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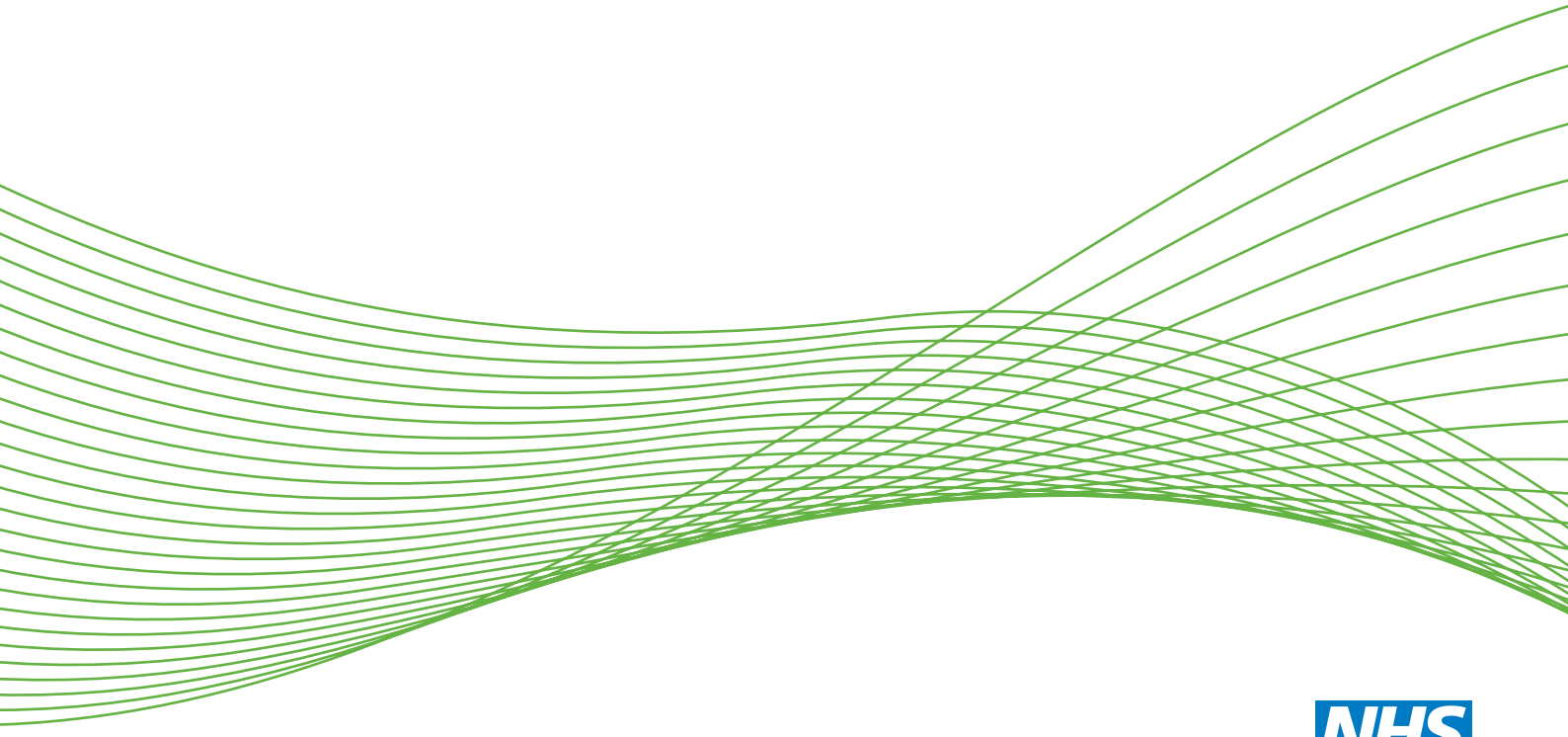

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Abstract

The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis

Eva Kaltenthaler,[1]* Christopher Carroll,[1] Daniel Hill-McManus,[1] Alison Scope,[1] Michael Holmes,[1] Stephen Rice,[2] Micah Rose,[3] Paul Tappenden[1] and Nerys Woolacott[4]

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Background: As part of the National Institute for Health and Care Excellence (NICE) single technology appraisal (STA) process, independent Evidence Review Groups (ERGs) critically appraise the company submission. During the critical appraisal process the ERG may undertake analyses to explore uncertainties around the company's model and their implications for decision-making. The ERG reports are a central component of the evidence considered by the NICE Technology Appraisal Committees (ACs) in their deliberations.

Objective: The aim of this research was to develop an understanding of the number and type of exploratory analyses undertaken by the ERGs within the STA process and to understand how these analyses are used by the NICE ACs in their decision-making.

Methods: The 100 most recently completed STAs with published guidance were selected for inclusion in the analysis. The documents considered were ERG reports, clarification letters, the first appraisal consultation document and the final appraisal determination. Over 400 documents were assessed in this study. The categories of types of exploratory analyses included fixing errors, fixing violations, addressing matters of judgement and the ERG-preferred base case. A content analysis of documents (documentary analysis) was undertaken to identify and extract relevant data, and narrative synthesis was then used to rationalise and present these data.

Results: The level and type of detail in ERG reports and clarification letters varied considerably. The vast majority (93%) of ERG reports reported one or more exploratory analyses. The most frequently reported type of analysis in these 93 ERG reports related to the category 'matters of judgement', which was reported in 83 (89%) reports. The category 'ERG base-case/preferred analysis' was reported in 45 (48%) reports, the category 'fixing errors' was reported in 33 (35%) reports and the category 'fixing violations' was reported in 17 (18%) reports. The exploratory analyses performed were the result of issues raised by an ERG in its critique of the submitted economic evidence. These analyses had more influence on recommendations earlier in the STA process than later on in the process.

Limitations: The descriptions of analyses undertaken were often highly specific to a particular STA and could be inconsistent across ERG reports and thus difficult to interpret.

Conclusions: Evidence Review Groups frequently conduct exploratory analyses to test or improve the economic evaluations submitted by companies as part of the STA process. ERG exploratory analyses often have an influence on the recommendations produced by the ACs.

Future work: More in-depth analysis is needed to understand how ERGs make decisions regarding which exploratory analyses should be undertaken. More research is also needed to fully understand which types of exploratory analyses are most useful to ACs in their decision-making.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

Adapted from the National Institute for Health and Care Excellence Technology Appraisal Process Guide (National Institute for Health and Care Excellence. *Guide to the Processes of Technology Appraisal*. 2014. URL: www.nice.org.uk/article/pmg19/chapter/foreword).

Appraisal Committee A standing advisory committee for the National Institute for Health and Care Excellence. It includes people who work in the NHS, people representing patient and carer organisations, lay members, and people from relevant academic disciplines and the pharmaceutical and medical device industries.

Appraisal consultation document Sets out the Appraisal Committee's preliminary recommendations to the National Institute for Health and Care Excellence.

Final appraisal determination Sets out the Appraisal Committee's final recommendations to the National Institute for Health and Care Excellence on how the technology should be used in the NHS in England.

Incremental cost-effectiveness ratio A statistic used to summarise cost-effectiveness. It is the ratio of the difference in the mean costs of a technology compared with the next best alternative to the differences in the mean outcomes.

Model An explicit mathematical framework that is used to represent clinical decision problems. It incorporates evidence from a variety of sources so that the costs and health outcomes can be estimated.

Multiple technology appraisal The process designed to appraise single or multiple products, devices or other technologies, with one or more related indications. The National Institute for Health and Care Excellence seeks relevant evidence from several sources.

Single technology appraisal The process specifically designed to appraise a single product, device or other technology, for a single indication. The process normally covers new technologies (typically, new pharmaceutical products or new licensed indications) and enables the National Institute for Health and Care Excellence to produce guidance soon after the technology is introduced in the UK. The National Institute for Health and Care Excellence seeks relevant evidence from several sources. The company submits the principal evidence.

List of abbreviations

AC	Appraisal Committee
ACD	appraisal consultation document
BMJ	British Medical Journal
CHE	Centre for Health Economics
CRD	Centre for Reviews and Dissemination
CS	company submission
ERG	Evidence Review Group
FAD	final appraisal determination
ICER	incremental cost-effectiveness ratio
LRiG	Liverpool Reviews and Implementation Group
MTA	multiple technology appraisal
NICE	National Institute for Health and Care Excellence
PAS	Patient Access Scheme
QALY	quality-adjusted life-year
ScHARR	School of Health and Related Research
STA	single technology appraisal
TA	technology appraisal

Plain English summary

In the National Institute for Health and Care Excellence (NICE) single technology appraisal (STA) process, independent researchers called Evidence Review Groups (ERGs) assess a company evidence submission. This assessment often includes exploring uncertainties in the information in the submission by conducting alternative analyses. We aimed to explore the number and type of these explorations undertaken by the ERGs. NICE requested that this work be carried out in order to better understand how ERGs conduct alternative analyses.

We looked at more than 400 documents to determine what analyses had been done by the ERGs, the reasons for these analyses and how this information was used. We separated the types of analyses into categories and summarised the reasons for and content of the analyses. We also looked at how the NICE Appraisal Committees (ACs) used this information in making their decisions.

We found that ERG reports had many differences in the amount and detail of their analyses. Over 93% of ERG reports had at least one of these analyses, with an average number of eight analyses per report. These analyses had more influence on recommendations earlier in the STA process than later on.

The ERGs frequently carry out analyses to better assess how uncertain information affects results. In this way, they aim to improve and clarify the information submitted by companies. These analyses are used by the ACs at NICE to help make their decisions on whether or not to recommend treatments.

Scientific summary

Background

The National Institute for Health and Care Excellence (NICE) single technology appraisal (STA) process is undertaken for a technology for a single indication. The process includes the production of a submission by the manufacturer of the technology. One of the nine independent Evidence Review Groups (ERGs) undertakes a critical appraisal of this submission. As part of the critical appraisal process the ERG may undertake exploratory analyses to explore uncertainties around the company's model and their implications for decision-making. The number and type of exploratory analyses undertaken varies between appraisals. The ERG reports are a central component of the evidence considered by the NICE Technology Appraisal Committees (ACs) in their deliberations. The findings of the committee are used to produce the appraisal consultation document (ACD) and, after further considerations and a consultation period, a final appraisal determination (FAD) is produced, which results in NICE guidance.

Objectives

The aim of this research was to develop an understanding of the number and type of exploratory analyses undertaken by the ERGs within the NICE STA process and to understand how these analyses are used by the NICE ACs in their decision-making process. For the purpose of this research, an exploratory analysis was defined as any additional analysis generating an incremental cost-effectiveness ratio (ICER) and included in the ERG report section 'Exploratory and sensitivity analyses undertaken by the ERG'. This is most commonly reported as Section 6 of an ERG report, based on the suggested ERG report template. The study aimed to address the following objectives:

1. to identify ERG reports that contain exploratory analyses conducted by the ERG, as defined above
2. to identify ERG approaches to exploratory analyses of economic evidence submitted by companies for NICE STAs and to categorise these approaches by type of analysis performed
3. to identify data sources used for exploratory analyses undertaken by ERGs
4. to identify factors that influence or predict the extent of ERG exploratory analyses
5. to identify whether or not companies were provided with the opportunity to provide the analyses as part of the clarification stage
6. to identify situations in which a committee requested the ERG to conduct additional analyses
7. to make an assessment of the degree to which the exploratory analyses influenced a committee's considerations and recommendations.

Methods

The 100 most recently completed STAs (from 2009) for which guidance has been published were selected for inclusion in the analysis. The documents associated with the 100 STAs and used in data extraction were:

- ERG reports (unredacted versions, including confidential information used by the ACs)
- clarification letters and responses
- the first ACD issued (subsequent ACDs were not considered)
- the last FAD issued (where more than one FAD has been produced).

More than 400 documents were assessed in this study. Information on the number of AC meetings for each STA was provided directly by NICE.

