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Research waste management: using HTA and guideline development as a tool for research priority setting the NICE way.

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3 **Research waste management: using HTA and guideline development as a tool for**
4 **research priority setting the NICE way.**
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Abstract

The National Institute for Health and Care Excellence (NICE) was established in 1999 and provides national guidance and advice to improve health and social care. Since then, NICE has been using its guidance production processes to systematically identify and prioritise research through systematic reviews, economic analysis and stakeholder consultation and then highlight those priorities by engagement with the research community. NICE also highlights its methodological areas for research to ensure the appropriate development and growth of the evidence landscape. This activity of NICE therefore supports the reducing research waste campaign by ensuring that the research it recommends has a beneficial impact on the health and care of the people.

Strengths and limitations of this study

- **Strengths**

- Highlights the importance of reducing research waste and the prioritisation of research as a key step in that process.
- Describes the systematic prioritisation of research done by NICE.
- Illustrates the methodological research undertaken from prioritised topics by NICE in recent years.

- **Limitations**

- This paper is limited to the prioritisation of research undertaken at NICE and does not reflect all the work the Institute does to reduce research waste.

Keywords: research waste, priority setting, research priorities, NICE, resource allocation

Introduction

There is no doubt that the substantial public and private investment in biomedical research (estimated to be around US\$240 billion in 2010),¹ has led to significant improvements to the quality of life of people. However, not all research yields such benefits and though some waste is unavoidable due to the nature of science, many improvements to the way we conduct our work, can be made to ensure that our investments are sound and the value of our research is increased.^{1,2} Getting the first step of the research cycle of priority setting or identifying the correct research question to fund, is key to this being successful.

Previous research has shown that there is a huge mismatch between the research that is funded and the research needed by the end users. A study found that only nine out of 334 research articles highlighted priorities relevant to patients or clinicians.² A second study found that whilst the majority of trials funded were related to drugs (about 40% non-commercial and 85% commercial), the end users were much more interested (80%) in research about “*education and training, service delivery, psychological interventions, physical interventions, exercise, complementary interventions, diet etc*”, compared to research in drugs (20%).¹

Another problem noted is that often the new research ignores what is already known about the problem and doesn't take into account previous research and therefore can duplicate information and give little additional value.^{1,2} Moreover, such research may miss the true knowledge gaps that need answering and this can often be compounded by the failure to publish negative research (publication bias) which can go undetected unless methodology such as funnel plots are used. Even if an appropriate research gap is identified, inappropriate design, or statistical analyses or the problem of ‘effect to bias ratio’ (where the magnitude of the effect size and biases like selection or confounding, are similar), may mean that the validity of any results may be questionable.^{3,4}

The National Institute for Health and Care Excellence (NICE) provides national guidance for health and social care and undertakes a thorough process of research prioritisation.^{5,6} The Science Policy and Research (SP&R) programme⁷ co-ordinates

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3 this activity at NICE and works together with various academic, health technology,
4 charity and research funding organisations to enable the appropriate research to be
5 done. It is now also working with life sciences companies, using European
6 Commission funding through the Innovative Medicines Initiative (IMI), to take this
7 work forward. In this paper we summarise these processes and the work that has been
8 undertaken through these mechanisms.
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13 **Guidance specific research priorities**

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15 NICE guidance is based on the synthesis of evidence primarily through the process of
16 systematic reviewing and, if appropriate, health economic modelling and cost
17 effectiveness decision analysis. The results of this work are then discussed by
18 independent advisory committees which can include a diversity of NHS staff,
19 healthcare professionals, social care practitioners, commissioners and providers of
20 care, patients, service users and carers, industry and academics. The committees,
21 through a process of guided deliberation of the evidence (which can include expert
22 opinions) reach conclusions by formally making draft recommendations. During a
23 period of public consultation, external stakeholders have an opportunity to comment
24 on draft recommendations before they are finalised and eventually published. The
25 evidence base supporting guidance recommendations are reviewed every few years to
26 ensure that any results potentially demonstrating a change in practice or care are
27 formally considered for potentially updating recommendations.
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38 Not only does this process explicitly describe the evidence base, but it also identifies
39 where there are gaps, uncertainties or conflicts, in the existing evidence. Many
40 uncertainties identified may be interesting to answer, but could have little impact on
41 people's care or NICE's ability to make appropriate evidence-based and evidence-
42 informed recommendations. Uncertainties can arise because there is no evidence
43 available or due to the absence of relevant research, or if research has been done, but
44 not yet published. Or there may be evidence available but there is still insufficient
45 information on which to base a recommendation (for example, due to inadequate
46 reporting), or the research is out of date (for example, a systematic review that needs
47 updating with recent trials or if clinical practice has changed). However, if these
48 uncertainties could have an impact, and support future NICE guidance
49 recommendations, it is important for the Institute to make recommendations for
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3 research (see Table 1). These recommendations are deliberated, discussed, agreed and
4 formulated by the independent advisory committees and the external community
5 (both specialist and public) are then invited to comment and contribute. The final
6 recommendations are then made clearly identifiable in the guidance and collated into
7 the publically available NICE research recommendations database.⁸ NICE then liaises
8 with the research community to ensure they are addressed. By making research
9 recommendations, NICE is looking to generate new evidence to inform the future
10 guidance update and review cycle. If gaps remain in the evidence base after several
11 years, the committee may consider keeping, removing or archiving the research
12 recommendations based on any new findings.
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21 In 2010 (updated in 2015), NICE established a formal guide to support this process
22 and to provide a route to ensuring they are picked up as key topics for research
23 funding.⁹ The guide describes a step-by-step approach to identifying uncertainties,
24 formulating research recommendations and research questions, prioritising them and
25 communicating them to researchers and research funders (see Figure 1).
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30 NICE works closely with National Institute for Health Research (NIHR, a
31 government body that supports health and care research of national research
32 priorities)¹⁰ to prioritise, promote and commission its research recommendations. The
33 identified topics are considered by a number of their different research programmes,
34 particularly the Health Technology Assessment, Public Health Research and the
35 Health Services & Delivery Research programmes. If they are found to be suitable
36 and fulfil their criteria, they enter the commissioning process. This process has
37 evolved over the last 10 years and since 2005, over £59million worth of these
38 research projects have been funded (see Table 2). In 2015, NICE and NETSCC
39 agreed a fast tracked route for the most important research recommendations, to be
40 flagged under the 'NICE Key Priority' designation. These research recommendations
41 have the potential to have the highest impact on future guidance recommendations
42 and people's care.
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52 **Methodological research priorities: 'research on research'**

