Evidence Review Group Report commissioned by the NHS R&D HTA Programme on behalf of NICE

Aripiprazole for the treatment of schizophrenia in adolescents (aged 15-17 years)

Produced by Southampton Health Technology Assessments Centre

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Rider on responsibility for the report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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J Jones (Principal Research Fellow) critically appraised the health economic systematic review and the economic evaluation and drafted the report; D Mendes (Research Fellow) critically appraised the health economic systematic review and the economic evaluation and drafted the report; GK Frampton (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report; P Harris (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report; E Loveman (Senior Research Fellow) critically appraised the clinical effectiveness systematic review; drafted the report; and project managed the review.

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LIST OF ABBREVIATIONS

AE	Adverse events
AIMS	Abnormal Involuntary Movement Scale
BNF	British National Formulary
BPRS	Brief Psychiatric Rating Scale
BPRS-C	Brief Psychiatric Rating Scale for Children
CAMHS	Child and Adolescent Mental Health Services
CE	Cost Effectiveness
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CGAS	Children's Global Assessment Scale
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression improvement scale
CGI-S	Clinical Global Impression severity scale
CHD	Coronary Heart Disease
CI	Confidence Interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, Text revision
CSR	Clinical Study Report
DES	Discrete Event Simulation
DSA	Deterministic Sensitivity Analysis
EPS	Extrapyramidal symptoms
ERG	Evidence Review Group
HES	Hospital Episode Statistics
HRG	Health Resource Group
HRQoL	Health Related Quality of Life
ICD-10	International Classification of Diseases, Tenth Revision
ICER	Incremental cost-effectiveness ratio
ITT	Intent-to-treat
K-SADS-PL	Schedule of Affective Disorders and Schizophrenia for School Age Children - Present and Lifetime Version
LOCF	Last observation carried forward
LS	Least squares
MIMS	Monthly Index of Medical Specialties
MS	Manufacturer's Submission
MTC	Mixed Treatment Comparison
OR	Odds Ratio
PANSS	Positive And Negative Syndrome Scale
PICO	Participants, Interventions, Comparators, Outcomes
P-QLES-Q	Paediatric Quality of Life and Enjoyment and Satisfaction Questionnaire
PPRS	Pharmaceutical Price Regulation Scheme
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
QoL	Quality of Life

RCT	Randomised Controlled Trial
RR	Relative Risk or Risk Ratio
SAE	Serious Adverse Events
SA	Sensitivity Analysis
SD	Standard Deviation
SE	Standard Error
SPC	Summary of Product Characteristics

SUMMARY

Scope of the submission

The manufacturer's submission (MS) does not fully reflect the scope of the appraisal issued by the National Institute for Health and Clinical Excellence (NICE). None of the active comparators specified in the scope issued by NICE (olanzapine, risperidone, quetiapine, amisulpride, clozapine) are included directly in the MS assessment of clinical effectiveness of aripiprazole. Olanzapine was included in the assessment of cost effectiveness. The MS included clozapine as a third line treatment in the health economic evaluation but a systematic search for data was not undertaken. A systematic review carried out by the manufacturer did not identify any relevant studies on any of the other comparators.

As a result of the lack of data on eligible comparators the MS focuses on the efficacy of aripiprazole relative to placebo, for which one relevant randomised controlled trial (RCT) was included. Two relevant single-arm open label studies of aripiprazole were also included, but the population characteristics of these trials deviate from the scope as they contain mixed populations of schizophrenia and bipolar I disorder patients or adolescent and adult patients.

Summary of submitted clinical effectiveness evidence

The clinical effectiveness evidence in the MS comes from:

- One three-arm phase III RCT comparing aripiprazole 10mg and 30mg against placebo – this is the primary source of evidence.
- Two phase III, single-arm, open label studies which were designed primarily to assess the safety of aripiprazole alongside the evidence from the included RCT.
- One phase III RCT comparing olanzapine against placebo which is paired with the aripiprazole-placebo RCT in an adjusted indirect comparison to elucidate the effectiveness of aripiprazole relative to olanzapine. This indirect comparison is used primarily to inform the economic model.

The primary outcome is the mean change in total PANSS score (Positive and Negative Syndrome Scale) from baseline to six weeks follow up. Both 10mg and 30mg aripiprazole groups of the RCT exhibited statistically significantly greater improvements in PANSS total score than the placebo group (which also exhibited some improvement from baseline). Secondary outcomes (positive and negative PANSS subscale scores; CGAS score (Children's

Global Assessment Scale); CGI scores (Clinical Global Impression) for severity (CGI-S) and improvement (CGI-I); and P-QLES-Q scores (Paediatric Quality of Life and Enjoyment and Satisfaction Questionnaire) also showed greater improvements from baseline to six weeks in the aripiprazole groups than the placebo group. For most comparisons these differences were statistically significant. Both the primary and secondary outcome measures suggest that aripiprazole appears to offer short-term benefit to patients, although the clinical significance of improvements in these questionnaire scores is unclear and not considered in the MS. The Evidence Review Group (ERG) received clinical advice that clinicians rarely use these specific tools to assess adolescents with schizophrenia.

Odds ratios (OR) and risk ratios (RR) for the adjusted indirect comparison indicate no statistically significant benefit of aripiprazole compared to olanzapine for the outcomes assessed (withdrawals due to adverse events, withdrawals due to lack of efficacy, withdrawals due to other reasons, significant increases in weight (≥7%), somnolence, and the number of patients receiving benzodiazepines (as a surrogate for extrapyramidal symptoms). Olanzapine was favoured over aripiprazole for withdrawals due to lack of efficacy.

Based on the limited available evidence, the ERG supports the conclusion of the MS that aripiprazole is generally well tolerated with the majority of adverse events (AE) being mild or moderate in severity and the incidence of discontinuations due to AE low. The MS omits a statistically significant change in questionnaire-based assessment scores for extrapyramidal symptoms (Simpson-Angus scale) favouring placebo over aripiprazole but the clinical implications of this omission are unclear and it appears unlikely that it would influence the overall conclusion concerning AE.

Summary of submitted cost effectiveness evidence

A systematic search of the literature did not identify any economic evaluations of pharmacological treatments for adolescent schizophrenia in the UK. An additional literature search for economic evaluations including adult aripiprazole was conducted and identified three studies. One further study was identified from hand searching of the NICE website. A narrative overview of each of the studies and an assessment of quality is provided, but few conclusions on the methodological quality or relevance of these studies is given. However, the MS does use this to conclude that a *de novo* economic evaluation was required.

The economic evaluation developed for the MS consists of a decision tree, followed by a Markov model to estimate the cost effectiveness of sequential treatment strategies (covering three lines of medication) rather than individual drug regimens. The results of the economic analysis are reported in terms of the incremental cost per Quality Adjusted Life Year (QALY) gained for aripiprazole as first line treatment followed by olanzapine as second line treatment and clozapine as rescue treatment (referred to in this report as first-line aripiprazole). This was compared with olanzapine followed by aripiprazole as second line treatment, and clozapine as a rescue option (referred to in this report as first-line olanzapine). This is a more limited comparison than outlined in the scope developed by NICE as noted above. The MS justifies the exclusion of other comparators due to the lack of data in adolescents, but does not discuss the relevance of the comparator chosen (or each component line of the first-line aripiprazole strategy) to clinical practice in England and Wales.

The states in the model - maintenance on current medication or relapse – characterise adolescent schizophrenia as a chronic disease with periodic acute episodes, and are consistent with previous economic evaluations in adult schizophrenia. The model adopted a three year time horizon, on the basis that this was the maximum duration an individual would remain in this patient group before being considered an adult (at which point other treatment options may be available). The model assumes that patients who discontinue treatment on first or second line treatment will switch to the next available line of treatment. Patients who relapse on the third line (rescue) treatment remain on that treatment following relapse – in the model no patients permanently discontinue treatment.

The MS reported that first-line aripiprazole dominated first-line olanzapine (was less costly and resulted in improved outcome). One-way sensitivity analyses indicated that the incremental cost effectiveness ratio (ICER) was most sensitive to variation in RR of relapse and daily cost of aripiprazole. In a probabilistic sensitivity analysis (PSA) first-line aripiprazole dominated first-line olanzapine in 80% of simulations and the MS reports a 96% probability of first-line aripiprazole being cost effective, at a threshold willingness to pay of £20,000 per QALY gained. The ERG identified errors in the model which affect the results presented in the MS:

- PSA results in the MS were based on undiscounted, rather than discounted, costs for first-line olanzapine leading to an over-estimation of the cost effectiveness of first-line aripiprazole compared with first-line olanzapine. The ERG re-ran the manufacturer’s PSA after correcting this error – in this analysis first-line aripiprazole dominated first-line

olanzapine in 57% of simulations and had a 73% probability of being cost effective, at a threshold willingness to pay of £20,000 per QALY gained;

- No management cost was applied for patients on first-line medication who relapsed in the second cycle of the model. Including these increases the cost of first-line aripiprazole relative to first-line olanzapine so that first-line aripiprazole no longer dominates in the base case (the ERG estimated the base case ICER, after correcting for this error, at £6,213 per QALY gained).

Commentary on the robustness of submitted evidence

Strengths

- The MS conducted a systematic search for clinical and cost-effectiveness studies of aripiprazole. It appears unlikely that the searches missed any additional clinical effectiveness or cost-effectiveness trials that would have met the inclusion criteria.
- The RCT comparing aripiprazole against placebo and the RCT comparing olanzapine against placebo were of reasonable methodological quality, and measured a range of outcomes that are relevant to the decision problem.
- The MS appears to present unbiased estimates of the primary outcome (PANSS total score at six weeks follow up) for aripiprazole versus placebo.
- The economic model is structurally consistent with models adopted for previous economic evaluations (in adults with schizophrenia). The appropriateness of applying this structure to the adolescent population was discussed with a relevant expert.
- The pre-model analysis methods used to derive input data for the economic model are generally appropriate. Sources of data are clearly identified and input values for model parameters are clearly presented in an Appendix to the MS.

Weaknesses

- The MS includes a very limited evidence base, which for clinical effectiveness is restricted primarily to a single RCT comparing aripiprazole against placebo. The MS does not directly include any of five eligible active comparators; it includes only one of these (olanzapine) in an adjusted indirect comparison.
- The adjusted indirect comparison comprises two RCTs and there is a lack of methodological information on how the adjusted indirect comparison was conducted.
- The chosen primary outcome (PANSS total score) is within the scope of the decision problem, but has unclear clinical meaning and appears to be used infrequently in clinical

practice; the MS does not justify how to interpret this outcome in a clinically meaningful sense.

- The MS considers short-term effects up to six weeks follow up.
- Generally, the MS presents an uncritical assessment of the evidence without consideration of potential biases. Claims about the advantages of aripiprazole are not fully grounded in the evidence presented.
- Some evidence about AE (weight gain and extrapyramidal symptom assessment scores) is omitted from the MS.
- The cost effectiveness model does not include all comparators listed in the scope – the MS states that this is due to a lack of placebo-controlled RCTs, which were required for inclusion in the adjusted indirect comparison.
- There was a lack of data specific to adolescents to populate the model. As a result, data on relapse, health state utility, disutility associated with treatment-related side effects and resource use assumptions are all derived from studies of adult rather than adolescent populations.
- The MS does not report discussion of the relevance, appropriateness or any quality assessment for studies used to derive key inputs to the model (such as RR of relapse).
- Clozapine was not included in the systematic review of clinical evidence and the MS offers no justification for the assumption that risks derived for aripiprazole can be applied to clozapine-treated patients.
- Some analytical errors were detected in the model. Where possible, corrected analyses have been presented by the ERG.

Areas of uncertainty

- Due to the lack of active comparators, the clinical effectiveness of aripiprazole relative to other atypical antipsychotic drugs is generally unclear. There is a lack of head-to-head trials comparing aripiprazole against other atypical antipsychotics in this population.
- The MS defined a clinically significant weight gain of ≥7%. No explanation for this threshold is provided. If a threshold is selected such that relatively few (or many) patients achieve it, this could influence interpretation of differences between groups.
- The potential for longer-term clinical effectiveness and AE is uncertain.
- There is uncertainty over the appropriateness of applying data derived from studies of adults with schizophrenia to the adolescent population.

- There is uncertainty over the appropriateness and relevance of key data inputs for the model, due to the limited discussion or critical assessment of data sources used to populate the model and in many cases no evidence of systematic targeted searches.

Key issues

- The MS presents a limited evidence base for the effectiveness of aripiprazole in the adolescent schizophrenia population due to a lack of information on eligible comparators.
- The cost effectiveness model does not include all comparators listed in the scope. The MS justifies the exclusion of other comparators due to the lack of data in adolescents, but does not discuss the relevance of the comparator (or each component line of the first-line aripiprazole strategy) to clinical practice in England and Wales.

1 Introduction to ERG Report

This report is a critique of the manufacturer's submission (MS) to NICE from Bristol Myers Squibb, Otsuka Pharmaceuticals on the clinical effectiveness and cost effectiveness of aripiprazole for the treatment of schizophrenia in adolescents aged 15-17 years. It identifies the strengths and weakness of the MS.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 26th May 2010. A response from the manufacturer via NICE was received by the ERG on 16th June 2010 and this has been included as an Addendum in the ERG report.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The MS generally provides a clear and accurate overview of schizophrenia in the adolescent population. Clinical advice to the ERG was that schizophrenia in adolescents is not a different disease than it is in adults (as suggested on p19 of the MS) but that adolescent symptoms are often more severe.

2.2 Critique of manufacturer's overview of current service provision

The MS provides very little discussion of the current service provision for aripiprazole or the comparator drugs. It is noted that only amisulpride and aripiprazole are licensed in adolescents, however the MS does not discuss what the typical patient pathway is in the treatment of adolescents presenting with schizophrenia. The ERG received clinical advice that risperidone is considered the standard first line therapy, but this is not taken into account in the MS.

2.3 Critique of manufacturer's definition of decision problem

2.3.1 Population

The population described in the decision problem is appropriate for the NHS.

2.3.2 Intervention

The description of the intervention in the decision problem reflects its use in the UK and is appropriate for the NHS. The licensed indication for aripiprazole in adolescents is for those aged

15-17 years. The dose of aripiprazole is typically 10mg per day although in individual cases up to 30mg per day can be used.

2.3.3 Comparators

The main comparator in the MS is olanzapine, with clozapine used as a third line treatment (only in the health economic model). The MS reports that the other treatments are not licensed in this population (quetiapine, risperidone), or infrequently used due to adverse events (amisulpride), and also that no Randomised Controlled Trial (RCT) evidence of these treatments in this population were identified and therefore these were not evaluated. As noted above, the ERG received clinical advice that risperidone is the most frequently used first line treatment in this population. The ERG also notes that olanzapine is not licensed for adolescents in the UK.

2.3.4 Outcomes

The outcomes included in the MS are standard outcomes used in research in this area; however, it is unclear how these relate meaningfully to patients. The ERG received clinical advice that clinicians rarely use specific tools such as these to assess adolescents with schizophrenia.