A data extraction tool was developed and piloted to ensure usability and to standardise extraction. The final categories of exploratory analyses were based on discussions with the project team and used an existing relevant published taxonomy; the categories of types of exploratory analyses included (i) fixing errors, (ii) fixing violations, (iii) addressing matters of judgement and (iv) the ERG-preferred base case. All data extractions were double-checked. A narrative synthesis of the extracted data was performed, summarising key data through text and tables to address the objectives. The mean number of exploratory analyses per ERG report was calculated as well as the median. The key data used in the synthesis were then reduced to whether a STA conducted more or fewer than the overall mean number of exploratory analyses.

Results

The level and type of detail in ERG reports and clarification letters varied considerably. The principal disease areas covered by the STAs were cancer (44%), blood and the immune system conditions (11%), cardiovascular conditions (10%) and musculoskeletal conditions (8%). Of the 100 STAs, 21% were assessed by the AC using end-of-life criteria. The vast majority (93%) of ERG reports reported one or more exploratory analyses with a range from 1 to 29 per report with an approximate mean of 8.5 analyses per report and a median of 7 analyses per report. The most frequently reported type of analysis in the 93 ERG reports that generated at least one exploratory analysis related to the category 'matters of judgement', which was reported in 83 (89%) of reports. The category 'ERG base-case/preferred analysis' was reported in 45 (48%), the category 'fixing errors' was reported in 33 (35%) and the category 'fixing violations' was reported in 17 (18%). ERG reports often included more than one type of exploratory analysis. The principal source of data used by the ERG was published literature.

The likelihood of an ERG performing eight or more exploratory analyses was not affected by the company's base-case ICER or disease area covered by the STA. The proportion of ERG reports with eight or more analyses appears to be relatively stable over time, although the number of exploratory analyses did vary by ERG.

Of the 93 STAs with at least one exploratory analysis, 65 (70%) ERG reports included at least one exploratory analysis that was covered in the clarification letter to the company. Overall, 36% (287/798) of the total exploratory analyses within the 93 reports were issues highlighted at the clarification stage. Almost all exploratory analyses performed were the result of any issue raised by an ERG in its critique of the submitted economic evidence, usually in the chapter in the ERG report preceding the section in which the exploratory analyses were presented.

Appraisal consultation document recommendations were clearly influenced by one or more of the mentioned ERG exploratory analyses in 55 out of the 76 STAs with ACDs (72%). This was reduced for FADs, as FAD recommendations were clearly influenced by one or more of the mentioned ERG exploratory analyses in 44 out of the 93 STAs with FADs (47%). The preferred ICERs reported in ACDs were 36% from ERGs and 11% from companies, while in 9% of ACDs, ICERs from both ERGs and companies were included or the ICERs from both were the same. This changed at FAD, where the preferred ICERs were 27% from ERGs and 23% from companies, with 17% of FADs using some ICERs from ERGs and some from companies.

Discussion

An ERG's judgement relating to perceived uncertainties or possible variation in the evidence base and model was the type of exploratory analysis appearing in the largest proportion of ERG reports. Rather than simply generating a single alternative ICER, exploratory analyses were conducted to present a number of scenario analyses.

As the most recent 100 STAs with guidance issued were included in this analysis, current practice is reflected. Extensive piloting and double-checking of data by experienced modellers helped to reduce inconsistencies and inaccuracies in the data extraction. By using a descriptive synthesis method, the likelihood of overstating relationships in the data was reduced.

Data extraction was difficult owing to the differences in the level and type of detail provided in the ERG reports and clarification letters so that data extractors had to exercise interpretation of some of the data. When grouping reports by indication, ICER or numbers of exploratory analyses, the numbers were too small to evaluate relationships in the data using basic statistical tests in a meaningful manner.

Conclusions

Evidence Review Groups frequently conduct exploratory analyses to test or improve the economic evaluations submitted by companies as part of the STA process. ERG exploratory analyses appear to often influence the recommendations produced in the ACDs and FADs issued within the NICE STA process. The influence appears to be greatest for ACDs and this influence is reduced by subsequent work between the ACD and the FAD. For the 79% of STAs with no ACD, the company ICER was < £20,000 per quality-adjusted life-year gained and the impact of the analyses was reduced. Caution should be used when drawing conclusions from the evidence, especially concerning the generalisability of the findings.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Historical perspective

The National Institute for Health and Care Excellence (NICE) in the UK provides guidance and advice to improve health and social care. NICE guidance contains evidence-based recommendations and includes technology appraisals (TAs), which are recommendations on the use of new and existing medicines and treatments within the NHS. The NICE single technology appraisal (STA) process is, in principle, undertaken for a single technology for a single indication, although more than one comparator may be included. The STA process began in 2005 and was introduced to enable the production of more rapid guidance than the existing NICE multiple technology appraisal (MTA) process so that new products could be approved as close to licensing as possible. Concerns were raised early on that although STAs resulted in more rapid guidance, there remained uncertainty concerning the extent to which STAs adequately addressed the specific decision problem under consideration.[1] There have been considerable changes to the STA process over time, such as the inclusion of scoping workshops, decision problem meetings, clarification letters and end-of-life criteria.

Previous research found the STA process to be slower than initially anticipated, primarily because of events outside NICE's control,[2] and that one-third of referred topics in the first 4 years of the STA process were either suspended or terminated. In their study comparing the NICE STA process with the Scottish Medicines Consortium process, Ford *et al.*[3] found that, overall, the STA process reduced the average time to publication compared with NICE MTAs (median 16.1 months compared with 22.8 months). However, for cancer medications, the STA process took longer than the MTA process (25.2 months compared with 20.0 months). Barham[4] also found that STAs took longer than anticipated, particularly for cancer drugs. A more recent analysis by Casson *et al.*[5] found STAs to be significantly faster than MTAs for all conditions. NICE aims to issue guidance as close to marketing authorisation as is possible.

National Institute for Health Research single technology appraisal process

Table 1 shows a brief description of the STA process.

The STA process is outlined in detail in NICE's *Guide to the Process of Technology Appraisal*[6] and includes the production of an evidence submission by the company producing the technology. The company submission (CS) to NICE forms the principal source of evidence for decision-making in the STA process. The company is expected to follow the decision-analytic approaches as described in the *Guide to the Methods of Technology Appraisal*[7] and the submission is expected to contain an evaluation of the clinical effectiveness and cost-effectiveness of the technology. Evidence Review Groups (ERGs) are charged with the task of critically appraising the CS to identify strengths, weaknesses and gaps in the evidence presented. Assessment by the ERG is conducted over an 8-week period. Templates exist for both the CS and the ERG report. Early in the process a request for clarification, covering any issues that are unclear in the submission, is made to the company, which is then given an opportunity to respond. As part of the STA process, the ERGs also undertake exploratory analyses to explore uncertainties around the company's model and the implications of these for decision-making. It is the responsibility of the ERG to determine what additional analyses are required and to undertake them. The ERG may also identify and correct technical or programming errors that are identified. This critical appraisal of the CS and additional work form the basis of the ERG's report. The number and type of exploratory analyses undertaken varies between appraisals, but they can contribute important evidence for consideration by an Appraisal Committee (AC). These ERG reports are a central component of the evidence considered by the AC.

TABLE 1 Single technology appraisal process

STA process	Weeks (approximately) since process start
Scope developed, sent out for consultation, discussed at scoping workshop and final scope agreed	Draft scope in week 1, scoping workshop weeks 7–9
Company discusses with NICE how the decision problem will be addressed	
	Weeks (approximately) after decision problem meeting and invitations sent
Company makes an evidence submission	9 (received by ERG)
ERG report developed: 2 weeks into the process the clarification letter is sent to the company	17
First AC meeting to develop the ACD or FAD (if no ACD produced)	21
Second AC meeting to develop the FAD, if an ACD has been produced at earlier AC meetings	29
After close of appeal period, NICE publishes guidance	38

AC, Appraisal Committee; ACD, appraisal consultation document; ERG, Evidence Review Group; FAD, final appraisal determination.

Little guidance is given to ERGs on how to produce their reports. Some assessment of process has been undertaken. For example, Wong *et al.*[8] assessed approaches used by ERGs to critically appraise search strategies within CSs. Previous research has highlighted issues with CSs that are particularly challenging to the ERGs.[9] Carroll *et al.*[10] suggested that company STA submissions could be improved if attention were paid to transparency in the reporting, conduct and justification of the review, and modelling processes and analyses, as well as greater robustness in the choice of data in the model and closer adherence to the scope or decision problem. Where this adherence is not possible, it was suggested that more detailed justification of the choice of evidence or data is required. Kaltenthaler *et al.*[11] also recommended the need for clear and transparent reporting of CSs, and for a clear and concise rationale for the synthesis of clinical data, the development of economic models and the assumptions used to develop models.

There are currently nine ERGs:

1. British Medical Journal (BMJ) Technology Assessment Group, BMJ Evidence Centre, BMJ Group
2. Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE), University of York
3. Health Economics Research Unit and Health Services Research Unit, University of Aberdeen
4. Kleijnen Systematic Reviews Ltd
5. Liverpool Reviews and Implementation Group (LRiG), University of Liverpool
6. Peninsula Technology Assessment Group, Peninsula Medical School, Universities of Exeter and Plymouth
7. School of Health and Related Research (ScHARR), University of Sheffield
8. Southampton Health Technology Assessment Centre, University of Southampton
9. Warwick Evidence, Warwick Medical School, University of Warwick.

An additional ERG, the West Midlands Health Technology Assessment Collaboration, undertook STAs during the period 2005–10.

The ERG report, together with other evidence, is considered by one of four NICE ACs. ACs can make four categories of recommendation: (1) recommended, (2) optimised (previously recommended under certain circumstances, e.g. to a subgroup within the licence), (3) only in research and (4) not recommended. Each appraisal may contain more than one recommendation. 'Only in research' recommendations are rare in any TA process.[12]

A recommendation is considered provisional if the AC recommendation is not recommended, limitations are recommended on the use of the technology or the company is asked to provide further clarification of their evidence submission. If the recommendation is provisional, an appraisal consultation document (ACD) is produced. At this stage, a 'minded no' preliminary recommendation may be issued, requiring more information from companies before a final recommendation can be made. Following the publication of an ACD, companies may submit additional evidence, which may include a Patient Access Scheme (PAS) proposal, and the ERG may produce a report that assesses the impact of the PAS. A PAS may also be submitted earlier on in the STA process. The AC, as part of its deliberations, considers the PAS as part of the evidence for the appraisal.

The AC meets to consider the consultation comments received on the ACD and any additional evidence produced. The ERG may be asked to critique any new evidence from the company. Final recommendations are made in the form of the final appraisal determination (FAD). At the end of the appeal period, NICE guidance is produced.

Aims and objectives

This study was commissioned by NICE and aims to investigate how ERGs undertake exploratory analyses within the NICE STA process and how these analyses are used by the NICE ACs in their decision-making process. For the purpose of this research, an exploratory analysis is defined as any additional analysis generating an incremental cost-effectiveness ratio (ICER) and included in the ERG report section 'Exploratory and sensitivity analyses undertaken by the ERG'. This is most commonly reported as Section 6 of an ERG report, if the suggested template is followed. This study aims to present an examination of the experiences and outcomes related to instances in which ERGs have conducted additional exploratory analysis and to examine what exploratory analysis have been done, and, where possible, why they were done and what the outcome of the analyses were in terms of how they were managed by the AC and used in the decision-making process. This is an under-researched area and this study was commissioned by NICE to develop understanding of this aspect of the STA process. This research is of interest to all key stakeholders in the STA process, including the ERGs, the pharmaceutical companies, AC members and NICE.