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54 The Edinburgh Reducing Waste conference in 2015 highlighted the importance of
55 being efficient in not only the 'what' but also the 'how' research is done. Whilst the
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3 basic methodology of systematic reviews and cost-effectiveness analyses may be well
4 established, there is still controversy about ‘best practice’ and challenges frequently
5 arise in the context of specific technologies, particularly when decisions are negative.
6 It is therefore vital that methodological research is undertaken. Inadequacies in the
7 evidence base have required the exploration of newer methods such as indirect
8 comparisons and the use of network meta-analyses.¹¹ Different perspectives exist
9 about what data constitutes as evidence and about what should be used for decision-
10 making. Due to the paucity of the evidence base for some interventions, particularly
11 in the public health and social care domains, NICE has always considered the ‘best
12 available’ evidence to inform its decisions, which moves beyond RCTs.¹² In order to
13 ensure that the evidence NICE receives is fit for decision-making, each of NICEs
14 guidance programmes have a methods guide which are regularly updated to
15 incorporate new developments. NICE Scientific Advice works directly with
16 commercial evidence producers on a fee-for-service basis to ensure the appropriate
17 evidence is available for decision-making.
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29 In 2008 NICE had its first comprehensive review of methodological priorities for
30 research, funded by the Medical Research Council (MRC) and NIHR joint
31 Methodology Research Programme (MRP).¹³ The methodological review identified
32 and prioritised methods research topics through a focused literature review,
33 interviews, an email survey, a workshop and web-based feedback exercise.
34 Participants were members of the NICE secretariat and its advisory bodies,
35 representatives from academia, industry, and other organizations working closely with
36 NICE. The first prioritised project the MRP funded in 2008 was on the appropriate
37 use of “only in research” decision¹⁴ and a further nine projects were funded through
38 another MRP call via their needs-led route in 2009 (over £2.3 million, see Table 3).
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46 To ensure that NICE had robust processes for timely identification, prioritisation and
47 communication of methodological research needs, an Internal Research Advisory
48 Group (IRAG, formerly the internal methods advisory group) was established in
49 2010. This group was tasked to develop the Institute’s methodological development
50 needs in both the short-term and long-term by continuing the systematic identification
51 and prioritisation of key research uncertainties on an on-going basis and working with
52 MRP to commission research.¹¹ The group consisted of representatives of the
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3 different guidance and non-guidance producing centres and programmes across
4 NICE, who were supported as and when needed by external research advisors from
5 academia who were methodological experts in the fields relevant to the work of
6 NICE. Each programme provided their methodological research priorities and 45
7 uncertainties were collated from across the Institute. These were clarified and re-
8 prioritised into themes that included modelling service delivery, using qualitative
9 evidence to capture patients experience, extrapolating data for co-morbid and
10 paediatric populations and using observational data from large datasets for decision-
11 making. These were then highlighted by MRC through a NICE specific funding call
12 (see Figure 2).
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21 Some of the prioritised topics did not receive any bids and other internal support
22 mechanisms were used to fund them as small scoping projects. This led to more
23 clarified research questions, of which one was undertaken internally by the SP&R
24 programme at NICE on the use of colloquial evidence¹² and the other to support the
25 use of observational data in clinical decision-making was put forward as a highlight
26 notice by the MRP in 2013. In 2015, the MRP added two further NICE priorities as
27 highlight notices on: improving cross-sector comparisons (beyond the QALY) and
28 determining the best methodology for eliciting expert opinion. The MRP has awarded
29 over £1.29 million for four research projects covering the three highlight notices'
30 topics, to date.¹⁵
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39 The SP&R programme has also participated in a project considering the role of social
40 values in priority setting as part of an international collaboration to try and unpick how
41 cultural contexts of well-being interacted with healthcare decision-making.^{16,17}
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43 Additionally, the programme supported the establishment of a Research Support Unit
44 (RSU) in 2013 to undertake short projects identified through internal prioritisation by
45 IRAG on methodological areas that included reviewing the literature on social value
46 judgements relevant for NICE and identifying and appraising promising sources of
47 UK clinical, public health and social care real-world data.¹⁸ Other arrangements for
48 NICE to access research commissioning include the Decision Support Unit, the
49 Technical Support Unit and the External Assessment Centres that facilitate
50 methodological research for health technology assessments (HTAs), clinical
51 guidelines and medical technologies evaluation work respectively. NICE has also
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3 recently partnered with Myeloma UK to explore how patient preferences could be
4 captured and included in HTAs more readily.
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8 NICE has also been looking at internationally important and relevant research
9 priorities that will potentially have a global impact on health and care decision-
10 making. It has been successful in gaining international co-operation and European
11 Commission funding through the IMI for some of the key priorities currently facing
12 the field. These include the use of real world data for early decision-making
13 (GetReal)¹⁹, the medicines adaptive pathways to patients (MAPPs) activities to foster
14 access to beneficial treatments for the right patient groups at the earliest appropriate
15 time in the product life-span in a sustainable fashion (ADAPT-SMART)²⁰ and using
16 big data for obtaining better outcomes for patients (BD4BO).²¹ The Institute has also
17 been actively involved with other European Commission funded projects such as
18 EUnetHTA (an effective and sustainable network for HTA across Europe)²² and
19 DECIDE (Patient and public focused strategies for communicating evidence-based
20 recommendations).²³
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31 In 2017 NICE published nine areas that it had, through the SP&R programme and the
32 IRAG, identified as priorities for methodological research. These are: (1) real world
33 evidence; (2) data science; (3) adaptive pathways; (4) patient preferences; (5)
34 improvements in cross-sector comparisons; (6) expert elicitation; (7) complex data
35 visualisation; (8) precision medicine, and (9) implementation of NICE guidance.
36 Methodological research in these areas will help NICE assess the need for
37 improvement in the methods and processes it uses to produce guidance and anticipate
38 and adapt to policy developments and changes in health and social care delivery in the
39 next few years.
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46 **Discussion**

