National Institute for Health and Clinical Excellence

Research Recommendations

Process and methods guide

Updated August 2011

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.

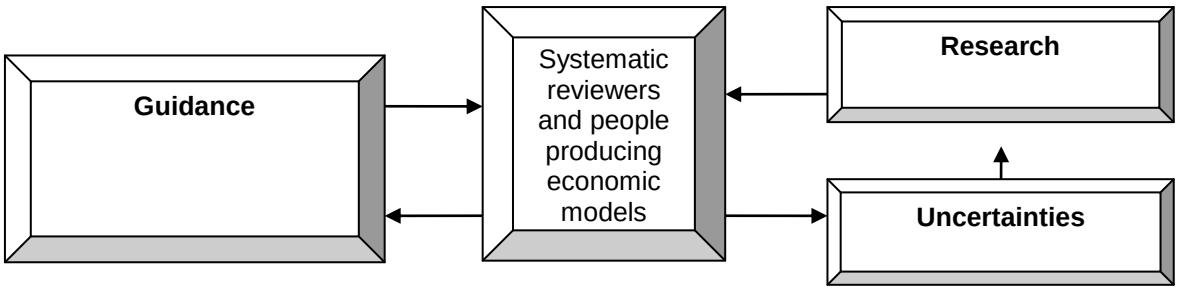
1.4 This updated process and methods guide has been developed to support guidance-producing centres in the process of making research recommendations. The guide describes a step-by-step approach to identifying uncertainties, formulating research recommendations and research questions, prioritising them 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).

1.6 The Medical Research Council (MRC) has funded a research project which will inform decision-frameworks for 'only in research' guidance recommendations[1]. Until the results of this study become available and their implications considered, guidance centres should continue with existing arrangements.

[1] The Methodology Research Programme funded a project in 2008 through its need-led process to consider when recommendations for 'only in research' should be considered by NICE's advisory committees. The project is led by Professor Karl Claxton at University of York and is entitled "Informing a decision framework for when NICE should recommend the use of health technologies only in the context of an appropriately designed programme of evidence development".

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

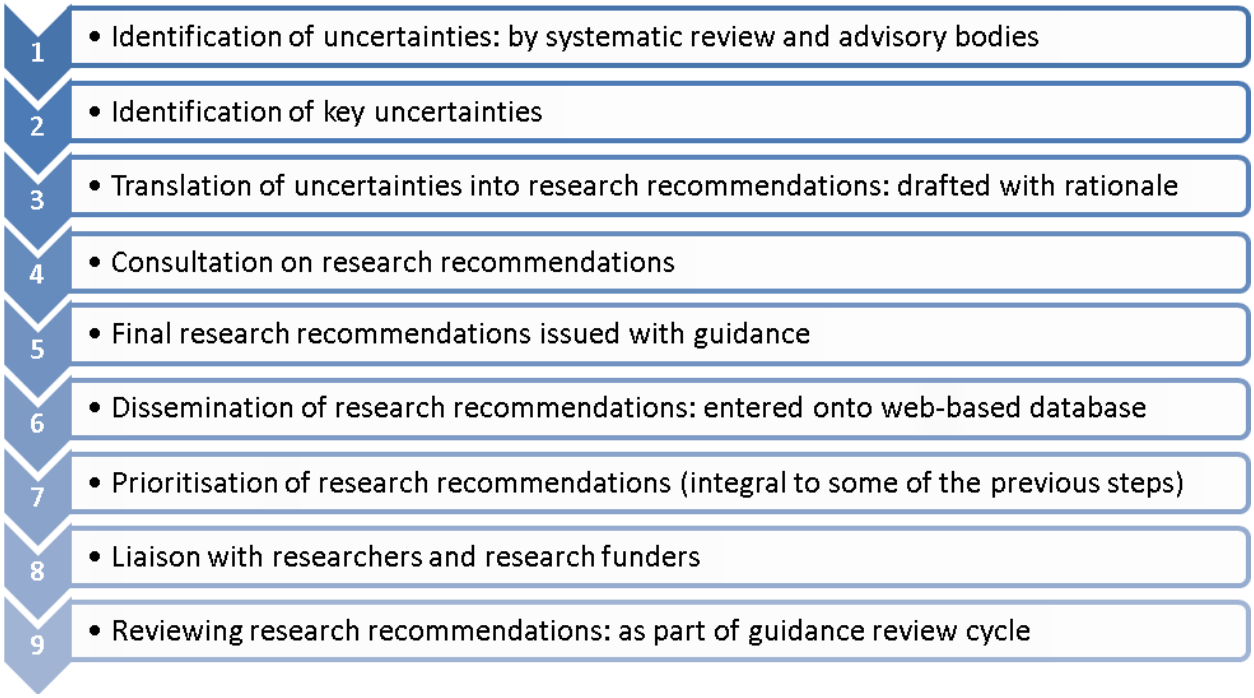


1.7 Research recommendations should be part of the full guidance production cycle (evidence synthesis through to funding opportunities, and reviews in updating guidance). Figure 1 demonstrates this:

- 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. The MRC-funded study will explore the utility of such methodology particularly in the context of technology appraisals (please refer to paragraph 1.6, above). It is anticipated that the results of this study will inform whether and when it may be appropriate to use this methodology.