The study seeks to address the following objectives:

1. to identify ERG reports that contain exploratory analyses conducted by the ERG, as defined above
2. to identify ERG approaches to exploratory analyses of economic evidence submitted by companies for NICE STAs and to categorise these approaches by type of analysis performed
3. to identify data sources used for exploratory analyses undertaken by ERGs
4. to identify factors that influence or predict the extent of ERG exploratory analyses
5. to identify whether or not companies were provided with the opportunity to provide the analyses as part of the clarification stage
6. to identify situations in which a committee requested the ERG to conduct additional analyses
7. to make an assessment of the degree to which the exploratory analyses influenced a committee's considerations and recommendations.

Chapter 2 Methods

This research was jointly undertaken by teams at ScHARR at the University of Sheffield and CRD and CHE at the University of York. The objectives addressed by this research were initially identified by NICE. A protocol was developed and peer reviewed and is available from the HTA website.[13] A content analysis of selected documents (documentary analysis) was undertaken to identify and extract relevant data, and narrative synthesis was used to rationalise and present these data.

Selection of single technology appraisals

The 100 most recently completed STAs (since 2009) for which guidance has been published were selected for inclusion in the analysis. It was considered among the team that 100 STAs represented the maximum number of appraisals that could be considered within the time and resource constraints of the project and that the 100 most recent appraisals would provide the most accurate reflection of current practice, as the process has changed substantially since the initial introduction of STAs in 2005. A list of the STAs included in this analysis is attached as *Appendix 1*.

All relevant documents for the 100 STAs were made available to the project team by NICE. The documents used in the data extraction were:

- ERG reports (unredacted versions used by the ACs)
- clarification letters and responses
- the first ACD issued (subsequent ACDs were not considered)
- the last FAD issued (where more than one FAD has been produced).

Information on the number of AC meetings for each STA was provided directly by NICE. The research required extraction of relevant data from more than 400 separate documents.

Data extraction

A sample data extraction template is attached as *Appendix 2*. The data extraction tool was formulated to extract relevant data to address the project objectives.[14] STA reports, clarification letters, ACDs and FADs all have a basic, standard structure, which facilitated data extraction. The ERG reports have a specific 'Exploratory' or 'Additional analyses' section, usually Section 6, from which the data on exploratory analyses were extracted. However, ERG reports and clarification letters and responses can vary greatly in their descriptions of analysis and level of detail. Pilot data extraction was initially undertaken by four extractors (AS, MH, SR and MR) on five STAs to develop and ensure the usability of the data extraction template. After modifications were made to the extraction form, a further pilot data extraction exercise was undertaken using three additional STAs in order to standardise extraction between the York and ScHARR teams. This process produced the final agreed data extraction tool (see *Appendix 3*). The final categories of exploratory analyses to be used in this study were created following this pilot process. They were based on discussions with the whole project team and an existing relevant, published taxonomy.[15] This approach was similar to framework analysis techniques for developing an a priori framework for coding qualitative data.[16] The categories were then defined in order to facilitate consistency of coding. The category 'matters of judgement' was originally composed of three more specific categories: (1) uncertainty and evidence variation, (2) alternative data and (3) ERG subjective judgement. However, it was found that the descriptions of the analyses in the reports were often inadequate for ensuring that the information was being interpreted and coded consistently into one of these categories. For this reason, a single, broader category of 'matters of judgement' was created. The final four agreed categories of exploratory analysis are listed below (*Table 2*). This simple scheme facilitated consistency of coding between data extractors.

TABLE 2 Summary of categories of exploratory analysis

Category	Definition
Fixing errors	The ERG considered that something was unequivocally wrong in the company's submitted model
Fixing violations	The ERG considered that the NICE reference case, scope or best practice had not been adhered to for one or more parameters or values, including missing out relevant comparators, and hence the model is not fit for purpose
Matters of judgement	The ERG did not consider that the submitted model was wrong as such, but amended the model by conducting an analysis (often a sensitivity or threshold analysis) to test uncertainties within the evidence or model, or because reasonable alternative assumptions could be applied. These could be hypothetical or based on alternative data in the published literature or provided by a company
ERG-preferred base case	The ERG conducted its own specific preferred base-case analysis. This might be the result of a series of exploratory analyses. This base case might still not be ideal from the ERG's perspective

The seven parts of the data extraction tool are outlined in *Table 3*.

All data extractions were double-checked by two researchers: > 90% were double-checked by just two team members (DHM and PT) in order to enhance the consistency of extraction and interpretation. The York team extracted data from 24 STAs and the ScHARR team extracted data from 76 STAs. In order to reduce possible bias in extraction, the York team extracted data from all of the ScHARR ERG reports and the ScHARR team extracted data from all of the York CRD/CHE reports.

The level and type of detail provided in and across the ERG reports and clarification letters could be very different, which made data extraction time-consuming, difficult and, at times, a matter of interpretation. Despite efforts to simplify the data extraction and coding process (e.g. a small number of well-defined, mutually exclusive categories of analysis), data extractors sometimes had to exercise interpretation for some data, principally for whether exploratory analyses were prespecified or hinted at in clarification letters. This issue of interpretation also affected the actual number of exploratory analyses undertaken by an ERG and the influence of specific exploratory analyses on AC recommendations, in that in some instances multiple analyses might be counted separately and in other instances they may be lumped together as a single analysis. A typical example can found in the STA, *Dabigatran Etexilate for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation* (TA249).[17] In this case, the ERG conducted many exploratory analyses, generating a range of ICERs, including an ERG-preferred base-case ICER of £24,173 per quality-adjusted life-year (QALY). As part of these analyses, the ERG aimed to test the impact of applying three different, but equally justified, sources of cost data for international normalised ratio monitoring; this produced three only very slightly different ICERs. However, this was interpreted as only one exploratory analysis, although it might arguably have been interpreted as three separate analyses. This ERG report was considered to have a total of 14 exploratory analyses overall. In order to address issues of interpretation such as this, the mean number of exploratory analyses was calculated. The key data used in the synthesis were then reduced to whether a STA conducted more or fewer than the overall mean number of exploratory analyses, and whether just 'one or more' exploratory analyses were explicitly cited as having an influence on a recommendation. These arbitrary selections were made as a means of making the most of the data to address the objectives of the project.

TABLE 3 Summary of data extraction tool

Section	Details of fields	Project objective
Basic characteristics	• STA title • ERG • Company • Disease area • Prespecified subgroups or end-of-life criteria applied? Extractors selected from a prespecified list of variables for most fields	4
Company's base-case ICER(s)	• What is the ICER for the single technology against the principal comparator(s)? • What are the ICERs for the technology against the next best non-dominated or baseline comparators? • What type of model was submitted?	4
Number and type of exploratory analyses conducted by ERG	• See *Table 2*. Extractors selected from a prespecified list of categories • Data extracted included the source(s) of alternative data, where reported	1, 2, 3
Clarification letter and responses	• Was the exploratory analysis mentioned or hinted at in the clarification letter questions?	5
ACD	• What was the preferred ICER and its source? • What was the recommendation (prespecified list of variables)? • Did the ACD mention one or more of the exploratory analyses and was an ICER mentioned? • Did one or more exploratory analysis influence the AC's recommendation (i.e. is the analysis or its ICER cited specifically in relation to the recommendation)?	7
Additional work	• Was additional work undertaken by the company and/or ERG between the ACD and the FAD?	6
FAD	• What was the preferred ICER and its source? • What was the recommendation (prespecified list of variables)? • Did the ACD mention one of more of the exploratory analyses and was an ICER mentioned? • Did one or more exploratory analysis influence the AC's recommendation (i.e. is the analysis or its ICER cited specifically in relation to the recommendation)?	7

Methods for analysis

A narrative synthesis was performed on the extracted data from the 100 ERG reports.[18] This involved summarising the key data through text and tables and then using narrative to highlight any potentially important patterns or relationships in the data. This approach was taken because the large number of reports and documents prevented meaningful, in-depth analysis of the text using qualitative methods, but the numbers were not large enough to permit meaningful statistical analysis of the data. The synthesis therefore described the incidence and frequency of exploratory analyses (objective 1); identified the types of exploratory analyses performed by ERGs, as well as their data sources, where appropriate (objectives 2 and 3); explored relationships between key variables and the presence and frequency of exploratory analyses (objective 4); described the role of exploratory analyses relating to the clarification process (objective 5) and additional analyses post ACD (objective 6); and assessed the possible influence of exploratory analyses on the recommendations of the ACs (objective 7). It was considered a priori that the disease area and a cost-effectiveness threshold of £20,000 per QALY were the key variables most likely to predict the incidence and frequency of exploratory analyses. This was because of the known impact of disease area on other elements of STAs[4] and the perceived importance of the £20,000 per QALY threshold for NICE decision-making.[19] An assessment was also made to identify any changes over time.

In conducting the synthesis, the following assumptions were made:

- Every exploratory analysis had to have a separately reported ICER. If an analysis combined the results of two or more exploratory analyses to calculate the third ICER, then this was considered to be a further, separate analysis.
- The ICER taken for comparison was for the technology against its principal comparator or in the principal scenario (its most likely use in clinical practice).
- When the base-case or preferred ICER reported by the company, ACD or FAD was a range or multiple ICERs (e.g. for subgroups or scenarios), then the lowest ICER was used.
- If the technology was considered to be a cost-effective use of NHS resources, then it was deemed to be so at a threshold of £20,000 per QALY gained.
- If the ACD or FAD simply stated that the technology was 'dominating', then it was assumed that it was cost-effective at the threshold of £20,000 per QALY gained.
- If the ACD or FAD simply stated that the technology was 'dominated', then it was assumed that it was not cost-effective at the threshold of £20,000 per QALY gained[19] (although a technology could simply be dominated by a very cost-effective comparator).
- The data on whether the analyses are mentioned by the ACD or FAD, or influenced their recommendation, relate to the exploratory analyses described in the ERG report or a specific addendum document (rather than any analyses conducted between the ACD and FAD).
- If any work was conducted by a company between an ACD and a FAD, it was assumed that it was critiqued by the ERG as a standard procedure (explicit requests by an AC for an ERG to conduct such work were rarely recorded in the ACD).
- Evidence of influence on a recommendation required a reference to an ERG's exploratory analysis or its ICER.

An example of the data extracted for a single STA, and used in the synthesis, is reproduced in *Appendix 3*.

Chapter 3 Results

General overview

Between September 2009 and September 2014, 100 STAs were undertaken by NICE that resulted in the production of guidance and formed the basis for these analyses. In these 100 STAs, 40 different companies submitted documents as part of the NICE STA process. The companies who were involved with the largest number of submissions were Roche ($n = 15$), Novartis ($n = 9$), GlaxoSmithKline ($n = 7$), Bristol-Meyers Squibb ($n = 7$) and Bayer ($n = 6$). The majority of companies made only one or two submissions (*Table 4*).

Ten ERGs conducted critical appraisals of these submissions. The principal ERGs were based at York CRD/CHE (18 reports), LR*i*G (17 reports), ScHARR (13 reports), Aberdeen (11 reports) and Southampton (10 reports). See *Table 5* for the number of reports completed by each centre in this period.

The principal disease areas covered by the STAs were cancer (44%), blood and the immune system (11%), cardiovascular conditions (10%) and musculoskeletal conditions (8%). The final scoping documents of the majority of the STAs (66%) included pre-specified subgroups. In 21% of the STAs, end-of-life criteria were considered by the AC (*Tables 6* and *7*).

