National Institute for Health and Clinical Excellence

Research Recommendations

Interim Process and methods guide

December 2014

1 Introduction

1.1 The foundation of NICE guidance is the synthesis of evidence primarily through the process of systematic reviewing. The results of the systematic reviews are then discussed by the independent advisory committees, which include NHS staff, healthcare professionals, patients and carers, service users or the target population, industry and academics. Stakeholders are then given the opportunity to comment on draft recommendations before they are finalised. Not only does this process explicitly describe the evidence base, it also identifies where there are gaps, uncertainties or conflicts in the existing evidence.

1.2 Many of these uncertainties, while interesting to resolve, are unlikely to have an impact on patient care or on NICE's ability to produce guidance. However, where these uncertainties are significant it is important for NICE to liaise with the research community to ensure they are addressed. NICE does this by making recommendations for research, which are communicated to researchers and funders. At the time guidance is issued, NICE's staff and advisory committees have oversight of the current evidence base and valuable insights into the priority uncertainties that need to be resolved. It is important that these insights are capitalised on.

1.3 In order to undertake its national role effectively NICE needs to ensure that:

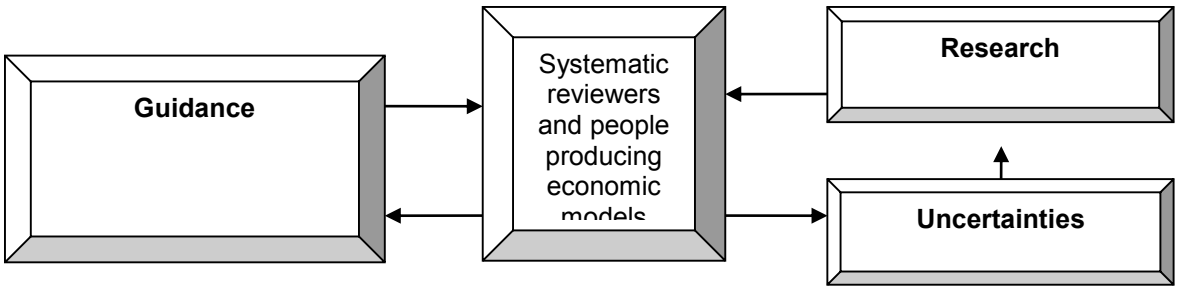
- the process of developing the research recommendations is robust, transparent and involves stakeholders
- the significant research priorities are identified
- all research recommendations are clearly identifiable within the guidance
- the research recommendations provide the information necessary to support the research commissioning process
- the research recommendations are accessible to researchers and funders
- research recommendations are kept up to date

- there are good communications with the research community.

1.4 This updated process and methods guide has been developed to support guidance-producing centres in the process of making research recommendations. The guide describes a step-by-step approach to identifying uncertainties, formulating research recommendations and research questions, prioritising them and communicating them to the NICE Research & Development (R&D) team and researchers and funders. It has been developed based on NICE R&D's experience of its interactions with research funders and researchers, as well as with guidance developers.

1.5 The process to achieve the steps and final research recommendations may vary between NICE guidance-producing centres and should be developed in the context of their process/methods manual(s).