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	If appropriate consider suggesting what might be the most appropriate study design to address the proposed question.
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 The draft research recommendations should be revised in light of any consultation comments, and the final recommendations published with the guidance.

2.4.3 The NICE R&D team should be notified of any research recommendations that are either considered to be priorities, or form part of the actual guidance to the NHS (for example 'only in research'/'with evidence development' recommendations). This will enable early engagement with research funders prior to finalisation and publication of the guidance (see also Step 7).

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.

2.5.2 Where a final research recommendation is not clear, clarification will be sought by the NICE R&D team from the guidance-producing centre.

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

2.6.1 Selected NICE research recommendations will be prioritised for funding purposes. Out of all the uncertainties identified and the key ones formulated into research recommendations/clear research questions, the NICE guidance-producing centres in consultation with the NICE R&D team should prioritise those that require funding to fill an existing evidence gap. The prioritised uncertainties/research recommendations should be identified via the criteria (see table 2) that will provide supporting explanations for why this research is required.

2.6.2 The prioritisation process will be based on the knowledge and expertise of staff within the centres – with regards to what is known of the existing state of the evidence (i.e. if any has come to light since publication of the guidance, or if the recommendation would continue to warrant support because there is no good evidence). These staff will advise their centre director(s) and/or discuss with NICE R&D to confirm the uncertainty/research recommendation as a priority. NICE R&D may require the centres to provide further information (if not already provided) such as writing a supporting statement against the criteria noted in table 2.

2.6.3 The process is iterative and based on consensus, and feeds into the annual meeting to prioritise and promote NICE research recommendations to the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme specifically and the NIHR Evaluations, Trials and Studies Coordinating Centre (NETSCC) more generally. This process is documented in appendix A.

2.7 Step 8 – Liaison with the researchers and research funders

2.7.1 The NICE R&D team liaises with researchers and research funders to make them aware of the key uncertainties that are highlighted during guidance

production. This includes national organisations such as NIHR, the UK Research Councils and research charities.

2.7.2 NICE works with NIHR, particularly the HTA programme, and the MRC. The NIHR HTA programme is one of five research programmes managed by NETSCC. NIHR HTA process the research recommendations from the NICE research recommendation database and explore their suitability for funding, either through the HTA or other NIHR programmes, including NIHR Public Health Research programme (PHR) and NIHR Service Delivery and Organisation (SDO). With these funding organisations now integral to the research functions of NICE, the Institute will be proactively exploring relationships with other research funders and the research community.

2.7.3 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 are considered alongside research recommendations from other sources.

2.7.4 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. Where a topic has arisen from NICE, NIHR HTA liaises with the NICE R&D team to identify the appropriate content expert who was involved in developing the research recommendation to comment on the vignette. NIHR HTA informs NICE R&D on the status of these priorities during subsequent stages of the process.

2.7.5 NIHR HTA and NICE R&D work together to identify priorities that would bypass the six NIHR HTA Advisory Panels and go directly as 'vignettes' to the NIHR HTA Prioritisation Strategy Group which meets four times a year. This is also an opportunity for those research recommendations that do not fit within the NIHR HTA remit to be referred to any of the other funding streams within the NIHR NETSCC portfolio, particularly the PHR and SDO

programmes, mentioned above.

2.7.6 The referral of topics process has been agreed by the NIHR HTA programme. The process at the NICE end is led by the NICE R&D team and continues to be undertaken annually. In order to ensure this prioritisation process is as efficient as possible, priority uncertainties should be highlighted to the NICE R&D team at the earliest opportunity so they can be passed directly to the research funders for consideration. This may include consideration of research recommendations into the standard processes at an early stage in the guidance production process and a specific discussion at advisory committee meetings.

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 Future developments

3.1 A process is being developed to enable the NICE guidance-producing teams to be more aware of NIHR-funded research that is in the process of being commissioned or is ongoing. This may inform potential review dates and avoid inadvertent challenges to ongoing research projects.