TABLE 4 Companies making evidence submissions within STAs included in the analysis

Company	Number of reports ($n = 100$)
1. Alimera Sciences	1
2. Alimta	1
3. Allergan Ltd	2
4. Amgen Inc.	2
5. Astellas Pharma	2
6. AstraZeneca	4
7. Bayer Healthcare	6
8. Biogen	1
9. Boehringer Ingelheim	3
10. Bristol-Meyers Squibb	7
11. Celgene	2
12. Cell Therapeutics Inc.	1
13. Eli Lilly and Company	5
14. Eliquis	1
15. Eisai Co. Ltd	1
16. Genzyme	2
17. GlaxoSmithKline	7
18. InterMune	1

continued

TABLE 4 Companies making evidence submissions within STAs included in the analysis (*continued*)

Company	Number of reports ($n = 100$)
19. Janssen Pharmaceutica	5
20. Laboratoires Servier	1
21. Movetis	1
22. MSD	2
23. Napp Pharmaceutical Group Ltd	1
24. Novartis Pharmaceuticals UK Ltd	9
25. Novo Nordisk	1
26. Otsuka Pharmaceutical	2
27. Pfizer	4
28. PharmaMar	2
29. Pharmaxis	1
30. Pierre Fabre	1
31. Roche	15
32. Sanofi-aventis	3
33. Savient Pharmaceuticals Inc	1
34. Schering-Plough	2
35. Stelara	1
36. Sucampo Pharma Europe	1
37. Takeda UK Ltd	2
38. The Medicines Company	1
39. ThromboGenics	1
40. UCB	1

MSD, Merck Sharp & Dohme.
The total is greater than 100 because six submissions were joint submission from more than one company.

TABLE 5 Evidence Review Groups responsible for producing reports within STAs included in the analysis

ERG	Number of reports ($n = 100$)
Aberdeen	11
BMJ	8
Kleijnen Systematic Reviews Ltd	7
LRiG	17
PenTAG	4
ScHARR	13
Southampton	10
Warwick	5
West Midlands	7
York CRD/CHE	18

PenTAG, Peninsula Technology Assessment Group.

TABLE 6 Disease areas relevant to STAs included in the analysis

Disease area	Number of reports ($n = 100$)
Blood and immune system	11
Cancer	44
Cardiovascular	10
Central nervous system	4
Digestive system	2
Endocrine, nutrition and metabolic	4
Eye	7
Infectious diseases	2
Mental health	2
Musculoskeletal	8
Respiratory	3
Therapeutic procedures	2
Urogenital	1

TABLE 7 Prespecified subgroups and end-of-life criteria assessed

Prespecified subgroups and end-of-life criteria	Number of reports[a] ($n = 100$)
With subgroups prespecified	66
With assessment for end-of-life criteria	21

a Some reports considered neither prespecified subgroups nor end-of-life criteria.

Finally, it should be noted that for 19 STAs (19%) no ACD was produced: decisions were simply recorded in the FAD. This means that some tables in the sections below do not report numbers for 100 STAs, but rather have a denominator of 81.

Exploratory analyses

Evidence Review Group reports that contain exploratory analyses

The vast majority (93%) of ERG reports for the STA process conducted and reported one or more exploratory analyses (*Table 8*): seven ERG reports did not contain any exploratory analysis that generated a new ICER.[20–26] In the 93 reports that did include an exploratory analysis, the number of analyses ranged from 1 to 29, with an approximate mean of 8.5 analyses per report and a median of 7.

TABLE 8 Summary of numbers of exploratory analyses

Exploratory analyses	Number
Proportion of reports with exploratory analyses	93/100 (93%)
Proportion of reports without exploratory analyses	7/100 (7%)
Number of exploratory analyses identified per report with analyses (mean) (number of exploratory analyses/number of reports with analyses)	8.5 (798/93)
Number of exploratory analyses identified per report with analyses (range)	1–29

Out of the 93 ERG reports with at least one exploratory analysis, a total of 40 (43%) included eight or more such analyses. For the 10 ERGs undertaking STAs, the mean number of exploratory analyses per report ranged from 2.3 (West Midlands) to 11.4 (ScHARR) (*Table 9*). It should be noted that no regression analyses were performed to explore the relationship between the mean number of analyses per report by ERG and other variables such as disease area and year, as well as other potentially influencing factors such as complexity and perceived quality of CSs, owing to the limitations of the data.

It is clear from the histogram (*Figure 1*) that the vast majority of ERG reports conducted nine or fewer analyses. Ten reports contained three or seven analyses, nine reports contained five analyses and six reports contained eight analyses.

TABLE 9 Mean number of exploratory analyses by ERG

ERG	Number of analyses/number of reports	Mean number of exploratory analyses per report
ScHARR	148/13	11.4
BMJ	83/8	10.4
CRD	173/18	9.6
PenTAG	38/4	9.5
Southampton	91/10	9.1
Warwick	44/5	8.8
Aberdeen	72/11	6.5
LRiG	96/17	5.6
Kleijnen Systematic Reviews Ltd	37/7	5.3
West Midlands	16/7	2.3
Total and mean	798/100	8

PenTAG, Peninsula Technology Assessment Group.

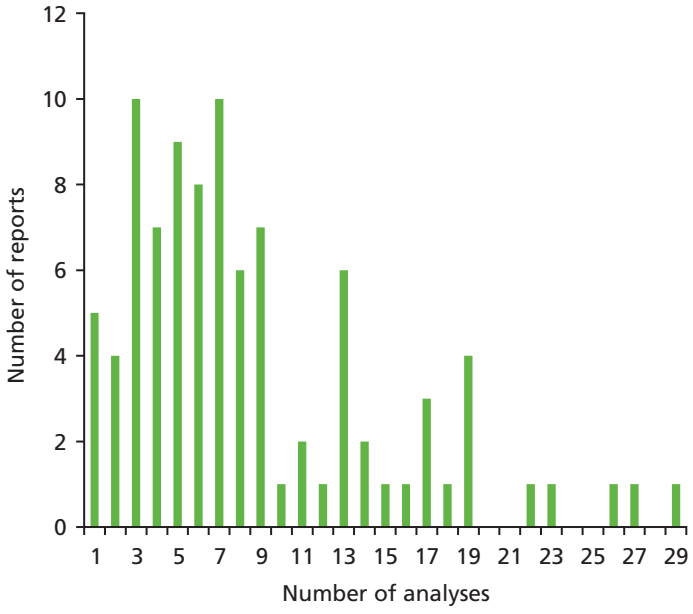


FIGURE 1 Distribution of exploratory analyses.

Categories of Evidence Review Group approaches to exploratory analyses of economic evidence

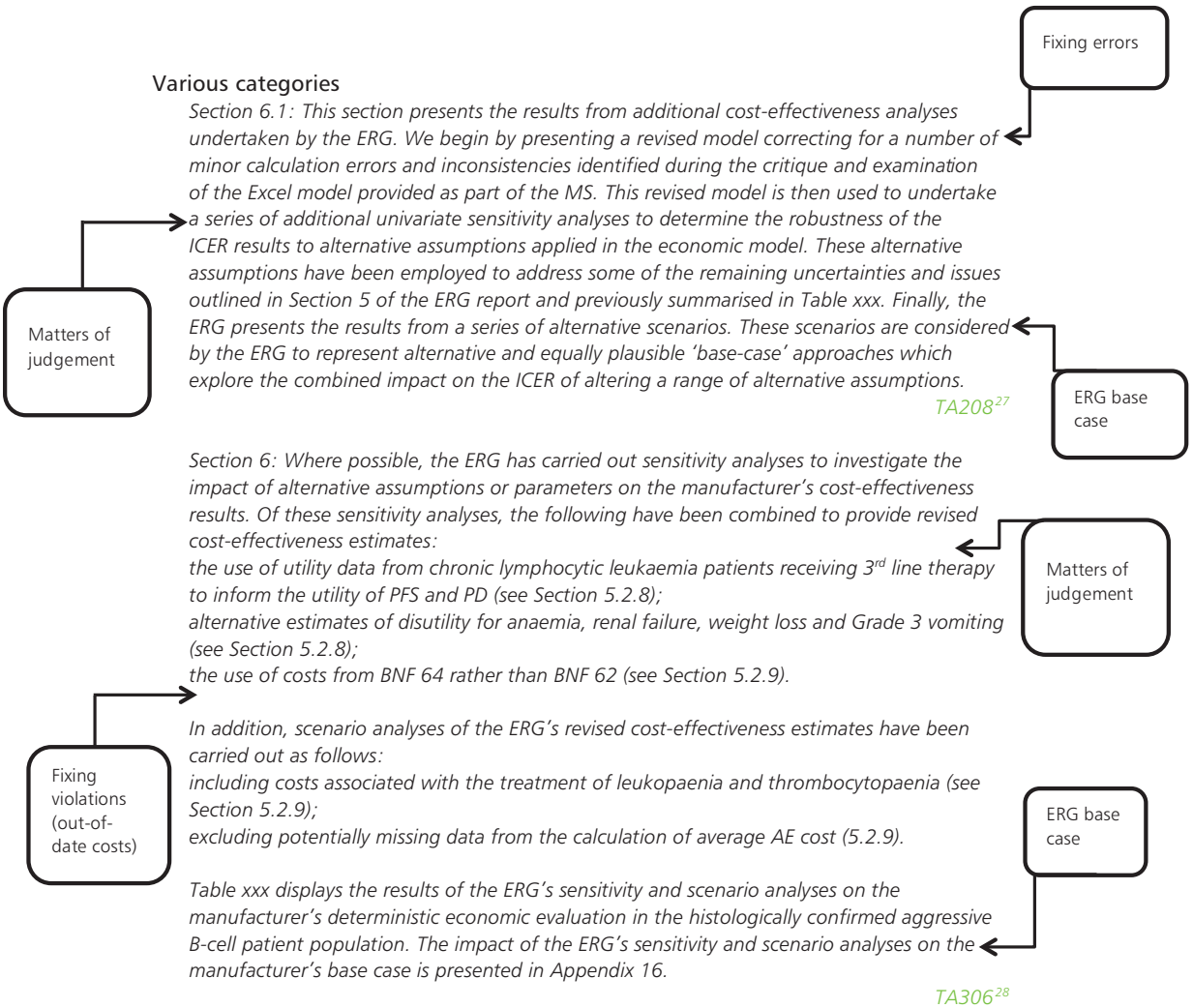
For the 93 ERG reports that generated at least one exploratory analysis, the type of analysis that appeared in the largest proportion of reports was the category of 'matters of judgement'; that is, the ERG considered there to be uncertainty or possible variation regarding the evidence used to populate the model. At least one such exploratory analysis was conducted in 89% of ERG reports. As a category of exploratory analysis, the calculation of a new base case by an ERG appeared in more ERG reports (48%) than analyses which were concerned with either fixing outright errors in the submitted models (35%) or fixing violations (18%) (*Table 10*).

Some examples of each of the categories are illustrated below based on extracts of text included in ERG reports.

TABLE 10 Proportion of reports with exploratory analyses for which the following categories were identified

Category	Number of reports (%) ($n = 93$)
Matters of judgement	83 (89)
ERG base-case/preferred analysis	45 (48)
Fixing errors	33 (35)
Fixing violations	17 (18)

Numbers add up to more than 100% because an ERG report could include more than one type of analysis.



Matters of judgement

Section 6.1 and 6.3: Opinion sought by the ERG suggested that it is far from certain that denosumab will be administered in a primary care setting, and so some analysis was undertaken based on assumptions that denosumab, zoledronate and ibandronate are administered entirely in a secondary care setting. . . . Tables xxx have been provided to show how the ICERs for denosumab change by subgroup using full secondary care costing assumptions for administration of denosumab and all the secondary comparators

TA204[29]

Sections 6.4.2 and 6.4.3: The ERG noted in its critique of the manufacturer's submission that some of the assumptions in relation to treatment initiation and monitoring costs were not considered to be sufficiently justified. The ERG examined a scenario which assumed that all treatments (as opposed to just dronedarone) could be initiated in an outpatient setting. The resulting effect on the ICERs was marginal and the overall conclusions on cost-effectiveness is not altered. . . . The ERG expressed some concern that the utility values applied in the economic model potentially imply a higher estimate of quality of life than that expected from the general UK population. In an attempt to address this issue, the ERG adjusted the constant value of the regression model used to estimate utility values to ensure that the values applied in the model do not exceed those of the general population. The adjustment was made to the regression constant such that the utility value estimated for a 70 year old AF [atrial fibrillation] male without any symptoms was reduced from 0.918 to 0.78, with the same adjustment applied throughout the model for all patients. The ERG recognises that this is not the most appropriate way to change the utility values but without access to the individual patient level data of the AFTER study this was the best that the ERG could do to take account of the manufacturer's potentially overly optimistic estimates of overall QALYs. Table xxx presents the ICERs for the base case populations incorporating the adjustment in HRQoL [health-related quality of life]. The implications for the cost-effectiveness results were limited.

