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**Title:**

What is the evidence from past National Institute of Health and Care Excellence (NICE) Single Technology Appraisals (STAs) regarding company submissions with base-case ICERs of less than £10,000 per QALY?

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## **Abstract**

### **Objectives:**

The National Institute for Health and Care Excellence (NICE) has recently proposed that company submissions with a base-case ICER of less than £10,000 per QALY might be eligible for a 'fast track' appraisal. The objective of this study was to explore outcomes relating to previously-conducted STAs with base-case ICERs of less than £10,000 per QALY.

### **Methods:**

All STAs with published guidance from 2009 to 2016 were included; those with company base-case ICERs of less than £10,000 per QALY were identified and analysed. A secondary analysis was also conducted for those with a company base-case ICER of £10,000-£15,000 per QALY. Relevant data were extracted and presented in a narrative and tables.

### **Results:**

In total, 15% (26/171) of STAs included a company submission with a base-case ICER of less than £10,000 per QALY. Of these, 73% (19/26) were given positive recommendations after the first Appraisal Committee (AC), while 27% (7/26) were initially given a Minded No before receiving a positive recommendation in the Final Appraisal Determination, albeit with restricted recommendations for three technologies. Five STAs had company base-case ICERs of £10,000-£15,000 per QALY and all received a positive recommendation after the first AC.

### **Conclusions:**

The majority of previous STAs with a company base-case ICER of £10,000 or even £15,000 per QALY received a positive recommendation after the first AC, but a number proved more complicated and required detailed appraisal, which influenced the final recommendation. This finding might have implications for the proposed NICE 'fast track' process.

## **Introduction**

The National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) process has been in existence since 2005. The process is undertaken for a technology for a single indication; it is outlined in detail in the Guide to the Single Technology Appraisal Process[1] and includes the production of a submission by the company that manufactures the technology. The company's submission (CS) to NICE forms the principal source of evidence for decision making in the STA process. The CS is expected to contain an evaluation of the clinical effectiveness and cost-effectiveness of the technology using decision-analytic approaches outlined in the NICE Technology Appraisals Methods Guide[2]. The submission should also include an incremental cost effectiveness ratio (ICER), expressed as cost per Quality Adjusted Life-Year (QALY), as the measure of the technology's cost-effectiveness. An independent, academic Evidence Review Groups (ERG) is charged with the task of critically appraising the CS to identify strengths, weaknesses and gaps in the evidence presented. The ERG also undertakes exploratory analyses to explore uncertainties around the company's model and resulting ICERs[3, 4]. The ERG report, together with the company's submission, is considered by one of the four NICE Technology Appraisal Committees (ACs) in their deliberations. The findings of the committee are used to produce the Appraisal Consultation Document (ACD); after further considerations and a consultation period, a Final Appraisal Determination (FAD) is produced that results in NICE guidance. In some cases, only a FAD is produced, without the need for an ACD. Within these documents are listed a company's submitted base-case ICER (or range), the ERG's preferred ICER (or range), the AC's preferred ICERs, as well as the committee's recommendations. On the whole, technologies are recommended for reimbursement if their ICER does not exceed the generally-accepted NICE threshold of £20,000-£30,000 per QALY[2, 5], although there is evidence that this threshold might sometimes be higher, even for technologies that do not satisfy criteria for end-of-life or being 'highly-specialised'[6, 7].

Changes to the NICE STA process have recently been proposed following consultation[8]. One of the proposals, and the focus of this paper, is that a new 'fast track' form of appraisal, a variant of the standard appraisal process, might be applied when a company submits a base-case ICER of less than £10,000 per QALY[8]. According to the consultation document, the stated intention behind the proposal appears to be twofold: to reduce the time from a technology's approval by the European Medicines Agency to its being made available in the National Health Service (NHS) in England and Wales; and to reduce resource use by the companies and

NICE by conducting an abbreviated technology appraisal process (shorter, less extensive evidence review processes by ERGs and fewer AC meetings)[8]. It is worth noting that a second NICE consultation took place, which also proposed an ‘Accelerated Technology Appraisal’ process. This particular process was intended to ‘fast track’ treatments that were ‘likely to provide similar or greater health benefits at a similar or lower cost than technologies already recommended in technology appraisal guidance for the same indication’.[9] Following the consultation this was integrated into the FTA process, but it is not the subject of this paper.

This project was designed to explore how many STAs (2009-2016) had an original company base-case ICER of less than £10,000 per QALY and how many, after the full appraisal process, were recommended in the first ACD and in the FAD. It also assessed whether and by how much the ICER(s) preferred by the AC and stated in the ACD and in the FAD were different from the original company base-case ICER(s), especially if the ICER exceeded the generally-accepted NICE threshold of £20,000-£30,000 per QALY[2, 5]. This enabled an evidence-based assessment of the outcomes for previous STAs with company base-case ICERs of less than £10,000 per QALY.

The research therefore aimed to answer the following questions:

How many STAs had a company submitted base-case ICER of less than £10,000 per QALY, or the technology dominated its principal comparator?