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49 Priority setting is an explicit method that considers what to fund by weighing the
50 trade-offs between the various options in the process.²⁴ It is imperative to avoid
51 research waste such that only key gaps in knowledge are fulfilled by undertaking new
52 research that help build a more complete evidence landscape for future policy
53 development and better clinical practice. Systematic approaches to research priority
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3 setting improve the transparency of research management and are often based on a
4 “research cycle” approach which includes the identification of research questions,
5 ranking their priority, identifying existing research, and setting priorities for primary
6 research, involving relevant stakeholders at key points throughout the cycle.²⁵ It is
7 therefore essential that a formal process of prioritisation of research be established
8 within guidance producing organisations, with the involvement of all legitimate
9 stakeholders, to increase the ownership of the ensuing research and the likelihood of
10 the results influencing practice and policy.²⁶

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16 Creating research recommendations is part of the guidance production cycle and they
17 should:

- 18 • Identify any uncertainties that may affect people’s care.
- 19 • Be developed using an appropriate technique to frame research question
20 development, for example PICO (population, intervention, comparator, outcome)
21 or EPICOT (evidence, population, intervention, comparator, outcome, time)
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- 23 • Go through a process of stakeholder consultation be reviewed as part of the
24 guidance review and update cycle.
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32 The NICE research recommendations are derived from the uncertainties identified
33 through the NICE guidance development process and are an integral part of the
34 guidance development and review cycles. They have the potential to identify waste
35 and support re-direction of resources to more valuable activities.²⁷ Publicly funded
36 guidance development bodies have a responsibility to ensure that they are guiding
37 appropriate future research based on identified need and gaps in the evidence base.
38 Methodological uncertainties derived from NICE also go through a process of
39 identification and prioritisation and are promoted to funders to encourage research
40 being funded into the various aspects of how to undertake the development of future
41 guidance. In recent years NICE has entered into a few international research
42 collaborations. These are becoming increasingly important as sources of research
43 funding, particularly within the current economic climate, are dwindling. Such
44 partnerships support the identification and prioritisation of cross-cutting research
45 needs and also potential joint funding routes. There should therefore be a shared
46 responsibility between research partners to ensure that key research is undertaken and
47 co-operation to allow sharing of information to avoid duplication and improve
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3 efficiency. NICE has partnered with The National Center for Biotechnology
4 Information so that there is now a PubMed bookshelf dedicated to methods
5 research, and the methodological research reports undertaken by organisations
6 like NICE are also indexed and accessible.
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11 A number of methods to identify priority areas for research have emerged. These
12 include measuring the burden of disease or the expected return from research as well
13 as estimates of the welfare losses resulting from variations in clinical practice.²⁸ The
14 value of information (VOI) analysis is a more novel approach to prioritising research
15 uncertainties that quantifies the expected net benefit from the results of the additional
16 research to society, against the cost of conducting that piece of research and its
17 implementation. Through this framework, the value of acquiring additional
18 information to inform the decision problem helps alleviate some of the uncertainty,
19 had less definitive evidence been used instead.^{29,30} This method has a firm foundation
20 in statistical decision theory and has been successfully used in other areas of
21 research.²⁸ It has also been employed for developing research recommendations from
22 a number of NICE guidance, but not yet been undertaken routinely.
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32 Other successful initiatives to identify, prioritise and promote research uncertainties
33 include the James Lind Alliance (JLA) Priority Setting Partnerships (PSPs). These
34 PSPs bring together patients, carers and clinicians using transparent methods to
35 prioritise 'known unknowns' that have been elicited primarily from evidence-based
36 knowledge.³¹ Until January 2016, these research priorities were collated and
37 published in the UK Database of Uncertainties about the Effects of Treatments (UK
38 DUETs). This was launched in 2006 to collate uncertainties from reports of
39 systematic reviews and clinical guidelines, protocols for systematic reviews (such as
40 those published in the Cochrane Database of Systematic Reviews) or from registered
41 information about ongoing clinical trials. Some of the treatment uncertainties came
42 directly from patients or carers, or from clinicians and cover a wide variety of health
43 problems, for example, cancer, mental health and skin disorders.³¹ Another good
44 example can be seen from the field of international development where the use of
45 evidence gap maps have been developed by the International Initiative for Impact
46 Evaluation (3ie). Evidence gap maps are evidence collections that map out existing
47 and ongoing systematic reviews or primary studies in a sector or subsector, such as
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maternal health, HIV/AIDS and agriculture. They present a visual overview of existing evidence and therefore highlight the areas of gaps within the evidence landscape.³²

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- **Conflict of interests:** All authors will complete the required forms as required but would like to declare that they do not have any conflict of interests. TS was an employee of NICE and the remaining authors are currently employees of NICE.
- **Ethics approval:** This study did not need any ethics approval.
- **Data Sharing:** All authors had complete access to the data and are happy to share it upon request.

Tables

Table 1: Example format for research recommendation rationale, to support prioritisation

Potential criterion	Explanation
Importance to patients, service users or the population	What would be the impact of any new or altered guidance on the population (for example, acceptability to patients or service users, 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 or evidence)? How important is the question to the overall guidance? <ul style="list-style-type: none"> • High: the research is essential to inform future updates of key recommendations in the guidance. • Medium: the research is relevant to the recommendations in the guidance, but the research recommendations are not essential to future updates. • Low: the research is of interest and will fill existing evidence gaps.
Relevance to the NHS, public health, social care and voluntary sectors	What would be the impact on the NHS, public health, social care and voluntary sector and (if relevant) the public sector of any new or altered guidance (for example, financial advantage, or effect on staff, strategic planning or service delivery)?
National priorities	Is the question relevant to a national priority area (such as a national policy or parliamentary paper)? If so, specify the document.
Current evidence base	What are the problems with the current evidence base? (That is, why is further research needed?) Is there any relevant ongoing research 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 on a technology, intervention or service 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 needed 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.