2.3.5 Economic analysis

The economic analysis in the MS decision problem appears to be appropriate, in terms of it being a cost utility analysis and in terms of the time horizon used. The exclusion of the comparators listed in the NICE scope however does not appear to be fully justified. This is particularly the case for risperidone as it is frequently used in these populations (albeit off licence). The MS states that there are no trial data for these treatments in adolescents; however, for the economic model it may have been appropriate to use other types of data, but a discussion of this is not provided. On page 22, the MS notes that risperidone has previously held a license for those aged over 15 years and this may suggest that there could be data on risperidone in the adolescent population, but this is not discussed.

2.3.6 Subgroups

No subgroups are noted in the decision problem. The ERG clinical advice concurs that this is appropriate.

2.3.7 Special considerations

The MS (p 25) notes that adolescents with other mental health disorders, such as learning disabilities, are not appropriate for the review. Clarification was sought to establish whether this means those with both schizophrenia and learning disabilities, as the ERG received clinical advice that this population is relevant. The response from the manufacturer can be seen in the Addendum below.

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach to systematic review

3.1.1 Description of manufacturer's search strategy

Overall the searches are appropriate, well documented and reproducible. Databases, dates of searches, and search strategies were specified and sufficient detail given to enable the methods to be reproduced. The ERG identified a few inconsistencies, as outlined below. The ERG did not re-run the searches, but did identify one publication of possible relevance; however the MS confirmed in their clarifications to the ERG (see Addendum) that this study was not of relevance.

3.1.1.1 Clinical effectiveness searches

The clinical effectiveness search strategies from each database have adequate documentation, enabling them to be reproduced. There is a mix of index terms, free text and application of a trials search filter. The different drugs searched for were not grouped in the same set, however the terms are all linked correctly. The searches are restricted to the appropriate age group using the Ovid limit mode, although without further free text or descriptors to represent adolescence or childhood. It is noted that while haloperidol, a typical antipsychotic, is used in the search strategy, clozapine, an atypical antipsychotic (and included in the NICE scope), is not included. Hand searching was reported to have been undertaken to check bibliographies, however clarification from the manufacturer suggests that this was of two reviews only (see Addendum). Searching for ongoing trials and other grey literature was not reported in the MS as confirmed in the clarifications sent by the manufacturer (see Addendum). An ongoing trials search was conducted by the ERG. Fifteen studies were identified, four of which had completed, however there were no studies which met the full scope of the appraisal.

No specific search for adverse event data was undertaken by the MS. The MS documents in Section 9.8 (Appendix 8) that it included two studies of relevance and that 'another review of the literature was deemed unnecessary.' The ERG conducted a search for adverse events but no relevant results were identified.

3.1.1.2 Cost effectiveness searches

The cost effectiveness search strategies are clearly documented and reproducible, using a mix of free text, index terms and a cost filter. The cost searches were less restrictive in terms of the population. The MS documents that the NICE website was searched to seek additional references, although there is no documentation of having searched for ongoing trials, conference proceedings or other grey literature. The ERG searched for ongoing cost effectiveness studies, but none were identified. The MS states that "in the interests of pragmatism, additional systematic searches were not carried out to identify specific UK resource use data for adolescents in the UK, as it is likely that these data are not available" (Section 6.5.3). No searches for relapse or re-hospitalisation literature were conducted.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection

The MS states clearly the inclusion and exclusion criteria for study selection (see Table 1 below). While included in the NICE scope and inclusion criteria (MS p28) as eligible treatments, the MS subsequently justifies not considering risperidone, quetiapine and amisulpride as comparators, due to an absence of adolescent data. The MS also justifies not considering clozapine as a comparator, because it is not routinely used in clinical practice to treat adolescents. The MS does consider the use of olanzapine to be an appropriate comparator, although the ERG notes that olanzapine is not licensed for adolescents under the age of 16 years in the UK. The MS includes an RCT[1] comparing olanzapine with placebo in the indirect treatment comparison and the economic analysis (see further discussion below).

In the inclusion criteria the MS includes recurrence (of psychosis) as an outcome, however this was subsequently excluded as an outcome due to a lack of data for aripiprazole.

With regard to the study design, the MS inclusion criteria prioritise RCT evidence, but also justify including non-RCTs for data on adverse events of aripiprazole. There are no limits placed on inclusion relating to the quality of the RCTs. While there are no restrictions on language in

the inclusion criteria used in the MS, the flow diagram on page 30 of the MS shows that non-English studies were excluded. No limits relating to the setting of the included evidence were specified.

The MS included one RCT[2] and two non-RCTs.[3,4] The included RCT[2] appears to be relevant to the decision problem stated in the submission and the licensed indication, and is relevant to the NHS. The two non-RCTs[3,4] may not be as directly relevant to the decision problem. One study[3] included a mixed study population of children and adolescents with schizophrenia (those who had completed the RCT[2]) or with bipolar I disorder (manic or mixed episodes with or without psychotic features from a different RCT undertaken by the manufacturer; MS p61) and as such is a single cohort extension study. While the MS reports safety data for the subgroup of participants with schizophrenia, it is unclear from the Clinical Study Report (CSR) whether these data were defined *a priori*. Aripiprazole is not currently licensed for treatment of adolescent bipolar disorder (acknowledged by the MS, Section 1.5, p14). The second non-RCT[4] included some adult participants as well as adolescents as it was a continuation of the aforementioned extension study and some participants had reached 18 years during the study.

Table 1: Eligibility criteria stated in the MS

Population	People with schizophrenia, aged 15-17 years.
Interventions	• Olanzapine • Risperidone • Quetiapine • Placebo • Haloperidol • Amisulpride • Aripiprazole
Outcomes	• Positive and Negative Syndrome Score (PANSS) • Brief Psychiatric Rating Scale (BPRS) • Clinical Global Impression (CGI) • Discontinuations • Discontinuations due to Adverse Events (AEs) • Treatment response (e.g. time to relapse) • AEs • Mortality (suicide) • Mental state (total symptoms, depression) • Social functioning • Recurrence • Health Related Quality of Life (HRQoL)
Study design	Randomised controlled trials
Exclusion criteria	

Population	• Adult (>17 years) or child (<13 years) other or mixed diagnosis, i.e. not schizophrenia alone
Interventions	• Clozapine • Other antipsychotics • Electro Convulsive Therapy • Behavioural interventions
Study design	• Non-systematic reviews, letters, commentaries, case report/series, surveys • Head to head studies with <2 arms including interventions of interest (as detailed in inclusion criteria)
Language restrictions	None

The MS provides a flow diagram (MS Section 5.2), identifying 1035 citations after de-duplication, plus an additional two references identified through hand searches. A flow-diagram provided reasons for the study exclusions, but the MS failed to provide a list of excluded references based on the full-text screening stage. This was subsequently provided and can be found in the Addendum to this ERG report.

The MS did not explicitly address any potential bias in the selection of studies or study assessment methods in the main body of the report. Details of the assessment methods employed were only reported in the Appendices (p135). While identified studies for the systematic review were independently assessed by two reviewers, with discrepancies resolved by a third party, it is unclear whether this process was also applied to the indirect treatment comparison (p 51) and the non-RCT evidence (p 57) (see clarifications from the manufacturer below). The MS omit details of the criteria used to identify the two non-RCTs[3,4] which the MS considers relevant to the appraisal of safety outcomes (p 57).

The MS exclude a phase II tolerability and pharmacokinetic non-RCT in adolescents due to the small participant numbers (n=21)[5] and deemed a conference abstract for risperidone insufficient for model parameters. The manufacturer was asked to clarify whether this conference abstract could have been included in the clinical review and responded that the data were insufficient to be included in the adjusted indirect comparison (see Addendum). The ERG has been unable to check whether the exclusion of either of these studies introduced any potential bias in the MS.

3.1.2.1 Identified studies

As stated earlier, the MS only identifies one RCT meeting the inclusion criteria (aripiprazole versus placebo),[2] and two non-RCTs for additional data on adverse events.[3,4] In addition, one

RCT was included for an indirect treatment comparison and to inform the economic analysis (olanzapine vs placebo).[1]

The included RCT,[2] compared aripiprazole 10mg, aripiprazole 30mg and placebo (see Table 2). The RCT included participants aged 13-17 years, while the scope of this appraisal specified children and teenagers aged 15-17 years as per the licensed indication. Summary details of trial design, intervention, population, patient numbers (eligible, randomised, allocated and drop outs), outcomes and statistical analysis (power/sample size calculations, description of ITT analysis) were provided. Reasons for drop-outs were not fully described in the MS.

Differences in baseline characteristics of participants appear to not have been statistically tested. The MS states that the three treatment arms were demographically similar and had similar baseline disease characteristics (p136). However, the ERG notes that there were differences between groups in gender, ethnicity and the proportion having used antipsychotic medication. There were also slight inconsistencies between baseline data presented in the MS and those presented in the RCT, although these are minor and are not anticipated to effect the efficacy estimates.

The RCT[2] included in the systematic review was conducted at 141 global sites according to the MS (Argentina, Bulgaria, Croatia, India, Jamaica, Mexico, Romania, Russia, Serbia, South Africa, South Korea, Ukraine and the US), but there appear to have been no sites in the UK. The journal publication of the RCT[2] refers to 101 centres and the relationship between sites and centres is unclear.

Electronic copies of the published papers cited in the MS were not provided with the original MS, but forwarded subsequently after a request by the ERG. The CSRs were submitted along with the clarifications sent by the manufacturer (17/6/1010). The ERG has not assessed the CSRs in detail, which range in size from 203 to 1507 pages.

The RCT included in the MS was sponsored by the manufacturer, although this is not explicit in the MS (the MS does state that the computer-generated randomisation codes were prepared by the sponsor's Biostatistics Department, p 33).

The MS appears to have identified all relevant RCTs meeting the inclusion criteria of the systematic review.

Table 2: Characteristics of the included RCT

Methods	Participants	Outcomes
Study 31-03-239, Findling et al[2] *Design:* phase III, multi-centre double-blind RCT *Interventions*: Grp1: 10 mg aripiprazole Grp2: 30 mg aripiprazole Grp3: placebo *Number of centres*: 141 sites/ 101 centres *Duration*: up to 10 weeks (28 day screening period, 42 day treatment period) *Length of follow-up:* open-label (Study 31-03-241) for six months or follow-up telephone call 30 days after the last dose to assess for any AEs	*Participant numbers:* n = 302 Grp1: 10mg n = 100 Grp2: 30mg n = 102 Grp3: n = 100 *Key Inclusion criteria*: Aged 13-17 years, with a K-SADS-PL* confirmed DSM-IV† diagnosis of schizophrenia and • PANSS score ≥ 70 at baseline (Day 1) • no mental retardation	*Primary endpoint:* Mean change from baseline to endpoint in the PANSS total score *Secondary endpoints:* PANSS total score, CGAS score, CGI severity score, CGI-improvement score, PANSS positive and negative subscale score, time to discontinuation *Others*: Number of hospitalisations for each patient, P-QLES-Q

*K-SADS-PL - Schedule of Affective Disorders and Schizophrenia for School Age Children - Present and Lifetime Version
†DSM-IV - Diagnostic and Statistical Manual of Mental Disorders, Fourth edition

The relevance of the RCT[1] included for the adjusted indirect comparison is somewhat less clear (see also section 4, economic evaluation below), as olanzapine is not licensed for the treatment of adolescents under the age of 16 years in the UK and is not routinely used in clinical practice. However, it is one of the named comparators in the NICE scope. The MS states that the baseline characteristics for participants in the olanzapine treatment group[1] and the aripiprazole treatment groups[2] were generally well matched for demographic and baseline characteristics, citing average age per treatment arm of participants as an example (p55 MS). However, there may be differences in the populations in terms of ethnic origin, but due to the characterisations used this is uncertain. In addition, in the olanzapine trial[1] some participants had previous experience with olanzapine and the placebo group of this trial included the highest percentage of participants having had previous antipsychotic treatment (85.7%). However, the baseline PANSS total scores per treatment arm were similar between the two RCTs, as were the CGI severity scale scores.

The unpublished included non-RCTs[3,4] were identified from manufacturer sources. As previously stated the methods of identification and selection were not reported. One of the studies[3] was an extension from the main RCT included in the MS and from another unpublished study (Study 31-03-240, p 61 of the MS). The second non-RCT[4] was a further continuation of the first non-RCT. The non-RCTs differed in their populations. The first non-RCT included children and adolescents aged 13–17 years with schizophrenia or aged 10-17 with bipolar I disorder, manic or mixed episode, with or without psychotic features.[3] However, the MS reported results for the schizophrenia subgroup only. The second non-RCT included adolescents also aged 13-17 years with schizophrenia, however some of these were aged 18 years or over.[4] Baseline characteristics of age, gender, height, weight, BMI and ethnic composition (%) appear to be similar between the studies (MS p63). The ERG considers that there is a potential for bias in the included studies given the factors noted above. In addition the two non-RCTs were sponsored by the manufacturer and data are presented in confidential CSRs and have not been subject to peer review.

Furthermore, a post-hoc subgroup analyses of adolescents aged 15-17 years was conducted, assessing similarities between this group and adults with schizophrenia treated with aripiprazole (p 38). It is unclear if the study was powered for this analysis.

3.1.3 Description and critique of the approach to validity assessment

The MS assessed the quality of the included RCT and the RCT used in the adjusted indirect comparison only, using criteria of the Centre for Reviews and Dissemination (2008),[6] which mirror the NICE criteria. Details of these assessments were provided in the appendices of the MS (p 136 and p 138). On the whole, the ERG agrees with the MS assessment of the study quality of the included RCT, with some exceptions (see Table 3). Quality of the non-RCTs was reported to have been assessed using a qualitative approach (p 139), however the appraisals appear to have mainly focused on attrition. Potential confounding does not appear to have been considered, for example. This is recognised as a risk of bias in observational studies.

Information contained in the MS (p 35) states that the three treatment arms were demographically similar, with similar baseline characteristics. However, the aripiprazole 10mg-group contained a higher percentage of female participants (55%) compared to the 30mg (36.3%) and placebo (39%) groups, with a lower proportion of Caucasians (54%) compared to

the 30mg (61%) and placebo (64%) group (p 35). The 10mg-group also contained a slightly higher percentage of participants with previous anti-psychotic medication use (53%) compared to the other two groups (both around 46%). No statistical analysis of baseline characteristic differences between the treatment groups was provided in the trial.[2] While statistical comparison is not strictly necessary between randomised groups, it does enable any chance of imbalance to be addressed by adjusting the statistical analysis for baseline variables.

According to the MS, the proportion of drop-outs were similar between groups (p 136), however, drop-outs accounted for 16% of the 10mg group, 18% of the 30mg group and 10% of the placebo group (MS flow chart p 39). The journal publication[2] reported non-significant p-values for pair-wise comparisons of drop-outs, which were not reported in the MS.