Figure 1: The role of research recommendations in the guidance production cycle

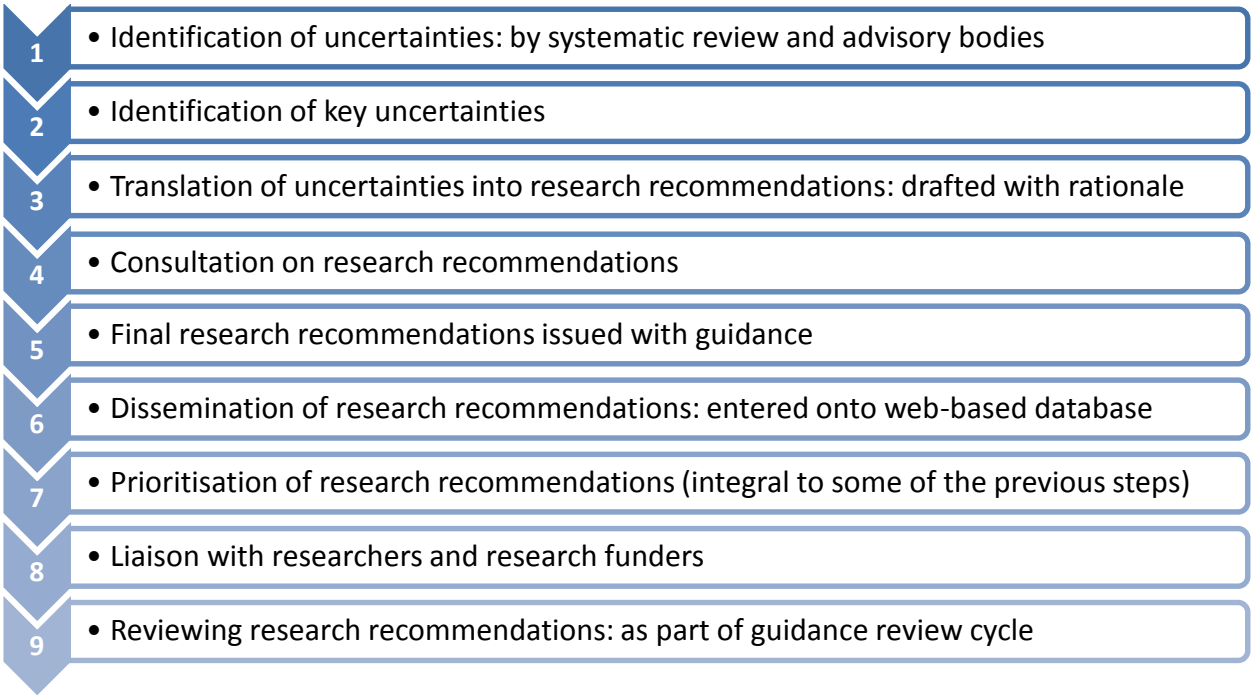


1.6 Research recommendations should be part of the full guidance production cycle (evidence synthesis through to funding opportunities, and reviews in updating guidance). Figure 1 demonstrates this:

- Guidance producers (including systematic reviews and those producing economic models) to take ownership of gaps (uncertainties).
- Develop high quality (PICO – population, intervention, comparator, outcome) research recommendations.
- Undertake consultation of research recommendations integral to the guidance.
- Review as part of the guidance review cycle.

2 NICE Research recommendations process

Figure 2: The NICE Research Recommendations process



2.1 Step 1 – Identification of uncertainties

2.1.1 The systematic review and economic modelling processes may identify uncertainties and gaps in the evidence base. These should be summarised in a clearly identifiable 'uncertainties' section in the evidence review. The summary is not intended to be exhaustive, but should be used as an aid in selecting the key uncertainties (Step 2).

2.1.2 There are different types of uncertainties and they may be related to any aspect of clinical/health/public health management. Examples include clinical and/or cost-effectiveness, diagnosis, test accuracy, prognosis, modes of delivery, optimal service design, quality of life, patient-defined outcomes etc.

2.1.3 Uncertainties may arise for many reasons (Box 1); because there is no

evidence available, or because the available evidence is not sufficient, robust, or conflicting.

Box 1: Examples of different reasons for uncertainties

There is no evidence available because:

a. the relevant research has not been done
b. the relevant research has been done, but not published
c. the relevant research has been done and published, but the searches have failed to identify it

Existing evidence is available but:

a. the publication contains insufficient information due to inadequate reporting
b. the research has been undertaken, but is not methodologically robust
c. the research has been undertaken, but the results were inconclusive (e.g. conflicting)
d. the research has been undertaken, but the study enrolled too few patients to be sure statistically that the results were not due to chance
e. research into the question has been undertaken, but the results cannot be applied to the population in question (for example, the setting or social and cultural context is not comparable, the patient population differs, a different dosage of drug has been used)
f. research has been undertaken into a related but different question (for example the comparator differs)
g. the research is out of date – for example, a systematic review needs updating with recent trials, or clinical practice has changed
h. the research cannot be understood due to language difficulties
i. studies have been done, but their findings are inconsistent