Table 2: Summary of the cost of National Institute of Health Research (NIHR) - funded projects (as at 31 March 2016)

	NICE Priority Topics		NICE Database Topics		Total	
	No of NETS projects	Funded cost (£)	No of NETS projects	Funded cost (£)	No of NETS projects	Funded cost (£)
HTA programme	24	£24,369,414	22 (I TAR)	£15,805,225	46	£40,174,639
PHR programme	4	£1,764,186	26	£16,448,522	30	£18,212,708
HS&DR programme	n/a	n/a	2	£738,188	2	£738,188
Total	28	£26,133,600	50	£32,991,935	78	£59,125,535

Source: NIHR Evaluations, Trials and Studies (NETS) Coordinating Centre (NETSCC)

HTA: Health Technology Assessment; PHR; Public Health Research; HS&DR: Health Services & Delivery Research; n/a: not applicable

Table 3: Methodological research projects funded through Methodology Research Panel (MRP) in 2009 (approximately £2.3 million)

Research Project	Principal Investigator	Primary Research Institute	Project duration (months)	Value funded
Widening the spectrum of health outcomes used in health technology assessment: integrated synthesis and mapping to QALYs	Professor A. E. Ades	University of Bristol	24	238,868
Use of generic and condition-specific measures in NICE decision-making	Dr L. Longworth	University of Sheffield	24	289,189
Preparatory study for the re-evaluation of the EQ-5D tariff	Dr A. Tsuchiya	University of Sheffield	18	242,969
Economic modelling of diagnostic/treatment pathways in NICE clinical guidelines	Dr J. Lord	Brunel University	24	284,471
Properties of statistical methods for indirect and mixed treatment comparison - a computer simulation evaluation	Dr F. Song	University of East Anglia	12	96,810
Methodological search filter performance: assessment to improve efficiency of evidence information retrieval.	Ms C. Lefebvre	NHS R&D Programme	24	95,833
Methods to estimate the NICE cost-effectiveness threshold	Professor M. Sculpher	University of York	24	351,357
Methods for the Indirect estimation of health state utilities	Professor C. McCabe	University of Leeds	24	194,949
Methods for strengthening evaluation and implementation: specifying components of behaviour change interventions	Professor S. Michie	University College London	36	509,200

Figures

Figure 1: The NICE research recommendations process

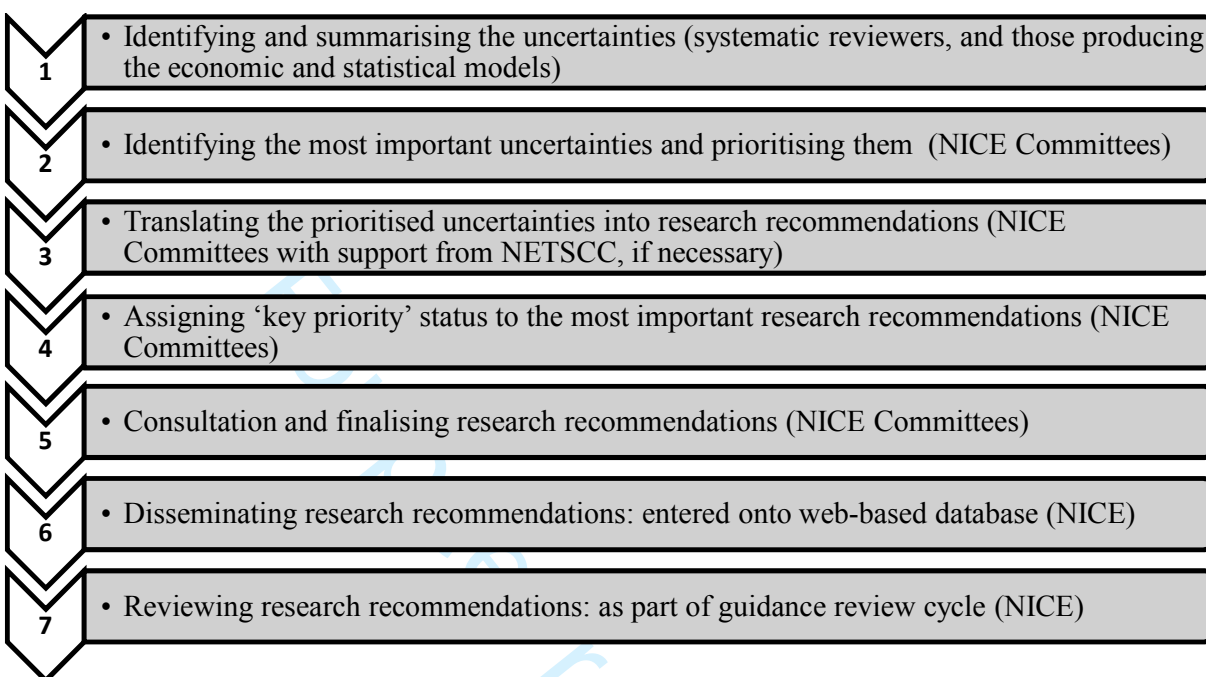
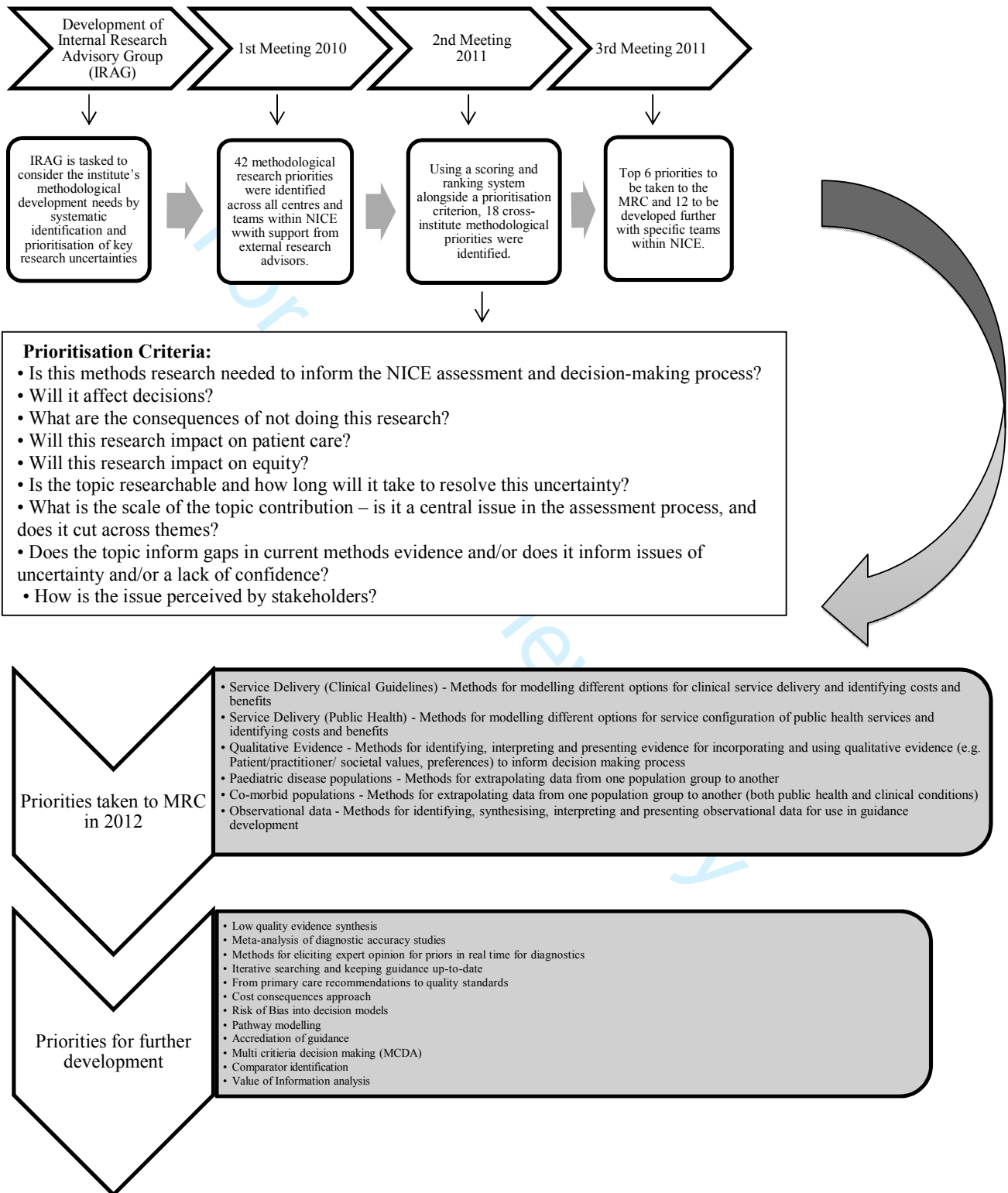