The ERG notes that some outcomes reported in the RCT were not reported in the MS. The journal publication[2] refers to the Simpson-Angus, Barnes and AIMS (Abnormal Involuntary Movement Scale) scales for assessing extrapyramidal symptoms (EPS) (p 1438), but these are not considered in the MS.

It is also unclear if the RCT used a true intention to treat (ITT) analysis. The MS assessment implied that only patients with a baseline and post-baseline assessment were included. However, it is also implied that everyone met this criterion (since anyone with missing post-baseline data had their data imputed by last observation carried forward, LOCF). For the efficacy analysis, the MS assessment states that all randomised participants were included using a LOCF dataset to account for missing data (missing data at a post-baseline visit was imputed with the value obtained at the nearest preceding visit, p136). However, the numbers of participants presented in the efficacy tables do not necessarily reflect the ITT populations.

Table 3: Manufacturer and ERG assessment of trial quality,[2]

NICE Quality Assessment Criteria for RCT	MS response	ERG response
1. Was the method used to generate random allocations adequate?	Yes	Yes
2. Was the allocation adequately concealed?	Yes	Yes
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Yes	Unclear
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Yes
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No

6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Yes
7. Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Unclear

3.1.4 Description and critique of manufacturer's outcome selection

The clinical effectiveness outcomes selected by the manufacturer match the NICE decision problem, with the exception that recurrence of psychosis, which was excluded as the MS found no data on this outcome (the trials that were eligible for inclusion did not report it – but they were short term studies). The effectiveness outcomes are widely used in the literature for assessing the effects of antipsychotic drugs. However, clinical advice to the ERG indicated that the questionnaire-based outcomes are rarely used in clinical practice in this population.

The stated primary outcome was the mean change from baseline to endpoint (six weeks) in the total PANSS score. The trial was powered statistically to detect a change of -11.4 in total PANSS score from baseline to six weeks. However, the meaning of this degree of change for adolescents is unclear (the MS states that it is equivalent to the median of the mean difference seen in aripiprazole studies with adults).

Secondary outcomes were stated in the MS as being PANSS total score at all other follow up weeks other than week six; mean change from baseline to endpoint in CGAS score; change from baseline in CGI-severity score; changes from one month in CGI-improvement score; changes from baseline in PANSS positive and negative subscale scores; time to discontinuation due to all reasons.

In addition, the MS reports 'other outcomes'. These were the number of hospitalisations per subject (reported in the MS as Confidential in Confidence (CIC) and do not appear in the journal publication[2]) and P-QLES-Q (Paediatric version of Short Form of the Quality of Life Enjoyment and Satisfaction Questionnaire) scores at screening and six weeks follow up. No explanation is given in the MS or the paper[2] as to why these outcomes are grouped separately from those classified as secondary outcomes, so clarification was sought from the manufacturer. The manufacturer's response was that P-QLES-Q is classified as an 'other' outcome as it is neither an efficacy nor a safety measure. No explanation was given for why the number of hospitalisations is classed as an 'other' outcome.

The P-QLES-Q is a validated measure of quality of life (QoL) that has been tested for its internal consistency and test-retest reliability. However, no clear information appears to be available on how to interpret the clinical meaning of P-QLES-Q scores (i.e. what is a meaningful change or difference in scores). detail The MS and a reference[7] provided by the manufacturer provide no guidance on this. Clarification was sought from the manufacturer, who confirmed that "there are no agreed parameters by which clinically meaningful changes/differences in PANSS, CGI, CGAS and P-QLES-Q can be pre-defined, and how they link with each other." (see Addendum). As stated above clinical advice to the ERG suggests that these measures are not routinely used in this population.

The analysis of P-QLES-Q was undertaken separately for the 'total' score and 'overall' score but it is not clear what this means, as no explanation is given in the MS or paper.[2]

[redacted]

Adverse events are reported in the MS. However, these are from only three studies: two non-RCTs[3,4] which the MS states, without any explanation, were identified from manufacturer sources; and the included RCT.[2]

Only a subset of the relevant outcomes was used in the adjusted indirect comparison, namely: adverse events; withdrawals due to lack of efficacy; withdrawals due to other reasons; significant weight increase; somnolence (drowsiness); and benzodiazepine use (as a surrogate for EPS). The reason for the choice of these outcomes appears (but is not stated) to be that these were relevant for the economic model. The adjusted indirect comparison is used solely to support the economic evaluation. No discussion is provided about whether other outcomes would have been available for a more detailed adjusted indirect comparison to support the clinical effectiveness assessment when comparing aripiprazole against olanzapine.

As noted above, data from three rating scales for assessing clinical effects of antipsychotic drugs are reported in the included RCT[2] and the CSR but not mentioned in the MS. These are: the Simpson-Angus scale for identifying antipsychotic-induced Parkinsonism; the Barnes rating scale for identifying drug-induced akathisia; and the AIMS scale for identifying drug-induced

dyskinesias. These instruments are relevant as they provide a means of objectively monitoring and classifying extrapyramidal adverse effects.

3.1.5 Description and critique of the manufacturer's approach to trial statistics

The MS reports results for all relevant outcome measures apart from those noted above that are relevant but omitted. Effectiveness results (PANSS, CGI, CGAS and PQ-LES-Q) are presented as LS (least squares) mean values for baseline and changes from baseline at follow up, together with sample sizes and p-values for group differences at each time point. No estimates of variance are reported in the MS for any outcomes obtained from the included RCT (however the paper[2] does provide standard error (SE) values for these outcomes). Follow up data are only presented as differences from baseline, both in the MS and paper.[2]

Data used in the adjusted indirect comparison (withdrawals, significant increases from baseline in weight, somnolence, and patients who received benzodiazepines [as a surrogate marker for EPS]) are reported as total numbers (N), numbers analysed (n) and percentages (%) for each study arm (time point not stated) with no variance estimates provided. The results of adjusted indirect comparisons for these outcomes are reported as ORs and RRs, each with 95% confidence intervals (CI).

Adverse events were reported in the MS as numbers and proportions. Means and standard deviations (SDs) for some adverse event outcomes (e.g. weight change) are available in the included RCT publication[2] but were not reported in the MS.

The MS states (p 39) in the flow-chart that all participants were included in the efficacy analysis. However, this contradicts the information in Table 11 (p 37) and the text on page 40, and the data tables themselves which show that different numbers were analysed for different groups and different outcomes. It is unclear why the numbers of LOCF vary between the different outcomes, for example CGAS and P-LQLES-Q as these assessments were undertaken at the same time. In particular there are differences between subscales of the P-QLES-Q. The ERG sought clarification from the manufacturer on justification of the LOCF approach and on how many observations in each week were carried forward (as bias could result if this differed between study groups). The manufacturer justified the LOCF approach but did not explain how many data were carried forward in each week (see Addendum).

Questionnaire-based outcomes (PANSS, CGI, CGAS and P-QLES-Q) are reported and interpreted uncritically in the MS, with emphasis given to the statistical significance of differences or changes in these outcomes but not their clinical relevance.

The primary outcome is change in PANSS total score from baseline to six weeks. Data for shorter follow up times are presented which the MS defines as secondary outcomes. However, in the synthesis and interpretation of these findings the MS appears to give equal weight to the six-week and shorter follow up data. No rationale is provided in the MS for the choice of follow up timescales employed. Clarification was sought from the manufacturer on why some outcomes were reported for baseline and individual weeks 1, 2, 3, 4, 5 and 6 whilst CGAS and P-QLES-Q were reported only for baseline and week six. The manufacturer explained that parameters relating to functioning and QoL are unlikely to show changes on a weekly basis and so measures [of CGAS and P-QLES-Q] at these times would be meaningless, (see Addendum).

3.1.6 Description and critique of the manufacturer's approach to the evidence synthesis

Overall there is good agreement between the MS and the respective study publications on information about study characteristics. Most of the results of the included studies are clearly tabulated for effectiveness outcomes, although as noted above, estimates of variance are omitted. The reporting of trial results for adverse events is less consistent. Interpretation of trial findings is rather uncritical and the structure of the results section does not easily facilitate synthesis of information across different trials, e.g. no overall integration of the findings on AEs from the RCTs and non-RCTs is provided.

A meta analysis was not considered appropriate by the manufacturer as only one aripiprazole RCT was identified. Instead, an adjusted indirect comparison was undertaken.

As noted, only two relevant RCTs were found by the manufacturer: one comparing aripiprazole against placebo,[2] the other olanzapine against placebo.[1] This is used as the justification for doing an adjusted indirect comparison by the manufacturer. The MS does not specify any aims of the adjusted indirect comparison and is uncritical with regard to the possible advantages and disadvantages of such an analysis. Details of how the data from the olanzapine trial were data extracted are not presented in the MS. The MS presents standard formulae for calculating OR and RR and their respective standard errors (SE) for individual RCTs based on dichotomous

input data (% of patients with or without outcome) for withdrawals, weight gain, somnolence, and patients receiving benzodiazepines. The MS also presents OR and RR with 95% CI for the outcome of the adjusted indirect comparison. However, no explanation is given for how these were generated from the ORs and RRs of the individual RCTs. Further, the MS does not provide any summary or interpretation of these results and the adjusted indirect comparison is not mentioned at all in the overall interpretation of the clinical effectiveness evidence (p 72 to 73).

To be eligible for an indirect comparison, ideally the individual trials should be as similar as possible in terms of their study characteristics. The aripiprazole and olanzapine RCTs appear to be broadly comparable in many respects but as noted above (section 3.1.2.1) the olanzapine placebo group[1] had higher prior use of antipsychotics than the aripiprazole placebo group.[2] It is also notable that the aripiprazole RCT recruited patients from a larger number of countries than the olanzapine RCT. These aspects of trial characteristics which are important for assisting interpretation of adjusted indirect comparisons are not considered in the MS, and no formal assessment of heterogeneity within the adjusted indirect comparison is presented.

3.2 Summary statement of manufacturer's approach

Taking into account the evidence synthesis overall (including the adjusted indirect comparison and the two non-RCTs) the ERG's view is that the approach with regard to searching for studies and reporting the studies in detail did not meet the quality criteria for a systematic review (Table 4). The MS did not fully assess the quality of all the included studies and no consideration of study quality was made when synthesising and interpreting the overall findings.

Table 4: Quality assessment (CRD criteria) of MS review

CRD Quality Item:	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. Inclusion and exclusion criteria are clearly stated.
2. Is there evidence of a substantial effort to search for all relevant research? i.e. all studies identified	Unclear. Searches were not conducted for adverse events (the MS states (p 140) that only two manufacturer-owned research studies are relevant for providing AE data but no scoping of the literature or other evidence to support this assertion is provided). The method of searching the manufacturer's own archives for relevant studies is not reported so it is not possible for the ERG to determine whether this was substantial, adequate and free of bias.
3. Is the validity of included studies adequately assessed?	Unclear. The primary RCT (MS, p 136) and a comparator RCT (MS, p 138) were appraised according to standard CRD

	criteria for assessing the quality of RCTs.[6] Quality assessment of two non-RCT studies was done narratively without reference to a checklist (MS, p 139 to 140). The MS states that this was due to a lack of validated checklists for single arm studies. For these non-randomised studies, the quality appraisal focused mainly on participant flow and attrition; blinding was not assessed. None of the quality assessments reported in the MS are considered further in relation to the synthesis and interpretation of the findings of the included studies.
4. Is sufficient detail of the individual studies presented?	Yes. The study design and Patient, Intervention, Comparator, Outcome (PICO) elements were tabulated for three of four included randomised and non-randomised studies. In response to a request from the ERG, the Manufacturer subsequently provided details for the fourth study by Kryzhanovskaya et al.[1] which was included in the adjusted indirect comparison.
5. Are the primary studies summarised appropriately?	No. The tables summarising the included clinical effectiveness studies are presented with limited if any introduction, explanation or narrative summary. A narrative synthesis which draws together all the clinical effectiveness results is missing from the MS. The interpretation of clinical evidence (MS, p 72) is limited and uncritical, with no indication of the strengths and weaknesses of the assembled evidence and no reference to the assessments of study quality that were made.

The process of study selection is mentioned on page 29 of the MS and the process of data extraction is mentioned on page 135 of the MS for clinical effectiveness studies. It is stated that study selection was undertaken by two reviewers with any disagreements resolved by discussion with a third party. Data extraction was undertaken by one reviewer and checked by a second reviewer, with any inconsistencies resolved through discussion. It is not explicitly stated in the MS how many reviewers conducted the quality assessments of the included studies. The details of the processes undertaken for the adjusted indirect comparison were not reported.

Overall there were no data on the other comparators which NICE had deemed relevant to the scope. It is also unclear whether other evidence submitted in the MS is sufficiently complete to fully address the decision problem. For example, no searches for AE were conducted and so relevant information may have been missed. The ERG ran some basic searches for AEs and did not identify any studies however. In addition, the risk of systematic error in the MS is unclear. There are several possible sources of systematic error in the MS but their importance is difficult to ascertain. Possible sources of systematic error noted by the ERG are: imbalances in the baseline characteristics of populations; ambiguity as to whether all relevant evidence was included (e.g. how the manufacturer's own studies were identified and selected, and whether

information on adverse events was missed); risk of confounding in single-arm trials; differences in attrition between groups; ambiguity in how the LOCF imputation was applied in statistical analyses; possible selective reporting (of manufacturer's trials and of trial outcomes (e.g. some statistically significant effects of aripiprazole were not reported in the MS; some outcomes were partially reported, e.g. weight gain)).

3.3 Summary of submitted evidence

In this section of the report, the ERG concentrates on the main outcomes of the included RCT[2] of aripiprazole after six weeks of treatment. Data have been checked by the ERG and summarised for each of the key outcomes below. For many outcomes the MS reports data at interim time points (weeks 1,2,3,4,5). In most cases this is presented as CIC information and as such has not been repeated here except where relevant a discussion of the statistical significance of these data is given. There were a few differences between the data presented in the MS and the data in the study publications; however these were generally minor discrepancies. The data presented in the tables below are the ERG checked data. In addition to the data provided in the MS, SEs are presented from the RCT publication and differences in scores between the groups have been calculated. The MS also presented data from the non-RCT extension studies and the data on adverse events from these studies has been checked by the ERG and are presented below. Occasionally data in the MS were presented from the trial CSRs in confidence.

3.3.1 PANSS

The stated primary outcome measure of the RCT was the mean change from baseline in total score of the PANSS at six weeks. The PANSS includes 30 items which can each be rated from 1 (symptoms absent) to 7 (extreme symptoms). The PANSS total score ranges from 30 – 210. Using the LOCF data Table 5 shows that at week six all groups showed a decrease (improvement) in symptoms as measured by the PANSS and there were statistically significant differences in the degree of improvement between the aripiprazole groups and the placebo group. The clinical significance of these differences is uncertain and no threshold to define treatment response has been provided in the MS, particularly given the placebo effect seen.

