price changes. Detailed analysis of prescribing costs and trends are presented against national indicators and stakeholders are alerted to the need for further local investigation. Accompanying text guides the user to national and local resources and where possible examples of successful prescribing initiatives are highlighted so that stakeholders are able to share best practice and support the aim of achieving cost-effective prescribing for their patient population.

The PWG is currently developing a patient information leaflet series to help inform decision making for patients.

A number of support tools containing local prescribing data have been developed that enable users to further interrogate cost drivers within therapeutic areas. By highlighting areas where savings could be made and cost effectiveness improved assists stakeholders to target therapeutic areas in their localities where further investigation may yield cost savings that enable more patients to be treated, and/or can be invested in other areas of prescribing or other services.

Stakeholders may also make informal requests for additional information or training to assist in influencing and challenging prescribing behaviours and also to address medicines optimisation issues not covered under existing publications. The PASU have provided bespoke education and training packages on various topics including, critical appraisal, academic detailing, medicines optimisation, and prescribing data.

In addition, the RDTC is keen to encourage the sharing of best practice between regions and continues to request that stakeholders submit any examples of successful initiatives or practices to the PASU in order that they can be highlighted and shared with other stakeholders.

17. Dealing with errors and omissions

Strict processes are in place throughout the preparation of each NDE to ensure that errors in the compilation, synthesis, interpretation and presentation of the evidence are avoided as far as possible. In the event of a suspected error being reported after publication the Clinical Editor will determine whether any corrections are necessary. Simple typographical errors may be rectified without seeking the views of the PWG. If an error is found that could potentially result in harm to patients or that which undermines the evidence on which a recommendation is based, the publication will immediately be removed from the website while the necessary corrections or changes are made in

consultation with the PWG. Depending on the significance of the error and the time since publication, stakeholders may also be notified of any corrections.

18. Archiving

Once published, all NDEs are available in electronic (pdf.) format only. In view of the time limited nature of these evidence-based publications, all NDEs are routinely archived five years after publication. In the interim period, if a NDE is updated, replaced or withdrawn, all previous versions of the NDE will be archived. Copies of archived publications are available to stakeholders upon request for reference purposes only. Copies of the literature searches, evidence tables, references, comments and other relevant materials are kept on file for a period of five years following the publication of the document.

Appendices

Appendix 1 . Methodology checklist for controlled trials (SIGN 2015)

SIGN	**Methodology Checklist 2: Controlled Trials**

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper a **randomised controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

SECTION 1: INTERNAL VALIDITY

In a well conducted RCT study…		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	Yes ☐ No ☐ Can't say ☐
1.2	The assignment of subjects to treatment groups is randomised.	Yes ☐ No ☐ Can't say ☐
1.3	An adequate concealment method is used.	Yes ☐ No ☐ Can't say ☐
1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	Yes ☐ No ☐ Can't say ☐
1.5	The treatment and control groups are similar at the start of the trial.	Yes ☐ No ☐ Can't say □
1.6	The only difference between groups is the treatment under investigation.	Yes ☐ No ☐ Can't say ☐
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Yes ☐ No ☐ Can't say ☐
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	

1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes ☐ No ☐ Can't say ☐ Does not apply ☐
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Yes ☐ No ☐ Can't say ☐ Does not apply ☐
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias? *Code as follows:*	High quality (++)☐ Acceptable (+)☐ Low quality (-)☐ Unacceptable – reject 0 ☐
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	
2.4	**Notes.** Summarise the authors' conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	

Appendix 2 . Methodology checklist for systematic reviews and meta-analyses (SIGN 2015)

SIGN

Methodology Checklist 1: Systematic Reviews and Meta-analyses

SIGN gratefully acknowledges the permission received from the authors of the AMSTAR tool to base this checklist on their work: *Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C,. et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology 2007, **7**:10 doi:10.1186/1471-2288-7-10. Available from http://www.biomedcentral.com/1471-2288/7/10 [cited 10 Sep 2012]*

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:

Before completing this checklist, consider:

Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO reject. IF YES complete the checklist.