Figure 2: Process of identifying methodological research priorities at NICE and relationship with Medical Research Council (MRC): Example 2010-2012



BMJ Open

Using HTA and guideline development as a tool for research priority setting the NICE way: reducing research waste by identifying the right research to fund.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019777.R1
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Primary Subject Heading:	Health policy
Secondary Subject Heading:	Research methods, Public health
Keywords:	research waste, priority setting, research priorities, NICE, resource allocation

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3 **Using HTA and guideline development as a tool for research priority setting the**
4 **NICE way: reducing research waste by identifying the right research to fund.**
5

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8 *Rejon-Parrilla, Senior Analyst^c; Dr Pall Jonsson, Associate Director^c and Professor*
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23 Abstract: 202 words

24 Manuscript: 3219 words

25 Tables: 3

26 Figures: 2

27 References: 36

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Abstract

Background: The National Institute for Health and Care Excellence (NICE) was established in 1999 and provides national guidance and advice to improve health and social care. Several steps in the research cycle have been identified that can support the reduction of waste that occurs in biomedical research. The first step in the process is ensuring appropriate research priority setting occurs so only the questions that are needed to fill existing gaps in the evidence, are funded. This paper summarises the research priority setting processes at NICE.

Methods: NICE uses its guidance production processes to identify and prioritise research questions through systematic reviews, economic analyses and stakeholder consultations and then highlights those priorities by engagement with the research community. NICE also highlights its methodological areas for research to ensure the appropriate development and growth of the evidence landscape.

Results: NICE has prioritised research questions through its guidance production and methodological work and has successfully had several research products funded through the National Institute for Health Research and Medical Research Council. This paper summarises those activities and results.

Conclusions: This activity of NICE therefore reduces research waste by ensuring that the research it recommends has been systematically prioritised through evidence reviews and stakeholder input.

Strengths and limitations of this study

- **Strengths**

- Highlights the importance of reducing research waste and the prioritisation of research as a key step in that process.
- Describes the systematic prioritisation of research done by NICE.
- Illustrates the methodological research undertaken from prioritised topics by NICE in recent years.

- **Limitations**

- This paper is limited to the prioritisation of research undertaken at NICE and it does not reflect all the work the Institute does to reduce research waste.

Keywords: research waste, priority setting, research priorities, NICE, resource allocation

Introduction

There is no doubt that the substantial public and private investment in biomedical research (estimated to be around US\$240 billion in 2010),¹ has led to significant improvements to the quality of life of people. However, not all research yields such benefits and though some waste is unavoidable due to the nature of science, many improvements to the way we conduct our work, can be made to ensure that our investments are sound and the value of our research is increased.^{1,2} Getting the first step of the research cycle, that is appropriate priority setting of research or identifying the correct research question to fund, is key to this being successful.¹

Previous research has shown that there is a huge mismatch between the research that is funded and the research needed by the end users. A study found that only nine out of 334 research articles highlighted priorities relevant to patients or clinicians.² A second study found that whilst the majority of trials funded were related to drugs, the end users were much more interested (80%) in research about “*education and training, service delivery, psychological interventions, physical interventions, exercise, complementary interventions, diet etc*”, compared with research in drugs (20%).¹

Another problem noted is that often the new research ignores what is already known about the problem and doesn't take into account previous research and therefore can duplicate information and give little additional value.^{1,2} Moreover, such research may miss the true knowledge gaps that need answering and this can often be compounded by the failure to publish negative research (publication bias) which can go undetected unless methodology such as funnel plots are used. Even if an appropriate research gap is identified, inappropriate design, or statistical analyses or the problem of ‘effect to bias ratio’ (where the magnitude of the effect size and biases like selection or confounding, are similar), may mean that the validity of any results may be questionable.^{3,4}

The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing evidence informed guidance on health and

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3 social care for England.^{5,6} NICE guidelines (clinical, public health and social care),
4 quality standards, health technology assessments (HTA) and other products help to
5 deliver the best possible care within the limited resources available.^{5,6} The Science
6 Policy and Research (SP&R) programme⁷ works together with various academic,
7 charity and research funding organisations to enable the appropriate research to be
8 done. It is now also working with life sciences companies, using European
9 Commission funding through the Innovative Medicines Initiative (IMI), to take this
10 work forward. In this paper we summarise these processes and the work that has been
11 undertaken through these mechanisms.
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18 **Research priorities identified through systematic reviews (guideline or HTA** 19 **production)**