[redacted]

[redacted] As noted above the numbers of participants included in these analyses are fewer than the numbers randomised to each study group.

Table 5: PANSS change from baseline total score at study completion (six weeks)

	Aripiprazole 10mg n=99	**Aripiprazole 30mg n=97**	**Placebo n=98**	**Aripiprazole 10mg versus placebo**	**Aripiprazole 30 mg versus placebo**
Least-squares (LS) mean (SE)	-26.7 (1.9)	-28.6 (0.9)	-21.2 (1.9)	Difference 5.5 p-value 0.05[a]	Difference 7.4 p-value 0.007[a]

[a]minor differences between MS, trial publication, and CSRs

PANSS subscale scores

The MS also reports the results of the positive and negative subscale scores of the PANSS. These consist of seven items each and scores for the subscales range from 7 (symptoms absent) to 49 (extreme symptoms). These data have been replicated in Table 6 below. As can be seen at study end (six weeks) the mean change from baseline on the positive subscale showed improvement (reduction in score) in all three groups. There was a statistically significant difference between the aripiprazole 10mg and the placebo group and between the aripiprazole 30mg and placebo group. The results on the negative subscale showed a similar pattern; all groups showed improvement and this change was larger in the treatment groups than it was in the placebo group, although this only reached statistical significance in the 10mg aripiprazole versus placebo comparison.

[redacted]

Table 6: PANSS positive and negative subscale scores at study completion (six weeks)

Aripiprazole 10mg n=99	Aripiprazole 30mg n=97	Placebo n=98	Aripiprazole 10mg versus placebo	Aripiprazole 30 mg versus placebo
PANSS positive subscale score, LS mean change (SE)				
-7.6 (0.6)	-8.1 (0.6)	-5.6 (0.6)	Difference 2.0 p-value 0.02[a]	Difference 2.5 p-value 0.002
PANSS negative subscale score, LS mean change (SE)				
-6.9 (0.6)	-6.6 (0.6)	-5.4 (0.6)	Difference 1.5 p-value 0.05	Difference 1.2 p-value 0.10

[a]minor differences between MS, trial publication, and CSR

3.3.2 CGAS

Mean change from baseline on the CGAS score was a secondary outcome of the included RCT. The CGAS scores range from 1-100, with higher scores indicating better functioning. Table 7 shows that there was an improvement on the CGAS (increased score) for all three groups and that there were statistically significant differences between each of the aripiprazole intervention groups when compared to the placebo group. No interim data were provided in the MS for this outcome. The clinical significance of these differences is uncertain.

Table 7: CGAS change from baseline score at study completion (six weeks)

	Aripiprazole 10mg n=97	Aripiprazole 30mg n=94	Placebo n=98	Aripiprazole 10mg versus placebo	Aripiprazole 30 mg versus placebo
LS mean - (SE)	14.7 (1.5)	14.8 (1.3)	9.8 (1.3)	Difference 4.9 p-value 0.005	Difference 5.0 p-value 0.004

3.3.3 CGI

The CGI severity score and improvement score were reported to be measured for change from baseline (Tables 14 and 15 of the MS). However, for the CGI improvement score the data presented in the MS were end-point scores rather than change from baseline scores (this supports the data presented in the trial publication[2]).

On the CGI severity score (ranges from 1-7) a decrease in score represents improvement. In all three groups the change from baseline showed improvement. A statistically significant difference in change scores was seen at six weeks between the aripiprazole 10mg versus placebo group, and between the aripiprazole 30mg versus placebo group. In the interim analyses, in the aripiprazole 10mg group statistical significance compared to the placebo group

was achieved at week 3 and week 5 but not at weeks 1,2 or 4 [redacted], whereas statistical significance was achieved at all interim time points in the aripiprazole 30mg versus placebo analysis except at week 2 [redacted].

On the CGI improvement score (ranges from 1-7, lower score indicates improvement) the mean scores were seen to be statistically significant between the aripiprazole 10mg group compared to placebo and between the aripiprazole 30mg group compared to placebo (Table 8). In the aripiprazole 10mg group statistical significance compared to the placebo group was only achieved at weeks 1 and 5 of the interim time points[redacted], whereas in the aripiprazole 30mg versus placebo analysis the difference was statistically significant except at the 2-week interim analysis.

Table 8: CGI severity (change from baseline) and improvement score at study completion (six weeks)

Aripiprazole 10mg n=99	**Aripiprazole 30mg n=97**	**Placebo n=98**	**Aripiprazole 10mg versus placebo**	**Aripiprazole 30 mg versus placebo**
CGI severity score, LS mean (SE) change from baseline				
-1.2 (0.1)	-1.3 (0.1)	-0.9 (0.1)	Difference 0.3 p-value 0.007	Difference 0.4 p-value 0.0016
CGI improvement score, LS mean (SE)†				
2.7 (0.1)	2.5 (0.1)	3.1 (0.1)	Difference 0.4 p-value 0.02	Difference 0.6 p-value 0.0004

†Change from baseline not appropriate for the improvement score.

3.3.4 P-QLES-Q

The MS also reports evidence on QoL from the included RCT.[2] The P-QLES-Q 14-item total score showed improvements in all three groups after study completion (six-weeks). There were, however, no statistically significant differences between the active treatment groups and the placebo group change from baseline scores (see Table 9 below). On the P-QLES-Q overall score (see above for detail) all groups improved (score increased) at study end-point, and the change from baseline scores were statistically significantly different between the aripiprazole 10mg group compared to placebo, and the aripiprazole 30mg group compared to placebo.

Table 9: P-QLES-Q scores at study completion (six weeks)

Aripiprazole 10mg n=95	**Aripiprazole 30mg n=87**	**Placebo n=89**	**Aripiprazole 10mg versus placebo**	**Aripiprazole 30 mg versus placebo**
P-QLES-Q total score, LS mean change (SE)				

5.2 (0.9)	5.9 (0.9)	4.5 (0.9)	Difference 0.7 p-value 0.55	Difference 1.4 p-value 0.26
P-QLES-Q overall score, LS mean change (SE)				
0.6 (0.1)	0.6 (0.1)	0.1 (0.1)	Difference 0.5 p-value 0.005	Difference 0.5 p-value 0.003

3.3.5 Sub-group analyses results

No sub-group analyses are reported in the MS

3.3.6 Indirect Comparison results

The MS reported that no head to head RCTs of aripiprazole and any other atypical antipsychotics in adolescents were identified. To fulfil the manufacturer's decision problem (see section 2.3 above for discussion of the decision problem) an adjusted indirect comparison was undertaken to provide comparative data between aripiprazole and olanzapine, the manufacturer's chosen comparator for the health economic evaluation. One RCT of olanzapine was identified and the data from this trial were compared to data from the aripiprazole trial using the placebo arms of each trial as a common comparator. Results of the analysis were applied in the subsequent economic evaluation (withdrawals for adverse events, lack of efficacy, and other reasons; significant weight increase from baseline of ≥ 7%; somnolence; and use of benzodiazepines). Results for these outcomes from each trial have been checked by the ERG and are presented in Table 10 below. There appear to be a large number of withdrawals due to lack of efficacy in the placebo group of the included olanzapine trial (51%).[1] Overall, the proportions withdrawing from the study are higher in the olanzapine trial (32% olanzapine vs 57% placebo) than the aripiprazole trial [redacted].

The results of the adjusted indirect comparison are presented in Table 11. As noted above (Section 3.1.6), the MS did not provide details of the methodology of the olanzapine trial or present all results, and did not provide a full description of the adjusted indirect comparison approach taken or a critique of this. The MS does not provide an interpretation of the results of the adjusted indirect comparison or any critical assessment of the results of the analysis. Results of the adjusted indirect comparison (p 55) suggest that aripiprazole was not favoured over olanzapine for these six outcomes (in three outcomes the ORs and RRs were seen to be better for aripiprazole however the 95% CI for the OR and RR included 1.0).

In the aripiprazole study the numbers of participants for weight increase are fewer than the total sample size, although no explanation for this is provided in the MS.

Table 10: Outcomes from the two RCTs included in the indirect comparison

	Aripiprazole 10mg, n=100	**Placebo, n=100**	**Olanzapine (flexible dose), n=72**	**Placebo, (n=35)**
Outcomes	**Number of participants with event, n(%)**			
Withdrawals due to adverse events	7 (7%)	2 (2%)	5 (7%)	0 (0%)
Withdrawals due to lack of efficacy	[redacted]	[redacted]	10 (14%)	18 (51%)
Withdrawals for other reasons	[redacted]	[redacted]	8 (11%)	2 (6%)
Significant weight increase from baseline ≥ 7%	n=84 [redacted]	n=89 [redacted]	33 (46%)	5 (14%)
Somnolence	11 (11%)	6 (6%)	17 (24%)	1 (3%)
Participants receiving benzodiazipines	[redacted]	[redacted]	21 (29%)	18 (51%)

†MS reports aripiprazole trial withdrawals due to lack of efficacy and withdrawals for other reasons as CIC (p53), however, these are not CIC in the flow chart, p39.

Table 11: Results of the indirect comparison of olanzapine versus aripiprazole

Outcome	**OR (95% CI)**	**RR (95% CI)**
Withdrawals due to adverse events	1.57 (0.06, 43.87)	1.55 (0.06, 40.30)
Withdrawals due to lack of efficacy	0.03 (0.00, 0.31)	0.05 (0.01, 0.50)
Withdrawals for other reasons	3.73 (0.48, 28.70)	3.40 (0.50, 23.11)
Significant weight increase from baseline ≥ 7%	0.51 (0.02, 11.50)	0.34 (0.02, 6.96)
Somnolence	5.34 (0.54, 53.01)	4.44 (0.50, 39.34)
Participants receiving benzodiazipines	0.39 (0.14, 1.08)	0.57 (0.30, 1.06)

3.3.7 Summary of adverse events

An overview of the safety of aripiprazole is provided in the MS based on evidence from the included RCT[2] and two non-RCTs.[3,4] As noted above, no additional systematic searches were undertaken by the manufacturer to look for data on adverse events of aripiprazole. The two non-RCTs included were identified from the manufacturer's own sources. Study 31-03-241[3]

was a six month study including participants from the published trial and from another trial undertaken by the manufacturer in adolescents with bipolar disease (MS Table 27, p 61). Data were presented in the MS for the schizophrenia subgroup only. The doses of aripiprazole were reported as being flexible, between 2-30mg but no details of mean dose have been provided. Some 24.3% of participants discontinued the study. Study 31-05-243[4] is a continuation study for those with schizophrenia in study 31-03-241. The dose of aripiprazole is stated as 5-30mg, no further details are provided. At the time of print (six months) 11.8% had discontinued.

The most common adverse events appear to be reported in the MS and have been checked by the ERG where data were available. Data reported include treatment-emergent adverse events identified in a defined proportion of participants (the proportions were inconsistently classified with a class of ≥ 5% in two studies, and ≥ 2% in the third study; also some data below these thresholds were included). The ERG has not reproduced these data on adverse events here (see Tables 32, 33 and 34 of the MS for further details) but a general discussion of the adverse events used in the subsequent economic model is given below. Other safety results reported were serious adverse events, clinical test parameters, and weight gain.

The manufacturer utilises some of the data presented in the adverse events section of the MS in their economic evaluation. These are weight gain and somnolence and were from the 10mg aripiprazole arm of the included trial only. However, the ERG have presented data here from the 10mg and 30mg aripiprazole arms of the included trial (and the placebo arm) and the two non-RCTs to illustrate the range of data presented for these adverse events. The proportions of participants reported to have gained ≥ 7% of weight and the proportions with somnolence can be seen in Table 12. The ERG are unclear how appropriate the 7% threshold is as no explanation has been provided in the MS. In the included trial publication the data are reported for a gain of ≥ 5%, and for the non-RCTs data are from unpublished CSRs. Whilst it would be inappropriate to formally compare the values from the different studies it can be seen on observation of the data that these rates vary widely. The ERG has also presented the actual changes in weight between the three groups of the included RCT for context (Table 13).

Table 12: Adverse events in the included studies

Adverse event	**Proportion of participants**
RCT[2], Aripiprazole 10mg, n=100, data collection six-weeks	
Weight gain ≥ 7%	[redacted]

Somnolence	11%
RCT[2], Aripiprazole 30mg, n=102, data collection six-weeks	
Weight gain ≥ 7%	5.2%
Somnolence	21.6%
RCT[2], Placebo, n=100, data collection six-weeks	
Weight gain ≥ 7%	1.0%
Somnolence	6%
Non-RCT[3] Aripiprazole dose ranged from 2-30mg, n=239, data collection six-months	
Weight gain ≥ 7%	24.5%[2,3]
Somnolence	13.8%[3]
Non-RCT[4] Aripiprazole dose ranged from 5-30mg, n=85, data collection six-months	
Weight gain ≥ 7%	12.7%[4]
Somnolence	[redacted]

[1] [redacted]

[2]appears to contradict the data in Table 32, page 65, which states that weight increased in 7.9% of participants.

[3]Unable to check this data in the CSR as the subgroup with schizophrenia was not presented

[4]appears to contradict the data in Table 33, page 67 which states that weight increased in [redacted] of participants, data not available to check in the CSR.

Table 13: Mean change in weight, baseline to six weeks (from included RCT[2]; not reported in the MS)

	Aripiprazole 10mg n=98	**Aripiprazole 30mg n=NR**	**Placebo n=99**	**Aripiprazole 10mg versus placebo**	**Aripiprazole 30 mg versus placebo**
Mean (SD) change from baseline, kg	0 (2.1)	0.2 (2.3)	-0.8 (2.6)	Difference 0.8 kg	Difference 1.0 kg
				p-value 0.009 aripiprazole versus placebo	

Other adverse events which were not utilised in the subsequent economic model but which may be relevant are EPS, serious adverse events (SAE) and prolactin levels, and these are therefore briefly discussed here. In the included RCT[2] akathisia, extrapyramidal disorder and tremor (symptoms which are associated with EPS) occurred respectively in 5%, 13% and 2% of those in the aripiprazole 10mg arm. In the aripiprazole 30mg arm these rates were 11.8%, 21.6% and 11.8% respectively. In study 31-03-241[3] 8.4% had akathisia, 19.2% extrapyramidal disorder and 6.3% tremor. In study 31-05-243[4] 2.4% had extrapyramidal disorder and 3.5% tremor. Akathisia was not reported. In addition EPS scores were reported in the RCT publication[2] but not in the MS. These data show that changes from baseline differed significantly between

aripiprazole and placebo for Simpson-Angus scale (0.5 aripiprazole 10mg; 0.3 aripiprazole 30mg, -0.3 placebo, p<0.007 aripiprazole 10mg vs placebo, p< 0.05 aripiprazole 30mg versus placebo). For the Barnes and AIMS scales the RCT states that there were no statistically significant differences although the data itself was not reported.

