A REVIEW OF THE NICE SINGLE TECHNOLOGY APPRAISAL PROCESS

REPORT BY THE DECISION SUPPORT UNIT

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SUMMARY

The Single Technology Appraisal (STA) process was introduced by NICE in 2005 as a means of undertaking "fast track" appraisals of single technologies, for single indications. Unlike the standard multiple technology appraisal (MTA) process, STA relies on a manufacturer evidence submission and an independent critique of that submission, rather than an independent analysis.

This project is concerned with how the STA process operates. Using the overarching themes of methodological robustness, transparency and inclusiveness, ten STAs were tracked as cases in the review. A range of data is drawn on to gain an insight into the STA process: documents and correspondence surrounding each case, attendance at Appraisal Committee (AC) meetings, interviews and surveys of stakeholders and AC members.

Low response rates to the surveys meant that the study is limited in its ability to report on the issues of transparency and inclusiveness, despite having increased the number and range of interviews conducted as a consequence.

A number of key findings are identified in relation to methodological robustness and other issues. These centre on issues to do with the requirements of the AC, the degree of reanalysis undertaken by Evidence Review Groups (ERGs), the burden of proof for manufacturers versus the Institute and the time taken for the Institute to issue guidance.

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CONTENTS

TABLES, FIGURES AND APPENDICES

Tables

Figures

Appendices

ABBREVIATIONS AND DEFINITIONS

AC	Appraisal Committee
ACD	Appraisal Consultation Document
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CHE	Centre for Health Economics
Consultee	Organisations that accept an invitation to participate in the appraisal.
Decision problem	The question addressed by the manufacturer/sponsor in its evidence submission
DSU	Decision Support Unit
ERG	Evidence Review Group
FAD	Final Appraisal Determination
HTA	Health Technology Assessment
LRiG	Liverpool Reviews and Implementation Group
MTA	Multiple Technology Appraisal
NICE	National Institute for Health and Clinical Excellence
NSCLC	Non small cell lung cancer
PenTAG	Peninsula Technology Assessment Group
PBAC	Pharmaceutical Benefits Advisory Committee
QALY	Quality Adjusted Life Year
ScHARR	School of Health and Related Research
Scope	Initial document describing the question to be addressed by an appraisal
SHTAC	Southampton Health Technology Assessments Centre
SMC	Scottish Medicines Consortium
STA	Single Technology Appraisal

1. INTRODUCTION

1.1. BACKGROUND

In late 2005, NICE launched the Single Technology Appraisal (STA) process to enable comparison of single products, normally with single indications, with one or more standard treatment comparators, close to their point of introduction into the UK.

The standard, multiple technology appraisal (MTA) process operated by the Institute since its inception in 1999 is perceived by many to be an international exemplar of good practice in health technology assessment (Hill et al, 2003). In particular, the MTA process is generally seen as being based on rigorous methodology, operating in a transparent and inclusive manner. However, despite these achievements, the Institute came under pressure to introduce a "fast track" assessment process to complement the MTA approach. The resultant STA process was aimed particularly at "life saving" drugs (NICE press Release 3rd November 2005) and particularly at cancer treatments with the aim of producing guidance between 6 and 15 months earlier than would be the case via MTA.

Overview of the STA process

The final STA process is described in detail by the Institute (NICE, 2006) and was developed following consultation with a wide range of stakeholders and the input from a working party convened by the Institute. A summary of the key components is provided here.

In principal, all technologies referred to the Institute by ministers can be assigned to the STA process if they are single technologies for a single indication. The STA process formally begins at the time NICE is notified that the manufacturer is applying to the regulatory authorities for a particular indication, or in cases where the STA is not related to a regulatory submission, at a time point determined by the Institute.

Scoping begins prior to formal referral of a topic to NICE. A draft scope is developed alongside the topic selection process and a final scope is issues after referral of a topic to the Institute taking into account comments on the draft scope through consultation.

NICE requests a formal submission from the manufacturer and supplies a template for that evidence submission to be completed over 8 weeks at a minimum.

After receipt of the manufacturer submission, an Evidence Review Group (ERG) prepares an independent review, also prepared according to a template provided by the Institute, over an 8 week minimum period. This is considered alongside submissions from other consultees by the AC who then make recommendations. If these recommendations are more restrictive than the terms of the licensed indication, the committee recommendations are considered preliminary and formally consulted on by issuing an Appraisal Consultation Document (ACD). Otherwise, the recommendations are considered final and a Final Appraisal Document (FAD) will be issued. The FAD is issued as NICE guidance and there is no formal consultation. Consultees can decide to lodge an appeal in relation to the FAD.

The entire process takes 32 weeks from appraisal initiation (defined as the point at which the manufacturer submission is requested) to publication of guidance if there is no appeal or ACD issued, 39 weeks where an ACD is issued, according to the STA process guide.

This review

The purpose of this review is to provide an input to the process of revising and updating the STA process guide (NICE, 2006), due in 2008.

The overarching themes which determine the scope of this review were specified by the Institute and are those which are the stated principles underpinning all NICE activities: methodological robustness, transparency and inclusiveness.

1.2. RESEARCH THEMES AND QUESTIONS

1.2.1. Methodological Robustness

Methodological robustness is the extent to which the process and methods are able to generate an appropriate evidence base to enable the NICE Committee to develop useful guidance for the NHS. The main question to be addressed is to assess whether the entirety of the evidence presented to the AC (including manufacturer submission,

ERG, supporting evidence from consultees and commentators and patient and clinical experts provides an adequate basis for the AC to make a decision.

The review of the manufacturer submission examined whether the decision problem in the submission reflected the question the NHS needed answering, as defined in the final scope, whether the submission was complete and comprehensive and what happened in the event that key information was missing. It looked particularly at whether appropriate patient subgroup analysis was undertaken by the sponsor and at particular complexities in interpreting the evidence put before the AC in each case including the use of indirect or multiple treatment comparisons methodology? The useful of both the manufacturer template and the ERG template was examined.

Overall, was the sponsor's submission sufficiently interrogated within the process to highlight the strengths and weaknesses of the submission?

It also took account of supporting evidence presented to the AC to establish whether evidence submitted to the AC by consultees and commentators, clinical specialists and patient experts helped contextualise the final scope and complement the manufacturer submission? In the event that inadequacies/problems were identified during the STA Review, to what extent could they have been due to the templates (content and structure) used for statements by consultees and commentators, invited specialists and patient experts?

1.2.2. Transparency

Transparency is the extent to which key evidence is made available to interested stakeholders and the public to allow the final decisions to be linked to the evidence base. The review focused on the extent to which stakeholders can identify the evidence that was presented to the AC, their interpretation and how they reached their decision? It explored how stakeholders received the information provided during the STA process, their understanding and their contribution to the process. It looked at whether additional steps such as clarification and iteration and formulation of a pre-meeting briefing document helped stakeholders interpret the evidence. In some cases, elements of the manufacturer's submission were classed as commercial/academic in confidence and we asked how important these elements were in relation to the AC decision making? Where confidential information could not be revealed, how much

did this limit understanding of end users of how the guidance section was arrived at as described in the ACD or FAD and/or the capacity of the consultees and commentators to contribute to the process?

1.2.3. Inclusiveness

Inclusiveness is the extent to which interested stakeholders are given the opportunity to participate and provide their input in the process. We reviewed the input of different stakeholders identified by the Institute (consultees and commentators) input at various stages of the appraisal (scoping, discussion of the decision problem, clarification, input to the ERG report, and the AC meeting), looked at whether they were aware of their ability to input in the process and the nature of their role.

2. MATERIAL AND METHODS

2.1. ELIGIBLE STAS

All STAs undertaken under the final STA process were eligible for inclusion in this study provided the expected date at which final guidance could be issued fell before October 2007. Each of these topics are illustrated in Table 1. Eight STAs met this criteria (1 to 8). However, none of these 8 STAs cover any oncology technology. This was considered a significant omission given the predominance of cancer drugs in the first wave of STAs. For this reason, two additional STAs (9 and 10, rituximab for follicular lymphoma and carmustine implants for glioma) were included in the study despite the fact that these appraisals were not expected to complete within the timescales of this study.

Table 1: Key characteristics of included STAs

No	***Technology***	***Earliest date Guidance could be issued***	***ERG***	***Development of the scope***
1	Rituximab for Rheumatoid Arthritis	June 07	LRiG	Stakeholder comments on scope
2	Alteplase for Stroke	June 07	SCHARR	
3	Natalizumab for multiple sclerosis	June 07	PenTAG	
4	Adalimumab for psoriatic arthritis	June 07	CHE York and Newcastle	
5	Abatacept for rheumatoid arthritis	Oct 07	LRiG	
6	Varenicline for smoking cessation	July 07	SCHARR	
7	Omalizumab for asthma	Aug 07	SHTAC	
8	Infliximab for psoriasis	Oct 07	SHTAC	
9	Rituximab for follicular lymphoma (3^{rd} line)	Jan 08	LRiG	STA Process included a scoping workshop
10	Carmustine implants for glioma	Dec 07	CHE York and Newcastle	

2.2. METHODS

2.2.1. Overview

The study uses a multiple case study design with each of the ten individual STAs treated as case studies. Quantitative and qualitative methods are combined to provide

in depth understanding of the STA process. Methods included documentary analysis of documents made available by NICE during the appraisal process, observation of pre-meeting briefings and AC meetings, interviews and surveys of stakeholders. All of the eligible STAs were examined using documentary analysis. In addition, five STAs were selected for in depth analysis where additional methods were employed, as illustrated in Table 2.

The five STAs selected for in depth analysis were chosen to include a representative sample of ERG teams, to include both technologies for cancer and other conditions and to select those appraisals most likely to be completed during the term of the study. By selecting the first four STA process, we hoped to allow the maximum time for each to complete whilst allowing some contingency planning to select alternatives in the event of unforeseen difficulties with one of the selected appraisals.

Table 2: Types of analysis for each STA

	STA	Manu/ERG	Documentary analysis of sponsor submission and ERG report	Observation of Committee discussion(s) and pre-meeting briefing	Interviews	Post-STA survey of Committee members, all consultees and all commentators (inc. ERG)
Group 1 STAs for in-depth analysis	**Natalizumab for MS**	Biogen Idec/PenTag	a	a	a	a
	Alteplase for stroke	Boehringer Ingelheim/ScHARR	a	a	a	a
	Abatacept for RA	BMS/Liverpool	a	a	a	a
	Omalizumab for asthma	Novartis/Southampton	a	a	a	a
	Carmustine implants for glioma	Link Pharma Ltd/York	No submission was made for this technology			
Group 2 STAs for less detailed analysis	**Rituximab for RA**	Roche/Liverpool	a			
	Adalimumab for PsA	Abbott Labs Ltd/York	a			
	Varenicline for smoking cessation	Pfizer/ScHARR	a			
	Infliximab for Psoriasis	Schering Plough/Southampton	a			
	Rituximab (3rd line) for follicular lymphoma	Roche/Liverpool	a			

2.2.2. Documentary analysis

The documentary analysis began at the start of the review of each technology and was carried out by the research team following the timetable laid down by the STA process guide. Each documentary analysis was initiated when the draft ERG report was received by NICE and the initial documentary review of the ERG report (with reference to the manufacturer's submission) had to be completed by the time of the pre meeting briefing telephone conference prior to the AC meeting. The documentary analysis provided an overview of the technology for the researchers and identified the specific issues which had arisen in relation to the manufacturer's submission, the views of the ERG and the areas of uncertainty which needed to be taken into account by the AC meeting in reaching their decision.

The documentary analysis also informed the researchers when they observed meetings of the Committees and Pre meeting briefings. Documentation available to the research team was;

Final scope for the appraisal
Matrix of consultees and commentators

Manufacturer/sponsor's evidence submission (confidential information removed)*
Clarification letters sent to the manufacturer/sponsor and the response to those*
Clarification letters to EMEA on marketing authorisation and response
Evidence review group (ERG) report*
Statements by consultees*
Premeeting briefing note of the NICE secretariat*
Final Appraisal Determination (FAD)*

If produced, the Appraisal Consultation Document (ACD), and resulting comments from consultees and

commentators on the ACD*

Summary of comments received via the web on the ACD
(where produced)*
Table prepared by the Technical Lead, showing the
Institute's responses to comments received on the ACD
(where produced)*

* Documents marked with an asterisk are released to consultees and commentators who have signed a confidentiality agreement before publication on the website.

Additionally, we included email exchanges between NICE and the manufacturer and those between NICE and AC members where relevant

A data extraction form was developed to allow recording of simple factual information relating to each of the STA projects with more detailed open ended questions. This was applied to all key documents (including manufacturer's submission and ERG report).

Recording included simple data;

- Decision by the AC and the rationale for 'minded not to recommend' decisions.
- Whether or not there is an ACD and if so, the number of consultees who respond.
- Number and source and basis of appeals (provided by NICE to the Reference Group)
- Whether an ACD was issued for consultation or whether the process goes straight to FAD.
- Whether or not there is a FAD, the number of unsolicited comments received.

- The lag between the product receiving marketing authorisation and NICE issuing guidance (for unlicensed products)
- The duration of each stage of the STA process.

The method of analysing documentation was developed involving in depth reading, summarising information using an Excel spread sheet format and producing a descriptive summary of the technology and related issues.

The ERG report was the main source material and was read at least three times. One reading served to familiarise the researcher with the technology. During the second reading, the researcher completed a proforma summarising the details of the technology and prepared a written summary as a briefing for the observation of the AC meetings. Issues raised by the ERGs which were considered substantial were tracked through other documents such as the manufacturer submission and subsequent correspondence to identify the source of the claims and at what point in the process they had been identified. Further details were added later once the outcome of AC meetings was known. This summary was checked with the technical lead for the particular STA for inaccuracies. The documentary analysis provided a detailed insight into the technology and factors which have been raised during the STA process. It informed both researchers for their observation of both the pre meeting briefing and the AC meetings.

2.2.3. Observation of meetings

Observation of pre meeting briefings and first AC meetings and in some cases where an ACD was issued, second AC meetings were carried out for those technologies studied in depth (natalizumab for multiple sclerosis, alteplase for stroke, and omalizumab for asthma, abatacept for rheumatoid arthritis). Both researchers attended the AC meetings to make field notes about the process, the decisions taken and the contributions to the debate by AC members. These notes were compared and discussed after the meetings and used as a basis for selection of AC members for interview and to set the agenda for those interviews.

2.2.4. Interviews with AC members

For those STAs examined in depth, two members of the AC were interviewed. Typically this meant the Chair and a member whose input appeared to have had a substantial influence in the discussions, as judged by the researchers. The aim of these interviews overall was to offer insights into the workings of the AC, individual perspectives on the evidence presented, the STA process and the factors which influenced the Committee decisions.

The specific aims of the interviews were;

- To gather the perspectives of AC members on decision making including insights into the differences associated with the nature of the uncertainties, the technologies or the evidence base presented.

- The view as to whether the AC member felt that the decision was 'correct' in the light of the evidence presented.

- To understand the nature and importance of the contributions by stakeholders (patient experts and professional experts)

- To capture the perspective of the chair on the process from scoping to the final decision.

Interviews were conducted by telephone as quickly as possible after the AC meetings. They used a semi structured format and are recorded and transcribed. Consent for recording was obtained prior to the interview.

All interviews were transcribed verbatim and entered into NUDIST qualitative software to support the analysis and aid retrieval of data. A sample of 10% of the data

gathered from interviews was coded by the second researcher to validate transcription codings.

2.2.5. Interviews with stakeholders

The protocol included interviews with five stakeholders not on the Appraisal AC to include one interviewee from each of the following;

- patient experts
- clinical experts
- commissioners
- manufacturers
- Evidence Review Groups

The purpose of these interviews was to gather a wider range of views to supplement the data gathered through survey of stakeholders (see below). However, there were sensitivities relating to the timing of interviews meaning that they were conducted at least fifteen days after FAD after which time no appeal could be made.

2.2.6. Survey of stakeholders

Three versions of the questionnaires were developed to survey the views of stakeholders (one version for consultees and commentators, one for ERGs and one for manufacturers). Draft questionnaires were prepared and revised in line with comments from manufacturer representatives on the Reference Group. In addition, we piloted the survey with ERG members in one institution.

The original proposal stated that piloting of the survey instruments would be conducted using the three STAs considered by the Institute immediately prior to those selected for this review project (erlotinib for NSCLC, cetuximab for head and neck cancer, pemetrexed for non small cell lung cancer NSCLC). However, each of these STAs have been subject to appeal. On advice from the Institute it was decided not to send surveys on these topics but instead to pilot the survey using even earlier STA

topics (gemcytabine for breast cancer, fludarabine for chronic lymphocytic leukaemia).

The piloting process indicated that response rates were likely to be low and responses not useful where surveys are sent to all consultees and commentators. The principal reason for this is that whilst the NICE matrix of stakeholders is typically broad, in practice very few contribute directly to any appraisal. Final versions of surveys were only sent to stakeholders that contributed to the STAs considered in this review.

2.2.7. Analysis

The case study approach is recognised as appropriate for exploratory, descriptive and explanatory analysis (Yin, 2003). The analysis combines review of documentation, direct observation of meeting and interviews and surveys of stakeholders. The analysis is iterative and is undertaken alongside data collection with methods informing and relating to one another. The documentary analysis and observation of meetings generates questions that are then pursued in interviews. The survey data will raise areas for further exploration in interviews.

In analysing the data, the researchers took account of the nature of the question and the level of the data. We began with 'within case analysis' to describe the story of the decision making process, the chronology and key themes using sequenced methods described. We then moved to 'across case comparisons' to identify themes which illuminate robustness, transparency and inclusiveness. We were mindful of the possibility that different methods might not converge within STAs and across the different STAs and apparently contradictory accounts might emerge from the different data sources. However, the aim was to provide a comprehensive and insightful account of the process including possible explanations for clear differences.

Qualitative analysis used a framework approach. Data were coded according to a pre-determined set of categories under the topics of methodological robustness, transparency and inclusiveness. The approach also allowed these categories to be

refined or for others to emerge in an inductive manner as the analysis was undertaken. The coding therefore combines evidence across the cases to allow general findings to be reported. As is typical with qualitative research findings, illustrative quotes are provided in reporting.

3. RESULTS

Results are presented in two sections. Firstly, each STA is described in turn, focussing on the outcome of different stages of the process and key issues raised at different stages of the process. We draw principally on the documentary analysis and AC observations to provide an account of the key issues considered in each appraisal, the interim, final and post appeal guidance. Secondly, we combine these data with the interviews and to a lesser extent survey data to highlight important findings that span several of the STAs studies. Where possible we provide verbatim quotes from interviews to illustrate recurrent issues and those unique issues raised by individuals. However, all interview participants did so on condition of anonymity and in order to preserve this we have on accession been unable to provide quotes due to the risk that the interviewee would be identifiable.

The status of the STAs considered in this review is reported in

Table 3. At the time of writing, final guidance had been issued for five technologies, two were at the ACD stage, one other at FAD stage. No submission was made by the manufacturer in relation to carmustine implants for glioma.

Table 3: Status of STAs selected for this review

Technology	*Components analysed*	*Status at 20th Sept 2007*
Rituximab for rheumatoid arthritis	Documentary analysis	Guidance issued
Alteplase for stroke	**Documentary analysis, interviews, meetings**	**Guidance issued**
Natalizumab for multiple sclerosis	**Documentary analysis, interviews, meetings**	**Guidance issued**
Abatacept for rheumatoid arthritis	**Documentary analysis, interviews, meetings**	**ACD issued**
Omalizumab for asthma	**Documentary analysis, interviews, meetings**	**FAD issued**
Varenicline for smoking cessation	Documentary analysis	Guidance issued
Adalimumab for psoriatic arthritis	Documentary analysis	Guidance issued
Infliximab for psoriasis	Documentary analysis	ACD issued
Carmustine implants for glioma	No submission from manufacturer	
Rituximab for follicular lymphoma (3rd line)	Documentary analysis	1st AC meeting held

Topics selected for in depth analysis are shown in bold

3.1. THE INDIVIDUAL STAS

The following summaries are based on analysis of documents made available to the research team. In the case of natalizumab for multiple sclerosis, abatacept for rheumatoid arthritis, alteplase for stroke and omalizumab for asthma they are also drawn from observations of AC meetings and Pre meeting briefings. The team offered interviews to fourteen AC members of whom only one did not make contact. Eight stakeholder interviews were also offered and of these only one did not make contact. Surveys of stakeholders who had contributed to the STA at some point were sent a survey to gather their views. However, although these requests were targeted to active contributors, the response rate was lower than expected. Only 16 responses were received: two from manufacturers, two from ERGs and twelve from consultees and commentators. Within the latter category, one competitor manufacturer responded, three patient groups, six professional organisations and two NHS trusts. The three questionnaires for ERGs, manufacturers and consultees and commentators were

designed to capture particularly distinct perspectives on the process. The diversity of the responses to the questionnaires and the small number of responses in any single category meant that the data was insufficient for any meaningful conclusions to be drawn. The results are shown in appendix 1 but are not discussed any further in this report.