3.2 NICE R&D will receive 6-monthly reports from the NIHR NETSCC (in March and September) for progress on all research recommendation prioritised since 2008. NICE R&D will subsequently share centre-specific updates.

3.3 The web-based research recommendation database is being developed further and a new version will be launched in 2011-12. As part of this development, historical content of the existing database will be transferred to a static list. Current research recommendations from the existing database will be transferred into the new database only if a review consideration process has confirmed that research has not been undertaken. Links will also be strengthened with the UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

3.4 To avoid a promising but unproven technology being excluded from use in the NHS, the Department of Health allows NICE to recommend that an intervention be used only "as part of a well-designed program of research"[2]. In practice, the lack of an identifiable pathway for such recommendations has meant that 'only in research' (OIR) decisions have often been viewed as "no" decisions. The conclusions from the MRC-funded project, will inform a decision framework for when NICE should recommend the use of health technologies 'only' in the context of an appropriately designed programme of evidence development (please refer to paragraph 1.6, above).

3.5 The White Paper, published in July 2010, places NICE as a key body in

[2] Department of Health (1999). Faster access to modern treatment: How NICE appraisal will work. London: Department of Health.

advising on research priorities and formalises the importance of the Institute's relationship with NIHR.

"*3.12 Progress on outcomes will be supported by quality standards. These will be developed for the NHS Commissioning Board by NICE, who will develop authoritative standards setting out each part of the patient pathway, and indicators for each step. NICE will rapidly expand its existing work programme to create a comprehensive library of standards for all the main pathways of care. The first three on stroke, dementia and prevention of venous thromboembolism were published in June. Within the next five years, NICE expects to produce 150 standards. To support the development of quality standards, NICE will advise the National Institute for Health Research on research priorities.*"[3]

[3] Department of Health (2010). Equality and excellence: Liberating the NHS. London: Department of Health.

Appendix A:

4 Annual prioritisation of NICE research recommendations with the NIHR NETSCC

4.1 Summary

4.1.1 NETSCC review the online NICE research recommendations database on a quarterly basis, and pick out research recommendations deemed as within remit. It would be useful to include (if not currently available) those deemed as priorities by NICE with a clear rationale.

4.1.2 NETSCC and NICE R&D meet quarterly to discuss research priorities and supporting processes.

4.1.3 NETSCC and NICE R&D hold an annual meeting to prioritise NICE research recommendations. Input from the guidance-producing centres is inclusive of the processes leading up to the meeting.

4.1.4 There are three levels of prioritisation that takes place:

1. Baseline – within advisory committees
2. Intermediate – within NICE guidance centres
3. High-level – between NETSCC and NICE

4.2 Note about the methods for prioritisation by the centres

4.2.1 Generally, NICE guidance recommendations (including research recommendations) are based on the available evidence, which are discussed and agreed by the advisory committees. Key recommendations are prioritised through consensus by the advisory committees that may choose to use a range of tools and templates to support prioritisation, including their own clinical experiences and knowledge. It is not the role of NICE to be

prescriptive about the tools and templates, as different topics will require different approaches. However, NICE would maintain that there is consistency in the methods used for a specific guidance/topic in development.

Box 3: NETSCC definitions of priority topics:

- 'Essential' topics bypass the first two meetings (refer to appendix B, for the 'commissioned work stream') of a NIHR HTA panel, and go straight to the Prioritisation Strategy Group. NIHR HTA will consider 3-5 NICE research recommendations to push through this route on an annual basis.
- 'Important' topics go to the first meeting of a NIHR HTA panel without a first sift of the topic. NIHR HTA will consider around 20-30 topics from NICE via this route.
- Topics that are picked up 'routinely' (either through nominations from the centres or directly by the NIHR HTA, from the research recommendations database) will go through the full process of the NIHR HTA commissioned work stream. Any number of topics can be considered through this route.

4.3 Breakdown of the prioritisation process

4.3.1 **Selection of research recommendations:** An annual collection of NICE research recommendations are consolidated to be reviewed and shared with NICE guidance-producing centres. The selection is usually from one calendar year (12 months) of published guidance, and will contain all research recommendations from:

- Cancer service guidance
- Clinical guidelines

- Diagnostics guidance
- Interventional procedures guidance
- Medical technologies guidance
- Public health guidance
- Technology appraisals guidance

This is referred to as the ‘long list’.

4.3.2 **Discussion of research recommendations:** Each guidance-producing centre director receives a ‘long list’ of all the research recommendations specific to the type of guidance they lead on. Centre directors will have the opportunity to review and share the research recommendations with their teams before discussing them with the NICE R&D team.

4.3.3 **Prioritisation of research recommendations:** Centre directors prioritise NICE research recommendations based on the criteria in table 2. These may require further input and clarification from the centres before a final ‘short list’ is produced.