In the included RCT[2] the MS does not report an overall incidence of SAEs, however, it does report the numbers of participants reporting a range of SAEs and from this the ERG can estimate that the rate of SAE in the aripiprazole 10mg arm was 6% and in the aripiprazole 30mg arm was 5%. In study 31-03-241[3] and study 31-05-243[4] the MS reports that SAEs were experienced by 5.9% of participants.

In the included RCT[2] prolactin levels in the aripiprazole 10mg arm decreased by 11.94 ng/ml by the end of the study. The incidence of low prolactin (<3ng/dl females and <2ng/dl males) was 33.7% in the aripiprazole 10mg arm. In the 30mg aripiprazole arm prolactin levels decreased by 16.74% and the incidence of low prolactin (as defined above) was 26.3%. The MS does not report the p-values for the differences between the groups, however, these are presented in the included RCT publication.[2] The change from baseline values for prolactin were statistically significantly different between the aripiprazole 10mg versus placebo arm (p<0.003) and between the aripiprazole 30mg versus placebo arm (p<0.0001). Similarly, the proportion of participants deemed to have clinically significant low prolactin levels was statistically significant between intervention and placebo groups (aripiprazole 10mg vs placebo, p<0.0001; aripiprazole 30mg vs placebo p<0.001) but this was not reported in the MS itself.

[redacted]

[redacted] In study 31-05-243 the MS states (p68) that "paired data were available for very few subjects and included three participants who completed month 12 and the end of treatment evaluations for withdrawn subjects' as having insufficient data to draw conclusions regarding the prolactin levels in this study". The ERG are unclear what is meant by this statement but the effect of this is that no prolactin data were presented.

On page 71 of the MS the overview of safety states that aripiprazole is generally well tolerated, with the majority of adverse events being mild or moderate in severity, and the incidence of discontinuations due to adverse events were low. Overall, the ERG would agree that this

appears to be a reasonable summary of the data presented. The MS also says that EPS were the most common treatment-emergent adverse events but that these rates are lower than that of first generation antipsychotics (reference provided). This concurs with advice received by the ERG that EPS are not a considerable problem. Hyperprolactinaemia is a potential adverse effect of atypical antipsychotics, however, these data show that prolactin levels decreased after treatment. No further discussion of these results was provided in the MS.

3.4 Summary

Within the reported study population of the MS, aripiprazole appears to show some short-term clinical benefit for adolescents with schizophrenia. While AEs appear to be moderate, the data presented cannot be fully compared with other treatments of this type. Although the ERG does not believe that any relevant trials have been missed, the MS contains only one single Phase III RCT comparing aripiprazole with placebo. Due to the lack of data on comparator treatments, the MS is unable to comment on the treatment effect within the decision problem as set by NICE.

Overall, the MS provides a limited and uncritical interpretation of the clinical evidence. In section 5.10 of the report in particular, the manufacturer reports on the advantages of aripiprazole, however, this is not based on evidence provided in the MS. In addition, the MS makes no reference to, or interpretation of, the placebo effect shown in the evidence, and there is no discussion of the clinical benefits of the outcome measures used or their meaning to patients. The ERG also notes that there may be some bias in the evidence of AEs, as a systematic search was not undertaken by the manufacturer, and some potentially important AE outcomes were omitted from the MS. The MS undertook an adjusted indirect comparison, however, this was based on limited outcomes, with minimal reporting of the methods employed. The MS interpretation of the evidence does not appear to the ERG to be fully justified on the basis of the evidence provided.

In summary, the MS is a reasonable approach to evidence synthesis within a restricted scope. The MS does not appear to sufficiently address the decision problem as set by NICE and it is unclear how the outcomes reported relate meaningfully to patients.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

i) a review of published economic evaluations of aripiprazole used in adult schizophrenia in the UK, since no economic studies were found in the systematic search conducted for pharmacological treatments for schizophrenia in adolescents (discussed further in section 4.1.1).

ii) a report of an economic evaluation undertaken for the present NICE appraisal. The cost effectiveness of aripiprazole as first line treatment followed by olanzapine as second line treatment and clozapine as rescue treatment (referred to in this report as first-line aripiprazole), is compared with olanzapine followed by aripiprazole as second line treatment, and clozapine as a rescue option (referred to in this report as first-line olanzapine). The results of the economic analysis are reported in terms of the incremental cost per Quality Adjusted Life Year (QALY) gained.

4.1.1 Manufacturer's review of published economic evaluations

A systematic search of the literature was conducted by the manufacturer to identify economic evaluations of pharmacological treatments for adolescent schizophrenia in the UK. An additional search for economic evaluations of aripiprazole (including adult schizophrenia) was performed due to the paucity of studies on adolescent and childhood schizophrenia. See section 3.1.1.2 for ERG critique of the search strategy.

The inclusion and exclusion criteria for the systematic review (listed in section 9.10.6 of the MS, p 147) specified that either cost-effectiveness, cost-benefit, cost-minimisation, cost-consequence or cost-utility studies regarding adolescent or child populations with schizophrenia or any of those studies involving aripiprazole (including those in adult populations) would be included. The MS excluded studies that did not include schizophrenia, aripiprazole (unless the population was adolescent or child populations), studies that are not relevant to the UK, and studies which did not consist of cost-effectiveness, cost-benefit, cost-minimisation, cost-consequence or cost-utility studies.

The MS states in section 6.1 that 52 potentially relevant studies were identified from screening 550 titles and abstracts. Of these 49 studies were excluded, mainly for not including aripiprazole

or not being relevant to the UK setting. Three studies were included for full review – Barnett and colleagues (2009),[8] Davies and colleagues (2008)[9] and Heeg and colleagues (2008).[10] Five additional studies were identified by hand-searching of the NICE website, two of which were excluded for not addressing the treatments or population scoped, and another two were excluded for having been superseded by the only additional included study - the current NICE clinical guideline on schizophrenia in adults[11] (details provided in MS Appendix 10, section 9.10.5). Therefore, in total, four studies were included.

A brief overview of each of the four included economic evaluations is provided in section 6.1.2 of the MS (p 75). Although all of the four studies used UK cost data, they all involved adult populations and hence were not considered to address the purpose of the MS. Apart from Barnett and colleagues (2009),[8] which is a cost-consequence analysis focused on diabetes and coronary heart disease (CHD) outcomes, the included studies consist of cost-utility analyses, two of them based on Markov models,[9,11] and one used discrete event simulation (DES).[10] The methodological quality of each study was assessed using the quality assessment checklist suggested in the NICE specification for manufacturer/sponsor submission of evidence.[12] These are presented in tables in Appendix 11 (Section 9.11, p 148) of the MS. No interpretation or conclusions of this quality assessment were provided in the MS.

Having briefly described the methodology, data sources, and results of each study, the manufacturer concluded, without further discussion, that no economic evaluations of the cost-effectiveness of aripiprazole in adolescent schizophrenia were identified and therefore a *de novo* economic evaluation was conducted for the current submission. Relevant methodological characteristics of the included published economic evaluations were not discussed in the MS (see section 4.2 of this report for further discussion of the methodology of these studies).

4.1.2 CEA Methods

A decision tree followed by a Markov model was developed by the manufacturer to estimate the cost-effectiveness of first-line aripiprazole compared to first-line olanzapine for the treatment of adolescent schizophrenia. The model incorporates first-, second- and third-line treatments, and patients switch to the next treatment when they discontinue or relapse. As discussed in section 6.2.6 of the MS, the model has a 3-year time horizon and cycle length of six weeks, with no half-cycle correction being applied.

The model was populated with clinical effectiveness data for adolescents aged 13-17 (MS section 6.2.1, p 79) and the base case analysis compares first-line aripiprazole with the alternative treatment strategy of first-line olanzapine. Results are presented in terms of total and incremental costs and QALYs, and incremental cost-effectiveness ratios (ICERs) between the two strategies (MS Tables 44 and 45).

4.1.2.1 Natural history

The model structure is intended to reflect the progression of schizophrenia in adolescents after an acute schizophrenic episode (MS section 6.2.5), and the clinical management of discontinuation and relapse, in order to capture the impact of first-line treatment on costs and patient outcomes until the age of 18 is reached (MS section 6.2.3). Disease progression was measured for both treatment strategies through the risk of relapse, adverse events and of treatment discontinuation due to lack of efficacy, adverse events or other reasons (MS section 6.3).

In the first two cycles, patients undergoing treatment may discontinue and switch to another antipsychotic drug. These are represented in the decision tree with the following health states: stable schizophrenia and withdrawal (due to lack of efficacy, adverse events or other reasons). In the second cycle, patients may relapse from treatment, thus this additional state is considered. Patients who do not relapse or discontinue treatment are assumed to continue on treatment in the stable schizophrenia state (section 6.3.8, p 91). Discontinuation was assumed to occur only in these first two cycles. From the third cycle onwards, patients are assumed to either continue in a stable condition with a given antipsychotic or to relapse and subsequently switch antipsychotic treatment. Hence, a Markov process was used involving only two states - maintenance on treatment and relapse - for the three lines of therapy. As shown in Figure 9 (page 81 of the MS) and stated in section 6.3.8, patients who discontinue or relapse on the second treatment are assumed to receive clozapine as a last resort treatment and to continue receiving clozapine after relapse. Death was not modelled (page 81 of the MS).

4.1.2.2 Treatment effectiveness

Treatment effectiveness is measured by each drug’s ability to maintain patients in the stable schizophrenia state (by avoiding discontinuation or relapse). The clinical parameters outlined in

section 6.3.1 (p 85) of the MS are: withdrawals (due to lack of efficacy, adverse events or other reasons), rates of adverse events and longer term rates of relapse. No indicator of disease improvement is considered for stable schizophrenia.

4.1.2.3 Health related quality-of-life

The aspects of schizophrenia identified in section 6.4.1 of the MS (p 92) as those that most affect patients' quality of life (QoL), were significant social, psychological and occupational dysfunction, social stigma, and behaviours related to psychotic symptoms. Though not clearly stated by the manufacturer, the model assumes that health states correspond to stages of disease progression and determine patients' QoL. The relevance of the impact of adverse events associated with antipsychotic treatment on patients' QoL was also highlighted and modelled. This is consistent with the previously published economic evaluations.[9,11]

According to MS sections 6.4.3 and 6.4.4, given that the EQ-5D was not used by the included RCT[2] and mapping was not used to transform the QoL data collected, the QoL estimates were derived from alternative sources. In the absence of data specific to adolescents, estimates from adult schizophrenia studies were assumed to be applicable and were used in the model.

4.1.2.4 Resources and costs

As detailed in section 6.5.3 of the MS, resource use data for adults provided by the NICE adult schizophrenia guideline[11] were used and amended as per recommendation of clinical experts to reflect the use of child and adolescent services. Besides the acquisition and monitoring of drugs (MS section 6.5.5), the included resources relate to the management of relapse, adverse events and switching treatment (MS sections 6.5.6, 6.5.7 and 6.5.8), adopting the perspective of the NHS and Personal Social Services (PSS) (MS sections 6.2.6 and 6.5). Relapse management includes acute hospitalisation, treatment in Child and Adolescent Mental Health Services (CAMHS) and medication. Unit costs were taken from the Personal Social Services Research Unit (PSSRU) 2009 report[13] and the NHS 2008-2009 Reference Costs,[14] as per MS section 6.5.6 and response to requested clarifications (see Addendum to this report).

Dosing data for aripiprazole and olanzapine were sourced from the relevant RCTs.[1,2] Section 6.5.5 of the MS shows that the daily dose and monitoring-related resource use for clozapine were estimated according to the Summary of Product Characteristics (SPC) of its most

prescribed formulation[15]. NHS Prescription Cost Analysis 2008[16] was used to identify the most frequently prescribed formulation of the drugs under analysis (p 110 to 111), and the acquisition costs were taken from the Monthly Index of Medical Specialties (MIMS online).[17]

4.1.2.5 Discounting

The discount rate applied to both future costs and benefits was 3.5% (p 83).

4.1.2.6 Sensitivity analyses

One-way sensitivity analyses were conducted, including all variables in the model and presented as a tornado plot showing the 20 most influential parameters, on page 109 of the MS. A series of scenario analyses were performed (p 112 to 121) to explore the relevance of assumptions related to: the most influential parameter (RR of relapse); the exclusion of EPS; different measures of treatment effect (RRs versus ORs); and accounting for utility decrements due to awareness of the potential for serious adverse events of clozapine. A probabilistic sensitivity analysis on the base case was conducted by running 10,000 simulations [model input parameters are available in Appendix 9.14 (p 163) of the MS] and the results are presented in Table 45 (p 110) of the MS. Additional PSAs were reported for each of the scenario analyses described above.

4.1.2.7 Model validation

The MS states that structural assumptions in the model were validated through discussion with a health economic expert prior to building the model, and that the electronic model was validated by having input data and calculations checked by at least two modellers or health economists and by checking whether the model results varied as expected when varying the value of input parameters.

4.1.2.8 Results

The model output for the base case analysis is presented in section 6.7 of the MS, showing Markov traces for each treatment strategy indicating the proportion of patients in each state over time (p 107). Deterministic results for the base case analysis are also given in Table 44 (p 108) in the MS reporting total and incremental costs and QALYs for each strategy, and incremental cost per QALY (dominance of one of the strategies over the other is used when negative ICERs are obtained, consistent with NICE methods guidance[18]). Probabilistic results are presented in

Table 45 (page 110) in the MS, using a cost-effectiveness plane (Figure 13, page 110 of the MS) and a cost-effectiveness acceptability curve (CEAC – Figure 14, page 112 of the MS).

In the base case analysis, first-line aripiprazole was found to be dominant, since it was less costly and more effective, compared with first-line olanzapine. Table 14 and Table 15 present the deterministic and probabilistic results of the base case analysis from the MS.

Table 14: Deterministic results presented for base case analysis (MS table 44)

Treatment strategy	Total Cost (£)	Total QALYs	Incremental Cost	Incremental QALY	ICER (£/QALY)
First-line aripiprazole	23,723	2.597	-69.21	0.004	Dominant
First-line olanzapine	23,792	2.593			

Table 15: PSA results presented for base case analysis (MS table 45)

Treatment strategy	Total Cost (£)	Total QALYs	Incremental Cost	Incremental QALY	ICER (£/QALY)
First-line aripiprazole	23,763	2.596	-1,016	0.008	Dominant
First-line olanzapine	24,778	2.589			

In the one-way sensitivity analyses the RR of relapse and the daily cost of aripiprazole were found to be the most influential parameters on the model results, followed by the OR of somnolence (page 109 of the MS).

The manufacturer performed a scenario analysis using estimates for RRs of relapse of the mixed treatment comparison (MTC) undertaken for the guideline for schizophrenia in adults.[11] The deterministic results showed that first-line aripiprazole would not be cost effective compared with first-line olanzapine. The results of additional scenario analyses conducted by the manufacturer are presented and discussed in detail in section 4.3.4.3 of this report.

4.2 Critical appraisal of the manufacturer's submitted economic evaluation

The ERG did not undertake an independent appraisal of the published economic studies identified by the MS, but considers that their analysis in further detail can provide information relevant to the decision problem.