- a. How many of these technologies received a positive recommendation in the ACD (or in the FAD, in those cases without an ACD)?
- b. How many of these technologies received a No or Minded No in the ACD?
- c. What reasons were given in the ACD for not recommending the technology?
- d. What was the final ICER and recommendation in the FAD?

A secondary analysis was also conducted on STAs with an original company base-case ICER of between £10,000 and £15,000 per QALY to determine if outcomes were any different for this group.

## **Methods**

A content analysis was undertaken of documents relating to all STAs conducted by NICE between 2009 and December 2016 by members of research teams from the University of Sheffield and the University of Liverpool. This study focuses on 2009 onwards because the STA process, after four years of development, had become largely standardised by this point[10]. A first screen was conducted to identify those STAs with a company base-case ICER of less than £10,000 per QALY, as reported in the first ACD (or FAD if there was no ACD). More extensive data were then extracted into a standard form from the ACD and FAD documents relating to these STAs. The data to be extracted included: Technology Appraisal (TA) number; title of STA; date of FAD; name of company; ERG; disease area; company base-case ICERs; AC-preferred ICERs in the ACD; ACD recommendation (and details); AC-preferred ICERs in the FAD; and the FAD recommendation (and details).

Data from the first 100 STAs with FADs had been collected for a previous project, which covered STAs from March 2009 to March 2014[3, 4, 6]. These data were extracted and checked by the two reviewers from the Sheffield team (CC, EK) and, in some instances, checked also by a member of the Liverpool team (RH). Where necessary, the original documents were all rechecked. The relevant documents of STAs from 1st April 2014 to December 2016 were publicly available on the NICE website and were checked and extracted by one member of the Liverpool team (RH) and double-checked by a second (AB). All ambiguous data were checked and discussed with all other members of the project team. The principal findings are summarised in a narrative and presented in tables, where relevant. Any instances where a technology was not recommended wholly in line with the original submission are discussed in detail, as are the issues that became apparent when examining these data.

## **Results**

Between September 2009 and December 2016, there were 171 STAs for which final guidance had been published. These did not include STAs that had been withdrawn or for which the process had started but had been suspended. Nor did it include STAs in which the relevant ICERs were commercial-in-confidence (e.g. TA410), where all the necessary documents are not available online (e.g. TA368, TA372, TA376, TA396) or in which no company base-case ICER was reported (a cost minimisation analysis) (TA191). Such STAs were

therefore excluded from this analysis because the ICERs were absent or unusable. The final total was 171 STAs, for which final guidance had been published. Out of these 171 STAs, 117 were excluded because none of the company base-case ICERs reported in the ACD or FAD was £10,000 per QALY or less (or dominated the principal comparator(s)). However, five of these STAs had company base-case ICERs between £10,000 and £15,000 per QALY (TA216, TA275, TA345, TA355 and TA400). These were considered a potential group of interest, so are considered separately below. Out of the remaining 54 STAs, 28 had multiple company base-case ICERs for the principal indication (due to the provision of ICERs for different scenarios, comparisons and subgroups), one or more of which was less than £10,000 per QALY and one or more of which was more than £10,000 per QALY. These were excluded from the primary analysis because they were unlikely to be ‘fast-tracked’ given the presence of ICERs of more than £10,000 per QALY for certain relevant subgroups or comparisons. These STAs are also considered in more detail below. The total number of STAs with company base-case ICERs that all either dominated current treatments or were less than £10,000 per QALY in all comparisons was 26, which represents 15% (26/171) of all STAs with usable ICERs and published guidance. This is consistent with the 15% figure quoted by NICE[8]. Details of the selection process are provided in Figure X.

<insert Figure: PRISMA flowchart of selection process>

### **STAs with all company base-case ICERs of less than £10,000 per QALY or dominating comparators**

The technologies in 19 out of these 26 STAs (73%) received a positive recommendation after the first AC meeting. In 13 of these 19 STAs (68%) only a FAD was issued, there was no ACD (see Table 1). In eight of these 13 STAs (62%), the companies’ base-case ICERs (or conclusion on dominance), as recorded in the committee documents, remained the preferred ICER of the committee (including technologies with a Patient Access Scheme [PAS] in the case of TA305). In the five other instances, the AC-preferred ICER in the FAD was not explicitly stated (due to a PAS in the case of TA294) in three cases and was higher in two, but each technology was stated to be cost-effective. For the six of the 19 technologies that generated positive recommendations, first in an ACD and then later, in the FAD, the AC-preferred ICER in the FAD was the same as the company’s base-case in one STA and higher than the company’s base-case in five STAs (but still below



£10,000 per QALY in four). In one STA (TA335), the AC preferred ICER in the FAD, and its relationship to the company base-case ICER, was unclear. The details of these 19 STAs are presented in Table 1.

<insert Table 1 here>

Seven of the 26 STAs with all company base-case ICERs of less than £10,000 per QALY received a Minded No in the first ACD. All of these technologies ultimately received a positive recommendation in the FAD, but in some cases this recommendation was restricted by subgroup. The details of these seven STAs are presented in Table 2. In each case, the AC considered that the analyses provided by both the company and the ERG were inadequate for making a decision, and the AC could not identify a plausible ICER per QALY based on the evidence and model as presented.