2.2 Step 2 – identification of key uncertainties

2.2.1 The summarised list of uncertainties is reviewed and key uncertainties are identified. The most important are those that the advisory committees consider need to be resolved to inform future updates of guidance recommendations, but also that there will be clear benefits and added value to the NHS. For example, the uncertainties may relate to key aspects of patient care or public health that must be addressed as a priority. There are no limits to the number of key uncertainties that are identified, and it may be that none are identified at all.

2.2.2 This process of identification/prioritising key uncertainties should be led by the advisory committees, with input from clinicians, researchers, patients and carers, service users or the target population, reviewers, health economists and Institute technical staff.

2.2.3 The selection of key uncertainties can also be informed by any economic modelling that is undertaken. For example, the results of an economic modelling exercise may be sensitive to specific parameter or structural assumptions that could be further informed by research.

2.2.4 Additional probabilistic sensitivity analysis with the models used in the decision-making could be a possible method for establishing the value for money of additional research to reduce evidential gaps and help prioritise future research efforts. These techniques are known as ‘value-of-information’ methods. While there is no requirement to routinely undertake such evaluations, they may be considered helpful in the process of identifying key uncertainties.

2.3 Step 3 – Translation of uncertainties into research recommendations

2.3.1 Each key uncertainty (if any have been identified) should be translated into a research recommendation with two components:

- a structured stand-alone statement that sets out the question(s) that needs to be answered (Table 1);
- an explanation of the rationale for why the uncertainty has been identified as being key (Table 2).

2.3.2 The research recommendations need to be stand-alone statements because they will be abstracted into a database and may not be read in the context of the guidance. Therefore, the information contained in the recommendation must be sufficient to characterise the research that needs to be undertaken and convey why it must be done. This should ensure that the recommendation will be picked up for further exploration.

Box 2: Example of structured statement and explanation:

- A randomised-controlled trial should be undertaken to determine whether benzoyl peroxide or adapalene is more clinically and cost-effective at reducing the number of non-inflammatory lesions in the treatment of acne vulgaris in adolescents. The study should also consider the impact of treatments on quality of life.
- Retinoids such as adapalene are currently recommended by many experts as first-line treatment for acne. The systematic review undertaken by NICE in 2009 did not identify any robust evidence comparing them with generic treatments, such as benzoyl peroxide, which have been demonstrated to be clinically and cost effective. Acne has a significant impact on quality of life. Acne is highly prevalent amongst teenagers, and therefore the preferential use of retinoids could have significant budgetary implications for the NHS. No ongoing trials have been identified.

2.3.3 The recommendations can include primary and secondary quantitative and qualitative research, for example, formative and summative evaluations, trials, longitudinal studies, secondary analysis, systematic reviews, and scoping papers of research needs. Methodological research and data collection exercises may also be recommended.

Table 1 Proposed format of research recommendations

Criterion	Explanation
Population	Define the population that the research needs to be undertaken in. Where appropriate, specify any of the following: • diagnosis • disease stage • co-morbidities • risk factors • gender • age • ethnic group • specific inclusion criteria • specific exclusion criteria • determinants of health • health status or setting (for example, community or secondary care)
Intervention	Specify the intervention that needs to be evaluated. This can be: • a drug • a device • a treatment • a management strategy • a psychological intervention • a behavioural intervention • a community intervention • an organisational or population intervention • a clinical prediction rule or prognostic factors. For public health this may also make reference to risk factors that the patient/population is exposed to. Where appropriate also consider providing information on: • the type, frequency, dose, and duration (for intervention or exposure); • any prognostic factor(s) or any diagnostic or screening test(s) that might be required. In the case of public health interventions the context and setting and method of delivery of the intervention may also need to be specified.