While Heeg and colleagues' DES-based model[10] considered four lines of antipsychotic treatment, both Davies and colleagues[9] and the NICE guideline for schizophrenia in adults[11] used Markov models which included three lines of antipsychotic medication and three health states – stable schizophrenia, relapse and death. Apart from the exclusion of the "death" state, the *de novo* analysis reported in the MS adopted an analogous approach to these Markov model-based studies[9,11] regarding treatment lines and health states.

Similarly to the MS *de novo* analysis, clozapine was the rescue option considered by Davies and colleagues [9] and Heeg and colleagues.[10] In contrast, in the NICE guideline,[11] the rescue alternative was assumed to always be a *depot* (long-acting injection) antipsychotic (namely, flupentixol decanoate). Longer cycle lengths than the six weeks used in the MS were employed in both of these studies using Markov models -18 weeks in Davies and colleagues [9] and 6 months in the NICE guideline[11].

Heeg and colleagues[10] found atypical antipsychotics less costly and more effective than typical antipsychotics, while Barnett and colleagues[8] found that aripiprazole was associated with fewer onsets of diabetes and CHD, and consequently lower long-term costs than olanzapine, quetiapine or risperidone. Moreover, Davies and colleagues[9] found aripiprazole-risperidone as the dominant sequence in terms of cost-effectiveness compared to 11 other pair sequences which also included the use of olanzapine and quetiapine. In contrast, despite showing olanzapine as more cost-effective than aripiprazole, given the high uncertainty, the NICE guideline for schizophrenia in adults[11] concluded that no option can be considered cost-effective compared to the other alternatives considered. The ERG suggest that the results presented by Davies and colleagues[9] show that risperidone may be a relevant comparator considering that the aripiprazole-risperidone sequence was found more cost-effective than the aripiprazole-olanzapine one.

4.2.1 Critical appraisal of economic evaluation methods

The ERG have considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 16 below, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[19]).

Table 16: Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	The decision problem addressed in the submission is presented in section 4 on pages 26 to 27. The MS estimated the cost-effectiveness of aripiprazole compared to olanzapine as first line therapy for adolescent schizophrenia.
Is there a clear description of alternatives?	Yes	The alternative strategies (aripiprazole – olanzapine – clozapine *versus* olanzapine – aripiprazole – clozapine) are stated in section 6.2.3 (p 81) of the submission.
Has the correct patient group / population of interest been clearly stated?	Yes	As per its final scope, the objective of the current STA is to appraise the clinical and cost effectiveness of aripiprazole in its licensed indication for the treatment of schizophrenia in adolescents (15-17 years). However, clinical effectiveness data of patients aged 13-17 years old were considered in the MS, given that the RCTs informing on the clinical effectiveness of aripiprazole and of the chosen comparator involved participants of that age range. A post-hoc subgroup analysis of 15-17 year old participants confirmed the comparable efficacy improvements of this age group with the overall adolescent dataset, the maintenance of effect in 15-17 year old patients and its similarity in terms of safety and tolerability with adult patients as reported in section 5.3.6 (p 38) and section 6.2.1 (p 79) of the MS.
Is the correct comparator used?	No	According to the MS section 4 (p 26), from the five scoped comparators, only olanzapine was included in the MS as a comparator due to the lack of evidence for the other scoped comparators in adolescents - risperidone, quetiapine, amisulpride and clozapine. Also note the only scoped comparator which is licensed for use in adolescents – amisulpride - was not analysed, and clozapine, which despite having been included as third line treatment in both alternative strategies of the model, was not accounted for as a comparator nor included in searches for clinical effectiveness estimates. ERG clinical advise suggests that risperidone is a relevant off-licence comparator.
Is the study type reasonable?	Yes	The conducted cost-utility analysis is appropriate to appraise the costs and health benefits in terms of HRQoL associated to each strategy and to identify the most cost-effective strategy through the incremental analysis.
Is the perspective of the analysis clearly stated?	Yes	The NHS and PSS perspective was adopted for costs as patient perspective was for outcomes, as per section 6.2.6 of the MS (p83).
Is the perspective employed appropriate?	Yes	In accordance with the NICE methods guide and the scope of this appraisal, sections 6.4 and 6.5 of the MS show that the perspective on costs is that of the NHS and PSS, and the perspective on outcomes considers health effects in terms of patients' quality of life and life expectancy (measured in QALYs).
Is effectiveness of the	Yes	The clinical evidence used in the model concerning

intervention established?		aripiprazole is based on the results from the included RCT (Findling and colleagues[2]), in which aripiprazole was found to be effective in adolescents compared to placebo. According to MS section 6.3.1 (p 85), aripiprazole's effectiveness was input into the model through the following parameters: withdrawal due to lack of efficacy, withdrawal due to adverse events, withdrawal due to other reasons and rates of adverse events (weight gain and somnolence). An adjusted indirect comparison was performed to obtain relative estimates of the effects of the two treatments. Given the short duration of the relevant RCT, Moeller and colleagues[20] provided long term relapse rates in adult patients with schizophrenia.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	A lifetime horizon would be appropriate to reflect all important differences between interventions given the chronic nature of schizophrenia. However, the justification provided on MS section 6.2.6 (p 83) for a 3-year time horizon consisted essentially of considering that the main differences between the technologies being assessed are before adulthood and that there is lack of data on long-term treatment outcomes.
Are the costs and consequences consistent with the perspective employed?	Yes	As described in the MS section 4, in accordance with the NHS and PSS perspective, the MS considered costs concerning acquisition of drugs, relapse treatment, adverse event treatment and costs of switching treatment. Patients' HRQoL was considered in the analysis in terms of QALYs, hence accounting for differences in both life expectancy and quality of life.
Is differential timing considered?	Yes	As per the NICE reference case, section 6.2.6 of the MS (p 83) shows that an annual rate of 3.5% was applied on both costs and benefits.
Is incremental analysis performed?	Yes	Deterministic results in terms of total and incremental costs and QALYs, and ICERs are reported for the base case analysis in table 44 (section 6.7.6, p 108) of the MS and for the PSA in table 45 (p 110).
Is sensitivity analysis undertaken and presented clearly?	Yes	PSA results are presented in section 6.7.8 (p 109 to 112), where a CE plane with confidence ellipses and a cost effectiveness acceptability curve (CEAC) can be found as well. Moreover, the MS undertook one-way deterministic sensitivity analyses and scenario analyses. According to the MS (section 6.6.2, p 104), all variables were included in the deterministic sensitivity analysis (DSA), using either the 95% CI reported in the adjusted indirect comparison or in the literature, or by assuming a 30% variation from the mean value of parameters for which no measure of variability was available. A tornado diagram was used to present the results of one-way SA, identifying the 20 most influential parameters (figure 12 section 6.7.7, p 109). This diagram does not explicitly show the ranges considered for each parameter though, which are available in Appendix 14 of the MS (p 163). Pages 112 to 121 of the MS present results of the scenario analyses performed on RR of relapse, EPS (with number of patients receiving benzodiazepines as a

		proxy), RR as alternative to OR as measures of treatment efficacy and accounting for disutility from clozapine.

NICE reference case

The NICE reference case[18] requirements have also been considered for the critical appraisal of the *de novo* economic evaluation of the MS, as summarised in Table 17 below.

Table 17: NICE reference case requirements

NICE reference case requirements (see detail in NICE report)**:**	Included in Submission
Decision problem: As per the scope developed by NICE	✓
Comparator: Alternative therapies routinely used in the UK NHS	?[a]
Perspective on costs: NHS and PSS	✓
Perspective on outcomes: All health effects on individuals	✓
Type of economic evaluation: Cost effectiveness analysis	✓
Synthesis of evidence on outcomes: Based on a systematic review	?[b]
Measure of health benefits: QALYs	✓
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	x[c]
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	✓
Source of preference data: Representative sample of the public	?[d]
Discount rate: 3.5% pa for costs and health effects	✓
Notes:✓=yes; x = no; ? = uncertain a) Only one of the scoped comparators was considered in the MS b) Study by Moeller and colleagues[20] that provided long-term relapse rates was not found via systematic review, nor was a systematic review for any clozapine data performed. c) Not standardised generic instrument, but health state descriptions were developed from literature review and expert opinion. d) Adult preferences were considered rather than adolescents.	

The manufacturer's analysis does not present disaggregated costs – by health state or by line of treatment, as suggested in the NICE template for submissions[12] – arguing that the model is not structured to provide such results. This appears to arise primarily from the structure, which separates out the first two cycles into the decision tree. However, if these first two cycles are incorporated into the Markov cohorts (undertaken by ERG in the electronic model submitted by the manufacturer), discounted costs disaggregated by line of medication and stages of clinical management (side effects, relapse and switching medication) can be estimated. Table 18 shows the dominating impact of costs of relapse in the evaluation, comprising approximately 80% of total costs for both treatment strategies. In contrast, medication costs comprise only 15% of total costs.

Table 18: Disaggregated costs, separating medication costs from management of side effects, relapse and additional costs of switching medication

Treatment strategy	Medication			Management			Total cost
	First-line	Second-line	Rescue	Side effects	Relapse	Switching	
First line aripiprazole	1,834	1,178	629	546	19,184	353	23,723
First line olanzapine	1,757	1,195	710	666	19,095	369	23,792

Table 19 reports disaggregated utilities by line of treatment and by health state (stable schizophrenia or relapsed). Disutility associated with side effects while on treatment were estimated for each line of treatment, but could not be distinguished between heath states.

Table 19: Disaggregated utilities, separating results for each line of treatment, identifying disutility from side effects

		First line		Second line		Rescue		Total	
		Stable	Relapse	Stable	Relapse	Stable	Relapse		
First line aripiprazole	Utility	1.2744	0.0523	0.7972	0.0269	0.4424	0.0131	2.606	2.597
	Disutility	0.0028		0.0053		0.0010		0.009	
First line olanzapine	Utility	1.1694	0.0534	0.8379	0.0292	0.4991	0.0148	2.604	2.593
	Disutility	0.0078		0.0019		0.0011		0.011	

Table 20 reports the distribution of patients across the three lines of treatment at the end of the model time horizon for both treatment strategies. A larger proportion of the modelled cohort is receiving third line treatment, at the end of the model time horizon, under the first-line olanzapine strategy compared with the first-line aripiprazole strategy. This largely arises due to the relatively high proportion of patients discontinuing treatment with olanzapine in the first cycle [redacted] and the higher risk of relapse on second-line treatment (with aripiprazole) for the first-line olanzapine strategy.

Table 20: Disposition of patient cohort across lines of treatment at end of model time horizon

	First line treatment		Second line treatment		Third line treatment	
	Maintenance	Relapse	Maintenance	Relapse	Maintenance	Relapse
First-line	0.232	0.012	0.353	0.017	0.369	0.017

aripiprazole						
First-line olanzapine	0.218	0.011	0.335	0.017	0.400	0.019

Summary

The methods adopted for the economic evaluation appear reasonable. The methods and data inputs to the model generally conform with NICE methodological guidance.[18] However, the economic evaluation only includes one of the comparators included in the NICE scope – excluding risperidone, which has been shown in a previous study (in adults with schizophrenia) to be a component of cost effective treatment strategies.[9,11]

Table 18 to Table 20 illustrate the comparatively small differences between costs and QALYs for the two treatment strategies included in the MS, and the major contribution of costs of managing relapse to total costs for both treatment strategies.

4.3 Critical appraisal of modelling methods in the manufacturer's economic evaluation

An outline critical review of modelling methods has been undertaken by the ERG. The review has used the framework for good practice in modelling presented by Philips and colleagues[21] as a guide, addressing issues of model structure, structural assumptions, data inputs, consistency, and assessment of uncertainty. The ERG presents the findings of this critical review and comments on issues identified.

4.3.1 Modelling approach / Model Structure

The model adopted for this submission is described in the MS as a decision tree model followed by a Markov model, and is evaluated using cohort simulation. A schematic for the decision tree is presented in Figure 8 (p 80) of the MS and a state transition diagram for the Markov model is presented in Figure 9 (p 81) of the MS. These are also included in the electronic model (on worksheets named '*Decision Tree'* and *'Markov Model').* The structure of the Markov model appears similar to that adopted for the NICE guideline on schizophrenia in adults,[11] though this is not discussed in the MS. Indeed the MS includes no discussion of the model structure in terms of clinical validation or comparison with models of schizophrenia in other patient populations. The MS does state that the model structure was discussed and externally validated by a health economist with an interest in mental health, prior to building the model.

The decision tree is used to determine whether patients remain on their current treatment or discontinue (due to lack of efficacy, adverse events or other causes) and is evaluated over two six-week cycles. Patients then enter the Markov model, in which they either experience relapse (switching from their current treatment to the next available line, unless they are already on the rescue treatment) or remain with stable schizophrenia. An alternative conceptualisation would be to incorporate the whole process within the Markov model and use cycle-dependent transition probabilities. In the first cycle, with all patients currently on first-line treatment, the relevant transition probabilities are those for discontinuation of first line treatment due to lack of efficacy, adverse events or other causes. In the second cycle the relevant transition probabilities are those for relapse on first line treatment and discontinuation of second line treatment due to lack of efficacy, adverse events, or other causes. In the third cycle (and all remaining cycles) the relevant transition probabilities are those for relapse on first line treatment, second line treatment and on rescue treatment. This alternative conceptualisation of the process is reflected in the presentation of Markov cycle traces (for all cycles, including those evaluated in the decision tree) in the electronic model, and in the MS (Figures 10 and 11, page 107 of the MS). It is not clear why the manufacturer chose to structure the model as a decision tree separate from the Markov model.

The states in the model - maintenance on current medication (which seems to be regarded as synonymous with stable schizophrenia) or relapse – appear to be reasonable as a characterisation of a chronic disease with periodic acute episodes and is consistent with the model developed in the NICE guideline for schizophrenia in adults.[11] There is no discussion in the MS on the appropriateness of treating non-relapse as a single state with a single utility value. This appears to ignore the clinical data on symptomatology presented in section 5.5 (p 40 to 50) of the MS. Moreover, there is no discussion in the MS of the rationale for excluding other states, such as “stable schizophrenia without anti-psychotic medication” that were included in the NICE model[11], from the model presented in the MS. There is limited discussion of the rationale for excluding mortality from the model, other than to state that there is no evidence of survival differences between treatments included in the model.

In contrast to the model developed for the NICE guideline for schizophrenia in adults,[11] the model presented in the MS makes no adjustment to drug costs for patients experiencing relapse. In the NICE guideline model all transitions were assumed to occur in the middle of the

annual cycle – all patients experiencing relapse would stop any existing antipsychotic medication and were then treated for the acute episode. Once they achieved remission they would return to their previous medication or switch to the next available line of treatment. In contrast, the model presented in the MS evaluates costs and outcomes at the end of each cycle – as a result, a patient who has a relapse accrues the full cycle cost of medication and the full cost of relapse, in the cycle that the relapse occurs. This implicitly assumes that patients/ carers are supplied with six weeks (or longer) of medication.