Details of the commercial in confidence material submitted is also given in the case studies. One of the principles of transparency is that all evidence pivotal to the AC decision should be publicly available. The amount of commercial in confidence (CIC material which includes academic in confidence material) varied across the technologies. The submission of CIC material is allowed within the process but may affect transparency when it appears to relate directly to a key area of debate in the AC meeting.

Full details of the documentation examined, the interviews conducted and the observations of AC meetings is included in Table 4.

Table 4: Data sources examined by STA

	STA	Manu/ERG	Documents reviewed	Observation of 1st AC	Observation of 2nd AC	Interviews (number completed)	Other stakeholders interviewed
Group 1 STAs for in-depth analysis	**Natalizumab for MS**	Biogen Idec/PenTag	MS, ERG, PMB, ACD, FAD, Cons	a	a	3	One patient expert One commissioner Two manufacturers Three ERG groups
	Alteplase for stroke	Boehringer Ingelheim/ScHARR	MS, ERG, PMB, FAD, Cons	a	NA	4	
	Abatacept for RA	BMS/Liverpool	MS, ERG, PMB, ACD	a	a	2	
	Omalizumab for asthma	Novartis/Southampton	MS, ERG, PMB, ACD, FAD, Appeal correspondence	a	a	4	
	Carmustine implants for glioma	Link Pharma Ltd/York	No submission made for this technology				
Group 2 STAs for less detailed analysis	**Rituximab for RA**	Roche/Liverpool	MS, ERG, PMB, ACD, FAD				
	Adalimumab for PsA	Abbott Labs Ltd/York	MS, ERG, PMB, ACD, FAD				
	Varenicline for smoking cessation	Pfizer/ScHARR	MS, ERG, PMB, FAD				
	Infliximab for Psoriasis	Schering Plough/Southampton	MS, ERG, PMB, ACD				
	Rituximab (3rd line) for follicular lymphoma	Roche/Liverpool	MS, ERG, PMB				

Key MS Manufacturer submission, ERG Evidence Review Group report, PMB Pre-meeting briefing, AC Appraisal Committee, ACD Appraisal Consultation Document, FAD, Final Appraisal Determination, Cons Consultation responses to ACD.
NA Not applicable

3.1.1. Rituximab for RA

Rituximab (Mabthera®, Roche) is licensed (May 2006) for the treatment of adults with severe, active rheumatoid arthritis following the inadequate response or intolerance of conventional treatment (disease modifying anti rheumatic drugs – DMARDs) including at least one tumour necrosing factor alpha inhibitor (anti TNF-α). It is given in combination with methotrexate intravenously by specialist physicians. Key characteristics relating to this STA are presented in table 5.

The manufacturer presented two scenarios. The first considered patients who fail one anti TNF-α and are then given either rituximab and methotrexate or leflunomide (a standard DMARD) and methotrexate. This is referred to as the NICE recommended scenario since this corresponds to current NICE guidance in relation to the sequential use of anti TNF-α's (infliximab, etanercept and adalimumab). The second scenario compared rituximab and methotrexate to adalimumab and methotrexate.

Subgroup analyses were carried out for three patient subgroups; those who had failed more than one anti TNF-α compared with those who had failed only one; samples recruited in the US (and considered to be less similar to UK populations) and those recruited in Europe; and patients who differed in terms of their rheumatoid factor (RF) status.

For the "NICE recommended" scenario, that is using a comparator of standard DMARD rather than sequential biologic therapy, the original company submission reports an incremental cost effectiveness ratio (ICER) of £14,690 per quality adjusted life year (QALY) gained. For the "sequential anti TNF-α" scenario, the ICER is estimated at £11,601 per QALY gained. The ERG raised numerous concerns with the manufacturer submission and re-calculated the ICERs using the manufacturers model and alternative parameter values. This resulted in estimates of £40,873 and £32,855 for the same two scenarios.
The submission included no commercial in confidence material.

At the first AC meeting discussion of the clinical effectiveness centred on concerns about long term efficacy data, the reliance on a single trial and pooled data from other RCTs, and assumptions about long term progression rates as modelled using HAQ

scores. Clarifications were sought from the manufacturer about disease progression rates, the possible loss of effectiveness over time, changing the definition of initial response and loss of response to reflect the definition of initial response in terms of DAS28 as used in the MTA of anti TNF-α's in rheumatoid arthritis (see 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' – final appraisal determination, 27 November 2006, section 1.3; available at www.nice.org.uk/page.aspx?o=388554)

The ERG also raised concerns about a range of parameter values used in the cost effectiveness model (for example, ACR response rates, HAQ progression rates whilst on treatment and after withdrawal).

The outcome of the first AC was a "minded no" with further analyses and clarifications to be conducted by the manufacturer in relation to some of the parameter values the ERG had raised concerns about, notably the HAQ progression rates and the definition of response used in the economic model. For consistency with previous NICE appraisals, HAQ progression rates that had been used in the assessment group model in the appraisal of etanercept, infliximab and adalimumab were requested.

At the second AC meeting on 8th May 2007, the revised manufacturer analyses were considered and the guidance issued as a result recommended rituximab in RA.

Table 5: Rituximab For rheumatoid arthritis – Key Issues

Rituximab for rheumatoid arthritis ***Manufacturer Roche*** ***ERG Liverpool*** ***Committee B***	
Two **comparators** conventional DMARDS and biologics (TNFis)	
Agreement on what constitutes BSC	Yes
Best supportive care	
Indirect comparisons	Yes
Populations	
Concerns about whether the study populations represented UK clinical populations?	No
Systematic review	
Was the search strategy complete?	Yes *
Was the search strategy given?	Partial *
Was the quality of papers included in the evidence submitted checked?	Partial *
Were inclusion and exclusion criteria given?	Partial *
Was submission judged to be comprehensive? (in terms of those studies included in the evidence base)	Yes *
Reliance on unpublished studies	No
Was additional material requested?	
Was it CIC?	No
Was it received in time?	Yes
Were subgroup analyses carried out?	Yes, post hoc
Cost effectiveness	
Micro simulation Markov model	
PSA was carried out	Yes
ERG had doubts about the validity of the model?	Yes
Other ERG concerns;	
Errors in mortality rates, treatment costs, in patient costs.	
Evidence base for rates of progression based on HAQ scores	
ICERs	
ICER Cost per QALY (MS) vs conventional DMARDs	£14,690
Vs sequential TNFis	£11,601
ERG vs conventional DMARDs	£37,002 - £80,198
vs sequential TNFis	£28,553 - £65,558

* As noted in the ERG report

3.1.2. Natalizumab for MS

Natalizumab (Tysabri®, Biogen Idec Inc) holds a marketing authorisation (July 2006) for use as a single disease modifying therapy in highly active relapsing remitting multiple sclerosis (HARRMS) for two patient groups - those in whom relapses occur at least twice in one year (the rapidly evolving severe, RES group) and those who continue to have active disease despite treatment with beta-interferon (the sub optimal therapy, SOT group). These groups are in line with the licensed indications. Natalizumab is administered intravenously at a dosage of 300mg every four weeks in a hospital setting and there are no limits on the duration of treatment. Key characteristics relating to this STA are presented in table 6.

The manufacturer compared natalizumab for multiple sclerosis with best supportive care, beta-interferon and glatiramer acetate (GA) using two scenarios as outlined in the scope; for the RES group, comparing treatment with beta interferon, GA or with best supportive care. For the SOT group, the comparison was made with GA and best supportive care. In the decision problem, the manufacturer argued that mitoxantrone (MTX) was not a valid comparator as it is only licensed only for use in oncology.

The manufacturer submitted that, in the RES group, natalizumab showed a cost per QALY of £32,000, £35,000 and £45,000 compared with beta-interferon, GA and best supportive care, respectively. Corresponding estimates in the SOT group were £43,000, £44,000 and £56,000 per QALY. The details of patient profiles in the RES sub group were commercial in confidence (race, disease duration, number of relapses, EDSS scores). Details of the relapse rates and disability progression used in the indirect comparisons were also CIC. Much of the discussion at the AC meeting centred on the extent of evidence of clinical effectiveness in the RES group which included a post hoc analysis suggesting a reduction in rates of relapse and disability progression.

At the first AC meeting on 6th March 2007, the discussion centred on clinical effectiveness including whether the RES & SOT groups are appropriately defined (because of the extent of the overlap between them) and the extent of evidence for effectiveness in these groups which was based mainly on a single trial. Follow up data

was available for two years only. The Committee explored the robustness of the cost effectiveness estimates. Particular considerations related to the economic modelling included limitations of the EDSS scores and the lack of quality data for costs and utilities. The AC also explored whether there were any characteristics of the patient population or technology that may justify positive guidance despite ICERs in excess of £30,000. The focus here was the comparison of natalizumab against BSC (£44,600) in the RES group. Importantly, the manufacturer considered that the existence of a risk-sharing scheme in this disease area specified a relevant threshold willingess to pay per additional QALY of £36,000 and that this would have to be adopted by the Institute. The MS risk-sharing scheme was devised by the Department of Health in conjunction with the manufacturers of beta interferon and glatiramer acetate and allows the provision of these treatments to some patients with MS in the NHS despite the fact that NICE did not recommend their use. The AC were clear that the MS risk-sharing scheme did not influence the way the Institute should assess the evidence of cost effectiveness.

At the first meeting the AC decided natalizumab should not be recommended. Therefore, an ACD was issued.

The 2nd AC meeting was held on 8th May 2007. The consultation period highlighted a general consensus that the appropriate comparator for the RES subgroup was in fact the disease modifying treatments, beta interferon and glatiramer acetate, despite the fact that these treatments were themselves not considered to be cost effective or recommended for use in the NHS by NICE. This choice of comparator was accepted by the AC.

In considering the manufacturer claim that the ICER compared to beta interferon was £32,000, the AC considered several uncertainties. These included the differences between the predictions of the economic model and the trial results on which the model was based, the time horizon, and the disutility of relapses. Considering all of these uncertainties the AC considered that the ICER presented by the manufacturer was unlikely to be accurate and that the true ICER may lie either above or below the estimate presented by the manufacturer.

The AC recommended natalizumab following a secret ballot. The FAD was published on 3rd July and stated that "the Committee concluded that the ICER of £32,000 per QALY for natalizumab compared with beta interferon presented by the manufacturer was more likely to be an overestimate." There was no appeal and Guidance was issued on 20th August 2007.

Table 6: Natalizumab for multiple sclerosis – Key Issues

Natalizumab for multiple sclerosis ***Manufacturer Biogen Idec*** ***ERG PenTAG*** ***Committee B***	
Three **comparators** one of which is unlicensed for the treatment of MS (MTX)	
Agreement on what constitutes BSC	No
Best supportive care	
Indirect comparisons	Yes
Populations	
Concerns about whether the study populations represented UK clinical populations?	Yes
Systematic review	
Was the search strategy complete?	No*
Was the search strategy given?	No*
Was the quality of papers included in the evidence submitted checked?	No comment*
Were inclusion and exclusion criteria given?	No*
Was submission judged to be comprehensive? (in terms of those studies included in the evidence base)	No*
Reliance on unpublished studies	No
Was additional material requested?	Yes
Was it CIC?	Yes
Was it received in time	Yes
Were subgroup analyses carried out?	Yes, post hoc criticised by the ERG
Cost effectiveness	
Markov process cohort model	
PSA was carried out	Yes
ERG had doubts about the validity of the model?	Yes
Other ERG concerns;	
Reliance on EDSS outcome measures (ERG)	
Reduced number of health states and bandings, allows for improving disability (ERG)	
Range of assumptions in the model (ERG)	
Pragmatic approach to cost effectiveness modelling	
ICERs	
ICER Cost per QALY (MS) RES group compared with IFN-B,	£32,000
GA	£35,000
BSC	£45,000
SOT group compared with IFN-B,	£43,000
GA	£44,000
BSC	£56,000
ERG	Not given

* As noted in the ERG report

3.1.3. Alteplase for stroke

Alteplase (Actilyse®, Boehringer Ingelheim Limited) has a UK marketing authorisation (September 2002) for the treatment of acute ischaemic stroke. Treatment must be started within three hours of onset after prior exclusion of intracranial haemorrhage (ICH) in adults under 80 years. It is administered intravenously under the supervision of specialist physicians in specialist centres.

The manufacturer submission compared alteplase for stroke with best supportive care without thrombolysis and generated ICERs below £20,000. The ERG supported the model structure and were generally in agreement that the central estimate of the ICER was below £30,000. The ERG did highlight their belief that these estimates were subject to a wide degree of uncertainty. The submission for alteplase included very little CIC material. Key characteristics relating to this STA are presented in table 7.

The AC met once only on 15th March 2007. The focus of the discussion in this meeting was an exploration of ERG concerns with the quality of the clinical evidence which relied mainly on a single study and the extent to which the available clinical results could be generalised to UK clinical practice. They also discussed whether the economic model captured the disease course and outcomes, and evidence for subgroups. There was also some discussion in the meeting of the implications of approval because of the requirement for alteplase to be given within three hours of symptom onset.

The decision was to recommend alteplase for stroke within the licensed indication. No ACD was issued and the FAD was issued on 8th May. There was no appeal and Guidance was issued on 27th June.

Table 7: Alteplase for ischaemic stroke- Key Issues

Alteplase for ischaemic stroke **Manufacturer Boehringer Ingelheim** **ERG /ScHARR** **Committee C**	
One **comparator –** best supportive care	
Agreement on what constitutes BSC	Yes
Best supportive care	
Indirect comparisons	No
Populations	
Concerns about whether the study populations represented UK clinical populations?	Yes
Systematic review	
Was the search strategy complete?	Yes*
Was the search strategy given?	Yes*
Was the quality of papers included in the evidence submitted checked?	Partially*
Were inclusion and exclusion criteria given?	Yes*
Was submission judged to be comprehensive? (in terms of those studies included in the evidence base)	Yes*
Reliance on unpublished studies	No
Was additional material requested?	Yes
Was it CIC?	No
Was it received in time?	Yes
Were subgroup analyses carried out?	Yes, post hoc and justified
Cost effectiveness	
State transition cohort model	
PSA was carried out	Yes
ERG had doubts about the validity of the model?	Yes
Other ERG concerns;	
Reliance mainly on a single study (ERG) and no account taken of the costs of getting patients to stroke centres in under three hours	
ICERs	
ICER cost per QALY (MS)	<£20,000
(ERG)	£26,000- £50,000

* As noted in the ERG report

3.1.4. Adalimumab for psoriatic arthritis

Adalimumab (Humira®, Abbott Laboratories Ltd) is licensed (September 2005) as a monotherapy for adult patients with active and progressive moderate to severe psoriatic arthritis (PsA) who have shown inadequate response or intolerance of at least two disease modifying anti-rheumatic drugs (DMARDs). It is available in two forms, as a 40mg pre filled pen or a pre-filled syringe at same dosage and can be administered by trained carers or self administered as a single subcutaneous injection every two weeks. Key characteristics relating to this STA are presented in table 8.

The scope indicated two comparators. Firstly, conventional management strategies for active and progressive psoriatic arthritis that has responded inadequately to previous DMARD therapy, excluding adalimumab and secondly, other TNF inhibitors etanercept and infliximab. The manufacturer approached the decision problem by comparing adalimumab versus conventional DMARDs, adalimumab versus etanercept, etanercept versus conventional DMARDs, adalimumab versus infliximab and infliximab versus conventional DMARDs

Existing NICE guidance for comparator treatments (NICE, 2006) states that;.

- Etanercept only given when peripheral arthritis with more than 3 swollen joints and more than 3 tender joints
- PsA has not responded to adequate trials of more than 2 DMARDs individually or in combination
- Infliximab in line with above if anti TNFs considered appropriate but etanercept contraindicated.

The ERG raised numerous concerns about the submission which they noted to be of poor quality. Although the manufacturer stated that the patient population considered in the decision problem should be in accordance with the licensed indication for adalimumab, the participants in the two pivotal RCTs were not entirely representative of that population. Neither study population was made up exclusively of patients who had failed to respond to at least two DMARDs (43% & 40% in M02-518, and 61% & 51% in M02-570 for the placebo and adalimumab groups, respectively). The trials also lacked patients with severe skin involvement. The ERG also expressed concerns about the complexity and accessibility of the methods used for the evidence synthesis,

inclusion criteria and key assumptions in the economic modelling. Independent expert clinical advice given to the ERG however, confirmed that the participants in these two trials represented a population with relatively severe PsA similar to those currently being treated in UK clinical practice. The clinical evidence submitted was based on only one study which had been fully published and three others published only as abstracts. The ERG noted that this had meant that they were unable to assess the validity and quality of these three studies.

At the first AC on 15th March, discussions focused on whether there was a sufficient evidence base for adalimumab, the application of research results to a UK setting, and implications of existing NICE guidance (as above). The AC also examined the cost effectiveness mindful of the ERG view that the economic model lacked validity.

The outcome of the first AC decision was a "minded no" and the ACD was published. The Institute requested that the manufacturer provide cost-effectiveness analyses for adalimumab compared with etanercept and infliximab using 12-week response data, without the constraint that the 12-week response rates should be equal to or lower than those reported at 24 weeks. It also requested that the results be provided separately for people with skin involvement (that is, 3% or more body surface area (BSA) affected by psoriasis) and for people without skin involvement (less than 3% BSA affected).

The second meeting was held on 16th May and the AC remained concerned about the methods used in the evidence synthesis including absolute response rates and ceiling adjustments and the use of 24-week data to predict 12-week response rates for which actual trial data were available. The AC accepted that the manufacturer had addressed some of these issues in the first revised submission When adjustments were made, the response rate for adalimumab decreased as expected. However, the calculated response rates for the other two drugs also decreased. The AC was therefore concerned as to whether the methods behind the second revised manufacturer's evidence synthesis were robust. The AC also remained concerned about the reliance on unpublished data. The AC concluded that adalimumab should be available as an option for the treatment of adults with active and progressive PsA when the person has three or more tender joints and three or more swollen joints, and when the disease

has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination.

There was no appeal and Guidance was published on 14th August 2007.

Table 8: Adalimumab for psoriatic arthritis – Key Issues

Adalimumab for psoriatic arthritis (PsA) **Manufacturer Abbott Labs Ltd** **ERG York** **Committee C**	
Two **comparators** Conventional management including DMARDs (excl adalimumab) Other TNF inhibitors (etanercept and infliximab)	
Agreement on what constitutes Best supportive care (BSC)	Yes
Indirect comparisons	Yes
Populations	
Concerns about whether the study populations	
represented UK clinical populations?	Yes
Systematic review	
Was the search strategy complete?	Probably yes*
Was the search strategy given?	Yes*
Was the quality of papers included in the evidence submitted checked?	No comment*
Were inclusion and exclusion criteria given?	No*
Was submission judged to be comprehensive? (in terms of those studies included in the evidence base)	Yes*
Reliance on unpublished studies	Yes
Was additional material requested?	Yes
Was it CIC?	Yes
Was it received in time?	No
Were subgroup analyses carried out?	Requested by ERG, not carried out
Cost effectiveness	
De novo cost effectiveness analysis based on probabilistic micro-simulation approach over a lifetime	
PSA was carried out	Yes
ERG had doubts about the validity of the model?	Yes
Other ERG concerns;	
Failure to consider all relevant trial data (exclusion of 12 week trial data) in estimating response rates for the economic model.	
Assumption of exchangeability of absolute response rates (after adjusting for severity of skin involvement) breaking randomised comparisons in the trials.	
Adjustments used to estimate 12 week response parameters from 24 week trial results	
Exclusion of potentially important comparator (palliative care)	
Assumptions about long term HAQ progression including treatment failure	
ICER cost per QALY (MS)	£25,991
(ERG)	>£30,000

* As noted in the ERG report

3.1.5. Varenicline for smoking cessation

Varenicline (Champix®, Pfizer Inc UK) is licensed (December 2006) in the UK for smoking cessation in adults who smoke tobacco products and wish to stop smoking. It is taken orally at a dosage of 1 mg twice daily following a one week titration.