<insert Table 2 here>

Four of the seven technologies were recommended fully in the FAD. However, it should be noted that, despite all four of these technologies originally dominating comparators or having company ICERs of less than £10,000 per QALY, almost all of the final ICERs preferred by the AC and stated in the FADs fell between £10,000 and £30,000 per QALY, based on the additional analyses requested by the AC and conducted by the company or ERG.

The remaining three of these seven STAs had more restrictive recommendations in the FAD. Two involved treatments for mental health conditions: aripiprazole for adolescent schizophrenia (TA213) and vortioxetine for major depressive episodes (TA367). In TA213 aripiprazole was originally indicated in the CS as a first-line therapy for the treatment of schizophrenia in adolescents (aged 15-17 years old) and the company base-case ICER was reported as £6,200 per QALY compared with olanzapine. However, the AC considered the principal comparator to be risperidone; ERG analyses had reported much higher ICERs for this comparison. Given that

the final ICERs for aripiprazole as a first-line therapy were in excess of £30,000 per QALY, the final recommendation restricted its use to first-line only for patients who were intolerant to, or contraindicated for, the principal treatment, risperidone. In a similar way, the CS in TA367 had restricted vortioxetine to second-line treatment, but the FAD recommendation restricted reimbursement to third-line treatment, i.e. for patients who had had an inadequate response to two antidepressants within the current episode. Once more, the initial Minded No recommendation was due in part to the AC stating that relevant comparisons were absent from the CS. The third STA with restricted recommendations was for rituximab for ANCA-associated vasculitis (TA308). The initial Minded No was because the AC was uncomfortable with uncertainties in the models submitted by the company and supplemented by the ERG, and therefore requested further analyses. As a result of these analyses, and contrary to the CS, the FAD only recommended rituximab for treatment-naïve patients in certain circumstances.

Overall, the principal reasons for the Minded No recommendations in these seven STAs, despite their low ICERs, might be summarised as follows (a single submission might be affected by a number of issues) : implausible results or ICERs due to the models' failure to reflect clinical practice (TA229, TA261, TA367) or uncertainties in the model parameters or assumptions (TA213, TA260, TA261, TA308, TA367). The need for additional analyses was also precipitated by a failure of the models to take into account or use the comparisons (TA213, TA229, TA367) or outcomes (TA312) that the ACs deemed most relevant.

### **STAs with company base-case ICERs of £10,000 to £15,000 per QALY**

Given that the proposed figure of £10,000 per QALY for NICE 'fast track' consideration is not an absolute, we present here the evidence from five further STAs from our sample in which all of the company base-case ICERs were less than £15,000 per QALY. That is, if one of the criteria for 'fast track' appraisal was to be set at £15,000 per QALY, then an additional five STAs become relevant to our analysis: thus, in total 31/171(18%) of previously completed STAs would be potentially eligible. These five additional STAs are summarised in Table 3.

<insert Table 3 here>

As with the majority of STAs with all company base-case ICERs of less than £10,000 per QALY that did not receive a Minded No in the ACD, all five of these STAs received a positive recommendation in the first AC meeting (and only a FAD was produced, there was no ACD). In three cases, the AC-preferred ICER in the FAD (the result of ERG analyses in each case) was higher than the original company base-case ICER, but all were below a cost-effectiveness threshold of £30,000 per QALY. Unlike the STAs considered in Table 1, this group includes two cancer technologies: bendamustine for chronic lymphocytic leukaemia (TA216) and nivolumab for advanced melanoma (TA400).

#### **STAs with company base-case ICERs ranging from less than £10,000 per QALY to more than £10,000 per QALY**

In total 28/171 (16%) of all of the relevant STAs in this sample had one or more company base-case ICERs of less than £10,000 per QALY as well as one or more ICERS of more than £10,000 per QALY (see Table 4). These were evenly spread across disease areas and ERGs, but it is noticeable that the last two years had more such STAs than the previous six years (15 for 2015-2016 compared with 13 for 2009-14). This perhaps reflects the increasing complexity of the assessments being conducted in the NICE STA process.

<insert Table 4 here>

It is no surprise that the picture for these 28 STAs is far more fragmentary than for those 26 STAs with all of the company base-ICERs below £10,000 per QALY. Only 39% (13/28) received an unrestricted, positive recommendation at the first AC. In seven of these, no ACD was produced at all, only a FAD, i.e. 25% (7/28) compared with 50% (13/26) in the group with company base-ICERs all below £15,000 per QALY. Further, technologies received a No or Minded No for all groups in 25% (7/28) of these STAs after the first AC and others were recommended in specific subgroups or circumstances only in 29% (8/28). All of the technologies in

these 28 STAs ultimately received a positive recommendation in the FAD, but in 32% (9/28) the recommendation was restricted to certain subgroups or lines of treatment and, in seven cases, was conditional on a PAS. In five of these seven cases, the PAS had been submitted along with the original company submission (see Table 4).