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21 NICE guidance is based on the synthesis of evidence primarily through the process of
22 systematic reviewing and, if appropriate, health economic modelling and cost
23 effectiveness decision analysis which are presented using GRADE profiles that allow
24 for a transparent representation of the confidence in the evidence available for
25 decision-making.⁸ The results of this work are discussed by independent advisory
26 committees (consisting of members external to NICE), which can include a diversity
27 of National Health Service staff, healthcare professionals, social care practitioners,
28 commissioners and providers of care, patients, service users and carers, industry and
29 academics. The committees, through a process of guided deliberation of the evidence
30 reach conclusions by formally making draft recommendations. During a period of
31 public consultation, external stakeholders can comment on draft recommendations
32 before they are finalised and eventually published.⁹ The evidence base supporting
33 guidance recommendations are reviewed every few years to ensure that any results
34 potentially demonstrating a change in practice or care are formally considered for
35 updating recommendations.
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47 Not only does this process explicitly describe the evidence base, but it also identifies
48 where there are gaps, uncertainties or conflicts, in the existing evidence. Many
49 uncertainties identified may be interesting to answer, but could have little impact on
50 people's care or NICE's ability to make appropriate evidence-based and evidence-
51 informed recommendations. Uncertainties can arise because there is no evidence
52 available or due to the absence of relevant research, or if research has been done, but
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not yet published. Or there may be evidence available but there is still insufficient information on which to base a recommendation (for example, due to inadequate reporting or poor quality), or the research is out of date (for example, a systematic review that needs updating with recent trials or if clinical practice has changed). However, if these uncertainties could have an impact, and support future NICE guidance recommendations, it is important for the Institute to make recommendations for research (see Table 1).

Table 1: Example format for research recommendation rationale, to support prioritisation

Potential criterion	Explanation
Importance to patients, service users or the population	What would be the impact of any new or altered guidance on the population (for example, acceptability to patients or service users, quality of life, morbidity or disease prevalence, severity of disease, or mortality)?
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Feasibility	Can the proposed research be carried out within a realistic timescale? Would the sample size needed 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.

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4 These recommendations are deliberated, discussed, agreed and formulated by the
5 independent advisory committees and the external community (both specialist and
6 public) that are then invited to comment and contribute.⁹ The final recommendations
7 are identifiable in the guidance and are also collated into the publically available
8 NICE research recommendations database.¹⁰ NICE then liaises with the research
9 community to ensure they are addressed as detailed in the paragraphs that follow. By
10 making research recommendations, NICE is looking to steer the research community
11 for them to generate new evidence to inform the future guidance update and review
12 cycle. If gaps remain in the evidence base after several years, the committee may
13 consider keeping, removing or archiving the research recommendations based on any
14 new findings. In 2010 (updated in 2015), NICE established a formal guide to support
15 this process and to provide a route to ensuring they are picked up as key topics for
16 research funding.¹¹ The guide describes a step-by-step approach to identifying
17 uncertainties, formulating research recommendations and research questions,
18 prioritising them and communicating them to researchers and research funders (see
19 Figure 1).
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32 NICE works closely with National Institute for Health Research (NIHR, a
33 government body that supports health and care research of national research
34 priorities)¹² to prioritise, promote and commission its research recommendations. The
35 identified topics are considered by a number of their different research programmes,
36 particularly the Health Technology Assessment, Public Health Research and the
37 Health Services & Delivery Research programmes. If they are found to be suitable
38 and fulfil their criteria, they enter the commissioning process. This process has
39 evolved over the last 10 years and since 2005, over £59million worth of these
40 research projects have been funded (see Table 2). In 2015, NICE and NIHR
41 Evaluation, Trials and Studies Coordinating Centre (NETSCC) agreed a fast tracked
42 route for the most important research recommendations, to be flagged under the
43 ‘NICE Key Priority’ designation. These research recommendations have the potential
44 to have the highest impact on future guidance recommendations and people’s care.
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Table 2: Summary of the cost of National Institute of Health Research (NIHR) - funded projects (as at 31 March 2016)

	NICE Priority Topics		NICE Database Topics		Total	
	No of NETS projects	Funded cost (£)	No of NETS projects	Funded cost (£)	No of NETS projects	Funded cost (£)
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Source: NIHR Evaluations, Trials and Studies (NETS) Coordinating Centre (NETSCC)

HTA: Health Technology Assessment; PHR; Public Health Research; HS&DR: Health Services & Delivery Research; n/a: not applicable

Methodological research priorities: ‘research on research’

The Edinburgh Reducing Waste conference in 2015 highlighted the importance of being efficient in not only the ‘what’ but also the ‘how’ research is done. Whilst the basic methodology of systematic reviews and cost-effectiveness analyses may be well established, there is still controversy about ‘best practice’ and challenges frequently arise in the context of specific technologies, particularly when decisions are negative. It is therefore vital that methodological research is undertaken. Inadequacies in the evidence base have required the exploration of newer methods such as indirect comparisons and the use of network meta-analyses, that allow for comparisons across different drugs and interventions where those trials have not been undertaken.¹³

Different perspectives exist about what data constitutes as evidence and about what should be used for decision-making. Due to the paucity of the evidence base for some interventions, particularly in the public health and social care domains, NICE has always considered the ‘best available’ evidence to inform its decisions, which moves beyond RCTs, using GRADE to determine the validity of the collective evidence.^{8-9,13}

In order to ensure that the evidence NICE receives is fit for decision-making, each of NICE’s guidance programmes have a methods guide which are regularly updated to

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3 incorporate new developments. NICE Scientific Advice works directly with
4 commercial evidence producers on a fee-for-service basis to ensure the appropriate
5 evidence is available for decision-making.
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9 In 2008 NICE had its first comprehensive review of the methodological research
10 needed for future development of the work of the Institute (methodological priorities
11 for research), funded by the Medical Research Council (MRC) and NIHR joint
12 Methodology Research Programme (MRP).¹⁴ The methodological review identified
13 and prioritised methods research topics through a focused literature review,
14 interviews, an email survey, a workshop and web-based feedback exercise.
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16 Participants were members of the NICE secretariat and its advisory bodies,
17 representatives from academia, industry, and other organizations working closely with
18 NICE. The first prioritised project the MRP funded in 2008 was on the appropriate
19 use of “only in research” decision¹⁵ and a further nine projects were funded through
20 another MRP call via their needs-led route in 2009 (over £2.3 million, see Table 3).
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29 To ensure that NICE had robust processes for timely identification, prioritisation and
30 communication of methodological research needs, an Internal Research Advisory
31 Group (IRAG, formerly the internal methods advisory group) was established in
32 2010. This group was tasked to develop the Institute’s methodological development
33 needs in both the short-term and long-term by continuing the systematic identification
34 and prioritisation of key research uncertainties on an on-going basis and working with
35 MRP to commission research.¹² The group consisted of representatives of the
36 different guidance and non-guidance producing centres and programmes across
37 NICE, who were supported as and when needed by external research advisors from
38 academia who were methodological experts in the fields relevant to the work of
39 NICE. Each programme provided their methodological research priorities and 45
40 uncertainties were collated from across the Institute. These were clarified and re-
41 prioritised into themes that included modelling service delivery, using qualitative
42 evidence to capture patients experience, extrapolating data for co-morbid and
43 paediatric populations and using observational data from large datasets for decision-
44 making. These were then highlighted by MRC through a NICE specific funding call
45 (see Figure 2).
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Table 3: Methodological research projects funded through Methodology Research Panel (MRP) in 2009 (approximately £2.3 million)