4.3.4 **NICE-NETSCC annual prioritisation meeting:** NICE R&D and NETSCC discuss the research recommendations prioritised by the NICE guidance-producing centres and their teams. The discussion explores each research recommendation and any rationale provided, which then will be defined as ‘essential’ or ‘important’ (see Box 3) NICE topics.

4.3.5 **Outcomes of prioritised research recommendations:** The ‘short list’ of prioritised research recommendations (including the ‘essential’ and ‘important’ NICE topics) can have a number of possible outcomes, notably:

- Rejected – primarily because they are not within the NETSCC remit; or there are ongoing studies, which may cover some aspects of the research recommendations.

- Pending – further discussion and/or information is required from the NICE guidance-producing centres and associated organisations (for example, the National Collaborating Centres) to clarify the nature of the research question.

- Accepted for consideration – a vignette (see appendix C) is prepared and taken forward to one of the six HTA panels, or straight through to the Prioritisation Strategy Group for discussion.

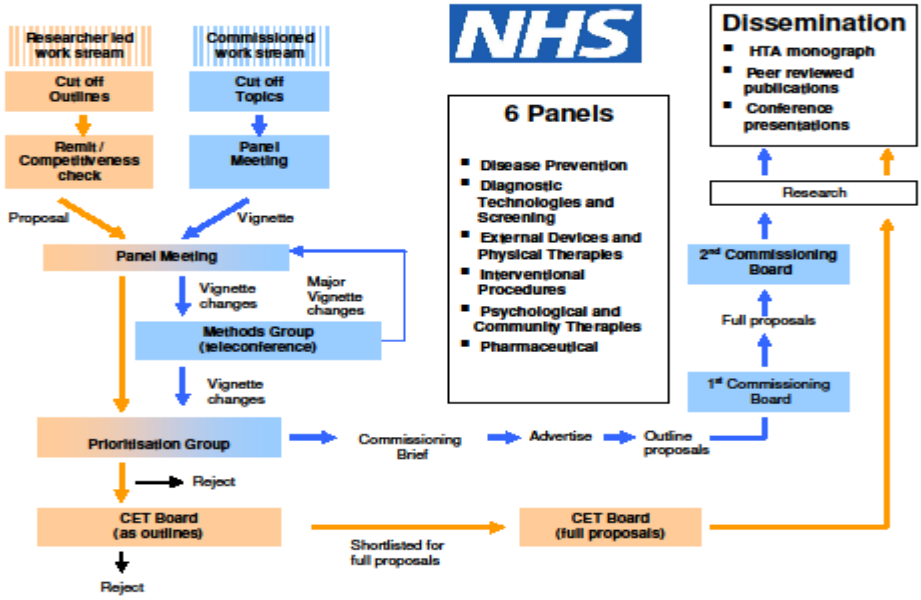
Appendix B:

5 NIHR HTA commissioned work stream

NIHR Health Technology Assessment programme

NHS National Institute for Health Research

Background to the HTA Programme



The Health Technology Assessment programme is managed by NETSCC, HTA as part of the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton.

Alpha House, University of Southampton Science Park
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Suggest a topic for research via our online form at www.hta.ac.uk/suggest

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www.hta.ac.uk

Appendix C:

6 NICE ESSENTIAL TOPICS - EXPERTS FOR VIGNETTES

6.1 Identifying and liaising with experts within NICE to comment on draft vignettes

6.1.1 The HTA Advisory panels meet four times a year, considering topic suggestions from a range of sources, including NICE topics flagged as essential priorities for research. The process proposed here details how the HTA programme team will liaise with NICE R&D to obtain expert input on vignettes being prepared for the NICE essential topics.

6.2 Proposed process

6.2.1 At the end of each round of panel meetings, NIHR HTA sends NICE R&D a list of the NICE topics for which a vignette will be written.

6.2.2 NICE R&D will provide NIHR HTA with contact details of the NICE experts to be approached for each vignette.

6.2.3 As they approach completion, NIHR HTA will circulate the draft vignettes to the relevant experts, who are given a maximum of three weeks to return their comments. Note: this will be part of NIHR HTA standard vignette process for consulting with external experts, and the NICE nominees will be amongst others consulted.

6.3 Timelines

6.3.1 The panels meet in January, April, June and October. The vignettes are usually timetabled to be sent to experts in November, March, May and August.

6.3.2 Occasionally, these timings might differ where NICE essential topic vignettes are to be considered outside the usual panel process. In this event, NIHR HTA will liaise with NICE R&D, as above, to identify and consult with the appropriate experts.