## **Discussion**

Twenty-six STAs in this sample would have satisfied the basic criterion for the proposed NICE ‘fast track’ appraisal process, i.e. all of a company’s submitted base-case ICERs for a technology and indication were less than £10,000 per QALY.. Following the example of previous STAs, this approach would make up to 18% of future STAs eligible for such a ‘fast track’ process. Our analysis found that to 73% (19/26) of these STAs received a straightforward, positive recommendation with an AC-preferred ICER in the FAD that fell below the £30,000 per QALY threshold of cost-effectiveness generally applied by NICE[2, 5].

However, the seven STAs with company base-case ICERs of less than £10,000 per QALY that received a Minded No in the ACD give particular pause for thought when considering the implications of these findings for the proposed ‘fast track’ process. In four of these STAs, the AC-preferred ICERs in the FAD, as a result of additional analyses performed by the company or the ERGs, had risen to almost £30,000 per QALY (still within existing thresholds of cost-effectiveness). Yet in the other three STAs (TA213, TA308 and TA367) the result was a recommendation restricted to certain subgroups or lines of treatment. In the case of TA213, the final preferred ICERs for the original proposal of first-line treatment were well in excess of the £30,000 per QALY threshold. The NHS could therefore have ended-up paying for a treatment for certain patients that might normally have been designated as “not cost-effective”, with the obvious implications and opportunity costs[5, 11, 12]. It might be the case that the health system would be willing to fund non-cost-effective treatments for certain subgroups in return for providing more timely access to new treatments and a faster, less expensive technology appraisal process[8], although some might disagree[12].

The NICE proposal has stated that criteria for inclusion in the ‘fast track’ process would be “the availability of strong evidence (with a low degree of decision uncertainty)” and that the ICER is indeed likely to be less than £10,000 per QALY. It was also anticipated that such technologies would be identified by NICE “following an

analysis of the company's submission, supported by external review"[8]. It is possible that STAs with issues, like the seven STAs with a company base-case ICER of less than £10,000 per QALY, and which received a Minded No in the ACD, might have been identified by this process and "re-routed" to the standard STA process. After all, the CS and models in four of these seven STAs were potentially easily identifiable as having a high degree of decision uncertainty on account of their failure to provide comparisons against the most relevant current treatments (TA213, TA229, TA367) and/or their failure to reflect UK clinical practice (TA229, TA261, TA367). However, it is questionable whether a more limited appraisal process might have identified the uncertainties in the model parameters and assumptions that affected five of these STAs (TA213, TA260, TA261, TA308, TA367). Indeed, the current process's heavy reliance on the ERGs to identify such issues is well known[3].

Based on the evidence, the group of 26 STAs with ICERs all less than £10,000 per QALY, and the group of five STAs with ICERs between £10,000 and £15,000 per QALY, all do appear to represent a generally quite homogenous type of STA. Only 13 of these 31 STAs had multiple ICERs and, of course, the range was very narrow (from the new technology dominating comparators to always being less than £15,000 per QALY). This means that 18 of these 31 STAs (58%) had only a single company base-case ICER. The groups and scenarios within these appraisals were fairly homogenous and thus required less complex methodology than other STAs. This accords with the NICE consultation proposal that "the weight and complexity" of the appraisals should be "in proportion to the technical challenges and the risks posed by the evidence that it considers." [8]. And thus, the 'fast track' appraisal process was only to be for "the appraisal of health technologies for which a confident judgement about value for money can be made at an early stage" [8]. However, such a judgement could not possibly be made, for example, for the 28 STAs with company base-case ICERs both less than and more than £10,000 per QALY, in which companies submitted multiple base-case ICERs for their technology, which might range from dominating to being dominated by comparators (e.g. TA349) on account of different subgroups, treatment lines or scenarios. Such technologies must be appraised via the standard process.

Another scenario arises when a relevant comparator product already has a confidential PAS in place with the Department of Health. In this case, an ERG is required to generate results taking into account all of the PAS discounts. In our dataset, two of the STAs (TA346 and TA366) with company base-case ICERs all less than £10,000 were subject to this additional process, as were two STAs (TA384 and TA415) within the group

containing multiple ICERs, some of which were below £10,000. This information can be identified at the outset and would allow some technologies to be quickly categorised as not being eligible for the ‘fast track’ process, if the presence of such an issue was deemed to require more work.

One particular pattern is noticeable in the 19 STAs with all ICERs less than £10,000 per QALY and with ‘straightforward’ positive recommendations. Six of the 19 (32%) comprise treatments for cardiovascular disease and four (21%) relate to treatments for eyes. We consider that these disease areas are disproportionately highly represented in this group. In a study of the first 100 STAs with published guidance (2009-2014), frequencies were 11% for cardiovascular disease therapies and 7% for eye therapies and treatments for cancer, for blood and immune system and musculoskeletal conditions, frequencies were all higher than 7% [4, 6, 10]. In our dataset, three of the four “eye” STAs evaluated aflibercept for different indications and this drug has a relatively low-intensity regimen (with relatively low associated costs) compared with currently licensed comparators[13], for example, ranibizumab, which was the subject of the fourth “eye” STA. The relatively higher proportions of cardiovascular and eye treatments in this sample of STAs might also be due in part to the lower costs of treatments for these particular disease areas relative to others, such as cancer or musculoskeletal conditions[14, 15]. There did not appear to be any particularly noticeable increase in these STAs over time (see Tables 1 and 2): there were the same number of STAs (n=4) with a company base-case ICER of less than £10,000 per QALY in 2011, 2012 and 2013, and only slight increases in 2014 (n=6) and 2015 (n=5). However, this might change in the future.