Research Project	Principal Investigator	Primary Research Institute	Project duration (months)	Value funded
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Preparatory study for the re-evaluation of the EQ-5D tariff	Dr A. Tsuchiya	University of Sheffield	18	242,969
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Methods for the Indirect estimation of health state utilities	Professor C. McCabe	University of Leeds	24	194,949
Methods for strengthening evaluation and implementation: specifying components of behaviour change interventions	Professor S. Michie	University College London	36	509,200

Some of the prioritised topics did not receive any bids and other internal support mechanisms were used to fund them as small scoping projects. This led to more clarified research questions, of which one was undertaken internally by the SP&R programme at NICE on the use of colloquial evidence¹³ and the other to support the use of observational data in healthcare decision making was put forward as a highlight notice by the MRP in 2017.¹⁶ They also funded two more NICE priorities on developing a reference protocol for expert elicitation in health care decision making in 2016¹⁷ and going beyond health related quality of life - towards a broader QALY measure for use across sectors in 2017.¹⁸

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4 The SP&R programme has also participated in a project considering the role of social
5 values in priority setting as part of an international collaboration to try and unpick how
6 cultural contexts of well-being interacted with healthcare decision-making.^{19,20}
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9 Additionally, the programme supported the establishment of a Research Support Unit
10 (RSU) in 2013 to undertake short projects identified through internal prioritisation by
11 IRAG on methodological areas that included reviewing the literature on social value
12 judgements relevant for NICE and identifying and appraising promising sources of
13 UK clinical, public health and social care real-world data.²¹ Other arrangements for
14 NICE to access research commissioning include the Decision Support Unit, the
15 Technical Support Unit and the External Assessment Centres that facilitate
16 methodological research for health technology assessments (HTAs), clinical
17 guidelines and medical technologies evaluation work respectively. NICE has also
18 recently partnered with Myeloma UK to explore how patient preferences could be
19 captured and included in HTAs more readily.
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29 NICE has also been looking at internationally important and relevant research
30 priorities that will potentially have a global impact on health and care decision-
31 making. It has been successful in gaining international co-operation and European
32 Commission funding through the IMI for some of the key priorities currently facing
33 the field. These include the use of real world data for early decision-making
34 (GetReal)²², the medicines adaptive pathways to patients (MAPPs) activities to foster
35 access to beneficial treatments for the right patient groups at the earliest appropriate
36 time in the product life-span in a sustainable fashion (ADAPT-SMART)²³ and using
37 big data for obtaining better outcomes for patients (BD4BO).²⁴ The Institute has also
38 been actively involved with other European Commission funded projects such as
39 EUnetHTA (an effective and sustainable network for HTA across Europe)²⁵ and
40 DECIDE (Patient and public focused strategies for communicating evidence-based
41 recommendations).²⁶
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52 In 2017 NICE published nine areas that it had, through the SP&R programme and the
53 IRAG, identified as priorities for methodological research. These are: (1) real world
54 evidence; (2) data science; (3) adaptive pathways; (4) patient preferences; (5)
55 improvements in cross-sector comparisons; (6) expert elicitation; (7) complex data
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3 visualisation; (8) precision medicine, and (9) implementation of NICE guidance.
4 Methodological research in these areas will help NICE assess the need for
5 improvement in the methods and processes it uses to produce guidance and anticipate
6 and adapt to policy developments and changes in health and social care delivery in the
7 next few years. By only highlighting methodological research areas to funders that
8 were systematically prioritised, NICE ensures that only questions whose answers will
9 impact its future work are studied therefore doing its part to reduce research waste.¹
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15 **Discussion**

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18 Priority setting is an explicit method that considers what to fund by weighing the
19 trade-offs between the various options in the process.²⁷ It is imperative to avoid
20 research waste such that only key gaps in knowledge are fulfilled by undertaking new
21 research that help build a more complete evidence landscape for future policy
22 development and better clinical practice. Systematic approaches to research priority
23 setting improve the transparency of research management and are often based on a
24 “research cycle” approach which includes the identification of research questions,
25 ranking their priority, identifying existing research, and setting priorities for primary
26 research, and involving relevant stakeholders at key points throughout the cycle.²⁸ It
27 is therefore essential that a formal process of prioritisation of research be established
28 within guidance producing organisations, with the involvement of all legitimate
29 stakeholders, to increase the ownership of the ensuing research and the likelihood of
30 the results influencing practice and policy.²⁹
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40 Creating research recommendations is part of the guidance production cycle and they
41 should:

- 42 • Identify any uncertainties that may affect people’s care.
- 43 • Be developed using an appropriate technique to frame research question
44 development, for example PICO (population, intervention, comparator, outcome)
45 or EPICOT (evidence, population, intervention, comparator, outcome, time)
- 46 • Go through a process of stakeholder consultation and be reviewed as part of the
47 guidance review and update cycle.
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53 This is the path that NICE has taken and therefore has a strong emphasis on reducing
54 research waste. The NICE research recommendations are derived from the
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3 uncertainties identified through the NICE guidance development process and are an
4 integral part of the guidance development and review cycles. The Institute therefore
5 reduces research waste by supporting the re-direction of resources to more valuable
6 activities.³⁰ By making its research priorities and funded research publically available,
7 it minimises the duplication of research. It also drafts research questions with
8 appropriate detail (e.g. type of study design, sample size required etc.), such that the
9 answers obtained from its commissioned research are meaningful. Publicly funded
10 guidance development bodies have a responsibility to ensure that they are guiding
11 appropriate future research based on identified need and gaps in the evidence base.
12 This is also true for research funders, who also have the same responsibility. NIHR
13 has shown that only 5 (11%) of the 47 trials funded over the two-year period (2006-
14 2008) were not based on identified gaps from systematic reviews, and they had valid
15 reasons for doing so.³¹