The manufacturer compared varenicline with bupropion, nicotine replacement therapy (NRT) and placebo (no therapy). Current NICE recommendations are for either buprupion or NRT as part of abstinent contingent treatment (where a smoker makes a commitment to stop smoking on a set date) and in this case, although GPs offer opportunistic advice, ideally, the patient will receive intensive support from NHS smoking cessation services. Varenicline for smoking cessation included details of an open label trial comparing varenicline with NRT transdermal patch, all of which were commercial in confidence. Key characteristics relating to this STA are presented in table 9.
In the manufacturer's base case analysis varenicline dominated NRT and bupropion over a lifetime horizon.

The ERG identified factors in the analysis that might affect cost-effectiveness estimates including assumptions about a single quit attempt, extrapolations of one year data to a lifetime horizon and computational errors in the model. They also criticised the use of indirect data when the direct trial data was available.

The AC met once only on April 18th 2007. The AC considered whether any one or a combination of these factors could lead to varenicline being considered not to be cost effective and decided that these concerns were not sufficient to undermine the inference that the use of varenicline in smoking cessation was likely to be a cost-effective use of NHS resources.

The decision of the AC was to recommend varenicline within the license indication and there was therefore no ACD consultation. The FAD was published on 30th May. There was no appeal and Guidance was issued on 25th July 2007.

Table 9: Varenicline for smoking cessation – Key Issues

Varenicline for smoking cessation **Manufacturer Pfizer** **ERG ScHARR** **Committee C**	
Three **comparators**	
Agreement on what constitutes BSC	No
Best supportive care	
Indirect comparisons	Yes (direct comparisons were available and not used)
Populations	
Concerns about whether the study populations represented UK clinical populations?	Yes
Systematic review	
Was the search strategy complete?	No*
Was the search strategy given?	No*
Was the quality of papers included in the evidence submitted checked?	No comment*
Were inclusion and exclusion criteria given?	Partial*
Was submission judged to be comprehensive? (in terms of those studies included in the evidence base)	No*
Reliance on unpublished studies	Yes
Was additional material requested?	Yes
Was it CIC?	Yes
Was it received in time?	Yes
Were subgroup analyses carried out?	No,
Cost effectiveness	
The BENESCO state transition model	
PSA was carried out	Yes
ERG had doubts about the validity of the model?	Yes
Other ERG concerns;	
Very complex model and multiple computational errors.	
Assumes a single quit attempt	
Extrapolates from one year's data to a lifetime horizon.	
Parameter values derived from US studies	
ICER Cost per QALY (MS) Base case over a lifetime	Dominates

* As noted in the ERG report

3.1.6. Omalizumab for severe persistent allergic asthma

Omalizumab for asthma (Xolair®, Novartis) is licensed for combined use in the treatment of adults and adolescents with severe persistent allergic asthma. It is given as 75-375 mg subcutaneous injections every 2 or 4 weeks by specialist physicians. Key characteristics relating to this STA are presented in table 10.

The manufacturer compared omalizumab as add-on therapy to standard therapy alone. Outcome measures included the rate of clinically significant asthma exacerbations, the rate of clinically significant severe exacerbations and the rate of emergency visits for asthma. In the manufacturer's submission, clinically significant exacerbations were defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids. Clinically significant severe exacerbations were defined as requiring treatment with systemic corticosteroids. The MS widened the scope to include rates of exacerbations (not requiring hospital admission) and severe exacerbations although definitions of exacerbations vary in the literature.

The manufacturer presented one post hoc analysis of a subgroup of severe high risk patients in the key trial cited in the submission (INNOVATE) but the post hoc analysis was criticised by the ERG. The manufacturer did not present any scenario analyses although the ERG did present scenario analyses for the primary intention to treat population (PITT). The base-case analysis for the INNOVATE PITT (primary intention to treat which excluded 13% of the randomised population) population produced an incremental cost effectiveness ratio (ICER) of £30,647 per QALY and an ICER of £26,509 per QALY for the high-risk hospitalisation subgroup. The manufacturer also presented an alternative base-case analysis using subpopulation data from the ETOPA (IA-04) trial that gave an ICER of £21,700 per QALY.

The manufacturer's submission presented a probabilistic sensitivity analysis that showed a mean ICER of £31,700 per QALY (95% CI, £23,200 to £48,200 per QALY). No probabilistic sensitivity analysis was performed for the high-risk hospitalisation subgroup. The MS for omalizumab for asthma included a key trial (INNOVATE) for which the true intention to treat (ITT) population was only available as commercial in confidence excluding the safety results. In the same

submission, details of baseline exacerbation rates, lung function (a secondary outcome) and interim recruitment and retention rates for an ongoing safety study were CIC.

The AC meeting considered scenario analyses for the PITT population using different assumptions carried out by the ERG.

The AC met twice on 16th May and 11th July. The ERG identified a number of issues with the parameters and uncertainties in the economic model. They had concerns about the limited number of parameters in the one way sensitivity analysis. The ERG showed that the key drivers of the economic model were utility values assigned to omalizumab responders, the costs of omalizumab and asthma mortality rate. The particular uncertainties were costing of omalizumab on a per mg basis, utility values assigned to non-severe clinically significant exacerbations and clinically significant severe exacerbations and asthma mortality rate.

The ERG therefore explored a number of scenario analyses on alternative assumptions for these parameters. The scenario analyses for the INNOVATE PITT population ranged from £33,300 to £40,900 per QALY while the scenario analyses for the high-risk hospitalisation subgroup ranged from £29,800 to £34,300 per QALY. The ERG performed an amended probabilistic sensitivity analysis that showed greater uncertainty around the ICERs for the INNOVATE PITT population than suggested in the manufacturer's economic analyses. The ERG's amended probabilistic sensitivity analysis showed a mean ICER of £38,900 per QALY (95% CI, -£253,100 to £224,500 per QALY). No probabilistic sensitivity analysis was performed for the high-risk hospitalisation subgroup.

The AC decided to approve omalizumab for asthma as an add-on therapy to be initiated under the following circumstances: **:**

- clinical confirmation of IgE (Immunoglobulin ECHMP) mediation of asthma
- two or more exacerbations of asthma requiring admission to hospital within the previous year

- a full trial, and documented compliance with all steps of therapy set out in the BTS/SIGN guidelines, and
- the patient should be a non-smoker or have successfully ceased smoking.

The AC met twice on 16th May and 11th July 2007.

The ACD stated that the AC had approved omalizumab for asthma for use in a high risk group only.

> Omalizumab add-on therapy should only be initiated under the following circumstances: **:**
>
> - clinical confirmation of IgE mediation of asthma
> - two or more exacerbations of asthma requiring admission to hospital within the previous year
> - a full trial, and documented compliance with all steps of therapy set out in the BTS/SIGN guidelines, and
> - the patient should be a non-smoker or have successfully ceased smoking.
>
> Omalizumab add-on therapy should be initiated and monitored by a physician experienced in both allergy and chest medicine in a specialist centre. Omalizumab add-on therapy should be discontinued at 16 weeks in patients who have not shown an adequate response to therapy. Response to treatment should be defined on the basis of all available clinical assessments including:
>
> - reported improvement in daily symptoms and in measurements of peak expiratory flow rate
> - reduction in the need for systemic corticosteroids
> - reduction in unplanned consultations for asthma.

The AC took advice from specialists about the need for careful identification of patients and discussed the effectiveness of omalizumab for asthma as add on to standard therapy for some particular patient groups. They debated parameters considered to be key in determining cost effectiveness in the INNOVATE trial population and in the high risk subgroup specified by the manufacturer.

- Asthma related mortality risk from clinically severe exacerbations

- Utility values assigned to omalizumab non-responders and standard therapy
- The time horizon
- The basis for estimating drug costs
- Adverse events

Overall, therefore, the AC concluded that there were a number of considerations which meant the ICER was higher than acceptable for patients with severe persistent allergic asthma. However, the AC was persuaded that for a narrowly defined severely affected group of asthmatics, at an elevated risk of asthma-related mortality, cost-effective treatment with omalizumab was possible, if therapy was discontinued in non-responders at 16 weeks and if vial wastage could be minimised to reduce costs. The AC recommended omalizumab. At the time of writing the institute were considering whether there were grounds for an appeal.

Table 10: Omalizumab for asthma – Key Issues

Omalizumab for asthma **Manufacturer Novartis** **ERG Southampton** **Committee C**	
One **comparator –** best supportive care	
Agreement on what constitutes Best supportive care (BSC)	Yes
Indirect comparisons	No
Populations	
Concerns about whether the study populations	
represented UK clinical populations?	No
Systematic review	
Was the search strategy complete?	Yes*
Was the search strategy given?	Yes*
Was the quality of papers included in the evidence submitted checked?	
Were inclusion and exclusion criteria given?	Partially*
Was submission judged to be comprehensive?	Yes*
(in terms of those studies included in the evidence base)	
Reliance on unpublished studies	No
Was additional material requested?	Yes
Was it CIC?	No
Was it received in time?	Yes
Were subgroup analyses carried out?	Yes, post hoc criticised*
Cost effectiveness	
Markov State transition model	
PSA was carried out	Yes but not for high risk subgroup
ERG had doubts about the validity of the model?	Yes
Other ERG concerns;	
Reliance mainly on a single study and robustness of evidence base for efficacy	
Robustness of post hoc sub group analysis	
Impact of uncertainties including asthma related mortality, utility values in model, costing on a per vial basis. And time horizon of economic model	
ICERs	
ICER cost per QALY (MS) Trial population;	£30,647
high risk group	£26,509
(ERG) Trial population	£36,362 - £40,8899
High risk group	£29,849 - £34,303

* As noted in the ERG report

3.1.7. Abatacept for rheumatoid arthritis (RA)

Abatacept for rheumatoid arthritis, (Orencia®, Bristol Myers Squibb) is licensed (March 2007) in combination with methotrexate (MTX) for the treatment of moderate to severe RA in adult patients who have had insufficient response to or intolerance of disease modifying anti rheumatic drugs (DMARDs) including at least one tumour necrosing factor alpha inhibitor (anti TNF-α). It is given as an intravenous infusion by specialist physicians. Key characteristics relating to this STA are presented in table 11.

The submission from the manufacturer focused on the use of abatacept in combination with methotrexate for the treatment of RA following the failure of an anti TNF-α. The manufacturer identified three possible comparators for abatacept: a return to conventional DMARDs, the use of a second anti TNF-α, and the use of rituximab. Only the first two of these comparators were considered in the assessment of cost effectiveness. A number of outcomes were reported in the submission including symptom measures, measures of physical function and measures of disease activity. A subgroup analysis was carried out for males.

The manufacturer estimated the incremental cost effectiveness ratio of abatacept compared with methotrexate to be £25,395 per quality adjusted life year (QALY) gained. The corresponding estimate in comparison with a second anti TNF-α was £22,628 per QALY gained. One-way sensitivity analyses suggested that the model was sensitive to assumptions about the time horizon, discounting, rate of underlying disease progression and the cost of abatacept. The manufacturer's probabilistic sensitivity analyses suggested that there was a high probability that abatacept was cost effective if the acceptable amount to pay for an additional QALY is £30,000. The ERG estimated that the ICER was at least £47k per QALY for the comparison with MTX alone and at least £125k per QALY compared to sequential anti TNF-α's. These ICERs would be even higher if the ERG preferred HAQ progression rates were accepted.

Abatacept is the single technology in this review where the STA process tracked the licensing application and included as commercial in confidence key findings from the

main trail which were used in modelling including details of non responders and HAQ change scores.

The AC met on 11th July and again on 12th September. Only the ACD issued after the first meeting was considered in this report since the outcome of the second meeting had not been published at the time of writing. The AC examined the evidence for clinical effectiveness in the manufacturer's submission but considered that it was a weakness in the evidence that there were no direct head-to-head comparisons of abatacept with alternative conventional DMARD regimens, anti TNF-α's or rituximab. The model did not include a sequence of treatments and abatacept was modelled as a final active treatment. The AC did not consider that this model structure would necessarily reflect clinical practice given current NICE guidance. However, it was aware of the evidence from clinical specialists that patients may have already tried a large number of conventional DMARDs before being prescribed anti TNF-α's, and that for these patients treatment options were limited. The AC heard from the ERG that it considered that the estimates of cost effectiveness were likely to be less favourable if a sequence of treatments had been modelled, but that this could not be formally explored without an alternative model structure. The AC also considered alternative disease progression rates whilst on treatment, after withdrawal from biologic treatment and after exhausting DMARD and biologic options.

An over-riding issue for the AC was the fact that no comparison of cost effectiveness had been made with rituximab which, as a NICE recommended option for RA patients after failure of an anti TNF-α (see section 3.1.1 above), was considered the relevant comparator. The MS had however, included an indirect comparison with rituximab in terms of clinical response which concluded there was no significant difference between the treatments. The AC were also clear that rituximab is significantly less costly than abatacept. Therefore, abatacept could not be considered a cost effective intervention compared to rituximab. Furthermore, the AC considered that the estimates from the ERG which generated high ICERs compare to DMARDs or sequential anti TNF-α's also made is unlikely that abatacept would be cost effective in patients for who rituximab was not an option. Abatacept was therefore not recommended for use in the ACD.

Table 11: Abatacept for rheumatoid arthritis – Key Issues

Abatacept for rheumatoid arthritis **Manufacturer BMS** **ERG Liverpool** **Committee C**	
One **comparator** - Management strategies without abatacept (including DMARDs and anti TNF-α agents).	
Agreement on what constitutes Best Supportive care BSC	Yes
Indirect comparisons	No
Populations	
Concerns about whether the study populations represented UK clinical populations?	No
Systematic review	
Was the search strategy complete?	Yes*
Was the search strategy given?	Yes*
Was the quality of papers included in the evidence submitted checked?	Yes*
Were inclusion and exclusion criteria given?	Yes*
Was submission judged to be comprehensive? (in terms of those studies included in the evidence base)	Yes*
Reliance on unpublished studies	No
Was additional material requested?	Yes
Was it CIC?	Yes
Was it received in time?	Yes
Were subgroup analyses carried out?	Yes,
Cost effectiveness	
Patient level state simulation model	
PSA was carried out	Yes
ERG had doubts about the validity of the model?	Yes
Other ERG concerns;	
Most appropriate comparator	
Can trial data be generalised to UK population likely to receive the drug?	
Submission of the model in the R-format	
Logic errors (discounting, sampling)	
Omission of treatment costs for MTX in the treatment arm	
No half cycle correction	
Parameter value adjustments	
ICERs	
ICER Cost per QALY (MS) vs BSC	£25,500
(ERG) vs BSC	£47,503 - £72,865
vs cycled TNFis	£124,661 - £210,053

* As noted in the ERG report

3.1.8. Infliximab for psoriasis

Infliximab for psoriasis (Remicade®, Schering Plough) is licensed (September 2005) for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or long wave ultra violet light (PUVA). It is given by specialist physicians as an intravenous infusion. It was compared with etanercept, efalizumab & standard treatment without an anti TNF-α or efalizumab. Key characteristics relating to this STA are presented in table 12.

The manufacturer based its evidence submission on the assessment report and model from 'Etanercept and efalizumab for the treatment of adults with psoriasis', NICE technology appraisal guidance 103 (TA103). The manufacturer's base-case analysis (for patients defined as 4th quartile Dermatology Life Quality Index (DLQI)) against continuous etanercept resulted in a cost of £26,095 per quality-adjusted life year (QALY) gained. The incremental cost-effectiveness ratio (ICER) for infliximab compared with best supportive care was £22,240 per QALY gained. The manufacturer carried out a series of one-way sensitivity analyses. These demonstrated that changes in response rates and patient weight had the greatest impact on the ICER. The probabilistic sensitivity analysis (PSA) gives a probability of being cost effective at £20,000 and £30,000 thresholds of 10% and 73%, respectively.

The ERG produced scenario analyses in which a number of changes from the manufacturer base case were combined. This increased the ICER for infliximab compared with continuous etanercept from £26,095 to approximately £41,000 per QALY gained when the drop out rate and inpatient costs were combined. When the all patient utility was included the ICER increased to approximately £77,000. The ERG also extended the manufacturer's PSA to include extra variables including annual drop-out rate, cost of infliximab, length of inpatient stay and number of outpatient visits. The combined result of these changes gave an ICER of £33,200 and a 38% probability of being cost effective at a £30,000 threshold.

The submission for infliximab for psoriasis was based on four RCTs, two of which included CIC information (details of subgroups) and the ERG noted that they were

unable to verify the information. Much of the discussion at the AC meeting focused on whether the patients in the most severe group were representative of the NHS patient population.

The AC met on 1st August and is due to meet again on 3rd October. In the first AC meeting, the AC noted that according to the clinical specialists, the patient experts, the manufacturer and the ERG, etanercept is given continuously in routine UK clinical practice. The AC was therefore persuaded that continuous etanercept was an appropriate comparator. The AC also discussed the extent to which the patients in the more severe group were representative of the broader population to be considered within the scope, the proposed decision problem and the clinical effectiveness evidence of the appraisal. No figures for the ICER compared with continuous etanercept were presented but the AC thought it was likely to be higher than £41,351 suggesting that infliximab would not be a cost-effective use of NHS resources in the broader population.

The AC considered that the manufacturer's base case was represented by a subgroup with particularly severe disease which had not been sufficiently defined and, because of this, it might not be reasonable to expect the same level of clinical response. Therefore the ICER of £26,095 was not considered a robust estimate of the cost effectiveness of infliximab compared with etanercept in the 4th quartile of DLQI subgroup.

The AC issued a "minded no" at the ACD stage for infliximab for the treatment of adults with moderate to severe plaque psoriasis. Additional work was requested which would assess the cost effectiveness of infliximab compared to continuous etanercept in the severe disease subgroup.

Table 12: Infliximab for psoriasis – Key Issues

Infliximab for psoriasis **Manufacturer Schering Plough** **ERG Southampton** **Committee B**	
Three **comparators** one of which is etanercept. NB The decision problems indicated etanercept at 25-50mg dosage whereas NICE Guidance states 25mg dosage.	
Agreement on what constitutes BSC	Yes
Best supportive care	
Indirect comparisons	Yes
Populations	
Concerns about whether the study populations represented UK clinical populations?	Yes
Systematic review	
Was the search strategy complete?	Probably Yes*
Was the search strategy given?	Limited*
Was the quality of papers included in the evidence submitted checked?	No*
Were inclusion and exclusion criteria given?	Yes*
Was submission judged to be comprehensive? (in terms of those studies included in the evidence base)	Probably yes*
Reliance on unpublished studies	No
Was additional material requested?	Yes
Was it CIC?	Yes
Was it received in time?	Yes
Were subgroup analyses carried out?	Yes,
Cost effectiveness	
Bayesian hierarchical Markov process model	
PSA was carried out	Yes
ERG had doubts about the validity of the model?	Yes
Other concerns;	
Reliance on EDSS outcome measures (ERG)	
Reduced number of health states and bandings, allows for improving disability (ERG)	
Range of assumptions in the model (ERG)	
Pragmatic approach (ERG)	
ICER Cost per QALY (MS)	£32,000-56,100
(ERG)	not given

* As noted in the ERG report

3.1.9. Rituximab (3rd line) for follicular lymphoma (FL)

Rituximab (Mabthera®, Roche) is licensed for the treatment of adults with relapsed/refractory FL responding to induction therapy with chemotherapy. Current NICE guidance (2006) recommends the use of rituximab as a first line treatment for follicular lymphoma. The focus of the STA was rituximab used 3rd line. Rituximab is given as a hospital based infusion as induction and maintenance therapy. Key characteristics relating to this STA are presented in table 13.

The manufacturer's submission (MS) presented two ways of using rituximab as a third line therapy: firstly, to induce remission in relapsed FL; secondly, as maintenance therapy after successful induction of remission. The MS claimed that there was no new evidence for the use of rituximab in adult patients with stage III-IV FL who are chemoresistant or are in their second or subsequent relapse after chemotherapy. Therefore the MS presented no new case for the use of rituximab in this patient population. The MS provided new clinical evidence from two randomized controlled trials (EORTC and GLSG-FCM). Both trials were included in the systematic review (SR) and compare the clinical effects of chemotherapy with or without rituximab in the induction of remission at first or second relapse and the clinical benefits of rituximab maintenance therapy versus the NHS current clinical practice of observation for FL patients. The submission did not include any commercial in confidence material.

The MS presents the results of two sets of economic evaluations. The first compares the use of rituximab maintenance (following response to an induction therapy) versus observation only (no treatment until relapse), the two arm model.. The second model compares the use of rituximab maintenance therapy with observation only for patients responding to chemotherapy with or without rituximab and tests whether the use of rituximab as an induction therapy in addition to maintenance therapy is cost effective, the four arm model.