Cycle length for the model appears to be entirely driven by the length of follow up in the included clinical trials.[1,2] Clinical advice to the ERG suggested that six weeks may indeed be a suitable duration for a therapeutic trial of a new medication in this patient group. However, there is no discussion in the MS of the appropriateness of the cycle length to progression of disease or rate of deterioration in this patient group.

The model has a three year time horizon. This is discussed in the MS in Table 3 (p 83) and the table in section 4 (p 26 to 27) of the MS outlining the decision problem. The selected time horizon is justified in the MS on the basis that: this corresponds to the maximum duration that an individual would remain in this patient group before being considered an adult (at which point other treatment options may be available); a lifetime model has been used for examining treatment options in adults (associated NICE guidance); and the lack of long-term evidence undermines the reliability of a lifetime model in this patient group. In this context the ERG considers the time horizon of three years reasonable for extrapolation from six week trials.

4.3.1.1 Structural Assumptions

The model assumes that all discontinuations due to adverse events, lack of efficacy and other reasons only occur in the first cycle of use with each line of treatment. This is consistent with the model developed for the NICE guideline for schizophrenia in adults[11] and with the clinical data used to populate the model, which had follow up data to six weeks. Discontinuation of current medication, in subsequent cycles, is only associated with relapse. However, there are no discontinuations with rescue medication, consistent with the model developed for the NICE adult guideline.[11] In the model presented in the MS, all patients who relapse on first or second line medication switch to the next available line – no patients are allowed to go unmedicated.

Patients on antipsychotic medication may experience treatment-related side effects that do not lead to discontinuation of treatment. These are accounted for in the model by applying a disutility for those patients experiencing a side effect (to account for the QoL impact of these side effects) and by applying estimated costs of managing the side effects. Different structural assumptions are applied, dependent on the type of side effect: it was assumed in the MS model that patients would only experience weight gain in first cycle of use with each line of treatment, whereas patients can experience somnolence and EPS in any treatment cycle. It is not clear from the MS whether the assumption regarding weight gain means that patients experience the weight gain in first cycle and remain overweight (thereby experiencing a QoL impact while they remain on the same medication) or whether the weight gain is assumed to resolve by the end of the first cycle. It appears, in the electronic model, that the latter assumption (that the QoL impact of weight gain only applied for the cycle in which weight originally occurs and not in subsequent cycles) has been applied (the impact of this assumption is explored in ERG scenario analyses reported in section 4.3.4.4).

It is assumed in the model that all patients who experience relapse on first or second line treatment will switch to the next line of treatment and will not remain on their current treatment. This assumption differs from that applied in the model developed for the NICE guideline for adult schizophrenia,[11] which allowed for 50% of patients to return to their current line of treatment following a relapse (with the assumption that they had temporarily stopped their current line of treatment while undergoing treatment for the relapse). It is not clear from the MS whether this assumption was discussed and validated by clinical experts.

4.3.2 Data Inputs

4.3.2.1 Patient Group

The MS states that the population considered in the economic evaluation is adolescents with schizophrenia aged 13-17. As stated earlier, this age range is wider than the UK marketing authorisation – the SPC for aripiprazole states it is not recommended for patients under 15 years of age due to insufficient data on safety and efficacy. The age range for patients in the model is consistent with the inclusion criteria for the RCT reported by Findling and colleagues[2] (reviewed in section 3.1.2.1 of this report). Further inclusion criteria for the trial were that patients should have:

o DSM-IV axis I primary diagnosis of schizophrenia (confirmed using K-SADS-PL)

- baseline PANSS score of 70 or higher.

The inclusion criteria are broadly similar to those for the trial reported by Kryzhanovskaya and colleagues[1] (used for the adjusted indirect comparison of aripiprazole with olanzapine) except that Kryzhanovskaya and colleagues:

- specified their diagnostic inclusion criterion as DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, Text revision) diagnosis of schizophrenia of the paranoid, disorganised, catatonic, undifferentiated and residual types (confirmed using K-SADS-PL).
- did not have any inclusion criteria based on PANSS score, but patients were expected to have a score over 35 on the anchored version of the Brief Psychiatric Rating Scale for Children (BPRS-C) scoring over 3 on at least of the hallucination, delusion or peculiar fantasies items.

The MS refers in section 6.2.1 (and earlier in section 5.3.6) to a post-hoc analysis of differences in outcomes between three age groups in the included trial reported by Findling and colleagues,[2] stating that outcomes in terms of long term symptom improvement, remission and maintained remission were similar across all three groups. No more detail is given in the MS and this analysis was not included as part of the submission. While the MS states similarity by age in outcomes such as long term symptom improvement, remission and maintained remission, these outcomes are not used in the model, whereas no information was provided on the relationship of age with variables that do enter the model (such as withdrawals due to lack of efficacy, adverse events and other causes).

Other than age, the MS contains no discussion on how the modelled population relates to the expected population likely to receive aripiprazole in clinical practice. In section 6.2.5 the MS describes the patient population entering the model as “in the acute phase of the disease with elevated PANSS scores” – but it does not discuss whether this is the expected population likely to receive aripiprazole in clinical practice.

4.3.2.2 Clinical Effectiveness

Clinical input parameters to the model are described in section 6.3 of the MS. Section 6.3.1 specifies the clinical parameters in the model and the rationale for their inclusion. Section 6.3.2 of the MS presents the base case parameter values, the sources and derivation of those values.

As discussed in section 4.3.1 of this report, the model adopted for the economic evaluation presented in the MS characterises schizophrenia as a chronic disease with periodic acute episodes, termed relapse in the model. The key clinical event in the model that is related to patients' current medication is the probability of relapsing in a given cycle. Other events included in the model are discontinuation of current medication and occurrence of treatment-related adverse events. Symptoms (outcomes reviewed in sections 3.3.1 to 3.3.4 of this report), which were the primary outcomes in clinical trials are not included in the model. This is consistent with the model developed for the NICE guideline for adult schizophrenia (the appropriateness of this assumption is discussed in section 4.3.1 of this report).[11]

The probability of discontinuing treatment (due to lack of efficacy, serious treatment-emergent adverse events and "other" causes) and the probability of experiencing treatment-related adverse events [weight gain ≥ 7%, somnolence and use of benzodiazepines (as a proxy for EPS)] were derived based on data included in the adjusted indirect comparison discussed in section 3.3.6 of this report. Event rates observed for aripiprazole in the included trial (Findling and colleagues[2]) were used as estimates of the probability of treatment discontinuation and adverse events for aripiprazole. To estimate treatment discontinuation and adverse events for olanzapine, the ORs estimated in the adjusted indirect comparison, were applied to the probabilities used for aripiprazole. In order to apply the ORs, the probabilities were first converted to odds – once the ORs were applied the odds were transformed back to probabilities. As noted in section 3.3.6 of this report, there is no discussion in the MS of the appropriateness of the methodology of the adjusted indirect comparison, nor any critical assessment of the results of the analysis. For example, there is no discussion of the validity of making an indirect comparison for withdrawals due to lack of efficacy, where [redacted] of placebo patients withdrew in one trial and 51% of placebo patients had withdrawn in the other. Moreover, the MS contains no discussion of the sensitivity of the results of the adjusted indirect comparison to the approach to dealing with zero-value cell counts. The adjusted indirect comparison of withdrawals due to adverse events and weight increase are both affected by zero-valued cells for the placebo arm in one of the included trials (see Table 10 in this report). Table 21 below illustrates the impact of a small change in the approach to dealing with zero-value cell counts on the OR estimated in the adjusted indirect comparison. Applying an adjustment of 1, rather than 0.5 (used in the MS), yields an OR for withdrawal due to adverse events that favours olanzapine (reversing the result from the MS) whereas the OR for significant

weight gain, while still favouring olanzapine, is closer to unity (the impact of applying alternative adjustments is explored in ERG scenario analyses presented in section 4.3.4.4 of this report).

Table 21: Impact of value adjustment in cells with zero values

Event	Add 0.5 to all cells in tables with zero-values (as in MS)		Add 1.0 to all cells in tables with zero-values	
	OR	95% CI	OR	95% CI
Withdrawal due to adverse event	1.57	0.06 to 43.87	0.86	0.06 to 12.59
Significant weight gain (≥7% over baseline)	0.51	0.02 to 11.50	0.91	0.08 to 10.18

Prescription of benzodiazepines is used in the pre-model analysis as a proxy for the presence of EPS, as a side effect of treatment, as (unlike the RCT reported by Findling and colleagues[2]) the RCT by Kryzhanovskaya and colleagues[1] did not report the proportion of patients in each trial arm experiencing EPS. Clinical advice to the ERG suggested that sexual dysfunction might also be an important side effect for adolescents receiving drug treatment for schizophrenia. However, neither of the included RCTs reported this outcome.

The MS does not discuss whether discontinuation due to other causes is an appropriate variable to be included in the analysis. The model is attempting to assess compliance in practice which is outside the context of the clinical trial. The withdrawals due to other causes appear to be primarily due to withdrawal of consent and to a large extent may reflect the ethics of conducting RCTs and therefore may have limited relevance to approaches to managing patients in normal practice. This may overstate the number of patients withdrawing from treatment in early stages. If withdrawal of consent is to be included in the model, it may have been more appropriate to include a state for patients who have withdrawn (temporarily or permanently) from drug treatment.

The MS does not report whether data on relapse were searched for, or identified in their main searches, nor does it report whether specific targeted searches were run for data on relapse with aripiprazole or other treatments. In the absence of data on relapse in adolescents with schizophrenia, the MS uses data on adults treated with aripiprazole compared with other atypical antipsychotics (termed “other SGAs” in the paper) from a study by Moeller and colleagues.[20] There is no information in the MS on how this source was identified or why it was chosen. There is no critical appraisal of the study included or any consideration of its appropriateness to the current context. The proportion of aripiprazole-treated patients who

experienced relapse within six months is reported by Moeller and colleagues[20] as 20% - this value is treated as the six month probability and is converted to a cycle probability, assuming a constant rate, using a standard formula described by Sonnenberg and Beck.[22] The proportion of other atypical antipsychotic-treated patients who experienced relapse by six months is reported as 19.4%. The RR of relapse reported in the study is 0.92 (95% CI 0.67 to 1.26). The manufacturer suggests that this value is an error, as it does not equal the ratio of the proportion of relapsed other atypical antipsychotic-treated patients divided by the proportion of relapsed aripiprazole-treated patients (0.194/0.2 = [redacted]) and this value is used in the model rather than the published value. Moeller and colleagues[20] do not explicitly state that the RRs they report have been stratified for baseline variables. However this seems a plausible explanation for why the RR does not equal the ratio of the crude proportions. Stratification by baseline variables would be an appropriate approach, given that a significantly higher proportion of patients treated with other atypical antipsychotics had depression as a comorbidity and that depression was shown to be a significant predictor of relapse in a Cox regression reported by Moeller and colleagues.[20] In the MS, the cycle risk for relapse associated with aripiprazole (5.02%) is multiplied by the RR of relapse (other atypical antipsychotic versus aripiprazole) to derive the probability of relapse associated with an other atypical antipsychotic (4.86%).

No systematic searches were undertaken for clozapine data. The MS justifies this on the basis that clozapine is a rescue treatment and not a relevant comparator – clarification was requested from the manufacturer on this (see Addendum, p 98). In the absence of relevant data for clozapine the MS assumes that the probability of adverse events with clozapine would be the same as for aripiprazole, without offering any justification. The risk of relapse for clozapine is based on data reported by Moeller and colleagues.[20]

4.3.2.3 Patient outcomes

HRQoL data, condition-specific symptom questionnaires (PANSS, CGAS, CGI) and general QoL (P-QLES-Q) were collected in the included trial reported by Findling and colleagues[2] (and are reviewed in sections 3.3.1 to 3.3.4 of this report). However these were not used in the model. The MS justifies the exclusion of QoL data from the trial only on the basis that the NICE reference case is not met as the EQ-5D was not used. The current guidance[18] does not require the use of EQ-5D, particularly in the case of non-adult populations. The ERG consider that more consideration could have been given to including HRQoL data from the included trials in the model, either through mapping or based on expert opinion.

The MS states in section 6.4.4 (p 93) that mapping was not used to transform QoL data from the trial(s). However it is not clear whether any searches were conducted to find existing mappings from PANSS, CGAS, CGI or P-QLES-Q to EQ-5D or to utility scales. If rigorous and methodologically sound mappings were not identified, it may have been possible to construct mappings based on expert opinion that could also have been considered as a scenario analysis to test the robustness of results to the exclusion of these QoL measures. Although the latter approach would be regarded as a methodologically weak option, it could have been used to explore uncertainty over the inclusion of a single stable schizophrenia health state (for example, by inclusion in a scenario analysis)

From the MS perspective (section 6.4.5, p 93), suitable QoL data from the trials were not available; hence, searches using “standard quality of life filters” applied “to the disease area search terms” were reported. The aim was to identify studies using preference-based or non-preference-based instruments (e.g. SF-12, SF-36) in adolescent/ child populations with schizophrenia. Three studies, using the SF-36, were identified which included subjects in the relevant populations. However, these did not report SF-36 scores for the health states included in the model and therefore, given the absence of suitable data for adolescents/ children with schizophrenia, studies included in the full search were reviewed to identify adult studies that reported utilities for the relevant health states. The MS reports that there were 35 studies identified, but only describes one study (by Briggs and colleagues[23]), which the manufacturer regarded as particularly relevant to the decision problem, in that it addresses the impact of schizophrenia on HRQoL and the impact of (some) treatment-related adverse events in a UK setting.

Briggs and colleagues[23] recruited 49 patients with stable schizophrenia and 75 lay people who each completed a utility interview, in which participants were asked to rate seven health states. Two of these were associated with the underlying condition - stable schizophrenia and relapse - and the remaining five related to side effects of treatment - weight gain, diabetes, hyperprolactinenia (male), hyperprolactinenia (female) and EPS. In addition, the 49 patients with stable schizophrenia completed the EQ-5D questionnaire, which was rated using a standard UK population tariff.[24] Lay participants were provided with a short passage of text explaining schizophrenia and watched a DVD showing an interview between a psychologist and a patient with schizophrenia. The utility interview was interviewer administered and consisted of first

rating the health states using a visual analogue scale and then using time trade-off (TTO). The aim of using the visual analogue scale was not to generate usable ratings, but to familiarise participants with the health state descriptions.

From the demographic data for patients with schizophrenia and lay participants reported by Briggs and colleagues,[23] large differences in marital status , and in highest educational level attained can be seen between the two groups of respondents, as shown in Table 22.