In 74% (23/31) of STAs with technologies with company base-case ICERs all below £15,000 per QALY, this represented the first time the technology was being assessed by NICE (for any indication). These cases therefore all potentially represented cost precedents for future submissions, even for different indications. In five of the remaining eight STAs (TA264, TA275, TA292, TA327, TA335), the technologies had received prior recommendations for essentially the same indication, either as long as five years before the relevant appraisal, e.g. alteplase for acute ischaemic stroke in 2007 (TA122) and 2012 (TA264), or as little as one year before the relevant appraisal, e.g. apixaban for embolisms in 2012 (TA245) and 2013 (TA275). In only three cases were there prior appraisals of the same technology for different indications: bendamustine for chronic lymphocytic leukaemia: TA216 (2011) had been preceded by bendamustine for non-Hodgkin’s lymphoma:TA206 (2010); rituximab for treating anti-neutrophil cytoplasmic antibody-associated vasculitis: TA308 (2014) had been

preceded by technology appraisals for a number of lymphoma indications and rheumatoid arthritis between 2002 (TA37) and 2009 (TA174); and finally ranibizumab for treating choroidal neovascularisation associated with pathological myopia: TA298 (2013) had been the subject of previous appraisals between 2008 and 2011 for macular degeneration and macular oedema (TA 155, TA229, TA237).

The strength of this research is that it represents an analysis of all NICE STAs with published final guidance from September 2009 to December 2016, and thus offers an excellent summary of current and recent practice. The double-checking of all key data across the 171 included STAs, by at least two experienced HTA researchers from two research teams (Sheffield and Liverpool), reduced the likelihood of inconsistency and inaccuracy in the data. In addition, the method of analysis was descriptive, which reduces the likelihood of overstating relationships in the data, and an inclusive approach was taken to managing data that were not straightforward, for example the presence of multiple ICERs.

There are however limitations to this study. There are inherent weaknesses in using documentary analysis in that the researcher is only able to analyse what has been reported. The level and type of detail provided in and across the ACDs and FADs could be very different, which made data extraction at times a matter of interpretation. The so-called original company base-case ICERs, as reported in the ACD or FAD, are possibly likely to be different in an unknown number of instances from the ICERs submitted by companies at the very start of the process because, as a minimum, they will have been subject to the clarification process led by the ERG[1], and so could have already been revised before the first AC meeting and that committee's request for any revisions or additional analyses. It is also unclear exactly how a new 'fast track' process might be operationalised, so assumptions have had to be made in this study and it is not possible to know exactly how far such a process might or might not identify STAs with issues requiring more extensive work. Finally, it is not possible to determine from the current study and analysis whether the proposed 'fast track' process will be adequate to identify all of the issues that might arise with a submission that has a company base-case ICER of less than £10,000 per QALY or how far the existence of this criterion might influence submissions; this study only explored what had happened with previous STAs that satisfied this basic criterion. These limitations suggest that caution should be exercised regarding some of the conclusions drawn from the evidence.

## **Conclusion**

The majority of previous STAs with a company base-case ICER of £10,000 or even £15,000 per QALY received a positive recommendation after the first AC, but a number proved more complicated and required detailed appraisal, which influenced the final recommendation. In 19 of the 26 STAs that satisfy the £10,000 per QALY threshold in this sample, the technologies received a positive recommendation after the first AC meeting with little or no amendment to the original company base-case ICERs in the FAD. The same finding applied to another group of five STAs with company base-case ICERs below £15,000 per QALY. However, in seven of the STAs with all company base-case ICERs below £10,000 per QALY, the technology received an initial **Minded No** and, in three cases (43%), the indicated patient groups were more restricted in the final recommendation than in the companies' original submissions. Additional analyses and work by the companies and ERGs had demonstrated that the relevant base-case ICERs might actually be much higher and the technologies might not be cost-effective for certain patient groups. It is uncertain whether a 'fast track' process would have identified these issues.