Checklist completed by:

Section 1: Internal validity

In a well conducted systematic review:		***Does this study do it?***
1.1	The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper.	Yes ☐ No ☐ **If no reject**
1.2	A comprehensive literature search is carried out.	Yes ☐ No ☐ Not applicable ☐ **If no reject**
1.3	At least two people should have selected studies.	Yes ☐ No ☐ Can't say ☐
1.4	At least two people should have extracted data.	Yes ☐ No ☐ Can't say ☐
1.5	The status of publication was not used as an inclusion criterion.	Yes ☐ No ☐
1.6	The excluded studies are listed.	Yes ☐ No ☐
1.7	The relevant characteristics of the included	Yes ☐ No ☐

	studies are provided.	
1.8	The scientific quality of the included studies was assessed and reported.	Yes ☐ No ☐
1.9	Was the scientific quality of the included studies used appropriately?	Yes ☐ No ☐
1.10	Appropriate methods are used to combine the individual study findings.	Yes ☐ No ☐ Can't say ☐ Not applicable ☐
1.11	The likelihood of publication bias was assessed appropriately.	Yes ☐ No ☐ Not applicable ☐
1.12	Conflicts of interest are declared.	Yes ☐ No ☐
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	What is your overall assessment of the methodological quality of this review?	High quality (++) ☐ Acceptable (+) ☐ Low quality (-)☐ Unacceptable – reject 0 ☐
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes ☐ No ☐
2.3	**Notes:**	

Appendix 3. New Drug Evaluation procedural template.

NEW DRUG EVALUATION

No. xxx Month Year

AGENT indication

Summary

This section is short and states what the drug is, what it is indicated for and should include a brief outline of efficacy and safety. It should clearly state when the drug should be used (if at all). The summary should contain enough information to leave the reader with a clear message about the drug, even if they do not read the rest of the document.

Level of evidence*		Level of evidence assigned to the evaluation must be based on a methodological assessment of the quality of the body evidence and the suitability of that evidence to address the issues under consideration.	PBR: Indicate whether the drug is included in the 'Payment by results tariff'
BNF: Use legacy BNF category			NICE: relevant NICE guidance with hyperlinks

The section titles of the NDE document are generally the same, although may change in some exceptional circumstances. The author should ensure the information under each heading complies fully with the objectives set out in the process manual.

What is it?

For clarity and consistency of presentation the recommended international non-proprietary name (rINN) should be given first followed by (brand name®▼, manufacturer). The proprietary (brand) name and manufacturer's name are generally only given in parentheses at first mention. The therapeutic class and/or mode of action together with dosage and administration details are given to highlight any potential service implications. This section may also include relevant information about why the product has been launched. Claims being made by the manufacturer about the drug may be included here for context only.

How effective is it?

All included trial data should be critically appraised in accordance with the methodology outlined in the process manual.

Clinical effectiveness data are synthesised through a narrative review with tabulation of results where necessary. The focus is on the primary outcome data of key published studies with patient-orientated outcomes specifically included where available. Decisions about whether to consider surrogate outcomes should be informed by available evidence regarding associations between the surrogate and the outcome of interest. If a European Public Assessment Report (EPAR) has been published, it is used to supplement the information included in the evaluation, if this is necessary.

Include study design, drutaion, sample size, key inclusion and exclusion criteria, primary outcome and key secondary outcomes if appropriate. Summarise the effect size and its precision (e.g. mean or percentage, P-value and confidence interval – use absolute figures where possible).

Trial limitations

The potential strengths and limitations of the evidence should be critically reviewed. Factors to highlight include:

- The reliability of the studies in the body of evidence, focussing on the quantity of evidence available and its methodological quality.
- The consistency of the studies in their conclusions including any conflicting results.
- The applicability of the data to the intended target population, focussing on the relevance of the populations, interventions, comparators or outcomes to the topic under consideration, including use of indirect (surrogate) outcomes.

How safe is it?

Clinical safety data are synthesised through a narrative review detailing the major and most common adverse effects, with an indication of frequency, where possible.

The focus is on those adverse effects that are considered by patients or clinicians as the most serious and/or severe and/or troublesome, or likely to lead to withdrawal from treatment. Explicit reference is made to information provided in the SPC (if available), relating to precautions, warnings, clinically important interactions and monitoring requirements, especially where a new drug differs significantly from that of currently available treatments. If an EPAR has been published, it is used to supplement the information included in the evaluation, if this is necessary. However, the content of this section is not intended to be exhaustive and therefore prescribers are expected to consult the respective SPC for full details of adverse effects, administration and monitoring requirements. Use precise means(s) or percentage(s) and P-value if available.