TA197[30]

Section 4.2.5: Pioglitazone costs

ISD Scotland prescription data notes the following balance between the three doses of pioglitazone in the year to December 2010 . . . Ignoring the 15mg dose still suggests that a significant proportion of patients may not titrate up to the maximum 45 mg. Given a rough balance of 60:40 for 30mg: 45 mg would imply an average annual cost for pioglitazone of £487 compared to the £516 of the base case: a reduction of £29. Over the initial 5 years of the modelling, on the basis of a discounted survival of 4.548 years in the pioglitazone arm this would be anticipated to reduce the pioglitazone total discounted costs by £130. In itself, this would only worsen the cost effectiveness estimate for once-weekly exenatide compared to pioglitazone from the £8,624 per QALY of the base case to £9,357 per QALY.

TA248[31]

Evidence Review Group base-case/preferred analysis

Section 5.5.3: New model results were generated by the ERG to take account of each of the issues previously identified (sections 5.5.2 and 5.5.3 above); the separate effect of each change is shown in the upper section of Table xxx compared to the manufacturer's submitted base case analysis. The most influential amendments are the removal of a limit on the number of cycles of treatment any patient could receive, and substitution of utility values based on the incidence of AEs [adverse events] reported in the JMEN trial. The combined effect of these changes is to increase the incremental cost attributable to use of pemetrexed by 35% as well as reducing the incremental QALYs gained by 2%, so that the ICER increases from £33,732 to £47,239 per QALY gained.

TA190[32]

Fixing errors

Section 5.5.3: A continuity correction is applied to models where a quantity is estimated at fixed time points, but the entity of interest (e.g. cost or survival) is accrued over the period between the fixed points. Relying only on values at either of the fixed points defining an interval may lead to systematic over or under-estimation. . . . The correct approach is to use the area under the curve (AUC) from the trial analysis unaltered, and then calculate 'mid-cycle' corrected estimates for the remainder of the model duration derived from a parametric model. When this approach is applied to the manufacturer's base case, the incremental utility gain is reduced by 3.5%, and the ICER correspondingly increased to £34,860 per QALY gained.

TA190[32]

Section 5.3.3: A minor error has been detected in calculating the proportion of patients assumed to receive docetaxel and erlotinib in second-line therapy. When this is corrected the ICER for the manufacturer's base case rises slightly to £33,817 per QALY gained.

TA190[32]

Fixing violations

Addendum: Can an indication of the cost effectiveness of the first-line aripiprazole strategy compared with a first-line risperidone strategy be provided using the estimated costs for risperidone (for adolescent schizophrenia) and the manufacturer's economic model? These issues were identified as important by NICE as risperidone is generally reported as the current standard first line treatment in adolescent schizophrenia, while the manufacturer's economic model includes olanzapine as the main comparator (due to inadequacies in the evidence base, discussed in the MS [manufacturer's submission] and the ERG report). Other comparators in the NICE scope were not modelled here. A limitation of this modelling is that data on risperidone is from one RCT [randomised controlled trial] only, not based on evidence from a systematic review.

TA213[33] *(e.g. failure to consider a key comparator in the scope)*

Section 5.3.3: Post progression costs and utilities are calculated in the submitted model by apportioning the overall mean survival between maintenance, second-line CTX [chemotherapy], BSC [best supportive care] and terminal care phases. Since apportioning is carried out on the basis of discounted overall survival estimates, and the costs are then discounted again, the post progression costs are double discounted in the model. In addition, the estimation of QALYs relies on the same discounted survival values and were similarly double discounted, so that incremental utilities are also affected. The net consequence of correcting this error in the manufacturer's base case is to increase incremental costs by a small amount (for BSC costs only), but to increase incremental QALYs by about 5.5%, so that the ICER falls to £32,091 per QALY gained.

TA190[32] *(a base-case error)*

Sources of evidence

It was difficult to ascertain the exact proportion of exploratory analyses that sourced data and to identify those sources, but it was apparent that published literature, rather than the company or clinical experts, was the principal source of data used by the ERGs, where a particular source was specified. Extractors categorised particular sources of alternative data used for exploratory analyses in a total of 86 reports (*Table 11*).

TABLE 11 Sources of alternative data

Source of data for exploratory analyses	Apparent sources of data for exploratory analyses ($n = 86$)
Literature	69 (80%)
Manufacturer	33 (38%)
Clinical advisors	15 (17%)
Other	41 (48%)
Unclear	8 (9%)

Numbers add up to more than 100% because an ERG report could include more than one type of analysis.

Factors that might influence or predict the presence of Evidence Review Group exploratory analyses

As noted above, this study aimed to test the possible influence of disease area, a cost-effectiveness threshold of £20,000 per QALY gained and changes over time as the factors most likely to predict the presence and numbers of exploratory analyses.

Disease area

Only five disease areas were the subjects of seven or more STAs. In this group, the blood and immune system had the highest proportion of its STAs, with eight or more exploratory analyses (64%), and cancer, the indication with the highest number of STAs, had the lowest (38%). However, the numbers were generally too small to suggest that disease area might predict a higher than average number of exploratory analyses (*Table 12*).

TABLE 12 Number of reports by disease area with eight or more exploratory analyses

Disease area	Number of reports with exploratory analyses (%) ($n = 93$)	Number of reports with eight or more exploratory (%) analyses
Blood and immune system	11 (12)	7/11 (64)
Cancer	40 (43)	15/40 (38)
Cardiovascular	9 (10)	4/9 (40)
Central nervous system	4 (4)	2/4 (50)
Digestive system	2 (2)	0/2 (0)
Endocrine, nutrition and metabolic	3 (4)	1/3 (25)
Eye	7 (8)	4/7 (57)
Infectious diseases	2 (2)	1/2 (50)
Mental health	2 (2)	1/2 (50)
Musculoskeletal	7 (8)	4/7 (50)
Respiratory	3 (3)	0/3 (0)
Therapeutic procedures	2 (2)	1/2 (50)
Urogenital	1 (1)	0/1 (0)

Company's base-case incremental cost-effectiveness ratio and the cost-effectiveness threshold of £20,000 per quality-adjusted life-year gained

Of the 93 companies' submissions that attracted one or more exploratory analyses by an ERG, the proportion submitting base-case ICERs that were cost-effective at the threshold of £20,000 per QALY was almost the same as the proportion at or above this threshold. The likelihood of an ERG performing eight or more exploratory analyses was not affected by the ICER: the proportion of reports that did so was approximately the same (41% and 45%) (*Table 13*).

It is therefore the case that the presence of exploratory analyses, or of eight or more exploratory analyses, is not obviously predicted either by the disease area covered by the STA or by a company's base-case ICER being less or more than the lower end of the cost-effectiveness threshold of < £20,000 per QALY.

Other factors that might determine the presence of exploratory analyses

The absence of exploratory analyses, or the presence of a relatively low number, could be caused by many factors. It could be that the submitted model was considered fit for purpose (e.g. TA267:[22] ERG report, section 5.3, 122: 'The ERG was satisfied with the estimates obtained from the manufacturer's model. Moreover, the sensitivity and subgroup analyses carried out by the manufacturer provided sufficient assessment of any areas of uncertainty'). Equally, it could be caused by the submitted model being perceived to be flawed to such a degree that additional analyses using the model and its data were deemed to offer no value for decision-making (TA310:[23] Section 6: 'In view of the serious nature of the major issues identified by the ERG, no attempt has been made to quantify the combined effect on the ICER per QALY gained of correcting the minor issues identified below. The ERG takes the view that to do so would give misleading credibility to the manufacturer's ICERs per QALY gained. Instead, the minor issues are described and the ERG's preferred input values have been presented to allow comparison with those used by the manufacturer.').

The proportion of ERG reports with eight or more analyses appears to be relatively stable over time (from 2011 to 2014 the proportion of these as a percentage of all STAs in 1 year was always between 38% and 45%), which suggests that there have not been any particular developments that appear to influence the frequency of exploratory analyses (*Figure 2*).

TABLE 13 Number of reports by company ICER with one or more exploratory analysis and eight or more exploratory analyses

ICER	Number of reports with one or more exploratory analyses
≤ £20,000 per QALY gained	44/93 (47%)
> £20,000 per QALY gained	49/93 (53%)
	Number of reports with eight or more exploratory analyses
≤ £20,000 per QALY gained	18/44 (41%)
> £20,000 per QALY gained	22/49 (45%)

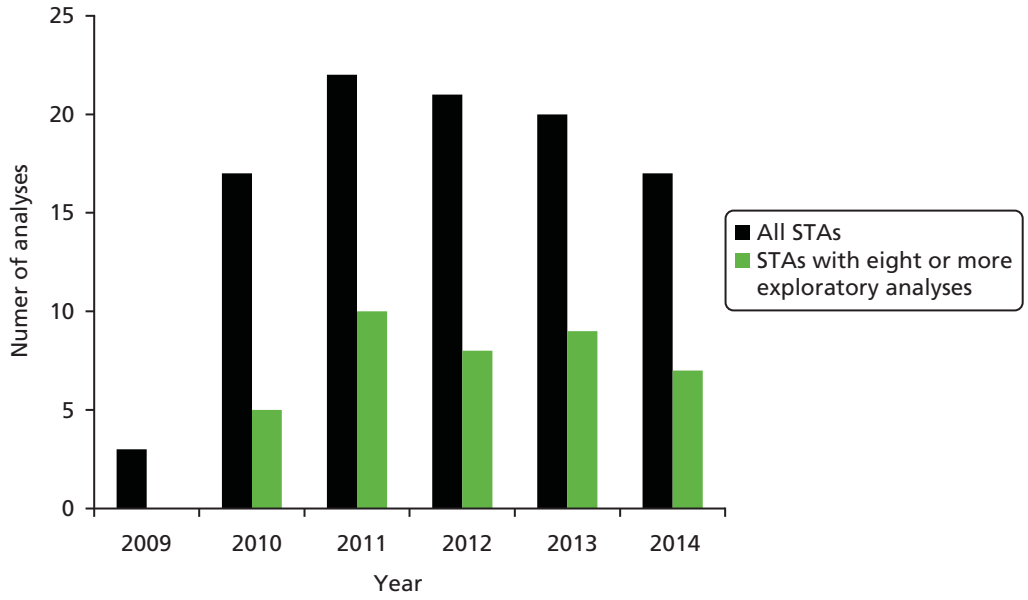


FIGURE 2 Single technology appraisals over time and proportions with eight or more exploratory analyses.

Relationship between clarification requests, Evidence Review Group critiques and exploratory analyses

After a company makes a submission, the ERG has only 2 weeks to read the submission and to request clarification or data from the company. The data presented here consider whether or not any of the exploratory analyses conducted by the ERG were specifically requested from the company but were not provided; were requested but could not be completed by the company for a particular reason; were based on data that were requested by the ERG in the clarification letter; or were 'hinted at' in the clarification process (*Table 14*).

The relationship between an exploratory analysis and a request made in a clarification letter was rarely very clear and might consist of little more than an analysis on an issue raised in the letter, without being directly based on that request. It is clear, however, that, even with such possible indirect associations between requests and the ERGs' exploratory analyses, the majority of exploratory analyses performed by ERGs (64%) were conducted for reasons other than the failure of the company to perform a specific, requested analysis; rather, because the ERG identified other issues with the model, including any which they had not had time to explore fully within the 2-week time frame for clarification.