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26 Methodological uncertainties derived from NICE also go through a process of
27 systematic identification and prioritisation and are promoted to funders to encourage
28 research being funded into the various aspects of how to undertake the development
29 of future guidance. Though this paper is limited to describing the prioritisation of
30 research undertaken at NICE, we feel it is an important part of the role of any HTA or
31 guideline-producing agency globally to undertake, in order to reduce research waste.
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37 In recent years NICE has entered into a few international research collaborations.
38 These are becoming increasingly important as sources of research funding,
39 particularly within the current economic climate, are dwindling. Such partnerships
40 support the identification and prioritisation of cross-cutting research needs and also
41 potential joint funding routes. There should therefore be a shared responsibility
42 between research partners to ensure that key research is undertaken and co-operation
43 to allow sharing of information to avoid duplication and improve efficiency. NICE
44 has partnered with The National Center for Biotechnology Information so that there
45 will be a PubMed bookshelf dedicated to methods research, and the methodological
46 research reports undertaken by organisations like NICE would also be indexed and
47 accessible in the future.
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3 A number of methods to identify priority areas for research have emerged. These
4 include measuring the burden of disease or the expected return from research as well
5 as estimates of the welfare losses resulting from variations in clinical practice.³² The
6 value of information (VOI) analysis is a more novel approach to prioritising research
7 uncertainties that quantifies the expected net benefit from the results of the additional
8 research to society, against the cost of conducting that piece of research and its
9 implementation. Through this framework, the value of acquiring additional
10 information to inform the decision problem helps alleviate some of the uncertainty,
11 had less definitive evidence been used instead.^{33,34} This method has a firm foundation
12 in statistical decision theory and has been successfully used in other areas of
13 research.³² It has also been employed for developing research recommendations from
14 a number of NICE guidance, but not yet been undertaken routinely.

22
23 Other successful initiatives to identify, prioritise and promote research uncertainties
24 include the James Lind Alliance (JLA, now part of NIHR and carried out via
25 NETSCC) Priority Setting Partnerships (PSPs). These PSPs bring together patients,
26 carers and clinicians using transparent methods to prioritise 'known unknowns' that
27 have been elicited primarily from evidence-based knowledge.³⁵ Until January 2016,
28 these research priorities were collated and published in the UK Database of
29 Uncertainties about the Effects of Treatments (UK DUETs). This was launched in
30 2006 to collate uncertainties from reports of systematic reviews and clinical
31 guidelines, protocols for systematic reviews (such as those published in the Cochrane
32 Database of Systematic Reviews) or from registered information about ongoing
33 clinical trials. Some of the treatment uncertainties came directly from patients or
34 carers, or from clinicians and cover a wide variety of health problems, for example,
35 cancer, mental health and skin disorders.³⁵ Another good example can be seen from
36 the field of international development where the use of evidence gap maps have been
37 developed by the International Initiative for Impact Evaluation (3ie). Evidence gap
38 maps are evidence collections that map out existing and ongoing systematic reviews
39 or primary studies in a sector or subsector, such as maternal health, HIV/AIDS and
40 agriculture. They present a visual overview of existing evidence and therefore
41 highlight the areas of gaps within the evidence landscape.³⁶

42 43 44 45 46 47 48 49 50 51 52 53 54 55 **Conclusions**

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3 It is important that HTA and guideline organisations use their systematic processes to
4 identify research gaps and then subsequently link with national research funders to
5 ensure they are addressed. NICE therefore supports the reducing research waste
6 campaign by ensuring that the research it recommends has a beneficial impact on the
7 health and care of the people, as it has been systematically identified as a genuine gap
8 in the health evidence or a method that needs further clarification or development.
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- **Data Sharing:** The data can be requested from NICE, UK.

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4 **Figures**
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6 Figure 1: The NICE research recommendations process
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9 Figure 2: Process of identifying methodological research priorities at NICE and
10 relationship with Medical Research Council (MRC): Example 2010-2012
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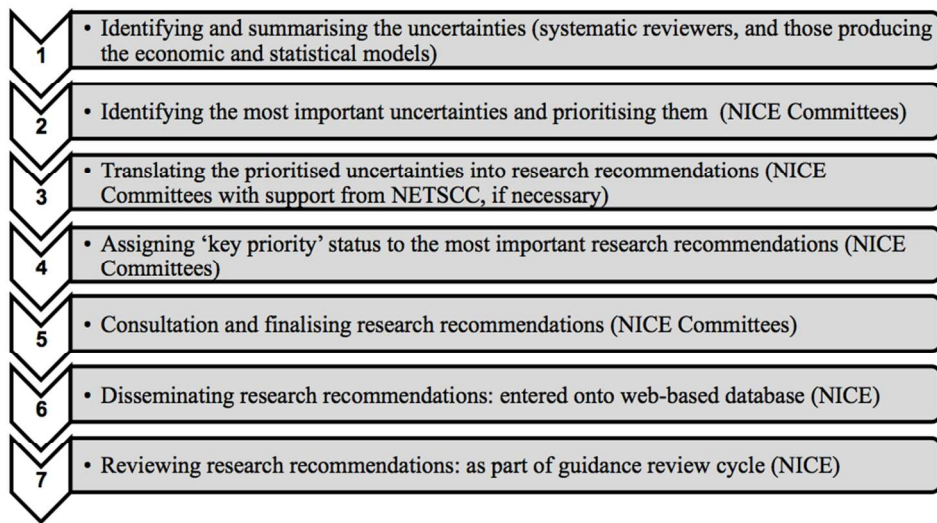


Figure 1: The NICE research recommendations process

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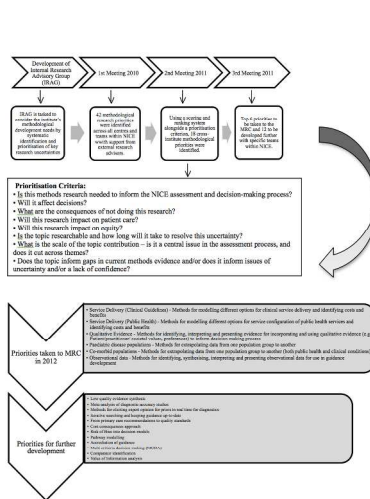


Figure 2: Process of identifying methodological research priorities at NICE and relationship with Medical Research Council (MRC): Example 2010-2012

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