The manufacturer reported an incremental cost-effectiveness ratio (ICER) of £7,721 per quality adjusted life year (QALY) gained for the two arm comparison. In the MS, when subject to extensive univariate and probabilistic sensitivity analysis (PSA), this

ICER was shown to be robust. In the MS, the 4-arm economic model illustrated that the greatest clinical effectiveness was achieved by R-CHOP followed by rituximab maintenance (R-CHOP>R). The MS concluded that R-CHOP>R is cost effective when compared to the second most clinically effective intervention of CHOP induction followed by rituximab maintenance therapy (CHOP>R); the estimated ICER is £16,749 per QALY gained. Again, in the MS, this ICER was shown to be robust.

The AC met once on 12th September. No details of this meeting were available to the research team at the time of writing.

Table 13: Rituximab (3rd line) for follicular lymphoma – Key Issues

Rituximab for follicular lymphoma **Manufacturer Roche** **ERG Liverpool** **Committee C**	
One **comparator (CHOP)**	
Two scenarios induction of remission and maintenance post remission	
Agreement on what constitutes Best supportive care BSC	No
Indirect comparisons	No
Populations	
Concerns about whether the study populations represented UK clinical populations?	Yes
Systematic review	
Was the search strategy complete?	Yes*
Was the search strategy given?	No*
Was the quality of papers included in the evidence submitted checked?	Yes*
Were inclusion and exclusion criteria given?	No*
Was submission judged to be comprehensive?	Yes*
(in terms of those studies included in the evidence base)	
Reliance on unpublished studies	No
Was additional material requested?	Yes
Was it CIC?	Yes
Was it received in time?	No
Clarification also sought by NICE regarding the licensing of rituximab.	Yes
Were subgroup analyses carried out?	Yes,
Cost effectiveness	
Two models Health state transition models.	
(three states 'maintenance model', five states' Induction and maintenance model')	
PSA was carried out	No
ERG had doubts about the validity of the model?	Yes
Other ERG concerns;	
No account of previous Rituximab use in 2-arm model	
Results of systematic review of rituximab monotherapy are not separated from overall results	
Uncertainty about the impact of exclusion of rituximab-naive patients.	
Need for clarification of the marketing authorisation	
Incomplete data from manufacturer meant that PSA could not be calculated.	
ICER Cost per QALY (MS) ICER R-CHOP>R vs R-CHOP 4-arm comparison	£16749
2-arm comparison	£7,721
ERG 4-arm comparison	Probably cost effective

* As noted in the ERG report

3.1.10. Summary of STAs

Of the nine STAs included in the review, three were recommended within their licensed indications at the first committee meeting and therefore a FAD was issued without an ACD (alteplase for stroke, rituximab for follicular lymphoma and varenicline for smoking cessation). Three "minded no's" were issued at the first AC meeting (adalimumab for psoriatic arthritis, infliximab for psoriasis and rituximab for rheumatoid arthritis). The two cases that had proceeded beyond the issuing of the "minded no" at the time of writing had both resulted in positive guidance being issued (adalimumab for psoriatic arthritis and rituximab for rheumatoid arthritis). Of the remaining STAs, two technologies were not recommended at the first AC meeting (abatacept for rheumatoid arthritis and natalizumab for MS) and another received positive guidance in a limited subgroup (omalizumab for asthma). The position on abatacept was maintained at the second AC meeting whereas the FAD (and final guidance) for natalizumab recommended its use in a limited subpopulation. The FAD for omalizumab maintained the position of the ACD.

There were 7 STAs where the ERG provided cost effectiveness estimates and in 6 of these cases, the base case ICER estimated by the ERG was higher than that suggested by the manufacturer (abatacept for RA, adalimumab for Psoriatic arthritis, alteplase for stroke, omalizumab for asthma, rituximab for RA, rituximab for follicula lymphoma). In the remaining case (varenicline for smoking cessation), the ERG and manufacturer agreed that the technology dominated.

ERGs identified significant methodological shortcomings in the majority of the STAs included in this report. In relation to the identification of evidence, the search strategy employed for the systematic review element of the manufacturer submissions was missing or incomplete in five cases (infliximab for psoriasis, natalizumab for multiple sclerosis, varenicline for smoking cessation, rituximab for follicular lymphoma, rituximab for rheumatoid arthritis). The majority of submissions did not report inclusion or exclusion criteria, only one provided details of procedures for checking the quality of included evidence (abatacept for rheumatoid arthritis).

3.2. METHODOLOGICAL ROBUSTNESS FINDINGS

3.2.1. The ERG Report and the requirements of the Appraisal Committee

The stated role of the ERG is to provide a technical review of the manufacturers submission, including to identify any evidence gaps. The STA process guide does not specify precisely what is covered by the term "review" and the distinction with "re-analysis" is one which can potentially be blurred. The document clearly states that the authors of these reports (the ERGs) have responsibility for their content and quality. Consequently, there is the potential for inconsistency between authors and between ERGs in terms of the content of ERG reports.

All ERGs involved in the STAs we have observed have provided reports that go beyond what might strictly be considered critical review. However, the extent to which additional analyses are undertaken differs markedly between groups. There are several reasons for this variability. First, there is an attitudinal difference between ERGs. Whilst all are prepared to go some way beyond the contractual obligations, some are prepared to consider the relationship with NICE as similar to a consultancy "client" with the ERG to provide whatever is required. Second, the ability of any group to provide alternative ICER estimates is dependent on the standard of the manufacturer submission. Where ERGs consider submitted models have structural or substantial other problems, it may be neither appropriate or feasible to produce an acceptable alternative. Third, the current contractual arrangements cover ERG involvement up to the 1st AC meeting. Any work required after that stage , for example in considering additional analyses requested of the manufacturer, must be negotiated with the Institute and the contractor via NHS NCCHTA.

> *"most teams hold them [NICE] to that [critiquing] and do not do any more than that."* [ERG member 1]

> *"The ERG reports have varied between something close to an MTA and something which takes the very strong line of 'all we are here to do is criticise and not to redo it but criticise what the company has presented us with.'" [AC member 1]*

"There are some of them [ERGs] that give more of a hint to it [most likely cost per QALY] if there is likely to be a disagreement with what the manufacturers said than others do." [AC member 2]

Several of the STAs studied as part of this project have highlighted a tension between the requirements of the AC and what ERG groups are contractually obliged to provide. In fact, the AC prefer analyses from the ERG groups that go beyond mere critical review by correcting model errors, estimating alternative parameter values and ultimately presenting reanalyses that the ERG believe to be credible. This was repeatedly emphasised by both AC chairs with reference to a recent appeal relating to bortezomib for multiple myeloma. On several occasions in interviews and in statements made to the AC, it was indicated that the appeal chair was not satisfied simply for the AC to claim an ICER was too optimistic but must suggest what they believed the ICER to be. This is an important issue as it highlights the existence of a gap between the requirements of the Institute and the information that ERG groups are contractually bound to deliver.

"The STA process is very vulnerable to imprecision but the deal with the ERG group is that they tell you what is wrong not what the effect of correcting what's wrong is . I don't think that is quite satisfactory and I now know it is even more unsatisfactory having heard the appeal panel say 'well what number do you think was right then if you don't like the one from the manufacturer ?' and we rather shrilly say it was already high and we know it would have been higher. 'Well that won't do they say' so we are stuck at appeal between an agreement with the ERG that they do not have to give us what we need and a view that is possibly emerging on appeal that we need some precision." [AC member 3]

"I think the STA process highlights and identifies issues which are concerns. It doesn't provide the answers. The TAR teams shouldn't feel that when they are doing an ERG tasks that they have to say, hey look I think there is an issue here – the model might be over or under estimating. We are not in a position to spend time addressing that

question in any detail.. we can raise the question but we don't have the answers." [ERG member 2]

As previously noted, several ERGs go beyond the required critiques in their reports. The motivation for this appears to lie in the goodwill the academic units have towards the Institute, a desire to provide the AC with the information required to make a decision, and professional pride.

"We want to produce a report product that is useful to the appraisal committee and often the manufacturer doesn't give you enough information or they don't do enough sensitivity analyses and we think that maybe the team needs to do a little bit more, NICE would be very keen for the teams to do more, maybe a little bit more analysis just to see."[ERG member 1]

"*It [the ERG report]seemed to be particularly obsessive, to go into all sorts of details and explore, they did little bits of simulation and things which seemed above and beyond the call of duty, someone had really taken it to heart I suppose which is not the case in some ERG's" [AC member 4]*

However, whether it is feasible for the Institute to sustain the STA process where ERGs provide additional analyses on the basis of goodwill has been questioned. We return to this issue in later sections. In addition to this, there have been concerns raised by one manufacturer, Bristol Myers Squib (BMS), in relation to the additional work undertaken by the ERG for the STA of abatacept for rheumatoid arthritis. BMS claim in their comments on the ACD that the ERG have gone beyond their remit as defined by the STA process guide and that the additional analyses undertaken by the ERG have not been subject to external review. This STA has not progressed sufficiently at this stage to be clear how this might resolve. Interviews with other manufacturers indicated that had positive guidance not been forthcoming for their products, similar grievances regarding the scope of ERG work might have been raised with the Institute.

3.2.2. The burden of proof

The key issue which distinguishes STA from the MTA process is the requirement for the manufacturer to submit evidence as opposed to an independent academic group. The process might therefore reasonably be expected to shift the burden of proof onto manufacturers – where the AC suspect a technology may be cost effective in certain subgroups or if assessed in a particular manner but the manufacturer has failed to demonstrate this then the AC should not recommend the use of the technology (Buxton and Akehurst, 2006).

From the outset of STA in 2005, many felt that this change in emphasis from the Institute to the manufacturer, coupled with assessment earlier in the lifetime of a product, would inevitably result in a greater number of rejected technologies. Certainly, several consultees on the original STA proposals emphasised the importance of the Institute having the ability and willingness to reject technologies on the basis of inadequate submissions. This expectation has been repeated in interviews with AC members.

> *"I suspect … the STA will lead to more no's than yes's on balance" [AC member 2]*

> *"I think if we do it properly there will be much more no's which I don't think was in anybody's mind when they wanted us to do things more quickly" [AC member 5]*

In the STAs that have operated under the final process and been selected as part of this review, all final guidance that has been issued to date recommends the technology for use (see Table 14). Given the relatively small number of topics caution must be exercised in drawing conclusions as to the overall balance of positive versus negative guidance in the STA process. However, it is worth noting how NICE recommendations compare to other international decision making bodies that have considered the same technologies, as illustrated in

Table 14. In terms of final recommendations, NICE differs from SMC, CADTH and PBAC in relation to natalizumab for MS and omalizumab for asthma. Whilst these decision making bodies operate in differing environments, including their own remit, and therefore decisions may be expected to diverge. In addition, it must be recognised in the case of omalizumab and a lesser extent natalizumab, that NICE guidance was positive in a restricted population only.

Greater scrutiny of these two appraisals does provide an indication that STA has not shifted the requirement for cost effectiveness to be demonstrated by the manufacturer rather than the Institute.

Table 14: Summary of recommendations by international HTA bodies for topics which NICE has issued guidance

		Rituximab for RA	Alteplase for stroke	Natalizumab for MS	Adalimumab for PsA	Varenicline for smoking- cessation	Omalizumab for asthma
NICE	England and Wales	**ü**	**ü**	**ü**	**ü**	**ü**	**ü**
SMC	Scotland	**ü**	**ü**	*X*	**ü**	**ü**	*X*
PBAC	Australia	**ü**		*X*	**ü**	**ü**	
CADTH	Canada	**ü**		*X*	**ü**	**ü**	*X*

In the case of the appraisal of omalizumab for asthma, the AC clearly was not convinced that the technology was cost effective in the high risk subgroup for which evidence was submitted. Final positive guidance was issued for a subgroup of even higher risk patients for whom no data were presented and no cost effectiveness estimate was made. Interestingly, the manufacturer questioned the arbitrary nature of this subgroup restriction. Several interviewees suggested that the outcome for this appraisal would likely have been a rejection under MTA since the independent assessment group would have provided an ICER estimate (see point 3.2.1 above).

> *"The big difference [with MTA] is that the ICER would have been much further outside, because there were several things in that model that were suspect anyway. If it had been an MTA and someone independent had done it I suspect we would have been looking at ICERS in the 50's and 60's instead of ICERS in the 23 pushed over the 30 by the ERG which would have made a difference. Faced with a 50 or 60 even the most sympathetic person wouldn't have said yes to it." [AC member 1]*

In the case of natalizumab for MS, positive guidance was issued in relation to the RES subgroup. In the manufacturer submission, an estimated ICER of £32k per QALY was presented for natalizumab compared to beta interferon with the manufacturer claiming that the appropriate threshold ICER for this appraisal should be £36k per QALY on the basis of the implied acceptable ICER under the Department of Health risk sharing scheme. The ERG report raised several issues concerning the cost effectiveness estimate, some of which could benefit the ICER and others which would worsen it. The net impact of these was not calculated either by the manufacturer or the ERG.

3.2.3. Quality and length of manufacturer submissions

The approach taken to dealing with poor quality manufacturer submissions in the STA process was highlighted by commentators from the outset in a similar vein to the overall concept of shifting the burden of proof to the manufacturer. Several sources suggested that a required component for a successful STA process is the ability of the AC to reject on the grounds of an inadequate submission. Other commentators

suggested that gaming behaviour by manufacturers might lead them not to provide usable submissions in some instances.

Manufacturer submissions included in this review have clearly been of variable quality. Those best placed to judge these submissions, the ERGs, have, on occasion, made some strong criticisms. This may be seen as inevitable to some extent given the academic nature of ERGs and their role as critical reviewers. Nevertheless, the tone of criticism in some reports coupled with interview evidence suggests that this is a genuine concern. ERG reports and other correspondence have, on several occasions, referred to “generally poor quality”, “fatally flawed analyses” and other highly critical phrases. This view was echoed by one AC member who suggested that the manufacturer submission for one of the STAs was the worst submission the AC had been presented with. Components of the assessment which appear to be poorly performed in several submissions are the transparency and justification for selection of clinical evidence, methods of performing indirect comparisons and the characterisation of uncertainty in implementing probabilistic sensitivity analysis.

The current STA process is not capable of resolving all concerns ERGs may have with a manufacturer submission and where manufacturers submit poor quality submissions the AC must nevertheless still rely on this as the principal review of the evidence.

In addition to concerns about the quality of manufacturer submission, several ERGs raised concerns about the quantity of material submitted. The specification for manufacturers states that the main body of the submission should not exceed 75 pages. However, this is regularly exceeded and sometimes by wide margins, as indicated in Section 3.1. For example, the submission for natalizumab for MS was 272 pages long. This is cited as an important pressure placed on the ERGs who are already working to extremely tight deadlines and hinders the extent to which information is transparent to stakeholders.

3.2.4. Dealing with uncertainty

The current guide to the methods of technology appraisal (NICE, 2004) states that probabilistic sensitivity analysis (PSA) "should be used" to represent the impact of parameter uncertainty on decision uncertainty. Manufacturers do routinely undertake PSA in their submissions although the quality with which uncertainty is characterised has been strongly criticised. ERGs have tended to replicate these analyses where they have changed parameter values.

The outputs from PSA are rarely presented at the AC meetings. In fact on only one occasion observed by the authors was the output from a PSA presented to the AC, in this example in the form of a confidence interval around the ICER. Even in this case the analysis had only been performed for a single subgroup. Parameter uncertainty is often considered by the AC as a series of one-way sensitivity analyses followed by a revised analysis based on a preferred set of parameter values.

However, this can cause difficulties if the particular scenario favoured by the AC has not been calculated by the ERG. The AC occasionally estimate the ICER for their favoured scenario in the meeting but this is obviously quite crude.

The absence of PSA results at the AC stage was criticised by some members of the AC.

> *"they didn't give it [PSA results] for the [subgroup] so what we are doing is basing our decision again on a point estimate and a one way around that point estimate which to me just seemed a bit poor."[AC member 6]*

> "*We don't talk about PSA at all in the meetings….I don't understand why when we are looking at national decision making levels it seems to me like we are going backwards and looking at things in a deterministic fashion. I understand it simplifies the discussion especially for people on the panel who aren't economists but most of those people still understand P values and confidence intervals." [AC member 7]*

In the case of abatacept, the manufacturer submission was performed in 'R' software, as opposed to the recommended Excel or Data Treeage format, to facilitate PSA with the patient level simulation model they developed. The review group did raise this as a concern at an early stage since ERGs cannot be expected to provide expertise in a wide range of software. Despite formal instruction from the Institute to use the recommended software, the submission was made in "R" with an excel version of the model provided. The excel version was the focus of ERG considerations and this did not include the capacity to perform PSA.

3.2.5. The role of the manufacturer and ERG templates

The submissions made by manufacturers and the reviews of those submissions by ERGs are made using templates designed by the Institute. We asked interviewees to comment on these designs in interviews and in some cases found a generally negative view of the manufacturer template from both ERGs and manufacturers, although equally there were many respondents who did not have any problem with the current design. A recurrent complaint was that in order to accurately fill out each section of the template the submission is required to repeat information in several places. This adds to the length of the document.

> *"..I think the template is an issue because there is a lot of repetition in it and it's not particularly conducive to allowing the flow of the story." [ERG member 4]*

In addition, some manufacturers claimed it was not clear what was expected within each section and the layout was not clear.

The ERG template was considered to be relatively flexible and some groups had not always followed it. Although some respondents expressed a dislike of the template, few specific reasons for this were given. There were some criticisms of the document in terms of lack of consistency with the manufacturer template and that it does not fit well with the types of evidence that are submitted to STA.

"… the templates were drawn up on the basis that there would be a systematic review of the literature and obviously because this is an STA you don't end up with many trials and so two things happen. One is you end up with the single trial and then you will have a review of the different literature and there is no mechanism within the template to talk about that." [ERG member 3]

3.3. TRANSPARENCY FINDINGS

In interviews with stakeholders, the transparency of the NICE process was universally praised. Despite the likelihood that STA might rely on commercial in confidence data to a greater extent due to the appraisal taking place earlier in the development of a technology, this has not been raised as a concern by any interviewee. However, caution must be exercised here since the only STA included in this review where the appraisal is tracking the license application is for abatacept for RA. Since this appraisal has not completed at the time of writing, it has not been feasible to interview stakeholders on this technology.

In other STAs, patient representatives suggested that whilst there are clearly technical issues discussed in some of the documentation that are difficult to understand, the summary documents provided by NICE and in particular the pre meeting briefing, are valuable in helping to understand the evidence and its role in the appraisal. In addition, the FAD was cited as providing a clear explanation of how the AC reached their conclusions, even where the interviewee did not agree with the actual decision made.

One manufacturer raised a concern about the degree of transparency prior to the first AC meeting, although felt that the process as a whole compared well with other decision making bodies.

"I think this is an issue as it's not as transparent as it was with the MTA and we don't get to see the ERG and that is a problem as we can't address any of the issues, which we can with the MTA, prior to the committee meeting and that would be helpful. Even if you only had 1 or 2

weeks to do it it would really help because I think there are frequently misunderstandings in their interpretation of the data" [Manufacturer 1]

3.4. INCLUSIVENESS FINDINGS

One patient representative who attended a AC meeting and provided extensive comments at various stages of the appraisal highlighted the burden of the workload involved in reading relevant materials if a useful contribution is to be made to the process.

Another concern raised by the same patient centred on the actual expectations of patient representatives attending the AC meeting versus the focus of the Institute itself.

"I want to tell the panel how this affects my family and especially me and the difficulty there is I am trying to inject a bit of emotion into the process and understandably so NICE are trying to take the emotion out and look at the pure facts. The difficulty is that there tends to be a mismatch of what people's expectations are." [Patient 1]

3.5. OTHER FINDINGS

3.5.1. Time

The rationale for the creation of the STA process was the requirement for the Institute to issue guidance earlier than would be the case under the MTA process. Whilst comparisons with MTA are not within the scope of this report, it is useful to describe the duration of the STAs observed as part of this project and to report the issues relating to time factors in the MTA process that were raised in interviews.