TABLE 14 Relationship between clarification letters and exploratory analyses

Clarification letter information	Proportion of clarification-letter-based analyses
Proportion of reports with exploratory analyses that performed at least one exploratory analysis that was covered in the clarification letter	65/93 (70%)
Clarification letter-based analyses as a proportion of the total exploratory analyses within these 65 reports	287/653 (44%)
Clarification letter-based analyses as a proportion of the total exploratory analyses within all 93 reports	287/798 (36%)

It is also clear that almost every exploratory analysis performed was the result of an issue raised by an ERG in its specific critiques of the submitted economic evaluation, usually in the chapter of the ERG report preceding the section given over to the exploratory analyses. Examples of ERG reports that do not justify their exploratory analyses in this way are very rare. For example, in TA196,[34] the exploratory analysis undertaken was to set the recurrence-free survival utility parameter equal to values of 0.95 and 0.90. This does not appear to be mentioned or hinted at in the ERG's critical appraisal.

Appraisal Committees and additional analyses

The majority of STAs involved additional work being performed between the production of the ACD and the FAD. However, it was rare for the ACD to mention a request for an ERG to conduct further specific analyses or critical appraisal. Where this did occur, it usually took place before the ACD. For example:

> *ERG Addendum: SHTAC were requested to provide additional analyses for the STA of aripiprazole for the treatment of schizophrenia in adolescents (aged 15-17 years).*
>
> *TA213*[33]

> *ERG Addendum: This document provides further comment from the ERG regarding the indirect comparisons of erlotinib and gefitinib presented by the manufacturer in the MS [manufacturer's submission]. It is provided in response to a NICE request arising from the pre-meeting briefing discussions.*
>
> *TA258*[35]

It was more often the case that the ACD would request additional work from a company. For example:

> *ACD, 4.10: The Committee concluded that it was difficult to establish the most plausible ICER for this treatment because sensitivity analyses to capture all preferred assumptions were not available. However, the Committee concluded that the ICER may be within the range that is consistent with an appropriate use of NHS resources. Therefore, because of these uncertainties, the Committee expects the manufacturer to respond to this appraisal consultation document by addressing the remaining uncertainties and by providing a revised cost-effectiveness analysis . . .*
>
> *TA226*[36]

> *ACD, 4.21: In summary, the Appraisal Committee could not assess whether gefitinib is a cost-effective treatment option because it did not have sufficient information to assess the most plausible ICER for gefitinib compared with standard platinum combination therapy or with pemetrexed and cisplatin. Therefore the Appraisal Committee is minded not to recommend gefitinb for the treatment of locally advanced or metastatic NSCLC [non-small-cell lung cancer]. It is recommending that clarification should be sought from the manufacturer, including analyses that use alternative survival extrapolations and application of hazard ratios, amended first-line chemotherapy costs and chemotherapy cycles, alternative prevalence rates of EGFR-TK [epidermal growth factor receptor tyrosine kinase] mutations and alternative assumptions about the cost of the EGFR-TK mutation tests.*
>
> *TA192*[37]

However, it was most often the case for there to be no specific request at all, but for a company to conduct additional work or resubmit with a PAS in response to a negative recommendation in the ACD (*Table 15*). It is often apparent in the FAD that this work was completed and also submitted for appraisal by the ERG or the NICE Decision Support Unit.

TABLE 15 Work conducted between the ACD and the FAD

Details of STAs with ACDs	Proportion satisfying criteria (%)
Proportion of STAs with additional work between the first ACD[a] and the FAD	60/81 (71)
Proportion of these STAs with a no or minded no recommendation in the ACD	58/60 (97)
Proportion of these STAs with an unspecified ICER in the ACD	20/60 (33)
Proportion of these STAs with a preferred ICER ≥ £20,000 per QALY gained in the ACD	38/60 (63)
Proportion of these STAs with a preferred ICER < £20,000 per QALY gained in the ACD	2[b]/60 (3)

a A total of 81/100 STAs had an ACD.
b One of these had a range of ICERs both below and above this £20,000 per QALYs threshold,[29] and the second had 'cost savings of £400,000 per QALY'.[38]

However, it should be noted that 19 out of 100 STAs did not produce an ACD; in these instances a FAD was issued without the prior publication of an ACD. In all 19 of these FADs, the technology received a positive recommendation. In the vast majority of these STAs, the company's ICER in its original submission was cost-effective at the threshold of £20,000 per QALY gained (15/19, 79%). These STAs also have a smaller proportion of ERG reports (32%) with eight or more exploratory analyses than does the sample as a whole (42%) (*Table 16*).

Table 17 shows the source of the ICERs preferred by the ACs as stated in the ACDs and FADs from the STAs included in this analysis. Often more than one preferred ICER was presented in the documents. The source of the preferred ICER was not always clear in the ACD and FAD. Of the 81 STAs with ACDs, for the majority of cases either there was no preferred ICER (38%) or the ICERs presented by the ERG were preferred by the AC (36%). In the 100 FADs, 27% of the preferred ICERs were from the ERG and 23% were from the company. The number of preferred ICERs including both company and ERG increased from 7 (9%) at the ACD to 17 (17%) at the FAD. It should be noted that in 7 of the 100 STAs no ERG exploratory analyses were undertaken.

TABLE 16 Single technology appraisals without an ACD

Details of STAs without an ACD	Number of STAs (%) ($n = 19$)
Proportion of these STAs with a company ICER of ≤ £20,000	15 (79)
Proportion of these STAs with eight or more exploratory analyses	6 (32)
Proportion of these STAs with a positive recommendation in the FAD	19[a] (100)

a Only one STA had a recommendation optimised.[39]

TABLE 17 Source of preferred ICERs for ACDs and FADs

ERG	Company	Both ERG and company	No preferred ICER	Unclear
ACD ($n = 81$)				
29 (36%)	9 (11%)	7 (9%)	31 (38%)	5 (6%)
FAD ($n = 100$)				
27 (27%)	23 (23%)	17 (17%)	24 (24%)	9 (9%)

Influence of the exploratory analyses on Appraisal Committees' considerations and recommendations

Of the 100 STAs, 76 had one or more exploratory analysis performed by the ERG and also had an ACD. In all but two of these STAs, the ACD made mention of at least one ERG exploratory analysis, and in a large majority (72%) at least one such analysis appeared to influence the ACD recommendation (*Table 18*).

All 100 STAs produced a FAD and 93 also had at least one exploratory analysis. Eighty-seven of these 93 FADs (94%) mentioned one or more of the original exploratory analyses from the ERG reports, but only 47% of STAs had final recommendations that appeared to be influenced by at least one of the exploratory analyses.

A full list summary of the ACD and FAD decisions is given in *Table 19*. Technologies received positive recommendations in < 18% of ACDs but subsequently received positive recommendations in 72% of FADs.

It is worthy of note that almost half (48%) of the STAs that had an ACD that reported a recommendation of no, only in research or minded no had moved to an outright recommendation or optimised recommendation in the FAD. Only one-third of STAs did not see a positive recommendation (*Table 20*).

TABLE 18 Influence of exploratory analyses on the recommendations

Type of recommendation	Number of reports (%)
ACD	
ACD mentions one or more exploratory analysis	74/76 (97)
ACD recommendation is clearly influenced by one or more of the mentioned exploratory analyses	55/76 (72)
FAD	
FAD mentions one or more exploratory analysis	87/93 (94)
FAD recommendation is clearly influenced by one or more of the mentioned exploratory analyses	44/93 (47)

TABLE 19 Decisions in ACDs and FADs

Decision	Number of reports (%)
ACD ($n = 81$)	
Recommended	10 (13)
Optimised	4 (5)
Minded no	19 (23)
No	48 (59)
FAD ($n = 100$)	
Recommended	51 (51)
Optimised	21 (21)
No	28 (28)

TABLE 20 Changes of recommendation from ACD to FAD

ACD to FAD recommendation	Number of reports (%) ($n = 81$)
No or minded no to recommended (including optimised)	39 (48)
No change positive recommendation (including from optimised to full recommendation)	14 (17)
No change negative recommendation	28 (35)

The ERG exploratory analyses apparently influenced the recommendation in a smaller proportion of FADs (47%) than ACDs (72%). This can be explained by taking into account the work conducted between the ACD and the FAD, reported in the section *Appraisal Committees and additional analyses*.

Patient Access Schemes

A total of 40 of the 100 STAs involved the submission of a PAS either as part of the original submission or after the first ACD. The influence of the PAS on the final recommendations, when submitted as part of the original appraisal, is unclear (*Table 21*). Almost half of companies that submitted a PAS did so from the start of the process (17/40). Seven of the submissions did not have an ACD and received a positive recommendation at the FAD. Of the remaining STAs, similar numbers received positive and negative recommendations in the FAD.

However, when a PAS was submitted after the production of the ACD, it led to a positive change in recommendation in 65% (15/23) of STAs (*Table 22*). This compares with 70% (7/10) when the PAS was submitted as part of the original submission. The likelihood of a final negative recommendation appeared to be slightly lower (24% vs. 35%) when a PAS was submitted as part of the original submission.

It is apparent that the ERG exploratory analyses are highly influential in the ACD but are necessarily superseded by the additional work of companies and ERGs later, after the ACD, especially with a PAS. However, *Table 18* also suggests that the recommendations of almost half of the FADs (44%) were apparently still influenced to some degree by one or more of the exploratory analyses performed by ERGs in the earlier stages of the appraisal process and the ACD comments and recommendation will naturally have influenced the FAD also.

TABLE 21 Patient Access Schemes submitted as part of the original submission

Number of STAs with a PAS	Change from ACD no to FAD positive recommendation	Change from ACD minded no to FAD positive recommendation	No change positive recommendation (no ACD)	No change negative recommendation
17/40	3/17	3/17	7/17	4/17

TABLE 22 Number with PAS submitted after ACD and before FAD

Number of STAs with a PAS	Change from ACD no to FAD positive recommendation	Change from ACD minded no to FAD positive recommendation	No change negative recommendation
23/40	11/23	4/23	8/23

A summary of decisions and incremental cost-effectiveness ratios

The perceived cost-effectiveness or otherwise of a technology is often considered to play a key role in decisions. For this reason, a summary of the ICERs submitted by companies, and the preferred ICERs of ACs, as outlined in the ACD and FAD, is tabulated below. It is apparent how many technologies appear to be cost-effective at a threshold of £20,000 per QALY gained in the original CSs (*Table 23*), and how few maintain that level of cost-effectiveness after appraisal and the production of the ACD.

The majority of ACDs record preferred or most plausible ICERs of > £20,000 per QALY gained or state that there is no plausible ICER owing to uncertainties within the evidence and model (*Table 24*).

By the production of the FAD, 37% of the STAs had achieved a preferred ICER at this level and 43% of the technologies were deemed to be cost-effective at a threshold of less than £30,000 per QALY (*Table 25*).