Criterion	Explanation
Comparator(s)	If appropriate, state what the intervention needs to be compared to. For example, placebo, routine NHS care, alternative treatment or management strategy. Where appropriate also consider providing information on: • the type, frequency, dose, and duration (for intervention or exposure); • any prognostic factor(s) or any diagnostic or screening test(s) that might be required.
Outcome	What will the researcher need to measure, improve, influence or accomplish to assess whether the intervention is effective? What are the clinical or patient-related outcomes of the intervention that should be measured to demonstrate this? If appropriate, consider providing information on: • outcomes to be measured (for example, mortality, morbidity, quality of life, patient perception). Any surrogate outcomes must be validated. • method and process of measurement (type, frequency or timing of measure) • length of follow-up required. In the case of public health interventions the causal pathway should be specified as leading either to individual or population level outcomes.
Study Design	It is seldom appropriate to specify the “most appropriate” study design to address the proposed question as there may be a number of alternatives depending on timescale and context.
Timeframe	Is there a timeframe in which the study needs to be completed? For example to inform a guidance review, or whether it is anticipated that the technology could be superseded before the results of any study are anticipated.

Table 2 Potential criteria to support prioritisation of key research recommendations

Potential Criterion	Explanation
Importance to patients or the population	What would be the impact of any new or altered guidance on the population (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease, or mortality)?
Relevance to NICE guidance	How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)? How important is the question to the overall guideline? • High: the research is essential to inform future updates of key recommendations in the guideline. • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates. • Low: the research is of interest and will fill existing evidence gaps.
Relevance to the NHS	What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning, or service delivery)?
National priorities	Is the question relevant to a national priority area (such as a National Service Framework or White Paper)? The relevant document should be specified.
Current evidence base	What are the problems with the current evidence base? (that is, why is further research required?) Are there any relevant ongoing trials that may resolve the uncertainty?
Equality	Does the research recommendation have any relevance to equality? For example, does it focus on groups needing special consideration, or focus on a technology that is not available for use by people with certain disabilities. What is known about the impact of the intervention on the health gradient?
Feasibility	Can the proposed research be carried out within a realistic timescale? Would the sample size required to resolve the question be feasible? Would the expense needed to resolve the question be warranted? Are there any ethical or technical issues?
Other comments	Any other important issues that should be mentioned, such as potential funders, outcomes of previous attempts to address this issue, or methodological problems.

2.4 Steps 4 and 5 – Consultation and finalisation of research recommendations

2.4.1 All research recommendations should be included in the draft guidance for consultation in a separate 'Research Recommendations' section. For guidelines this section should be included within both the full and the NICE versions of guidance. The recommendations may be included within the body of the text, but they must always be listed in the allotted research recommendations section. Information about research currently in progress should not appear in the 'Research Recommendations' section, but in a separate 'Ongoing Research' section.

2.4.2 In some cases, the relevance and importance of research recommendations may be enhanced by making Committee members aware of the remit and scope of the National Institute for Health Research (NIHR) research programmes and the types of research questions they can consider. This may be aided by engaging committees with the work of the **NIHR Evaluations, Trials and Studies Coordinating Centre (NETSCC)** at an early stage in the process prior to the formulation of some research recommendations.

2.4.3 During guidance development the involvement of NETSCC can ensure that the NICE advisory body is made aware of any relevant ongoing research commissioned by NETSCC. NETSCC may also advise on structuring clear and actionable research recommendations that fall within the remit of certain NIHR research programmes. This approach is routinely applied in the development of NICE public health guidelines and is increasingly applied to clinical guidelines.

2.4.4 The draft research recommendations should be revised in light of any consultation comments, and the final recommendations published with the guidance.

2.4.5 Where a research recommendation is viewed by the advisory committee chair and centre director as particularly important and a candidate for NICE Key Priority designation (see step 7), **NIHR Evaluations, Trials and Studies Coordinating Centre (NETSCC)** should be engaged early and prior to finalisation and publication of the guidance. The NICE R&D team should be notified of any such potential research recommendations.