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**Table 1: Summary of STAs with company base-case ICERs <£10,000 per QALY that received a positive recommendation at first time of asking**

TA number	FAD date	Technology	Disease area	ERG	ACD, FAD	FAD-preferred ICER	Relative to original ICER
230	2011	Bivalirudin	Cardiovascular	ScHARR	FAD	Dominates	Same*
236	2011	Ticagrelor	Cardiovascular	LRiG	ACD, FAD	<£10,000	Higher
264	2012	Alteplase	Cardiovascular	ScHARR	FAD	<£10,000	Same†
267	2012	Ivabradine	Cardiovascular	BMJ Evidence	ACD, FAD	<£10,000	Same
290	2013	Mirabegron	Urogenital	BMJ Evidence	ACD, FAD	<£10,000	Higher
292	2013	Aripiprazole	Mental health	ScHARR	FAD	Dominates	Unclear
294	2013	Aflibercept	Eye	Aberdeen	FAD	Dominates (with PAS)	Same†
298	2013	Ranibizumab	Eye	Aberdeen	FAD	Dominates	Same
305	2014	Aflibercept	Eye	Warwick	FAD	<£10,000 and dominates (with PAS)	Same
318	2014	Lubiprostone	Digestive system	CRD York	FAD	Dominates	Same
325	2014	Nalmefene	Alcohol dependence	ScHARR	ACD, FAD	<£10,000	Higher
327	2014	Dabigatran etexilate	Cardiovascular	BMJ	FAD	Unclear but within acceptable range	Higher
335	2015	Rivaroxaban	Cardiovascular	ScHARR	ACD, FAD	Unclear but within acceptable range	Unclear
346	2015	Aflibercept	Eye	Aberdeen	ACD, FAD	Unclear but within acceptable range (with PAS)‡	Higher

<b>TA number</b>	<b>FAD date</b>	<b>Technology</b>	<b>Disease area</b>	<b>ERG</b>	<b>ACD, FAD</b>	<b>FAD-preferred ICER</b>	<b>Relative to original ICER</b>
350	2015	Secukinumab	Psoriasis	Aberdeen	FAD	Unclear but within acceptable range (with PAS)	Unclear
366	2015	Pembrolizumab	Cancer	LRiG	FAD	Unclear but within acceptable range (with PAS)‡	Unclear
407	2016	Secukinumab	Musculoskeletal	Kleijnen SR	FAD	<£10,000 (with PAS)	Same
408	2016	Pegaspargase	Blood & Immune	Kleijnen SR	FAD	Dominates	Same
418	2016	Dapagliflozin	Diabetes	Warwick	FAD	Unclear but within acceptable range	Higher

\*Different figures, but still dominates. PAS: Patient Access Scheme. †A specific final ICER was confidential or not reported. ‡Includes PAS for comparators

**Table 2: Summary of STAs with company base-case ICERs <£10,000 per QALY that received an initial Minded No recommendation in the ACD**

TA number	FAD date	Technology	Disease area	ERG	ACD reason for decision	FAD decision	FAD ICER (source)
213	2011	Aripiprazole	Mental Health	Southampton	4.7, 4.12: The AC requested more evidence on comparisons other than olanzapine, especially for risperidone, the principal, routinely-used comparator in UK clinical practice. 4.14: The AC was concerned that, due to a number of uncertainties in the model, the ICER could be as high as £233,000 per QALY gained (in line with sensitivity analyses conducted by the ERG) and that aripiprazole was dominated by risperidone in the ERG's exploratory analyses	1.1: Recommended only in a subgroup of the original indication (people aged 15 to 17 years who are intolerant of risperidone, or for whom risperidone is contraindicated, or whose schizophrenia has not been adequately controlled with risperidone)	4.12: As first line, the ICERs ranged from £52,750 to £108,800 when compared with treatment sequences in which risperidone is used first (company's updated base-case analysis)
229	2011	Dexamethasone implants	Eye	Aberdeen	4.35: Submission did not compare the new technology with any of the active comparators listed in the scope and identified by the ERG along and other stakeholders ... Cost of treatment and extrapolations beyond data from the trial "were not plausible and did not reflect clinical practice in the UK"... The Committee were therefore unable to estimate the most plausible ICER	1.1: Recommended	4.20: £26,300 (company's updated base-case analysis)
260	2012	Botulinum toxin type A	Chronic migraine	Warwick	4.19: On the basis of the evidence submitted to the AC, it was unable to conclude whether botulinum toxin type A was cost effective compared to standard care. The central estimate of probabilistic ICER was not presented and there was uncertainty in many of the modelled parameters.	1.1: Recommended	4.15: £18,900 (ERG analysis of company's updated base-case analysis)
261	2012	Rivaroxaban	Blood & Immune	SCHARR	1.2, 4.13, 4.15, 4.16: The main limitation of the model from the AC's point of view was that patients were only treated with the drug for 12 months yet in practice people may need ongoing anticoagulation. The AC also considered the assessment of cost-effectiveness in different subgroups to be uncertain and therefore requested further evidence to support the assumptions.	1.1: Recommended	4.13, 4.16: Most likely ICERs based on length of treatment duration ranged from dominating comparators (3 months) to £19,400 per QALY for people who need treatment beyond 12 months (ERG analysis)