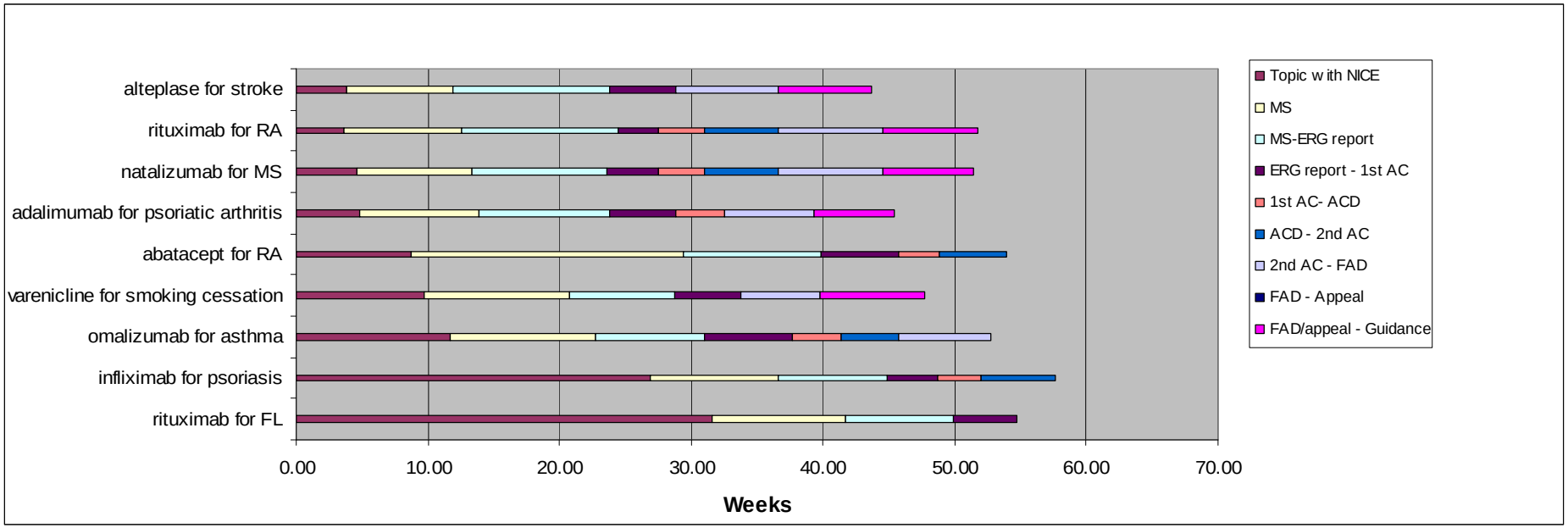
Figure 1 shows the time taken, in weeks, for each stage of the STA process for each of the topics selected as part of this review. The average time from referral of a topic to NICE to the publication of guidance is 49 weeks across the 5 STAs for which guidance had been published at the time of writing. In the cases of alteplase for stroke and varenicline for smoking cessation, where no ACD was issued, this was 44 and 48 weeks respectively. Interestingly, it was suggested in interviews that the reason the

appraisal of alteplase was so straightforward was because the product has been on the market for 4 years, had been though appraisal by SMC which had improved the quality of the manufacturer submission and has gained support from clinicians from its use in practice. The three of these STAs for which an ACD was issued lasted 51-52 weeks.

From the point at which the manufacturer submission begins, the time to issue guidance is an average 44weeks. For alteplase for stroke, this was 40 weeks and for varenicline for smoking cessation this was 38 weeks (compared to the 32 weeks cited in the STA process guide). For the three other STAs, where an ACD was issued, the duration of the process was 46-48 weeks (compared to 39 weeks cited in the STA process guide). None of these technologies have been the subject of an appeal. The duration of the only STA where the NICE appraisal process is tracking the licensing of the technology (abatacept for RA) is currently 57 weeks from the referral of the topic to NICE and 48 weeks from the start of the manufacturer submission. As can be seen in Figure 1, the period for the manufacturer submission has been extensive in this instance due to delays in the licensing process.

Therefore, within the cases examined as part of this review, the operation of the STA process is slightly slower than the benchmark identified in the process guide. The causes of these delays may be varied and not within the control of the institute. For example, since the Christmas holidays fell within the process for several of these appraisals there is likely to be some additional time required. The licensing process is at least one relevant factor that the Institute does not have under its control. Nevertheless, the end of the process which is relevant to the NHS and other stakeholders is the issuing of guidance. The cause of delays must be considered, whether or not these are factors within the control of the Institute, when assessing how STA currently operates and how potential changes may impact on the length of time it takes for the Institute to issue guidance.

Figure 1: Duration of selected STAs from time of referral to NICE



Many respondents suggested that the feasibility of producing an independent submission within comparable timelines to the STA process should be considered. Common to each of these suggestions was the proposal that whilst the time required to produce the independent submission could not be shortened from the current approximate 24 weeks, other aspects of the process could be speeded up or run concurrently.

> *"The difficulty with the MTA and the timelines in the MTA is not to delays within the group, it is delays from when topics are identified to when they are approved by the DoH till when they actually get scheduled by NICE. So it wasn't the groups holding up the topics it was factors that were slow in that process." [ERG member 3]*

> *"There is a lot of fluff on either end [of the appraisal process] that is just wasted time for NICE..... and that certainly could be cut down." [ERG member 2]*

> *"When the STA process was introduced it was supposed to be trimming things down...., it was all going to be a very much trimmed down process. I believe it has evolved back into the TAR process almost without solid evidence based input from a TAR team and I think that is wrong." [ERG member 2]*

> *"I don't think the overall process from having the initial scope through to the final guidance is much different (to MTA). I believe some of the early STAs are still rambling around somewhere." [ERG member 4]*

There were several occasions where it was pointed out how changes to schedules, however small, and particularly if not communicated to the relevant parties can cause substantial difficulties. Manufacturers cited instances where release of ACD and FAD documentation were delayed for a few days by the Institute, without consultation, and stressed the difficulties this can cause for them where meetings involving colleagues travelling from overseas are scheduled around these dates. There was a feeling that

delays to the process from the Institute are particularly frustrating when timelines are so strictly enforced for submissions from manufacturers and ERGs.

3.5.2. Sustainability of the process for ERGs

ERGs consist of academics based in UK universities and there are a number of potential tensions that the current STA process places on these groups. These tensions are potentially important for the process as a whole if there is an expectation that reviews will continue to be performed by these organisations and if there is no suitable alternative.

Firstly, unlike the assessment reports produced under the MTA programme, there is little scope for original, publishable output from the production of ERG reports. In smaller assessment groups, and with a greater STA workload from the Institute, the pressure to "publish or perish" could have serious conflicts with the ability to recruit and retain appropriately qualified individuals to undertake these reviews.

> *"..you won't get any career progression and it has to be senior staff." [ERG member 1]*

Secondly, ERGs have indicated that the STA is much less rewarding at a personal level and much more stressful compared to MTA.

> *"..you get no publications, its very stressful because you don't have time. One of the things people like about working in health technology assessment, you can take your time to do it right and build a model that makes sense and this is too frenetic." [ERG member 1]*

> *"We have to go along [to the AC meeting] prepared to say 'sorry we don't know the answer to that', which sometimes is a change for the team who normally go along having spent 9/12 months on a topic and feeling comfortable about most of the ins and outs….The ERG process is almost a consultancy/peer review thing." [ERG member 2]*

Thirdly, the contractual basis for provision of ERG reports was consistently cited as being an under-representation of the amount of work involved, despite the fact that this has been increased since the start of STA. The extent to which current arrangements undervalue the work provided by ERGs relates to the points raised in section 3.2.1 above.

> *"if they simply want the critique then it is sustainable for us to critique the submissions, send it back and tell them what's missing. If we are requested to continue to put into the process the same amount we have over the last ones…we would have to do some thinking about that." [ERG member 3]*

3.5.3. Scoping workshops

Scoping workshops did not occur for all STAs included in this review. Manufacturers were generally favourable of these where they did occur. However, because these meetings include other stakeholders, potentially including comparator manufacturers, their value can be limited. A submitting manufacturer is unwilling to disclose many details in this setting but it was felt that confidential discussions with the Institute and possibly the ERGs at this stage can be extremely beneficial.

> *"I think that confidential discussions at the beginning would make things so much easier and smoother and to miss that out or not to have had that with the manufacturer I think they are missing out on a lot of information which would help right at the beginning." [Manufacturer 1]*

3.5.4. Consultation prior to the first AC meeting

Both manufacturers suggested that because they do not see the ERG report prior to the first AC meeting, an opportunity for clarifications is missed. There may be instances of misunderstandings and this stage would provide an opportunity to rectify these. However, this would clearly have implications for timescales although there may be occasion where this might save time later in the process.

3.5.5. Other issues

The pre-meeting briefing was cited as an extremely constructive component of the process by a large number of interviewees representing all stakeholders. One ERG group raised concerns about inaccuracies in this document given that it is such a key document.

STA AC meetings centre on a presentation by the NICE technical lead and the importance of this presentation was highlighted by several interviewees. However, the AC can be a daunting arena to present and this is magnified for technical leads that have little time to become confident with the clinical issues and may be relatively junior or inexperienced staff.

> *"I think the technical lead is in the same position as the TAR team, the ERG have not really had the opportunity in the technology and the condition and maybe find themselves struggling a little bit." [ERG member 5]*

4. SUMMARY AND IMPLICATIONS

This review has tracked five STAs in significant detail, and five others to a lesser degree, in order to gain insights into how the current process operates using the overarching themes of methodological robustness, transparency and inclusiveness.

4.1. LIMITATIONS

Comparisons with the NICE MTA process are not part of this review. The authors have not observed AC meetings where technologies that are being appraised using MTA are considered, nor has the evidence or decisions from MTA been reviewed. Therefore, it is not generally possible to be clear that issues observed are any different to those which would arise using a different process.

One element of the research was the use of postal surveys to ERGs, manufacturers and other stakeholders. These were designed to provide significant information on the themes of inclusiveness and transparency. However, only a very low number of useable responses have been received. Interviews form the other principal data source which provides information on these two themes. However, the study is lacking in its ability to report on these two themes.

In addition, STAs were selected on the basis of the dates on which they were being considered by the Institute. There are two reasons why this selection may not be fully representative of the types of technologies likely to be considered under this process. Firstly, STA was designed to permit guidance to be issued close to the time of licensing. However, only one STA considered in this review was for a technology tracking the licensing process (abatacept for rheumatoid arthritis). In fact, there have been suggestions that the most straightforward STAs are those which concern technologies that already have a history of use in the NHS. There is often less uncertainty surrounding these technologies due both to the quantity of published evidence and clinical experience of using the technology. Secondly, whilst oncology topics dominated earlier waves of STAs, none of the topics we have considered in detail are in this field. STAs added to this review in order to address this concern have

provided relatively little information. The STA of carmustine implants for glioma has been suspended and rituximab for follicular lymphoma is still in its early stages.

The report does not provide a de novo review of the methodological robustness of the manufacturer submission. We rely on the ERG reports as the principal source of evidence to provide this critique. In addition, the reliance on qualitative interviews takes place in a context where interviewees are aware of the process by which this report will be used by the Institute. There is therefore a greater potential for respondent sensitivity to influence their accounts than may be the case in many other research projects. Within the qualitative data there is a tendency to focus on those components of the process that respondents feel do not operate well. Therefore, there is not explicit comment on each stage of the process and there is a tendency to accentuate the negative rather than the positive elements of STA. In addition, given the selection of STAs where positive guidance was issued in relation to each of those technologies for which interviews were conducted, it is perhaps not surprising that manufacturers have relatively little to say about the process.

Due to the fact that the appraisal process for abatacept for rheumatoid arthritis is yet to conclude, we have been unable to conduct interviews with stakeholders or send out surveys in relation to this topic. With a technology so close to licensing, it is likely that there is substantial reliance on commercial in confidence material. How this impacts on the ability of stakeholders to understand how guidance has been developed has not been addressed because of the lack of interview and questionnaire responses.

Not all ACs have been observed as part of the review. Committee A has not dealt with any of the STAs selected for in-depth analysis. The potential for differences across these ACs may therefore have been lost in this project in favour of a case selection strategy that covered a range of ERGs, topics and manufacturers.

4.2. ISSUES FOR CONSIDERATION

The following issues are those that arise from the findings of this report and which may usefully be considered by the Institute and its advisors when considering changes

to the STA process. This is not intended to be an exhaustive list and are not intended to be considered as recommendations for changes.

- The issue of the burden of proof underpins the design of the STA process. The role of the manufacturer and the ERGs and the options available to the AC are driven by this issue. However, there is currently no explicit statement of where the burden of proof lies. The conclusion of the evidence identified in this report is that a view is emerging from the appeals panels that the burden remains with the Institute. The Institute should consider issuing an explicit statement about the burden of proof that is upheld at appeal.
- Many other issues for consideration can only be resolved once the issue of the burden of proof is clarified. Nevertheless, the Institute should consider revising the stated role of the ERGs in order to fulfil the requirements of the AC. This should consider the role of the ERG both in terms of content (in particular the extent to which critique of the manufacturer submission alone is sufficient) and the timescale of their involvement. Currently, ERG input can be required post ACD, particularly where a minded no is issued, and pre and post-appeal. However, there is no clear contractual arrangement to cover this additional work. Clarity around the role of the ERG may be required and consideration should be given to the potential legal challenges the Institute may face if there is variation from these arrangements.
- The potential for basing the STA process on a manufacturer submission accompanied by an independent critique may require reconsideration, particularly in the light of the issue of the burden of proof. In particular, some would suggest that the absence of an independent submission is not compatible with a process which does not place the burden of proof on the manufacturer. The Institute should consider this point in revising the STA process.
- The requirement for the Institute to issue guidance quickly underpins the creation of STA. The extent to which changes to the process will impinge on these performance measures, and how external pressures on the Institute might view these changes, must be considered. In particular, in considering the feasibility of an independent submission, their may be components of the existing process that could be shortened or excluded in order to minimise the

time delay this would inevitably have. The opportunity cost of limiting or eliminating particular components of the process must be considered. A wider range of STAs than have been considered in this report should be used to judge the timelines the process currently operates to and compared with those operating under the MTA process.

- In the absence of a full independent submission, consideration should be given to the issue of how the Institute deals with uncertainty, poor quality or incomplete manufacturer submissions. An important element to this may be the willingness to reject technologies for these reasons even though it is not possible for the Institute to demonstrate they are unlikely to be cost effective. In this situation, it may be important to establish a link with the MTA process. The current process guide does refer to the potential for MTA as part of the appraisal review but lacks detail of the criteria used to make this decision and implies that this would be a longer term consideration as part of NICE's updating process rather than an immediate referral as the result of a submission to STA that is not considered complete.
- There may be value in involving the lead members of the AC in the presentations at the committee meetings.
- Both the manufacturer and ERG templates require revision. The manufacturer template currently is repetitious and this makes it difficult to present the evidence in a clear, concise and transparent fashion.
- Consideration should be given to the role of software that is not currently recommended in the methods guides. There are instances where such software is more appropriate for the types of cost effectiveness models required yet not all ERGs have expertise in all types of software.

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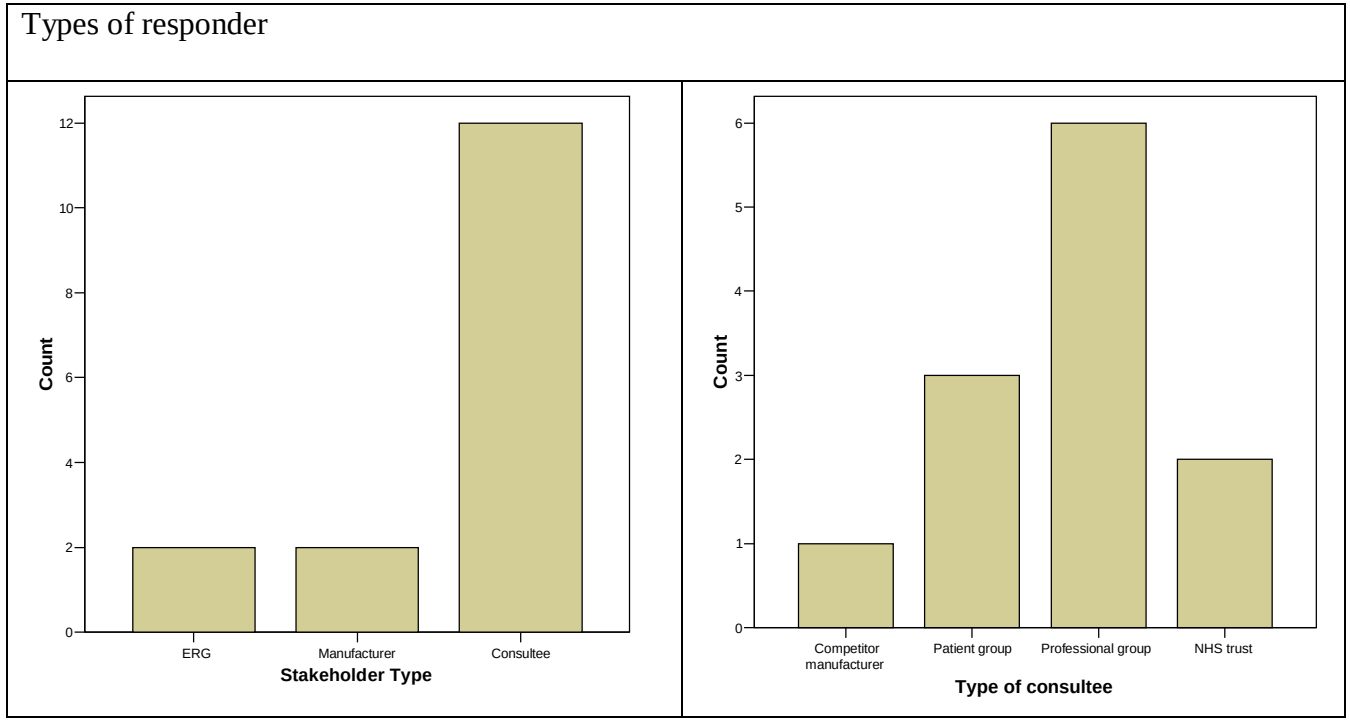
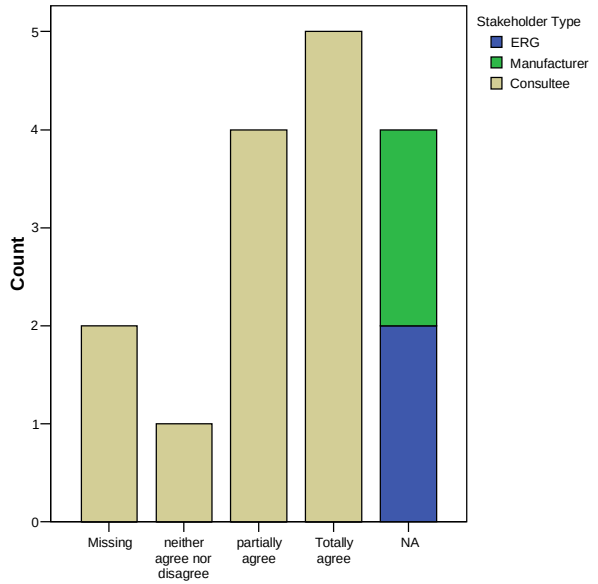
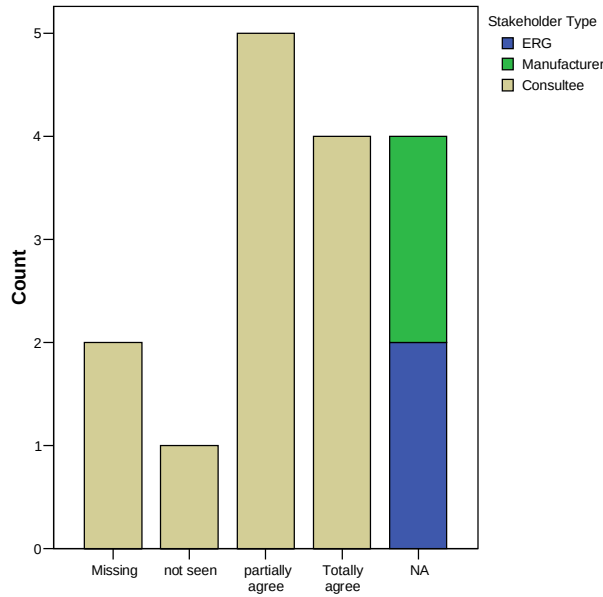
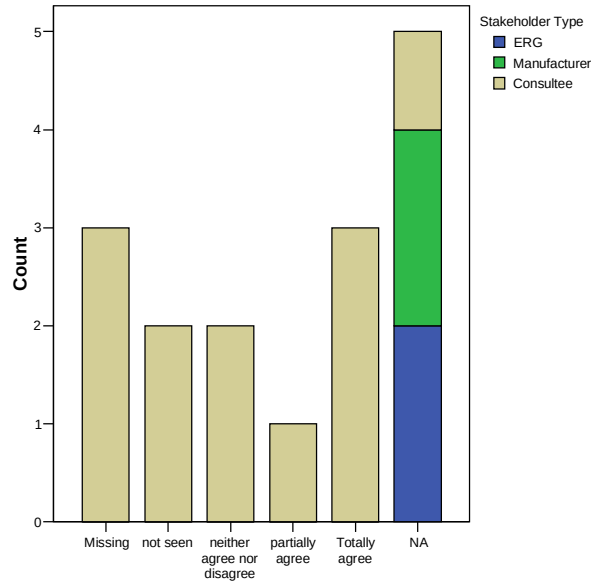
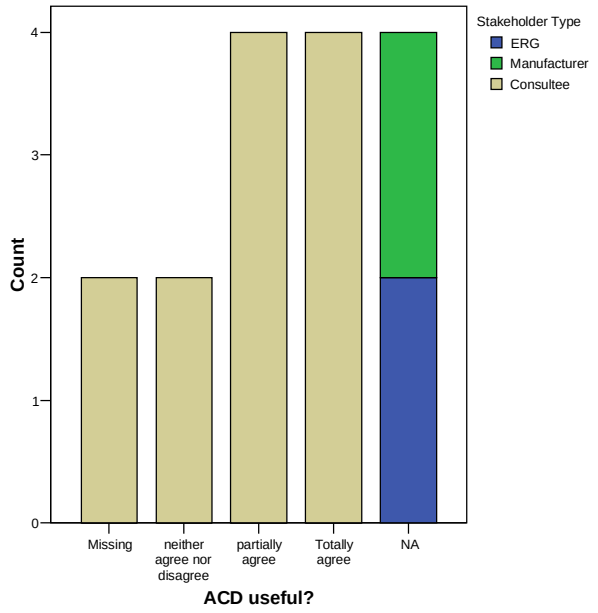
Appendix 1: Results of surveys