2.5 Step 6 – Dissemination of research recommendations

2.5.1 The NICE R&D team extracts all the final research recommendations that are published and adds them to the research recommendation database on the NICE website. The database is available online, it is searchable, and it is monitored by research funders. NETSCC actively reviews all NICE research recommendations and considers those that are within the remit of the programmes they manage.

2.6 Step 7 – Prioritisation of research recommendations (but integral to some of the previous steps)

2.6.1 Careful application of the criteria in table 2 and where appropriate, the early engagement of NETSCC should result in high quality research recommendations from NICE advisory bodies. Increasingly, the NICE research recommendations data base should contain only important research recommendations and the active surveillance of these by NETSCC and other research funders should ensure that appropriate priority is assigned through their normal prioritisation processes. Further information on NETSCC and the prioritisation processes used is shown in Appendix 1.

2.6.2 In some cases, it may be apparent to NICE that a research recommendation is particularly important and that it wishes to signal special priority to NETSCC. NETSCC has agreed to a “NICE Key Priority” designation and

once accepted by NETSCC, these research recommendations will be fast-tracked through the NETSCC development and review processes.

2.6.3 The NICE Key Priority designation can only be made where the NICE advisory body chair and Centre Director agree that special priority needs to be signalled. Prior to formally making the designation, NETSCC must also be consulted, prior to the guidance being finalised, such that the final research recommendation is clear and actionable and takes account of any research started or commissioned since the systematic reviews that informed the NICE advisory body. Due to the resources needed for collaboration in the late stages of guidance development, NETSCC can accept up to a maximum of 10 research recommendations with NICE Key Priority status each year. NICE R&D maintains a list of NICE Key Priority research recommendations and liaises with NETSCC and the NICE guidance producing centres as required.

2.6.4 NICE and NETSCC have an annual meeting to review progress on taking forward and funding research from NICE research recommendations. This includes monitoring progress and total spend on all NICE research recommendations as well as considering those with the NICE Key Priority designation.

2.7 Step 8 – Liaison with the researchers and research funders

2.7.1 NICE works closely with NETSCC in the prioritisation of research recommendations as outlined in section 2.6 above. The NICE R&D team also liaises with other researchers and research funders to make them aware of the key uncertainties that are highlighted during guidance production. This includes national organisations such as the UK Research Councils and research charities.

2.8 Step 9 – reviewing research recommendations

2.8.1 It is important that as part of the guidance-review cycle that the research

recommendations are checked to see if the necessary research has been undertaken.

2.8.2 This process should be undertaken in conjunction with the development of a review proposal. The literature searches that are undertaken as part of the review proposal process will identify whether the necessary research has been undertaken or is in progress. If the research has been undertaken the NICE R&D team should be notified so that the uptake of the recommendation can be highlighted in the database, and where necessary removed completely.

3 Appendix A: Further information on NETSCC

NICE works with NIHR, particularly through NETSCC and the NIHR Public Health Research and the NIHR Health Technology Assessment (HTA) programmes. The NIHR HTA programme is one of five research programmes managed by NETSCC. NETSCC reviews the research recommendations from the NICE research recommendation database and explores their suitability for funding, either through the HTA or other NIHR programmes it manages, including the NIHR Public Health Research (PHR) programme and the NIHR Health Services & Delivery Research (HS&DR).

To date, NICE has worked with NIHR HTA leads in identifying important research recommendations within the remit for NIHR HTA research. The NIHR HTA programme's commissioned work stream is independent from NICE and the research recommendations arising from NICE guidance (other than the ones with NICE Key Priority designation) are considered alongside research recommendations from other sources. During the NIHR HTA programme commissioning process, topics are initially sifted and, if found to be suitable, a vignette is drafted by NIHR HTA for consideration by the NIHR HTA Advisory Panels.

Research recommendations with the NICE Key Priority designation may bypass the six NIHR HTA Advisory Panels and go directly as 'vignettes' to the NIHR HTA Prioritisation Group which meets three times a year. Processes for other NETSCC programmes may vary.