TA number	FAD date	Technology	Disease area	ERG	ACD reason for decision	FAD decision	FAD ICER (source)
308	2014	Rituximab	Blood & Immune	ScHARR	4.17: The AC concluded that none of the ICERs presented by the manufacturer and the ERG provided an accurate cost-effectiveness estimate due to uncertainties pertaining to model parameters, such as unrealistic outpatient costs and utility values and incomplete and inappropriate treatment sequences. Additional analyses were needed.	1.1: Recommended only if: further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose; or cyclophosphamide is contraindicated or not tolerated; or the person has not completed their family and treatment with cyclophosphamide may materially affect their fertility; or the disease has remained active or progressed despite a course of cyclophosphamide lasting 3–6 months; or the person has had uroepithelial malignancy	4.18: £12,100 for people who can have cyclophosphamide, less than £30,000 for those who cannot (ERG analysis)
312	2014	Alemtuzumab	Central Nervous System	Southampton	4.10, 4.11: The AC concluded that the primary outcome measure for the MTC should be sustained accumulation of disability lasting 6 months because this was a co-primary outcome in the clinical trials. The number of QALYs accumulated over the lifetime of the model was deemed to be implausibly low.	1.1: Recommended	4.21: ICER considered to be between £13,600 and £24,500 compared to glatiramer acetate and (4.22) £8,900 compared to fingolimod for a different population (company's updated base-case analysis)
367	2015	Vortioxetine	Mental Health	York CRD	1.2, 4.12, 4.20: The only population modelled was for second-line treatment; AC was interested in other comparisons / lines. 4.12, 4.13, 4.16: AC thought the model structure lacked validity and that the resource use and costs did not reflect the pathway of care for the indicated population.	1.1: Recommended only in people who have had an inadequate response to two antidepressants within the current episode (3rd line)	4.12: All scenario ICERs against all comparators were less than £9,000 when equal efficacy between treatments is assumed (company's updated base-case analysis)

ACD: Appraisal Consultation Documents; FAD: Final Appraisal Determination; ICER: Incremental Cost-Effectiveness Ratio; AC: Appraisal Committee; MTC: Mixed Treatment Comparison

**Table 3: Summary of STAs with company base-case ICERs £10,000 to £15,000 per QALY**

<b>TA number</b>	<b>FAD date</b>	<b>Technology</b>	<b>Disease area</b>	<b>ERG</b>	<b>ACD, FAD</b>	<b>FAD-preferred ICER</b>	<b>Relative to original ICER</b>
216	2011	Bendamustine	Cancer	PENTAG	FAD	<£10,000	Lower (£12,000)
275	2013	Apixaban	Cardiovascular	BMJ Evidence	FAD	<£20,000	Higher
345	2015	Naloxegol	Digestive system	Kleijnen SR	FAD	<£13,000	Same
355	2015	Edoxaban	Cardiovascular	LRiG	FAD	<£16,000	Higher
400	2016	Nivolumab	Cancer	BMJ Evidence	FAD	<£30,000* (with PAS)	Higher

\*As long as combination technology is costed according to its Patient Access Scheme PAS).

**Table 4: Summary of STAs with company base-case ICERs ranging from less than to more than £10,000 per QALY**

TA number	FAD date	Technology	Disease area	ERG	ACD decision	FAD decision
182	2009	Prasugrel	Cardiovascular	LRiG	Recommended	Recommended
186	2010	Certolizumab pegol	Musculoskeletal	West Midlands	Minded No	Recommended (with PAS*)
197	2010	Dronedarone	Cardiovascular	York CRD	Not recommended	Recommended for second line only
203	2010	Liraglutide	Blood & Immune	Aberdeen	Restricted recommendations	Recommended (in certain subgroups)
248	2012	Exenatide	Blood & Immune	Warwick	Recommended	Recommended
249	2012	Dabigatran etexilate	Cardiovascular	York CRD	Minded No	Recommended
252	2012	Telaprevir	Hepatitis	Southampton	No ACD	Recommended
253	2012	Boceprevir	Hepatitis	Southampton	No ACD	Recommended
287	2013	Rivaroxaban	Blood & Immune	Southampton	No ACD	Recommended
293	2013	Eltrombopag	Blood & Immune	Aberdeen	Recommended	Recommended
315	2014	Canagliflozin	Endocrine	Southampton	Restricted recommendations	Recommended (in certain subgroups)
317	2014	Prasugrel	Cardiovascular	LRiG	Recommended	Recommended
326	2014	Imatinib	Cancer	Southampton	Recommended	Recommended
330	2015	Sofosbuvir	Hepatitis	Southampton	Minded No	Recommended



<b>TA number</b>	<b>FAD date</b>	<b>Technology</b>	<b>Disease area</b>	<b>ERG</b>	<b>ACD decision</b>	<b>FAD decision</b>
331	2015	Simeprevir	Hepatitis	Southampton	Restricted recommendations	Recommended
336	2015	Empagliflozin	Endocrine	Warwick	Minded No	Recommended (in certain subgroups)
341	2015	Apixaban	Cardiovascular	LRiG	No ACD	Recommended
342	2015	Vedolizumab	Digestive system	SCHARR	Restricted recommendations	Recommended (with PAS*)
349	2015	Dexamethasone implants‡	Eyes	BMJ Evidence	Restricted recommendations	Recommended (in certain subgroups)
354	2015	Edoxaban	Cardiovascular	BMJ Evidence	No ACD	Recommended
359	2015	Idelalisib	Cancer	Warwick	Minded No and No	Recommended (in certain subgroups) (with PAS*)
363	2015	Ledipasvir / sofosbuvir	Hepatitis	SCHARR	Restricted recommendations	Recommended (in certain subgroups) (with PAS)
364	2015	Daclatasvir	Hepatitis	York CRD	Restricted recommendations	Recommended (in certain subgroups) (with PAS)
365	2015	Ombitasvir / paritaprevir / ritonavir +/- dasabuvir	Hepatitis	Southampton	Recommended	Recommended
384	2016	Nivolumab‡	Cancer	Southampton	No ACD	Recommended