TABLE 23 Company and ACD ICERs

Company base-case ICER to ACD-preferred ICER	Number (%) of reports ($n = 81$)
No change (≤ £20,000)	9 (11)
From ≤ £20,000 to > £20,000	4 (5)
From ≤ £20,000 to 'no preferred' or 'no plausible ICER'	20 (25)
From ≥ £20,000 to 'no preferred' or 'no plausible ICER'	13 (16)
No change (> £20,000)	35 (43)

TABLE 24 Appraisals consultation document ICERs

ACD finding	Number (%) of reports ($n = 81$)
With preferred ICER of ≤ £20,000 per QALY gained	9 (11)
With preferred ICER of > £20,000 per QALY gained	39 (48)
AC unable to specify a preferred ICER	33 (41)

TABLE 25 Final appraisal determination ICERs

FAD finding	Number of reports ($n = 100$)	Proportion (%) of recommendations
With preferred ICER of ≤ £20,000[a]	37	37/37 (100)
With preferred ICER of £20,000–30,000	6	6/6 (100)
With preferred ICER of > £30,000	36	17/36 (47)
AC did not specify a preferred ICER[b]	21	12/21 (57)

a Including range with at least one ICER of < £20,000 or an acknowledgement that the technology is cost-effective at £20,000 threshold.
b Includes FADs without an ICER where the analysis was based on 'costs' alone.[25,39]

All 43 STAs with a FAD-preferred ICER of < £30,000 per QALY gained received positive recommendations, as did a further 29 in which the FAD did not specify a preferred ICER or reported one that was > £30,000 per QALY, yet the technology was still considered a cost-effective use of NHS resources. Therefore, 40% (29/72) of recommendations were for technologies with an ICER that fell outside the perceived threshold of cost-effectiveness, and only 8 of these 29 took end-of-life criteria into account. However, it is noteworthy that 90% (19/21) of STAs that took into account end-of-life criteria (see *Table 7*) resulted in a FAD with an unspecified ICER or one in excess of £30,000 per QALY.

The ICERs preferred by ACs were, therefore, often higher than the base-case ICER submitted by a company, principally as a result of the exploratory analyses of an ERG. However, it is not the case that these ERG analyses always generated a single, higher ICER than that submitted by the company. The analyses would most often generate a number of different ICERs, with the aim of testing the findings of the submission and providing useful information for the committees based on different thresholds or scenarios. A typical example can be found in one STA, *Dabigatran Etexilate for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation* (TA249).[17] The CS reported a base-case ICER of £7940 per QALY for dabigatran 150 mg versus its principal comparator, warfarin. The ERG conducted 14 exploratory analyses generating a range of ICERs, including an ERG-preferred base-case ICER of £24,173 per QALY. The conclusion of the first AC was that the preferred ICER was between £6300 and £24,000 per QALY and the final decision was that the most plausible ICER was < £20,000 per QALY. The company's ICER was, therefore, relevant and exploratory analyses generated the highest ICER, but the final decision was made based on consideration of the range of ICERs.

Chapter 4 Discussion

Statement of principal findings

Over 400 documents were analysed from the 100 STAs included in this analysis. The ERGs performed at least one exploratory analysis in 93% of all STAs (objective 1). An ERG's judgement relating to perceived uncertainties or possible variation in the evidence base and model was the type of exploratory analysis appearing in the largest proportion of ERG reports (objective 2). Where alternative data for an exploratory analysis were identified, published literature such as trial evidence was the most frequent source (objective 3).

As demonstrated by the frequency, number and type of analyses performed, ERG exploratory analyses were not simply conducted to generate a single, alternative ICER, but rather presented a number of scenario analyses, presumably with the intention of allowing an AC to decide which ICER they preferred. The aim was to ensure that the AC had sufficient information in order to reach a decision. Where it was deemed that the company had not provided this, it was the ERG who was responsible for undertaking what they determined to be the most appropriate exploratory analyses. In essence, ERGs plug the gaps in the evidence. They play in important role in reducing the uncertainty associated with the AC decision-making process through their critical appraisal of the CS and undertaking exploratory analyses. Not only do they test the company model, they aim to anticipate what information the AC will need in order to make their decisions.

The incidence and frequency of ERG exploratory analyses do not appear to be related to any developments in the process between 2009 and 2014, the disease area covered by the STA or the company's base-case ICER. There is no clear pattern to the presence or frequency of these analyses, although there does appear to be a pattern in the mean number of analyses by ERG (objective 4). However, this association has not been tested in a regression analysis to confirm whether or not the ERG centre is an independent predictor of the number and extent of exploratory analyses. It might be affected by many variables, such as disease area and year, as well as the complexity and perceived quality of CSs. Therefore, this finding should be interpreted with caution and more research is needed to determine the relationship between ERG and the number and extent of exploratory analyses. The number of exploratory analyses undertaken may also vary according to the skills, experience and judgments of the ERGs and that of individuals within the ERGs. This issue was not explored within this study.

The numbers of STAs undertaken by individual companies was small. Companies do not always produce their submissions 'in-house' and may commission health economics consultancy organisations to produce their submissions. This issue was not addressed in this study.

Fewer than half of the exploratory analyses were requested or hinted at in the clarification letters submitted to companies (objective 5). This may be because of the clarification letter being submitted so early on in the process that the ERG had not had time to develop a full understanding of the model and what information may be needed. However, it was rare for an exploratory analysis not to be justified in a preceding chapter of the ERG report in the critique of the submitted model.

For the majority (71%) of STAs, additional work was submitted by the company and ERG between the ACD and the FAD. The ACD for almost all (97%) of these particular STAs made a 'no' or 'minded no' recommendation (objective 6). Approximately one-fifth of STAs did not produce an ACD; a large majority of these STAs had a company ICER that was cost-effective at the threshold of £20,000 per QALY gained and all received a positive recommendation in the FAD and required fewer exploratory analyses than the sample as a whole.

At least one of the exploratory analyses conducted and reported by an ERG is mentioned in 97% of ACDs and had a clear influence on more than two-thirds of ACD recommendations. The influence of these exploratory analyses is reduced in the FAD, although they still had a direct influence on the final recommendations in almost half of STAs. The preferred ICERs reported in ACDs were 36% from ERGs, 11% from companies and 9% from both. This changed at the FAD, where the preferred ICERs were 27% from ERGs, 23% from companies and 17% from both. The findings of work conducted by the company and ERG between the ACD and the FAD appear to reduce the influence of the original ERG exploratory analyses on the final recommendation, although the original analyses help to shape the ACs preferred assumptions and inform further work (objective 7).

It cannot be assumed that the number of exploratory analyses is an indicator of the quality of a CS. As stated above, with reference to STAs with no such analyses, this absence might be as a result of a model being deemed by the ERG to be of either very good quality or very poor quality. If a model is considered to be of very poor quality, the ERG may decide that it is pointless to undertake any exploratory analyses at all. The type of analysis is more informative regarding quality. Analyses that are categorised as matters of judgement might indicate an ERG exploring multiple scenarios relevant to an otherwise essentially sound model and submission. This represented the principal type of analysis in this sample of STAs: 89% of ERG reports with analyses contained at least one such analysis (see *Table 10*). However, if the ERG is conducting analyses to fix errors or violations then this suggests that there were issues with the perceived quality of the submitted model. In this sample, ERGs conducted at least one such analysis, respectively, in 35% and 18% of STAs.

Strengths and limitations of the assessment

A strength of this research is that this was an analysis of the most recent 100 STAs, which offers a good summary of current and recent practice. The development of a simple coding scheme, the extensive piloting of the data extraction tool and the double-checking of all key data across the 100 STAs by at least two experienced cost-effectiveness modellers reduced the likelihood of inconsistency and inaccuracy in the data. In addition, the method of synthesis was principally descriptive, which reduces the likelihood of overstating relationships in the data, and a reductive approach was taken to managing data that might be affected by interpretation or by poor reporting in the original documents.

There are, however, some limitations in this research. The descriptions of analyses undertaken were often highly specific to a particular STA and could be inconsistent across ERG reports and, thus, difficult to interpret. The source of ICERs cited in ACDs and FADs could also be unclear or open to interpretation. There are inherent weaknesses in using documentary analysis in that the researcher is able to analyse only what has been reported. The level and type of detail provided in and across the ERG reports and clarification letters could be very different, which made data extraction time-consuming, difficult and, at times, a matter of interpretation. Documents varied greatly in their description of analysis and the level of detail presented. Despite efforts to simplify the data extraction and coding process, data extractors sometimes had to exercise interpretation for some data. It was often difficult to understand from the documents alone the decision-making process that was being undertaken. In addition, the data did not permit a deeper exploration of the nuances and complexities within the types of analyses (e.g. using the fields types of models and nature of the implementation of the exploratory analysis, including data sources).

Data extraction was undertaken by only two research teams, who between them had undertaken nearly one-third of the STAs. Although this introduced a potential source of bias, it was overcome to some extent by having neither team extract data from their own reports. In addition, the inside knowledge obtained from working on so many STAs was crucially important in interpreting the data.

It was not possible to report reliably exactly what proportion of the 100s of exploratory analyses was actually mentioned in ACDs or FADs, or influenced their recommendations, and so this has been reduced simply to whether 'one or more' exploratory analyses were mentioned or had an influence in any particular STA. When grouping reports by disease area or ICER or numbers of exploratory analyses, the numbers were too small to evaluate relationships in the data using basic statistical tests in a meaningful manner. Further exploration, for example by assessing more STAs, might be able to determine whether or not disease area is a predictor not only of the number of analyses but also of the type of analysis undertaken. These limitations suggest that only cautious conclusions should be drawn from the evidence, especially concerning the generalisability of any findings.

Chapter 5 Recommendations

From the available evidence, it is not possible to specify the most useful type of ERG exploratory analysis, or the optimal number of analyses, for any particular STA, so ERGs can only continue to follow current approaches, unless there are changes to the time frame or quality and breadth of the models submitted by companies. It is important to recognise that exploratory analyses introduce greater transparency into the evidence presented to the AC, providing a range of options from which the Committee can decide which judgements it considers most reasonable. As such, the inclusion of exploratory analyses in the STA process must be encouraged.

Any recommendations generated from this research are best developed in conjunction with all key stakeholders including companies, NICE and the ERGs. The following are suggested recommendations for consideration:

1. The ERGs spend a considerable amount of time identifying errors, inconsistencies and testing assumptions in company models. In some instances the company provides verification of the model already. However, where this is not the case, companies may wish to further explore the value of additional peer review processes to identify such errors before submission.
2. Unequivocal errors in the CS could be listed and dealt with in a separate section of the ERG report, distinct from other exploratory analyses undertaken by the ERG. The results from the correction of these errors and no other changes could be presented in this section. If possible, these can be rechecked by the company and agreement reached on the correct company ICER.
3. Where possible, companies should be asked at clarification letter stage to undertake exploratory analyses identified as potentially important by the ERG and NICE at this early stage. However, the ERG would still be required to undertake further exploratory analyses that are identified after the clarification letter stage.
4. We recommend that a common terminology be used to describe the types of issues identified within STA models and to describe the types of exploratory analyses undertaken by the ERGs. The taxonomy used in this report may provide a useful starting point for ensuring consistency in the use of such terminology.

Chapter 6 Conclusions

Implications for service provision

The exploratory analyses undertaken by the ERGs appear to plug some of the gaps in the evidence received from CSs, reduce uncertainty and support AC decision-making. They frequently influence both ACD and FAD recommendations. Therefore, the use of ERG reports in the STA process appears to be highly effective, in that all relevant information needed to reduce uncertainty is presented to the AC in a timely and transparent manner, although the process can be resource- and time-intensive. It is often only by the ERGs undertaking exploratory analyses that uncertainties in the evidence base are addressed and ACs have enough evidence to make decisions on technologies. The number and extent of exploratory analyses undertaken appear to be consistent over time and across disease areas. ERGs frequently conduct exploratory analyses to test or use more appropriate parameters in the economic evaluations submitted by companies as part of the STA process. ERG analyses are often highly influential in the first recommendations of ACs. Their influence might then be superseded by later work (though they necessarily do indirectly impact on the work conducted between an ACD and a FAD), but might still have an influence on a recommendation in as many as half of all FADs. The provision of a longer period of reflection for ERGs to identify all the possible issues or uncertainties with submitted evaluations might permit the development of more comprehensive clarification letters and allow companies to perform more of the required additional analyses.

Suggested research priorities

Future research priorities include:

- Undertaking a more in-depth analysis of how ERGs make decisions regarding which exploratory analyses should be undertaken. This could take the form of a prospective qualitative study of a limited number of STAs.
- Qualitative research with ACs members to determine when and which type of exploratory analyses are most useful in their decision-making so that energies can be focused on these analyses.
- In-depth analysis of the category of ‘matters of judgement’. This could be done by prospectively categorising the nature of the implementation of any exploratory analysis and the data sources used, for example whether an analysis was based on different but equally valid assumptions or different but equally valid sources of data. More in-depth analysis could be undertaken to explore how the presence and extent of the exploratory analyses may vary according to the skills, experience and judgments of the ERGs.