If there is a lack of long-term safety data, this should be highlighted and the standard Yellow Card statement should be included as follows:

All suspected adverse reactions to black triangle drugs such as AGENT NAME should be reported to the MHRA via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

What other options are there?

This section should briefly outline the overall pathway of care and the alternative treatments that are available, including use of unlicensed comparators (if appropriate) are summarized along with the recommendations of relevant National Guidelines. Where appropriate, this will include signposting to applicable NICE pathways and quality standards. The preference of each option should be indicated where possible (such as alternative, first-line, second-line)

This section should provide details of expected prevalence, incidence and uptake with estimates of likely cost per population cohort – compared with alternatives, where possible or appropriate.

When should it be used?

Recommendations on the place in therapy of a new drug are produced using a considered judgement process informed by systematic reviews of the best available evidence. Authors must ensure they consider all patient-orientated outcomes, including those for which limited data may be available.

Potentially significant patient and service implications should be highlighted where appropriate, along with any uncertainties concerning the proposed recommended place in therapy

All recommendations should be clear, concise and unambiguous and where possible include a definite statement as to when, or indeed if the new drug should be prescribed, and to whom in relation to existing therapies. Any recommendation should ensure they highlight any potentially significant patient and service implications, along with any uncertainties concerning the proposed recommended place in therapy. Potential financial and organisational barriers to implementation should also be considered especially if it may involve other agencies or professionals across a care pathway. It may also be useful to briefly discuss any change in practice that will be needed for example training programmes or shared care arrangements.

Economic Impact

How much does it cost?

Use standard cost-chart Excel spreadsheet to produce a cost-chart comparing a range of appropriate drugs for that particular indication. Show comparative costs at basic NHS prices and except where indicated otherwise, each show the cost of one-year of treatment at a standard daily dose. These charts are not intended to be exhaustive. The doses shown are for comparison purposes only and are not intended to imply therapeutic equivalence. Cost information is obtained from the current electronic Drug Tariff, or if the product is not listed there, eMIMs, BNF online, or the manufacturer. If the cost of the new drug is not available at the time of publication the NDE will be updated once pricing information becomes available.

This chart is not intended to be exhaustive of all available treatment options. Doses shown are for general comparison only, and do not imply therapeutic equivalence.

References

Use Ednote® and customised RDTC short output style

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New Drug Evaluation No: xxx
Name and indication - Month Year

Date of evidence search DD/MM/YYYY

New Drug Evaluations should be read in conjunction with the relevant Summary of Product Characteristics (SPC) and the BNF. They are intended to be used as a local decision making aid and DO NOT constitute formal guidance.

Due to the time limited nature of New Drug Evaluations they are published with the expectation that they will not be routinely scheduled for review, see process manual. In view of the continued emergence of new evidence, readers are recommended to re-check the biomedical literature after 18 months beyond the publication date of each NDE.

Agents which have been reviewed by the National Institute for Health and Clinical Excellence (NICE) are indicated by the presence of a (N) after the drug name. Please refer to the **NICE** website to access guidance for these agents.

All New Drug Evaluations are subject to external peer-review. Details of the core sources, date ranges, search strategy and inclusion and exclusion criteria are available upon request.

Declarations of interest: All members of the Publications Working Group (PWG) and external reviewers are required to comply with the RDTC Conflicts of Interest Policy. In addition to declaring interests, all members of the PWG are required to conduct themselves in accordance with RDTC policy and guidance for interacting and joint working with the Pharmaceutical Industry.

No member of the **PWG** or **external reviewers** declared any potential conflicts of interest (specific or non-specific, financial or non-financial) with respect to the topic of this New Drug Evaluation.

ANNOTATE ACCORDINGLY PRIOR TO FINAL DRAFT

New Drug Evaluations – Process Manual

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Revisions to text:
Section 4.1 and 4.6
Appendix 3. Procedural template

Review Date: 20th October 2018

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