<b>TA number</b>	<b>FAD date</b>	<b>Technology</b>	<b>Disease area</b>	<b>ERG</b>	<b>ACD decision</b>	<b>FAD decision</b>
413	2016	Elbasvir–grazoprevir	Hepatitis	Kleijnen SR	No ACD	Recommended (with PAS*)
415	2016	Certolizumab pegol	Musculoskeletal	ScHARR	Restricted recommendations	Recommended (in certain subgroups) (with PAS*)
424	2016	Pertuzumab	Cancer	ScHARR	Not recommended	Recommended

‡Includes PAS for comparators \*PAS submitted with original company submission.

## Appendix: STAs cited within the manuscript

All documents are available from the NICE website: <https://www.nice.org.uk/>

<b>NICE TA number</b>	<b>Full Appraisal Title</b>
TA182	Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention
TA186	Certolizumab pegol for the treatment of rheumatoid arthritis
TA189	Sorafenib for the treatment of advanced hepatocellular carcinoma
TA191	Capecitabine for the treatment of advanced gastric cancer
TA197	Dronedarone for the treatment of non-permanent atrial fibrillation
TA203	Liraglutide for the treatment of type 2 diabetes mellitus
TA213	Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years
TA216	Bendamustine for the first-line treatment of chronic lymphocytic leukaemia
TA229	Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion
TA230	Bivalirudin for the treatment of ST-segment-elevation myocardial infarction
TA236	Ticagrelor for the treatment of acute coronary syndromes
TA248	Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes
TA249	Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation
TA252	Telaprevir for the treatment of genotype 1 chronic hepatitis C
TA253	Boceprevir for the treatment of genotype 1 chronic hepatitis C
TA260	Botulinum toxin type A for the prevention of headaches in adults with chronic migraine
TA261	Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism
TA264	Alteplase for treating acute ischaemic stroke
TA267	Ivabradine for treating chronic heart failure
TA275	Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation
TA287	Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer
TA290	Mirabegron for treating symptoms of overactive bladder
TA292	Aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder
TA293	Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura
TA294	Aflibercept solution for injection for treating wet age-related macular degeneration
TA298	Ranibizumab for treating choroidal neovascularisation associated with pathological myopia
TA305	Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion
TA308	Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis
TA312	Alemtuzumab for treating relapsing-remitting multiple sclerosis
TA315	Canagliflozin in combination therapy for treating type 2 diabetes

TA317	Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes
TA318	Lubiprostone for treating chronic idiopathic constipation
TA325	Nalmefene for reducing alcohol consumption in people with alcohol dependence
TA326	Imatinib for the adjuvant treatment of gastrointestinal stromal tumours
TA327	Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism
TA330	Sofosbuvir for treating chronic hepatitis C
TA335	Rivaroxaban for preventing adverse outcomes after acute management of acute coronary
TA336	Empagliflozin in combination therapy for treating type 2 diabetes
TA341	Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism
TA342	Vedolizumab for treating moderately to severely active ulcerative colitis
TA345	Naloxegol for treating opioid-induced constipation
TA346	<u>Aflibercept for treating diabetic macular oedema</u>
TA349	Dexamethasone intravitreal implant for treating diabetic macular oedema
TA350	Secukinumab for treating moderate to severe plaque psoriasis
TA354	Edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism
TA355	Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation
TA359	Idelalisib for treating chronic lymphocytic leukaemia
TA363	Ledipasvir–sofosbuvir for treating chronic hepatitis C
TA364	Daclatasvir for treating chronic hepatitis C
TA365	Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C
TA366	Pembrolizumab for advanced melanoma not previously treated with ipilimumab
TA367	Vortioxetine for treating major depressive episodes
TA368	Apremilast for treating moderate to severe plaque psoriasis
TA372	Apremilast for treating active psoriatic arthritis
TA376	Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases
TA384	Nivolumab for treating advanced (unresectable or metastatic) melanoma
TA396	Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma
TA400	Nivolumab in combination with ipilimumab for treating advanced melanoma
TA407	Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors
TA408	Pegaspargase for treating acute lymphoblastic leukaemia
TA410	Talimogene laherparepvec for treating unresectable metastatic melanoma
TA413	Elbasvir–grazoprevir for treating chronic hepatitis C
TA415	Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor
TA418	Dapagliflozin in triple therapy for treating type 2 diabetes
TA424	Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer

Figure: PRISMA flowchart of STA selection process