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Eva Kaltenthaler led the project, developed the protocol and undertook data extraction.

Christopher Carroll developed the protocol and undertook data extraction and data analysis.

Daniel Hill-McManus undertook data extraction and data checking.

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Michael Holmes developed the protocol and undertook data extraction.

Stephen Rice developed the protocol and undertook data extraction and data checking.

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Paul Tappenden developed the protocol and undertook data checking.

Nerys Woolacott developed the protocol.

All members of the project team contributed to the writing of the report.

Data sharing statement

Non-confidential data used in this report can be obtained by contacting the corresponding author.

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Appendix 1 List of 100 single technology appraisals

NICE TA number	Appraisal title	NICE document ID number
TA181	Pemetrexed for the first-line treatment of non-small-cell lung cancer	35
TA182	Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention	25
TA183	Topotecan for the treatment of recurrent and stage IVB cervical cancer	102
TA185	Trabectedin for the treatment of advanced soft tissue sarcoma	24
TA186	Certolizumab pegol for the treatment of rheumatoid arthritis	28
TA189	Sorafenib for the treatment of advanced hepatocellular carcinoma	22
TA190	Pemetrexed for the maintenance treatment of non-small-cell lung cancer	72
TA191	Capecitabine for the treatment of advanced gastric cancer	100
TA192	Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer	120
TA193	Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia	119
TA196	Imatinib for the adjuvant treatment of gastrointestinal stromal tumours	82
TA197	Dronedarone for the treatment of non-permanent atrial fibrillation	55
TA198	Tocilizumab for the treatment of rheumatoid arthritis	26
TA201	Omalizumab for the treatment of severe persistent allergic asthma in children aged 6–11	123
TA202	Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab	126
TA203	Liraglutide for the treatment of type 2 diabetes mellitus	68
TA204	Denosumab for the prevention of osteoporotic fractures in postmenopausal women	61
TA205	Eltrombopag for the treatment of chronic immune (idiopathic) thrombocytopenic purpura	13
TA208	Trastuzumab for the treatment of HER2-positive metastatic gastric cancer	59
TA211	Prucalopride for the treatment of chronic constipation in women	125
TA212	Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer	47
TA213	Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years	122
TA214	Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer	105
TA215	Pazopanib for the first-line treatment of advanced renal cell carcinoma	69
TA216	Bendamustine for the first-line treatment of chronic lymphocytic leukaemia	343
TA218	Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia	11
TA219	Everolimus for the second-line treatment of advanced renal cell carcinoma	71
TA220	Golimumab for the treatment of psoriatic arthritis	353
TA221	Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura	14

NICE TA number	Appraisal title	NICE document ID number
TA222	Trabectedin for the treatment of relapsed ovarian cancer	51
TA225	Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs	19
TA226	Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs	57
TA227	Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer	45
TA229	Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion	349
TA230	Bivalirudin for the treatment of ST-segment-elevation myocardial infarction	338
TA232	Retigabine for the adjunctive treatment of partial onset seizures in epilepsy	404
TA233	Golimumab for the treatment of ankylosing spondylitis	53
TA234	Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs	360
TA235	Mifamurtide for the treatment of osteosarcoma	36
TA236	Ticagrelor for the treatment of acute coronary syndromes	67
TA237	Ranibizumab for the treatment of diabetic macular oedema	369
TA238	Tocilizumab for the treatment of systemic juvenile idiopathic arthritis	318
TA239	Fulvestrant for the treatment of locally advanced or metastatic breast cancer	331
TA244	Roflumilast for the management of severe chronic obstructive pulmonary disease	341
TA245	Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults	307
TA248	Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes	336
TA249	Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation	94
TA250	Eribulin for the treatment of locally advanced or metastatic breast cancer	359
TA252	Telaprevir for the treatment of genotype 1 chronic hepatitis C	459
TA253	Boceprevir for the treatment of genotype 1 chronic hepatitis C	460
TA254	Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis	63
TA255	Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen	400
TA256	Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation	420
TA258	Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer	473
TA259	Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen	465
TA260	Botulinum toxin type A for the prevention of headaches in adults with chronic migraine	462
TA261	Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism	437
TA263	Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer	54
TA264	Alteplase for treating acute ischaemic stroke	536
TA266	Mannitol dry powder for inhalation for treating cystic fibrosis	85

NICE TA number	Appraisal title	NICE document ID number
TA267	Ivabradine for treating chronic heart failure	484
TA268	Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma	73
TA269	Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma	498
TA271	Fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema after an inadequate response to prior therapy	419
TA272	Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract	320
TA275	Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation	500
TA282	Pirfenidone for treating idiopathic pulmonary fibrosis	334
TA283	Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion	328
TA284	Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer	435
TA285	Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer	490
TA287	Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer	569
TA288	Dapagliflozin in combination therapy for treating type 2 diabetes	427
TA289	Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis	510
TA290	Mirabegron for treating symptoms of overactive bladder	542
TA291	Pegloticase for treating severe debilitating chronic tophaceous gout	521
TA292	Aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder	305
TA293	Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura	589
TA294	Aflibercept solution for injection for treating wet age-related macular degeneration	519
TA295	Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy	538
TA296	Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene	499
TA297	Ocriplasmin for treating vitreomacular traction	544
TA298	Ranibizumab for treating choroidal neovascularisation associated with pathological myopia	555
TA299	Bosutinib for previously treated chronic myeloid leukaemia	495
TA303	Teriflunomide for treating relapsing–remitting multiple sclerosis	548
TA305	Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion	578
TA306	Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma	414
TA307	Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy	514
TA308	Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis	567

APPENDIX 1

NICE TA number	Appraisal title	NICE document ID number
TA309	Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer	489
TA310	Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer	556
TA311	Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation	610
TA312	Alemtuzumab for treating relapsing-remitting multiple sclerosis	539
TA313	Ustekinumab for treating active psoriatic arthritis	607
TA315	Canagliflozin in combination therapy for treating type 2 diabetes	554
TA316	Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen	600
TA318	Lubiprostone for treating chronic idiopathic constipation	725
TA319	Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma	74
TA320	Dimethyl fumarate for treating relapsing-remitting multiple sclerosis	585
TA321	Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma	605
TA322	Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality	480

ID, identification.

Appendix 2 Sample data extraction template

NICE document number	STA title	ERG team	Company	Disease area	Pre-specified subgroups	Assessed for end-of-life criteria (yes/no)?	Company's base-case ICER		
							List	Deterministic/ probabilistic	Next best non-dominated or baseline comparator (list treatment comparator for final ICER)

Exploratory analyses undertaken by ERG						Is the exploratory analysis mentioned/hinted at in the clarification questions? If so give details (including question numbers)	Committee decision at ACD	Is the exploratory analysis mentioned in the first ACD? Is the ICER for the analysis mentioned?	Did the exploratory analysis influence the committee's ACD recommendation?	Exploratory analyses undertaken by ERG. Analysis number (including page numbers)
Analysis number (including page numbers)	Type of exploratory analysis	Nature of exploratory analysis	Category of data source	ICER of exploratory analysis	Next best non-dominated or baseline comparator (list treatment comparator for final ICER)					

Additional work requested by AC and done by ERG (yes/no)?	Committee decision at FAD	Is the exploratory analysis mentioned in the final FAD? Is the ICER for the analysis mentioned?	Did the exploratory analysis influence the committee's FAD recommendation?	FAD preferred ICER and source	Additional submission from company (yes/no)?	Number of AC meetings	Number of ACDs	Number of FADs	Extracted by	Checked by

Appendix 3 Example data extraction

Data extraction was undertaken from NICE TA 190.[32]

NICE document number	STA title	ERG team	Company	Disease area	Pre-specified subgroups	Assessed for end-of-life criteria (yes/no)?	Company's base-case ICER		
							List	Deterministic/ probabilistic	Next best non-dominated or baseline comparator (list treatment comparator for final ICER)
72	Pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)[32]	Liverpool Reviews and Implementation Group, University of Liverpool	Eli Lilly and Company	Cancer	All stage IIIb/IV patients who have received four cycles of first-line CTX (S0) As above but with adenocarcinoma (S1)	Yes	£33,732 (S0) £39,364 (S1)	Unclear Unclear	Watch and wait/BSC Watch and wait/BSC

Exploratory analyses undertaken by ERG						Is the exploratory analysis mentioned/hinted at in the clarification questions? If so give details (including question numbers)	Committee decision at ACD	Is the exploratory analysis mentioned in the first ACD? Is the ICER for the analysis mentioned?	Did the exploratory analysis influence the committee's ACD recommendation?	ACD preferred ICER and source
Analysis number (including page numbers)	Type of exploratory analysis	Nature of exploratory analysis	Category of data source	ICER of exploratory analysis	Next best non-dominated or baseline comparator (list treatment comparator for final ICER)					
1.	Uncertainty and evidence variation	All cycles of pemetrexed and revised CTX (Chemo) costs	Other	£43,179	Watch and wait/BSC	No	Not recommended	Yes (p. 17 s4.14, no ICER)	Yes, via No. 9	> £51,000, ERG
2.	Uncertainty and evidence variation	Revised utility values	Literature	£36,798	Watch and wait/BSC	No		Yes (p. 17 s4.15, no ICER)	Yes, via No. 9	
3.	Fixing errors	Continuity correction	Not applicable	£34,860	Watch and wait/BSC	No		Not specifically	Yes, via No. 9	
4.	Fixing violations	Correct double discounting	Not applicable	£32,091	Watch and wait/BSC	No		Yes (p. 18 s4.18, no ICER)	Yes, via No. 9	
5.	Fixing violations	Discounting assumptions	Not applicable	£33,640	Watch and wait/BSC	No		Yes (p. 18 s4.18, no ICER)	Yes, via No. 9	
6.	Uncertainty and evidence variation	Include monitoring costs	Not applicable	£34,651	Watch and wait/BSC	No		Yes (p. 13 s3.24, no ICER)	Yes, via No. 9	
7.	Fixing errors	Correct arithmetic	Not applicable	£33,817	Watch and wait/BSC	No		Not specifically	Yes, via No. 9	
8.	ERG base-case/ preferred analysis	All of the above	Not applicable	£47,239	Watch and wait/BSC	No		Not specifically	Not specifically	
9.	ERG base-case/ preferred analysis	All of the above + IPD survival analysis	Not applicable	£51,192	Watch and wait/BSC	Yes, C1		Yes and ICER (p. 18 s4.18)	Yes (p. 20 s4.21)	

BSC, best supportive care.

Additional work requested by AC and done by ERG (yes/no)?	Committee decision at FAD	Is the exploratory analysis mentioned in the final FAD? Is the ICER for the analysis mentioned?	Did the exploratory analysis influence the committee's FAD recommendation?	FAD preferred ICER and source	Additional submission from company (yes/no)?	Number of AC meetings	Number of ACDs	Number of FADs	Extracted by	Checked by
Unclear	Recommended	Yes, Yes s.3.17	Yes, via No. 8 and 9	About £47,000 (confidently less than £50,000)	Not requested but performed by company and ERG	2	1	1	DHM	PT
		Yes, Yes s3.21	Yes, via No. 8 and 9							
		Not specifically	Yes, via No. 8 and 9							
		Not specifically	Yes, via No. 8 and 9							
		Not specifically	Yes, via No. 8 and 9							
		Not specifically	Yes, via No. 8 and 9							
		Yes, Yes s3.23	Yes, via No. 8 and 9							
		Yes, p. 19 s4.16	Yes, s4.16							
		Yes, p. 19 s4.16	Yes, s4.16							

EME
HS&DR
HTA
PGfAR
PHR

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