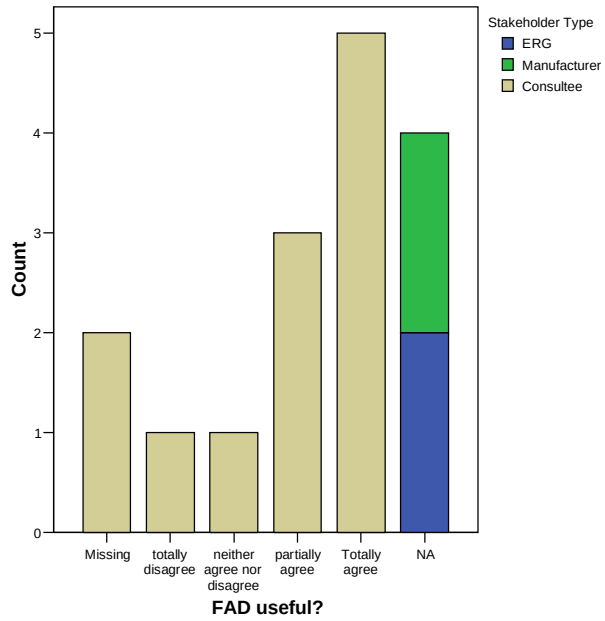




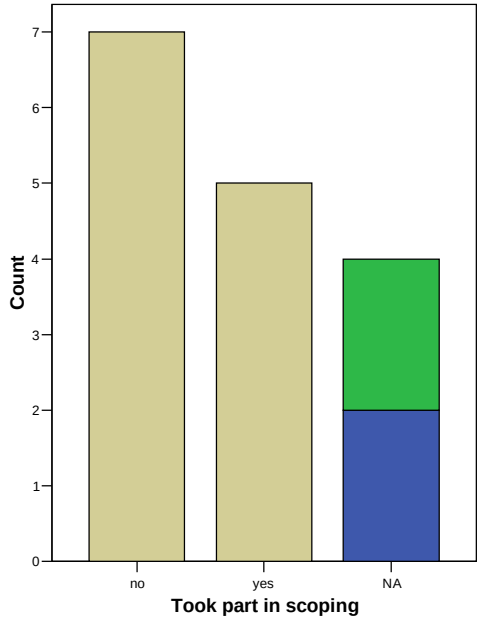


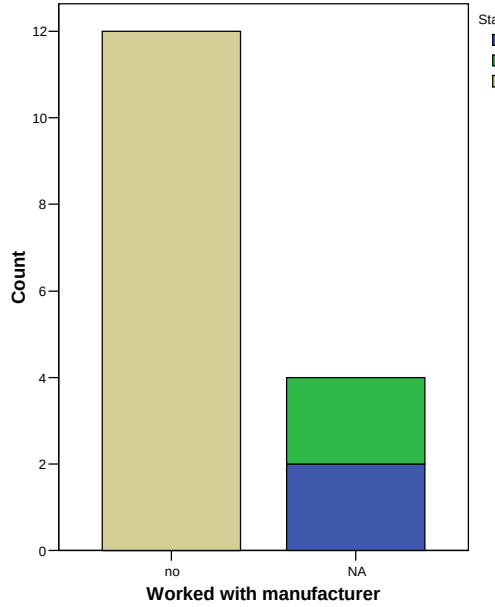


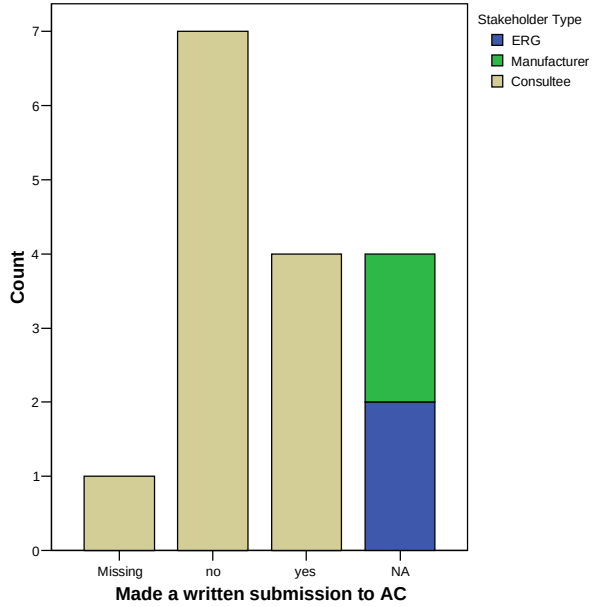


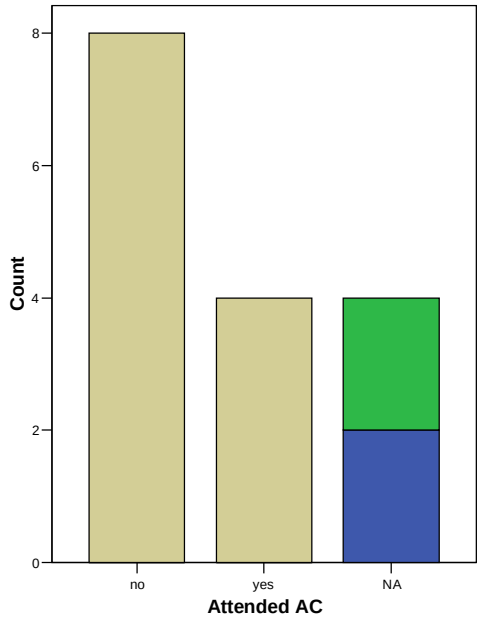


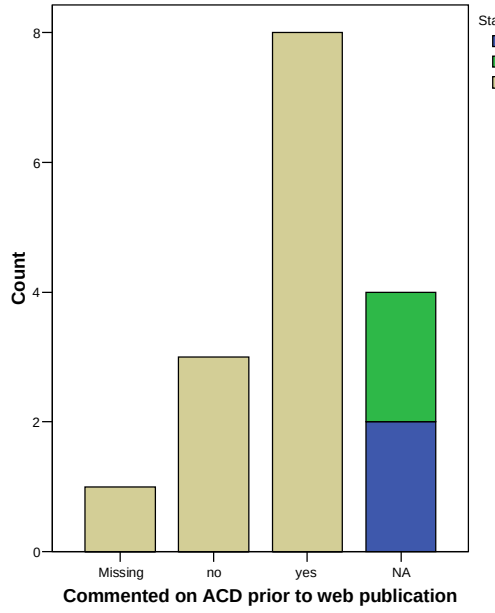
Value of documents to consultees/stakeholders

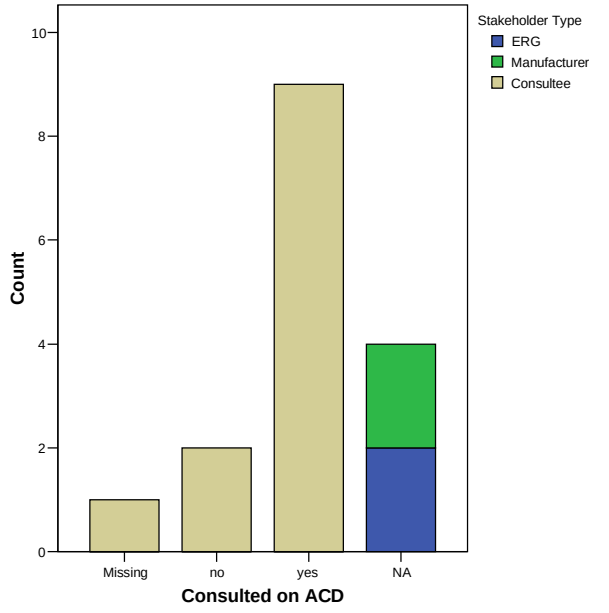






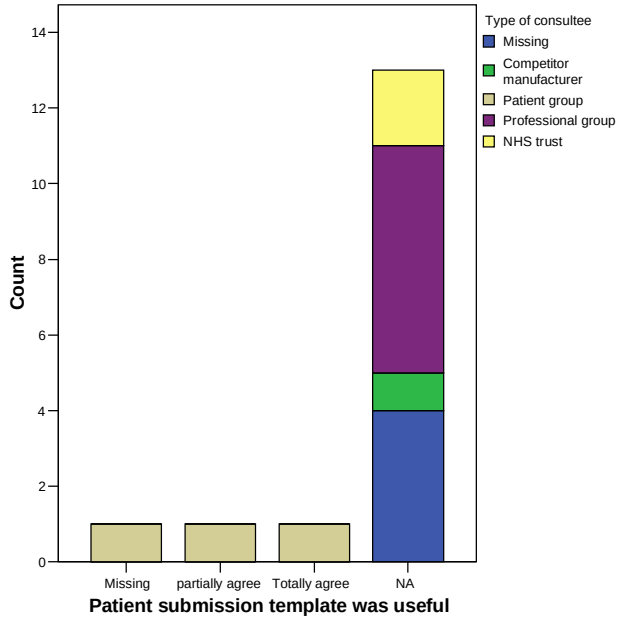


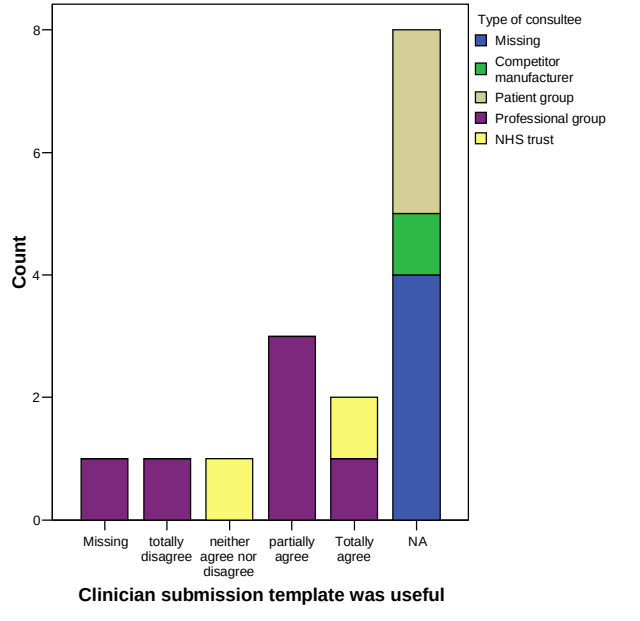


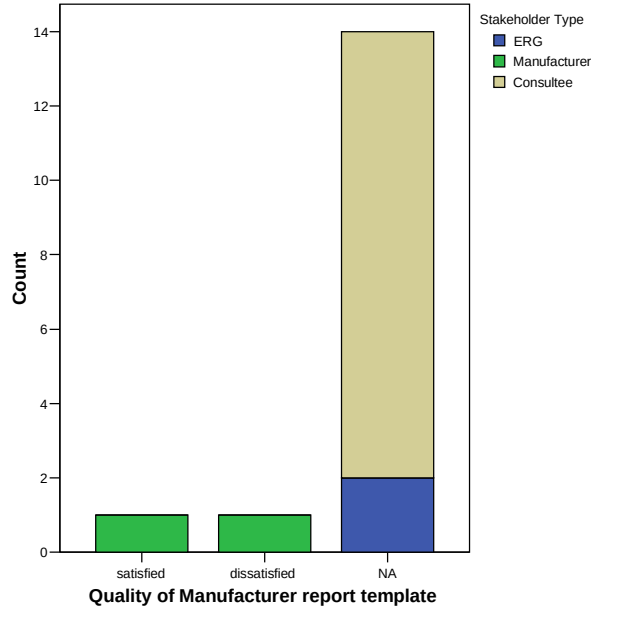


My organisation took part in ….

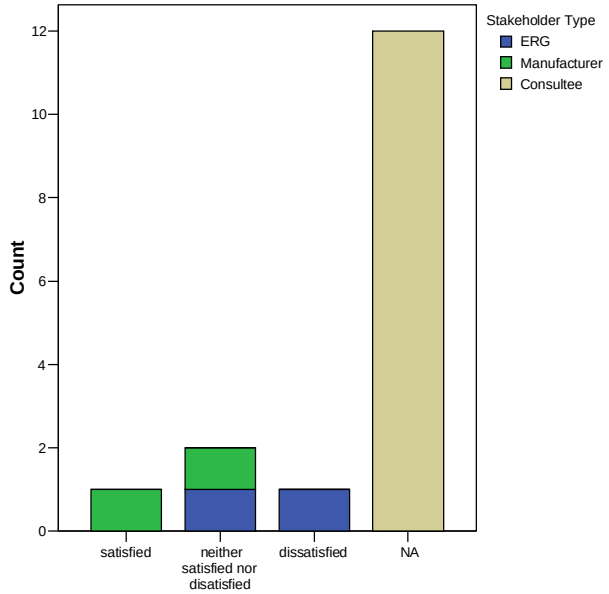
Value of submission templates

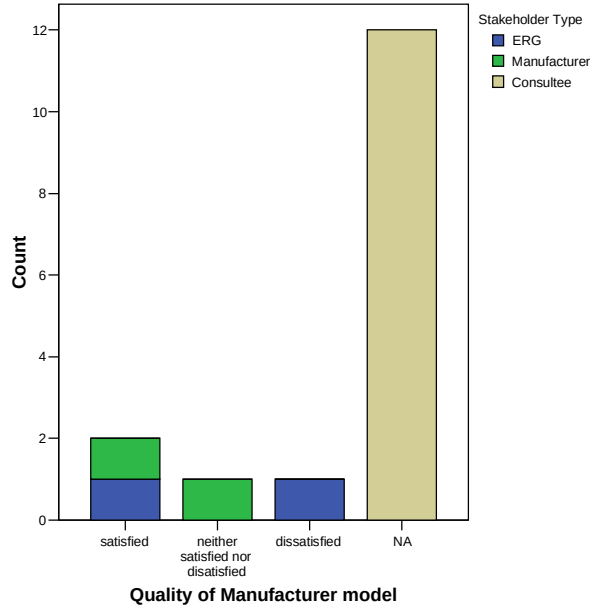


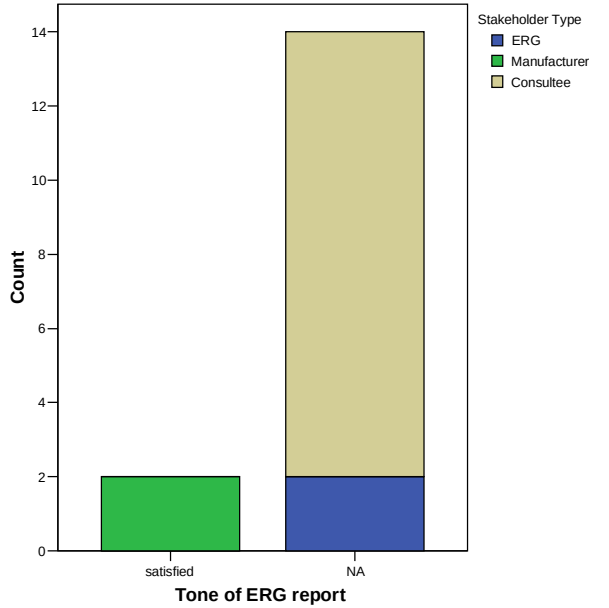


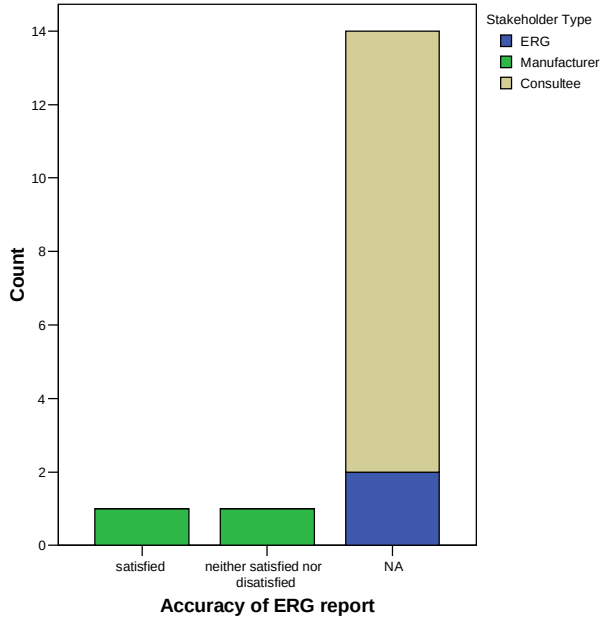


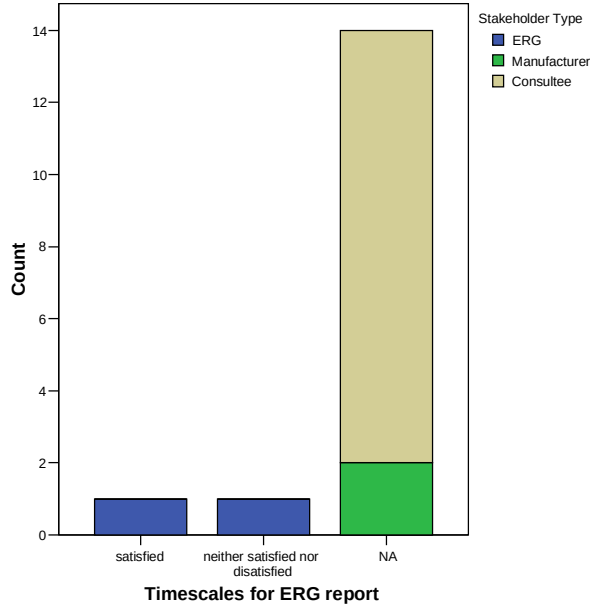
Manufacturer and ERG views on process

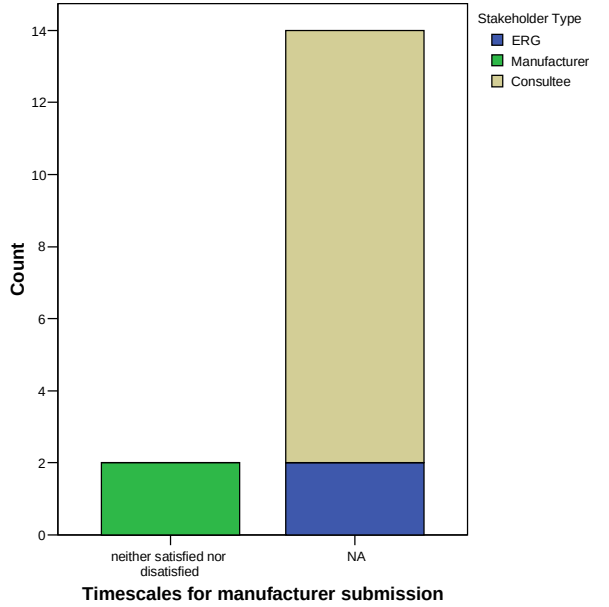


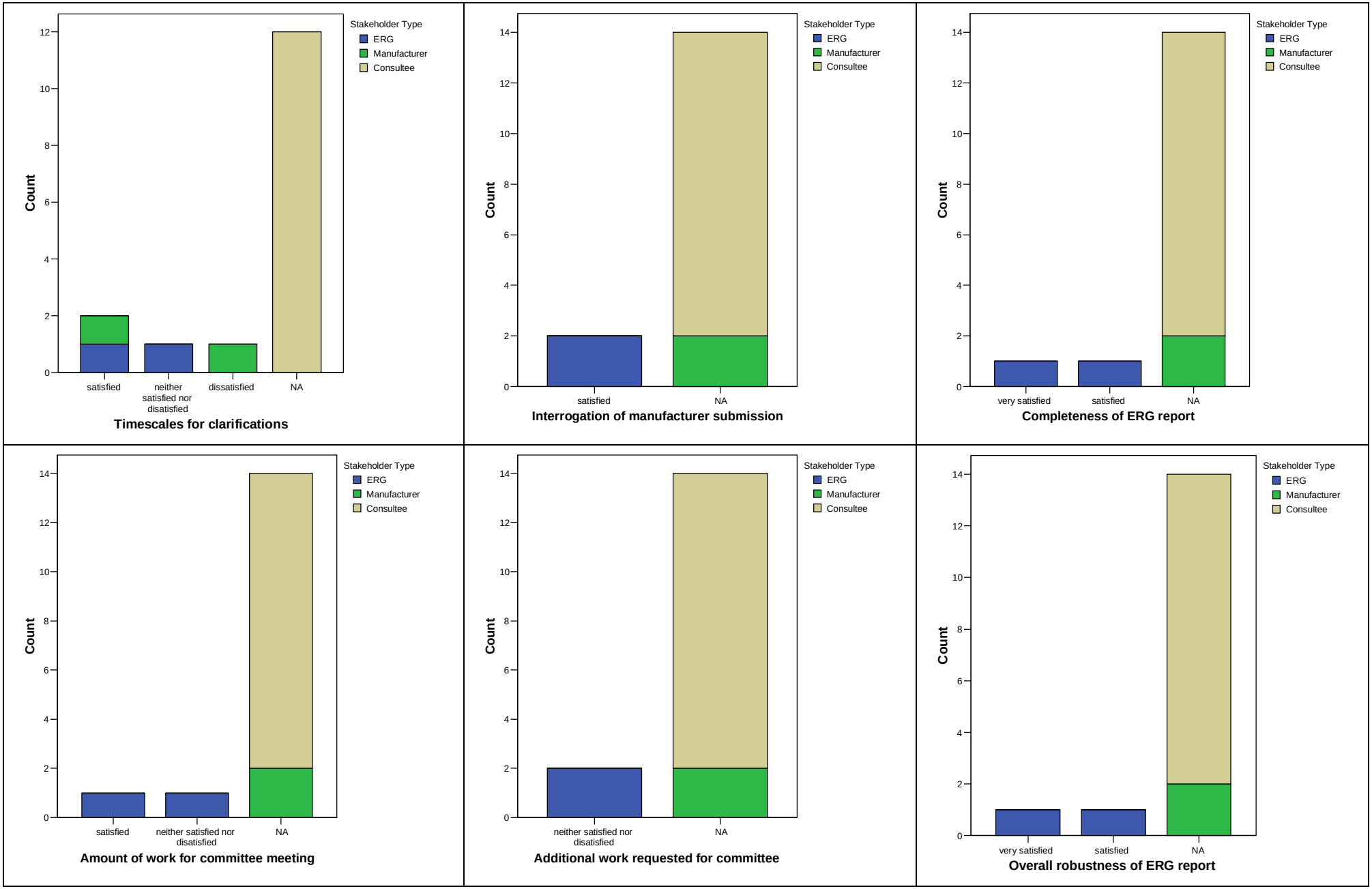








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ERG
Manufacturer
Consultee
Count
satisfied
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dissatisfied
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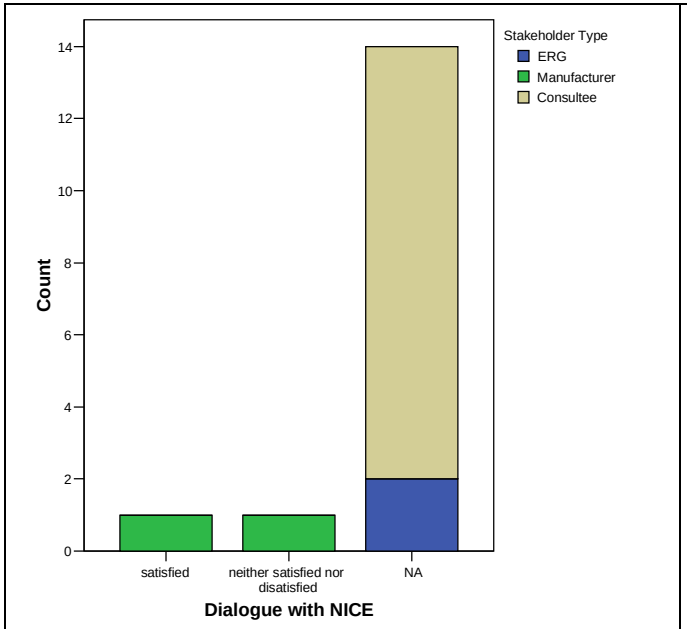
Timescales for clarifications
Interrogation of manufacturer submission
very satisfied
Completeness of ERG report
Amount of work for committee meeting
Additional work requested for committee
Overall robustness of ERG report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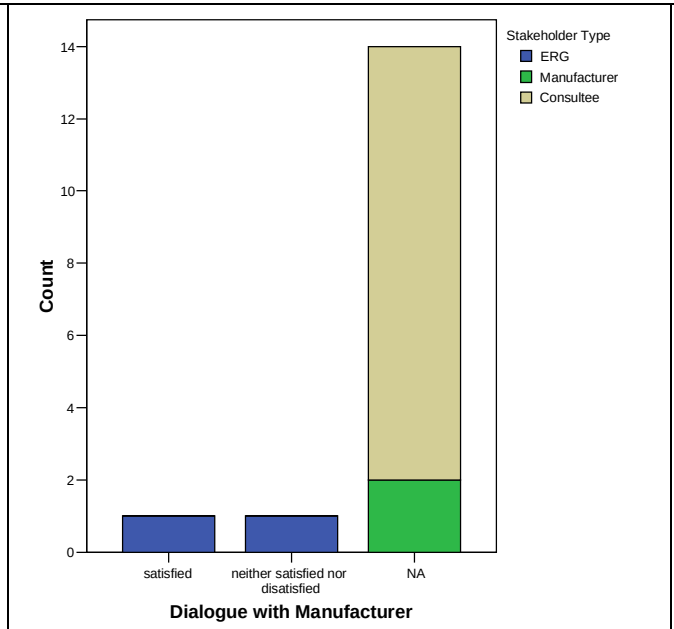
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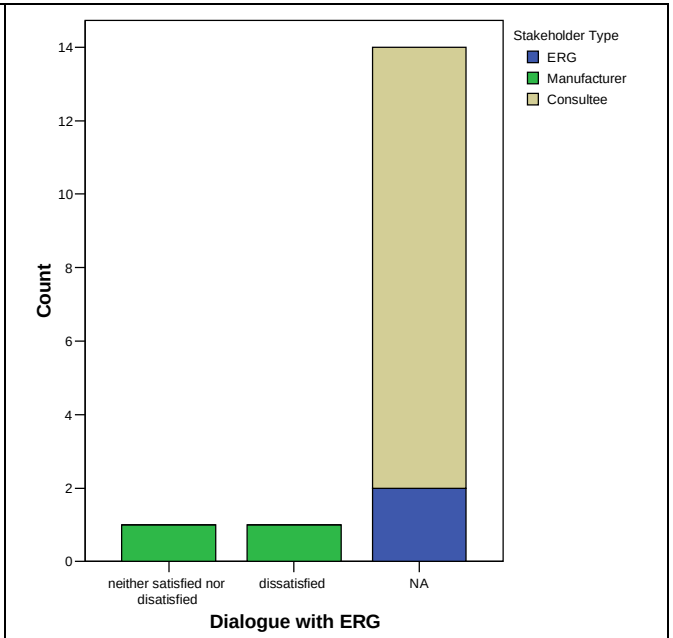
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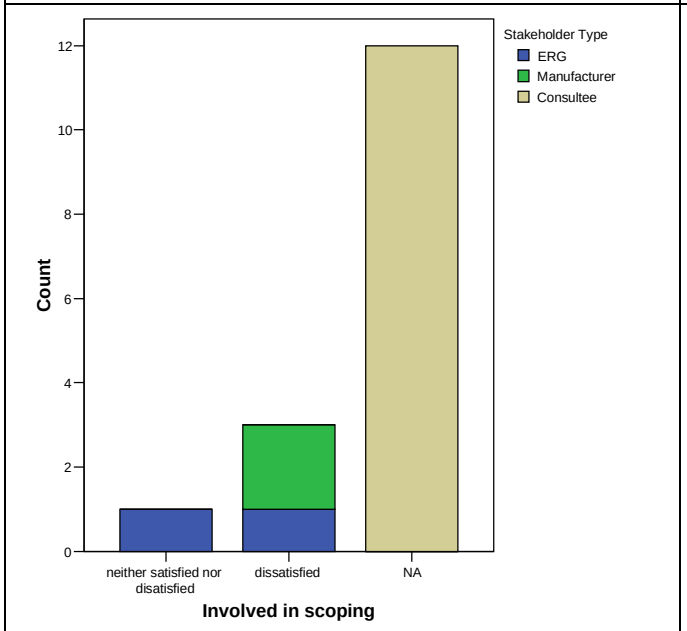
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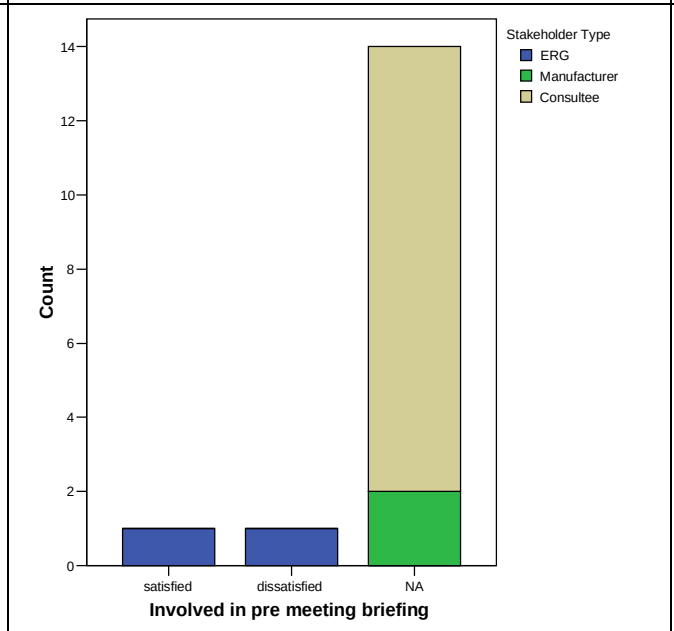
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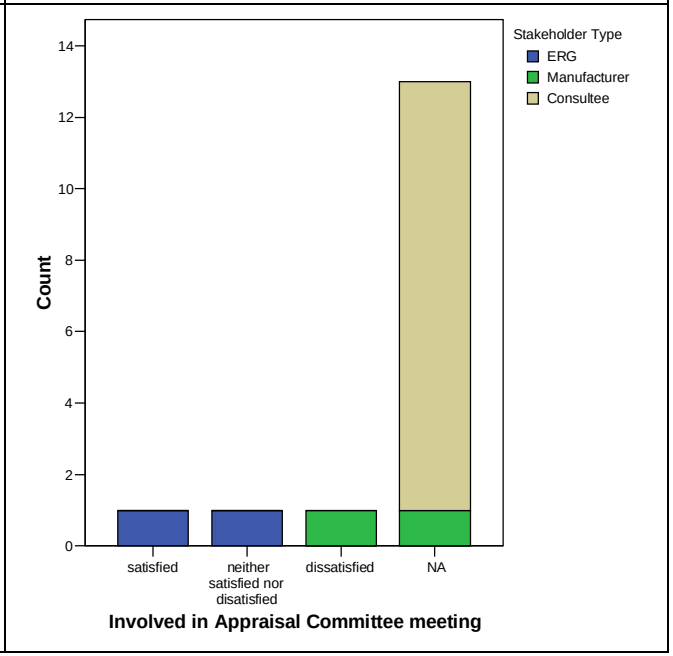
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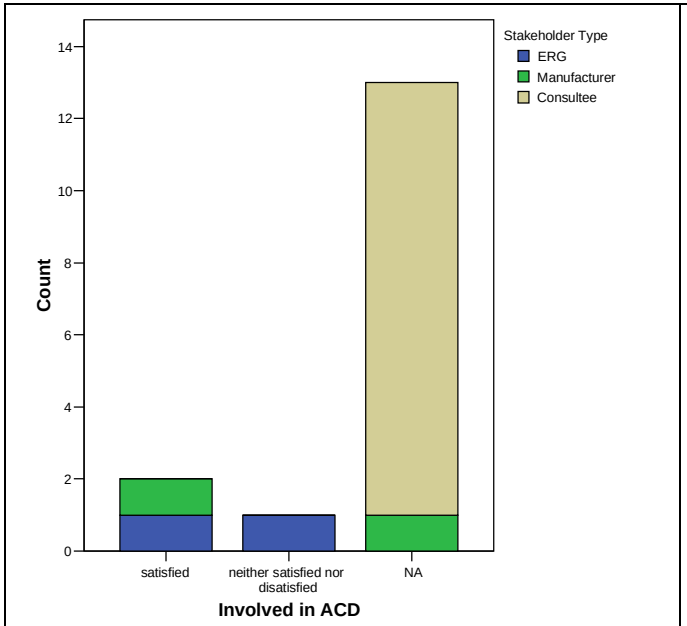
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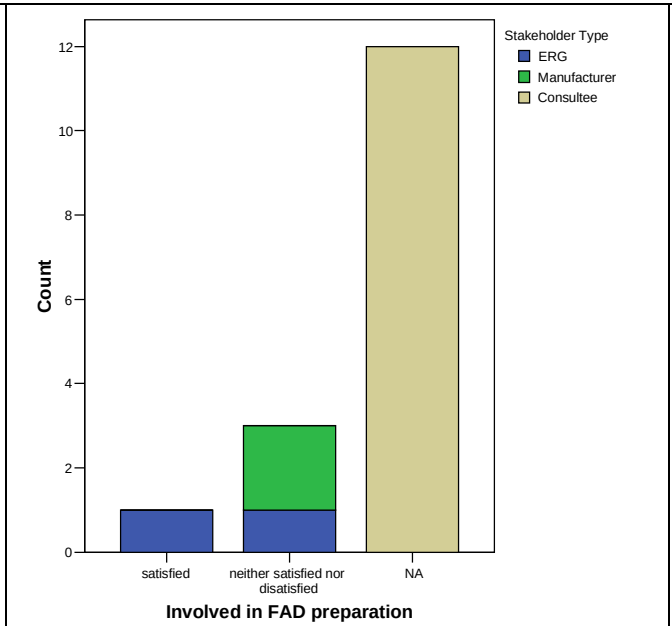
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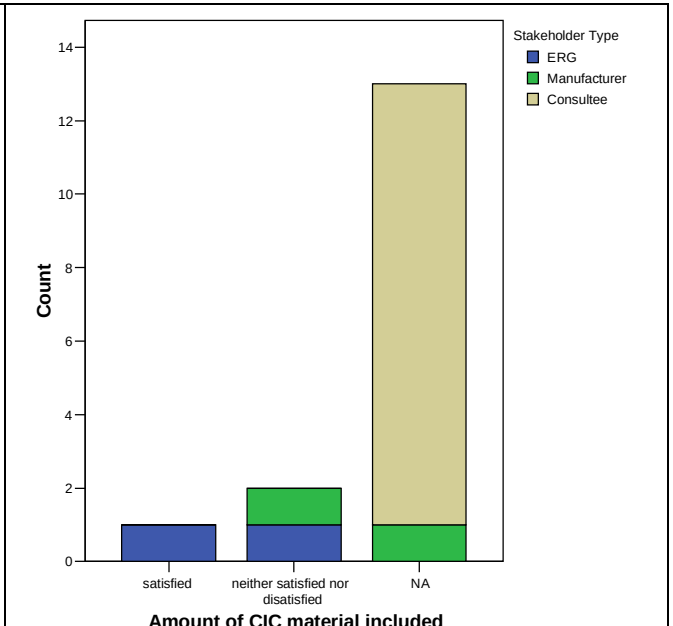
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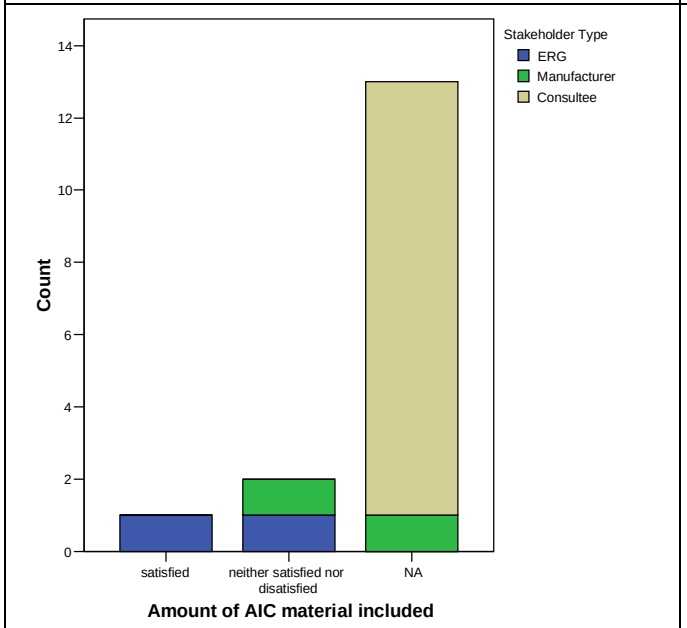
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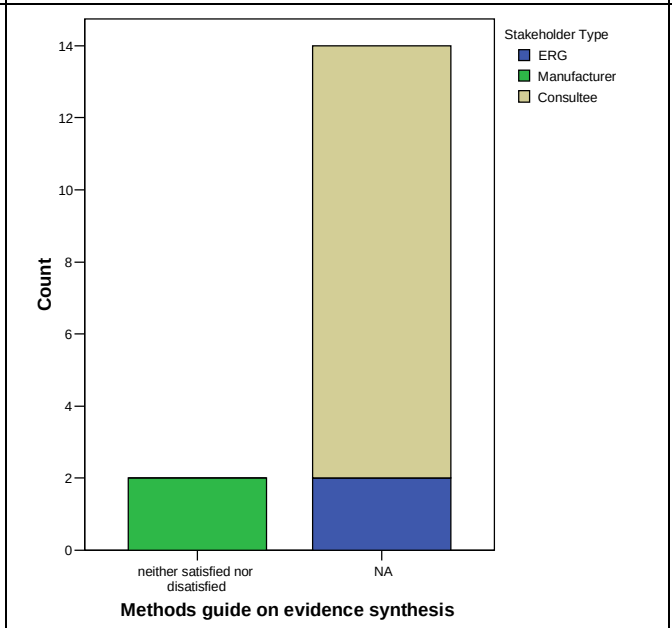
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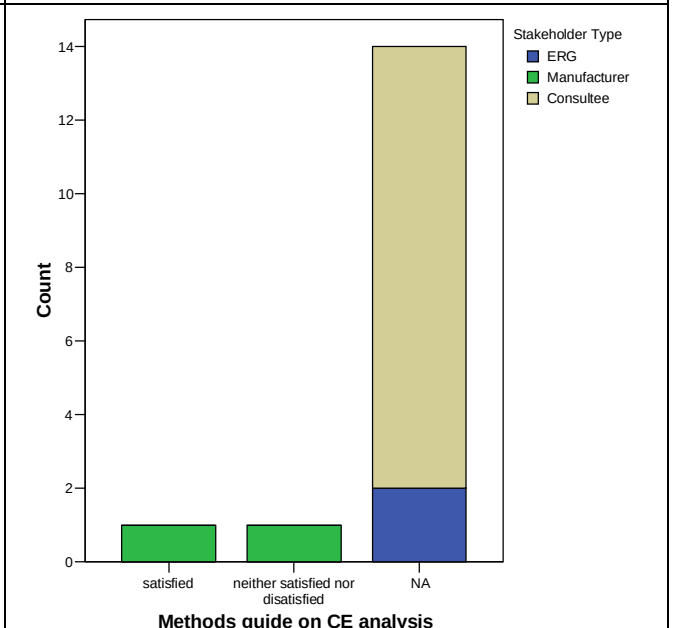
Manufacturer
Consultee
Count
neither satisfied nor disatisfied
NA
Methods guide on evidence synthesis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Consultee
Count
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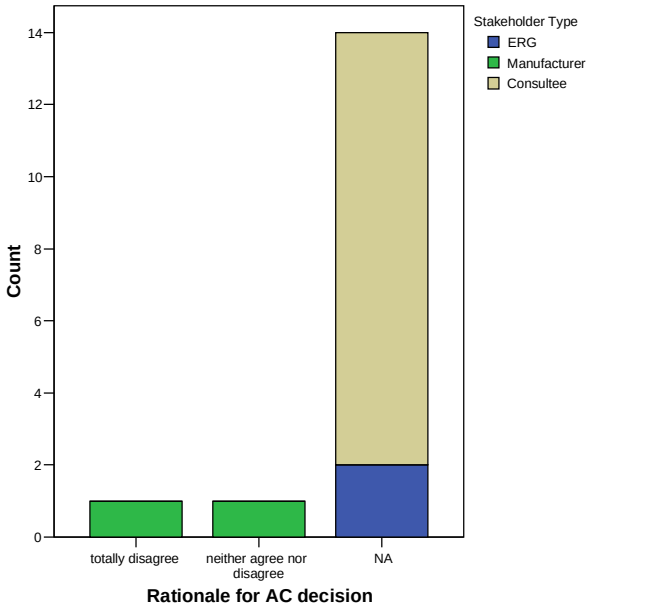
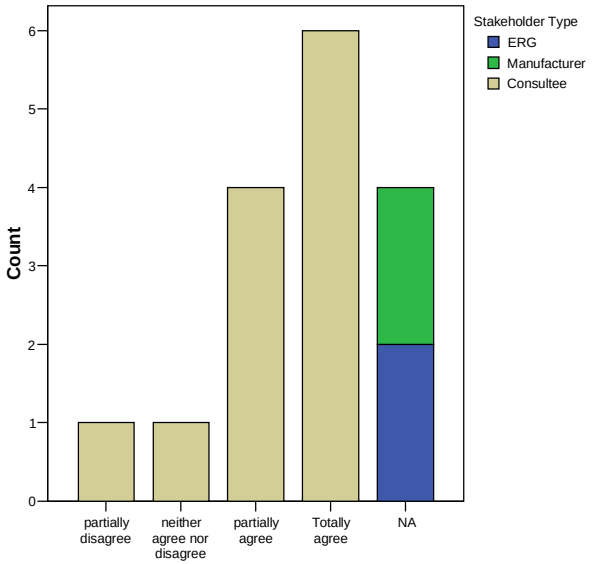
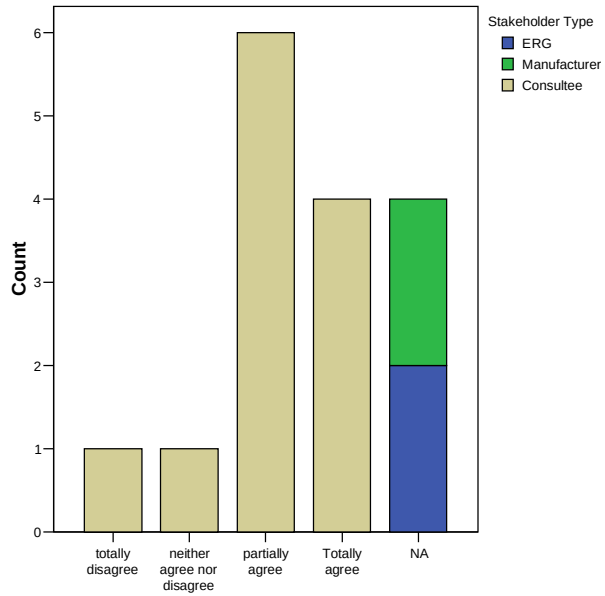
neither satisfied nor disatisfied
NA
Methods guide on CE analysis

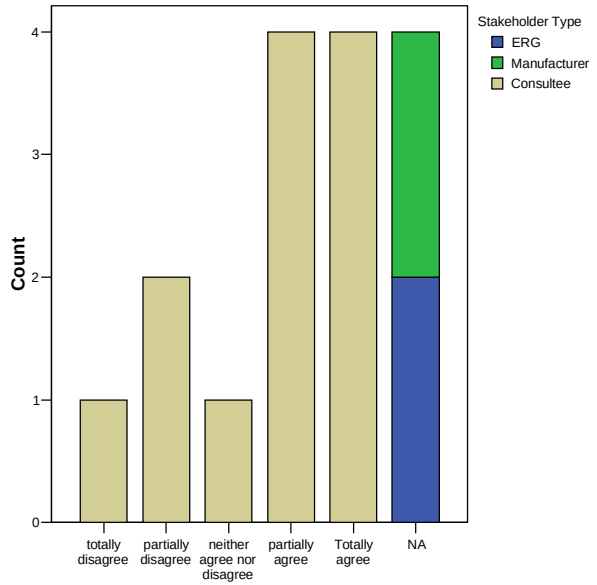

Stakeholder Type
ERG
Manufacturer
Consultee
Count
14
12
10
8
6
4
2
0
totally disagree
neither agree nor disagree
NA
Rationale for AC decision



It is clear what evidence was presented to the AC

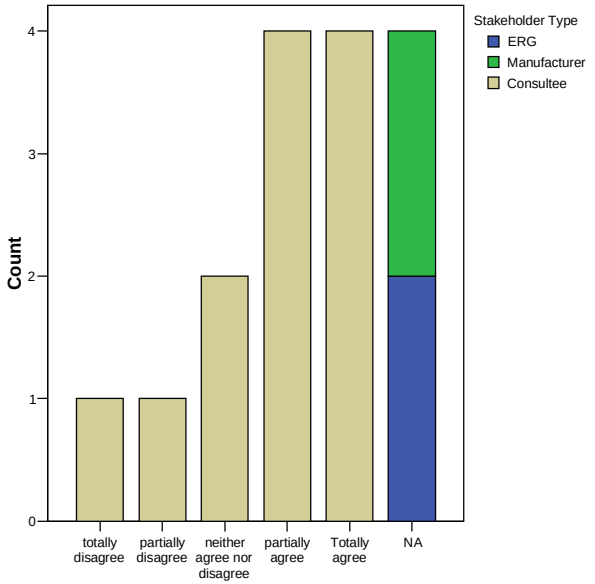


It is clear how evidence was interpreted

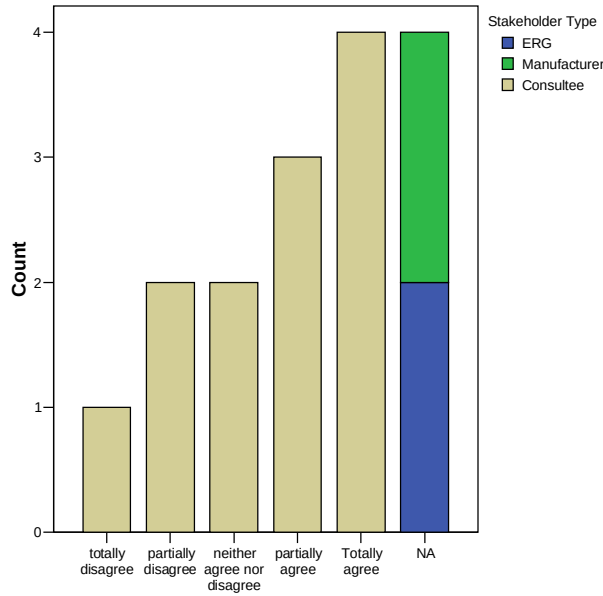


It is clear how it led to the decision

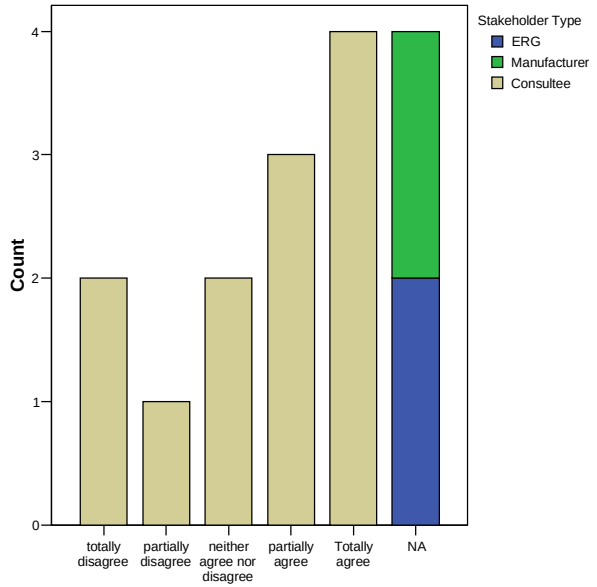
The Appraisal considered…



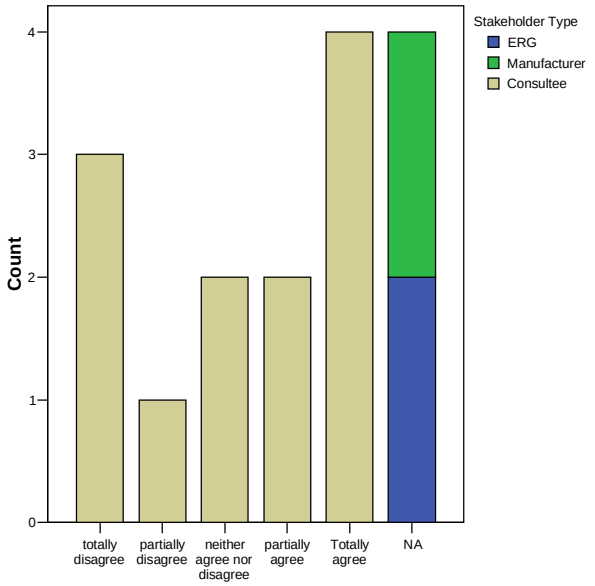
the relevant clinical problem for the NHS



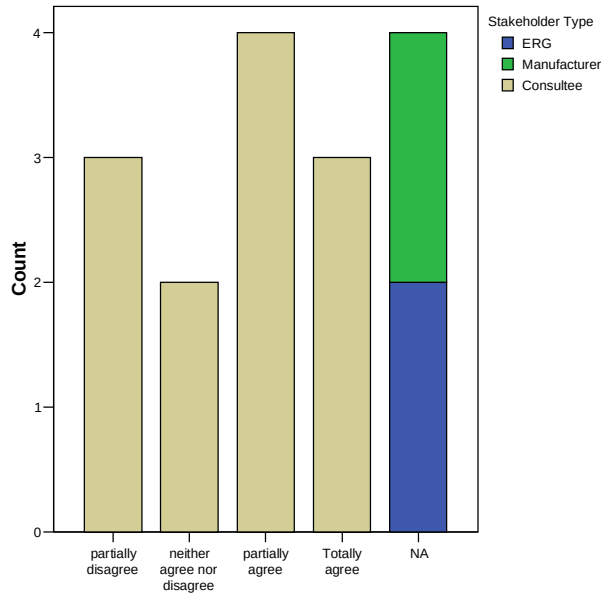
the relevant population



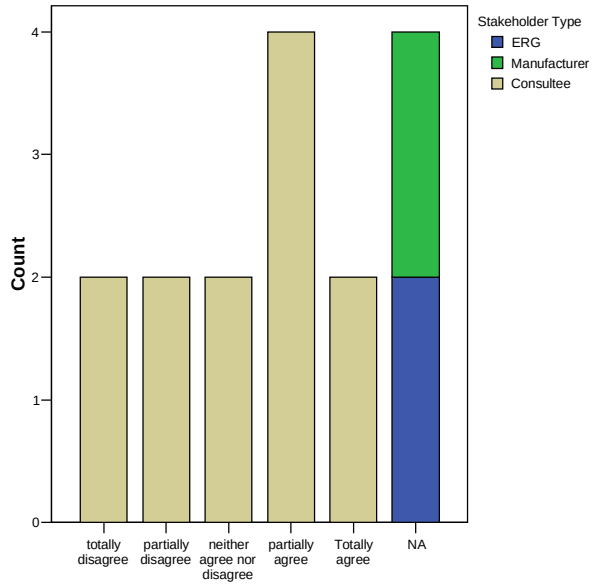
the way that the technology is used in the NHS



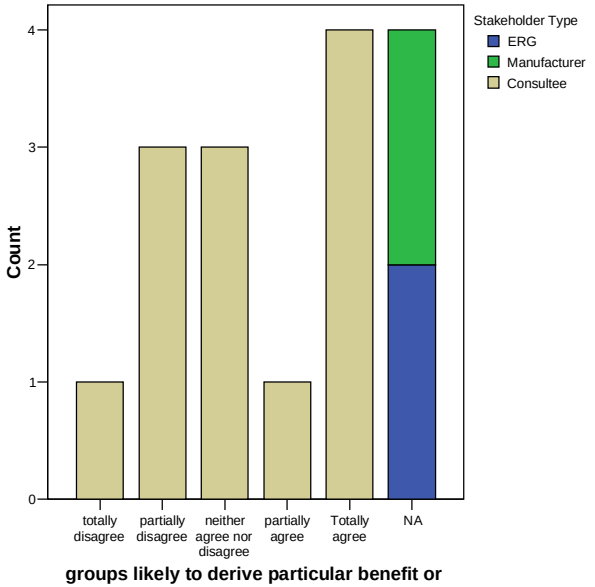
other appropriate treatments



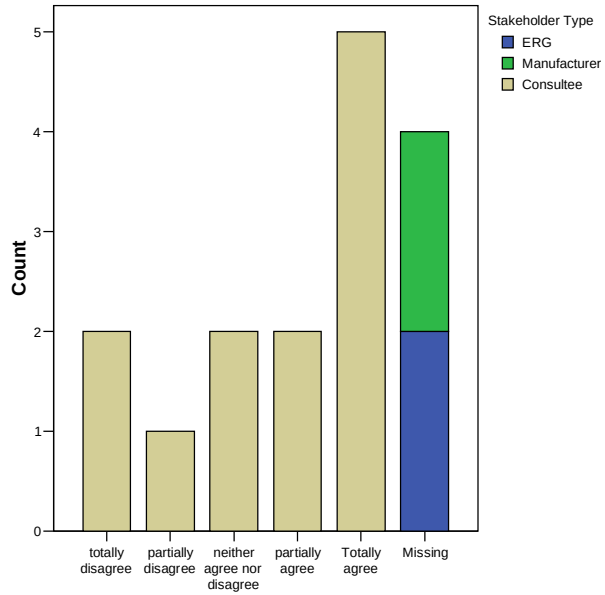
relevant outcomes



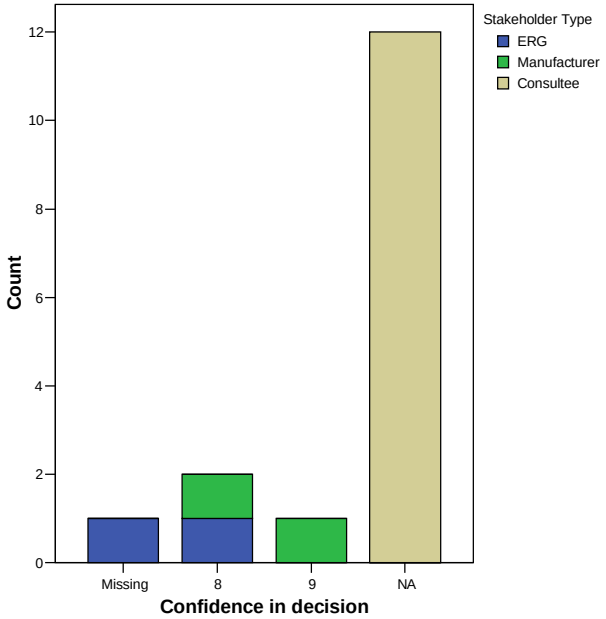
realistic timescale for costs and benefits

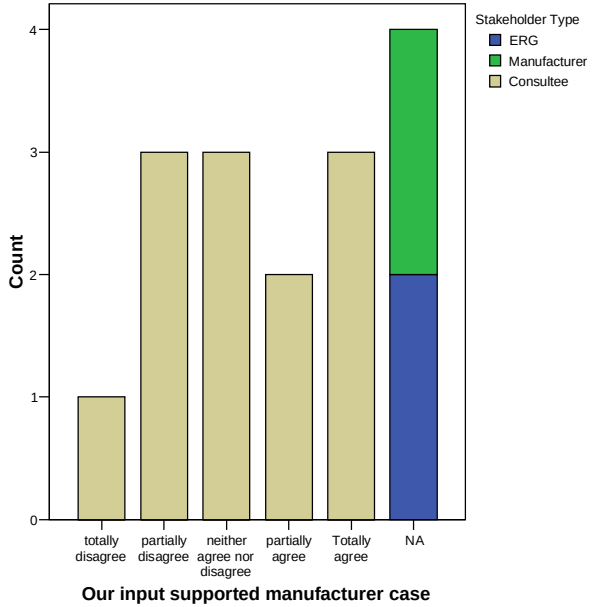


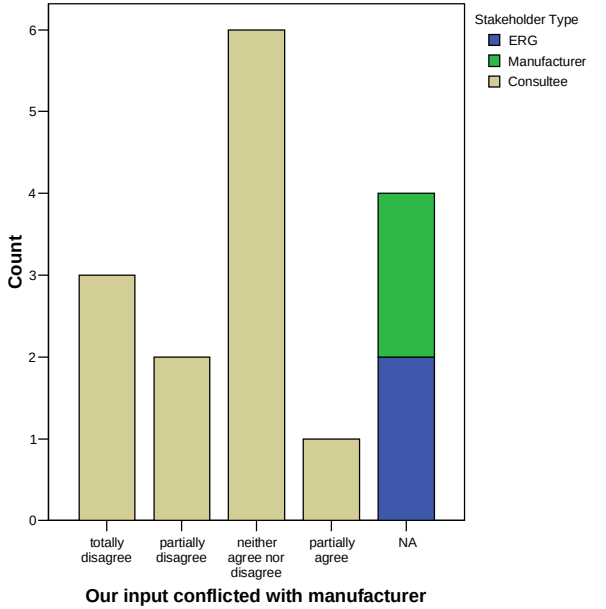
groups likely to derive particular benefit or harm

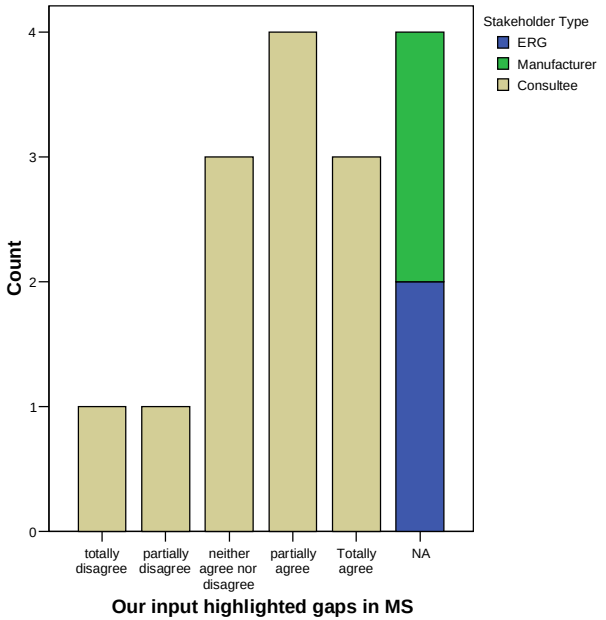


All available evidence


Stakeholder Type
ERG
Manufacturer
Consultee
Count
12
10
8
6
4
2
0
Missing
8
9
NA
Confidence in decision


Stakeholder Type
ERG
Manufacturer
Consultee
Count
4
3
2
1
0
totally disagree
partially disagree
neither agree nor disagree
partially agree
Totally agree
NA
Our input supported manufacturer case


Stakeholder Type
ERG
Manufacturer
Consultee
Count
6
5
4
3
2
1
0
totally disagree
partially disagree
neither agree nor disagree
partially agree
NA
Our input conflicted with manufacturer


Stakeholder Type
ERG
Manufacturer
Consultee
Count
4
3
2
1
0
totally disagree
partially disagree
neither agree nor disagree
partially agree
Totally agree
NA
Our input highlighted gaps in MS