Table 22: Demographic characteristics of participants in study by Briggs and colleagues[23]

Characteristic	Layperson sample (n=75)	Patient sample (n=49)
Male/ female	35/40	22/27
Mean age (yrs)	39.4 (17-76)	43.5 (21-64)
White ethnicity	93.3%	93.9%
Marital status		
Single	21.3%	51.0%
Married	65.3%	30.6%
Cohabiting	8.0%	12.2%
Divorced	2.7%	2.0%
Widowed	2.7%	4.1%
Highest educational level		
Did not complete high school	1.3%	28.6%
Minimum school age (GCSEs)	24.0%	59.2%
A levels	10.7%	8.2%
Degree or equivalent qualification	52.0%	4.1%
MSc degree/ PhD	12.0%	0%

The ratings derived by Briggs and colleagues[23] are shown in Table 23. Given the differences noted above, the use of patients' valuation is more appropriate than lay persons. However, considering that these were derived in adults, the generalisability of these valuations to the adolescent population is open to question. The MS reports discussions with two clinical experts on the appropriateness of using adult-derived valuations for adolescent populations. The experts suggested that there were likely to be differences between valuations from adults and from adolescents, but were unable to agree on the likely direction of these differences. Clinical advice provided to the ERG suggested that the impact of weight gain, as a side effect of treatment, on QoL may be more significant in adolescents than in adults.

Table 23: Health state utility values derived in study by Briggs and colleagues[23]

Health state	Mean utility (SE)		t-test for difference[a]
	Patient	Lay person	
Stable schizophrenia	0.919 (0.023)	0.865 (0.021)	p=0.087
Weight gain	0.825 (0.028)	0.779 (0.024)	p=0.216
Diabetes	0.769 (0.036)	0.712 (0.028)	p=0.215
Hyperprolactinemia	0.815 (0.030)	0.783 (0.025)	p=0.415
Relapse	0.604 (0.042)	0.479 (0.033)	p=0.022
EPS	0.722 (0.037)	0.574 (0.032)	p=0.003
Notes [a] unequal variance t-test			

The study authors noted that the mean utility for patients' current health state (0.86 - based on responses to the EQ-5D and rated using the general population tariff) is lower than the value for patients in the rating exercise elicited using TTO, but almost identical to that elicited from the lay person sample.

The MS does not compare the valuations reported by Briggs and colleagues[23] with those adopted in other economic evaluations. Though such a comparison would not address the question of whether these values apply to adolescents, the ERG suggest that this could give some reassurance that Briggs and colleagues[23] data have e face or convergent validity. It should be noted that Briggs and colleagues'[23] analysis was restricted to a sample of 49 patients and hence it may be unlikely to support rigorous conclusions. The comparison with other valuations could also provide a basis for revised lower/ upper limits to apply in further sensitivity or scenario analyses.

Briggs and colleagues[23] study concluded that the PANSS score did not influence the utility score, independently of the health state, which may lend some support for not accounting for symptoms in the stable schizophrenia state in the model. However the sample size (n=49) may not support definitive conclusions and there remains uncertainty over how applicable results derived in adults may be to the adolescent population.

4.3.2.4 Resource use

Four types of resource were identified and costed in the MS (see 6.5 of the MS for details):

1) Drug acquisition (section 6.5.5 of MS)
2) On-treatment monitoring (section 6.5.5 of MS) and switching of medication (section 6.5.8

of MS)

3) Management of adverse events (section 6.5.7 of MS)
4) Health state costs – associated with relapse requiring either hospital in-patient admission or community support from child and adolescent mental health services (section 6.5.6 of MS)

Treatment costs have been calculated using daily drug dosages from SPCs, supported by mean/ median dosages in the included trials reported by Findling and colleagues[2] and Kryzhanovskaya and colleagues[1] (mean daily dose of aripiprazole in the 10mg arm was 9.8 mg, while the median dose of olanzapine in the trial reported by Kryzhanovskaya and colleagues[1] was 12.5 mg). The SPC of the most prescribed formulation of clozapine states that doses should be between 200 and 450 mg per day, with a usual dose of 300mg (the MS uses the mid-point dose of 325mg). Table 24 below reports the drug dosages and unit costs used in the MS model. Drug costs per cycle of treatment were calculated by the manufacturer and applied in the decision tree and subsequent Markov model. The full cycle costs of drug management were applied for patients experiencing a relapse during a cycle.

Table 24: Drug dosage and acquisition costs in MS

Drug	Dose (mg per day)	Price per pack (£)	Packaging	Cost per day (£)
Aripiprazole	10	95.74	28 x 10mg tablets[a]	3.42
Olanzapine	12.5	79.45	28 x 10mg tablets[b]	3.55
Clozapine	325	24.64	28 x 100mg tablets[c]	2.86

[a] aripiprazole is available in 5, 10, 15 and 30mg tablets in packs of 28 tablets. Packs of 5, 10 and 15 mg tablets each cost £95.74. Packs of 30mg tablets cost £191.47. Also available as orodispersible tablets and oral solution. Costing uses 10mg tablet pack based on most commonly prescribed formulation in prescription cost analysis
[b] olanzapine is available in 2.5, 5, 10, 15 and 20mg tablets in packs of 28 tablets. Also available as 7.5 mg tablets in packs of 56. Costs for packs of 2.5, 5, 10, 15 and 20 mg tablets are £21.85, £43.70, £79.45, £119.18 and £158.90 respectively. Packs of 7.5mg tablets cost £131.10. Costing uses 10mg tablet pack based on most commonly prescribed formulation in prescription cost analysis
[c] clozapine is available under a number of proprietary brands. Unit costs in the MS were based on Clozaril – the most commonly prescribed brand in UK prescription cost analysis. Costing uses 100mg based on most commonly prescribed formulation in prescription cost analysis

The package size and tablet dose used in the drug acquisition costs in the MS were based on the most commonly prescribed brands and packaging in a UK prescription cost analysis, using data from 2008. The data used in the prescription cost analysis were not limited to prescription of included drugs for schizophrenia nor to the adolescent population. It is therefore not clear whether the selected costings apply directly to providing these treatments in the patient

population relevant to this appraisal. The estimated cost per day used in the MS (reported in the final column of Table 24) implicitly assumes perfect divisibility of prescribed medications – that is the daily cost was estimated by multiplying a derived cost per milligram by the relevant daily dosage. This is appropriate for aripiprazole, but may be less reasonable for olanzapine and clozapine. For example, a daily dosage of 12.5mg cannot be provided exactly using 10mg tablets. Costing the exact dosage (assuming one 10mg and one 2.5 mg tablet are provided) gives a daily cost for olanzapine of £3.62 (resulting in a cycle cost of £152 and annual cost of £1,321, compared with £149 and £1,295 in the MS model). This could be regarded as a conservative assumption that biases the analysis against aripiprazole.

The costing for aripiprazole takes no account of the specification for initiation of treatment in adolescents outlined in the SPC, which states that treatment should be initiated at 2 mg (using oral solution 1 mg/ml) for two days, titrated to 5 mg for two additional days to reach the recommended daily dose of 10 mg. While the cost per milligram for the oral solution is greater than for tablets (£0.68 vs £0.34) the lower initial dosage means that drug costs may be slightly lower in the first week of treatment compared with subsequent weeks (£23.25 vs £23.94). It is not clear whether the initiation of treatment with aripiprazole in adolescents may require closer supervision than other medications. The preceding costings also assume that the required dosages of oral solution (available in 150mL packs at a concentration of 1mg/mL) can be provided to patients without any wastage.

While some additional resource use is included in the model, for monitoring patients being treated with clozapine and for patients switching drug treatment, the model does not include any ongoing costs for drug administration or clinical management of patients on treatment. It appears to be implicitly assumed that such resource would be the same for all treatments and therefore can be left out of the evaluation. However, this assumption is not discussed in the MS. Patients treated with clozapine require additional monitoring. According to the SPC all patients treated with clozapine require regular monitoring of white blood cell (WBC) counts and absolute neutrophil count (ANC) – this should be weekly for the first 18 weeks of treatment and then at least every four weeks subsequently. In the MS this regularity of monitoring was equated to two-to-three blood tests per six week cycle – this was subsequently assumed, in the model, to equate to one hour of mental health nurse time (however this assumption is not justified in the MS).

Resource use associated with switching medication was based on three 20-minute visits to a the psychiatrist – this assumption appears to be based on the NICE adult schizophrenia guideline.[11] There is no discussion in the MS whether this assumption is appropriate to the adolescent population. Clinical advice to the ERG suggested that this assumption was reasonable.

Resource use associated with adverse effects of drug treatment adopted in the model were based on assumptions made in the NICE adult schizophrenia guideline[11] for weight gain and EPS, and on clinical opinion for somnolence. All patients experiencing weight gain were assumed to make two visits to their GP and 20% received specialist advice from a dietitian (comprising three visits, the first lasting one hour and the following two visits lasting 30 minutes each). Patients experiencing EPS were assumed to require one visit to the psychiatrist and receive treatment with 2mg of lorazepam (this differs slightly from the assumptions in the NICE guideline where patients with EPS were treated with procyclidine). Patients experiencing somnolence were assumed to require one 20 minute visit to the psychiatrist in each cycle that the adverse event occurred. There is no discussion in the MS whether resource use or treatment assumptions developed for adult patients are appropriate to the adolescent population, other than a statement on page 103 of the MS referring to validation by clinical experts. Clinical advice to the ERG suggested that this assumption was reasonable.

Resource use associated with relapse applied in the model was based on the NICE guideline on schizophrenia in adults.[11] The economic analysis, reported in the NICE guideline, assumed that 77.3% of relapsed patients were treated as inpatients (with the remaining 22.7% managed in the community by CAMHS). There is no discussion of whether the assumptions are appropriate to the adolescent population. Clinical advice to the ERG suggested that the proportion having in-patient management may be lower for adolescents as they are more likely to have support from a parent/ guardian and are less likely to be living on their own. As a result the deterioration of their condition may be picked up earlier and a smaller proportion may reach the stage of requiring in-patient admission. The duration of treatment for relapse (both in-patient length of stay and time under management of CAMHS in the community) is assumed, in the model, to be one cycle (i.e. six weeks). This assumption is not discussed or justified in the MS. The assumed duration of six weeks (42 days) contrasts with the length of stay used in the economic analysis reported in the NICE guideline, which was 111 days (based on average duration of hospitalisation for people with schizophrenia, schizotypal and delusional disorders -

International Classification of Diseases, Tenth Revision (ICD-10) codes F20-F29 - in England in 2006/07 reported in Hospital Episode Statistics (HES)). There may be a justification for a shorter average duration of stay based on the average length of stay (46.25 days) reported in 2008/09 NHS Reference Costs[14] for Health Resource Group (HRG) PA52 “behavioural disorders” (which includes data from non-adult patients admitted with a primary diagnosis of schizophrenia). However, HRG PA52 also covers a range of mental health diagnoses in all admitted patients under 18 years of age and is not specific to schizophrenia. Reference cost data are not sufficiently specific to the patient group covered by this appraisal (adolescents (15-17) with schizophrenia) to provide a conclusive answer. Standard queries available for HES data[25] provide information on patients with primary diagnoses of schizophrenia (ICD-10 codes F20-F29) but include adolescents with the adult population (only reporting average length of stay of 107.7 days for all admitted patients). The impact of alternative assumptions for duration of in-patient and community-based care for relapse is explored in ERG scenario analyses presented in section 4.3.4.4 of this report.

4.3.2.5 Costs

There was a discrepancy between the main submission and the electronic model on the source of unit costs for ariprazole, olanzapine and clozapine. The MS reported using MIMS online[17] while the electronic model reported the source as the British National Formulary.[26] Unit costs for ariprazole reported in the MS were slightly lower than those in the current BNF (No 59 published March 2010).[26] A clarification was requested from the manufacturer (see Addendum), which confirmed MIMS online[17] (accessed April 2010) as the source for drug acquisition costs, noting that the lower cost in MIMS reflects a reduction under the Pharmaceutical Price Regulation Scheme (PPRS) which occurred after the publication of the current BNF.

Other unit cost data were taken from NHS Reference Costs,[14] (cost per day for in-patient admission associated with relapse) and from Unit Costs of Health and Social Care[13] (cost of mental health nurse time, GP, dietitian and psychiatrist time). All costs were assumed by the manufacturer to be current costs with no uprating to take account of inflation. The publication year for NHS Reference Costs was not stated in the MS or in the electronic model and a clarification was requested from the manufacturer (see Addendum to this report). The manufacturer’s response states that NHS Reference Costs included in the model are for 2008/09, the most recently published data available.

There also appeared to be an error in the estimate of the acute hospital cost per day for use in the model. The MS stated that the cost was based on the national average unit cost for HRG code PA52. However the value used appears to have been that for HRG code PA53B (Eating Disorders with length of stay 8 days or more). A clarification was requested from the manufacturer. This stated that the value used in the model was incorrect and a set of corrected results was supplied (see Addendum to this report).

4.3.3 Consistency

4.3.3.1 Internal consistency

The electronic model is coded in MS Excel and is fully executable. It contains several worksheets, including a deterministic analysis, sensitivity analysis and PSA. The results of the deterministic analyses (DSA) are presented on the '*Results*' worksheet. Deterministic one-way sensitivity analyses are run from the '*Data & References*' worksheet with the results displayed using a tornado diagram. The range for input variables in the one-way sensitivity analyses are based on 95% confidence intervals (where these are available) or were set at ± 30% of the base case value. PSA is run from the '*Simulation*' worksheet with results copied to the '*CE Plane*' worksheet. Random checking of the model has been undertaken for some of the key equations in the model (results of this are described below). However, the ERG has not undertaken a comprehensive check of all cells in each model.

Worksheets containing parameter inputs for the model are generally well laid out and are organised logically (for example with separate sheets for efficacy, adverse events and relapse parameters). However, the worksheets containing the model processes (named '*Engine Ari then Ola*' and '*Engine Ola then Ari*') are poorly presented and difficult to understand. The separation of the first two cycles – into decision tree calculations, which are laid out vertically – from the Markov model (which is laid out horizontally on the worksheet) makes the model structure very difficult to follow. It also appears to have led to an error whereby no costs have been applied for patients (on the first-line medication) experiencing relapse in the second model cycle (see below).

The MS reports (section 6.8.1) the processes undertaken for internal validation of the model. According to the MS:

- all input data were double extracted and “double checked”
- calculations in the model were checked by “at least two modellers/ health economists”
- face/ predictive validity of the model was tested by varying model parameters according to a model checklist to review expected versus actual results. This checklist was not provided in the MS nor were any results of this process presented.

The ERG has checked the input data and these correspond with data inputs specified in the MS. The main data manipulations in the model (for example, transforming six-month probabilities to six week probabilities) appear to be correct. However, the ERG have identified some errors in the model. These are presented below along with corrected deterministic base case results.

Errors identified by the ERG in the model

- the separation of the “decision tree” and the Markov model has lead to a discrepancy where the utility effect of relapse in patients on first-line medication (in the second cycle) is included, but no cost is applied. Including these costs leads to results shown in Table 25 below:

Table 25: Correcting base case results for exclusion of cost of relapse in cycle 2

Treatment strategy	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£ per QALY gained)
First-line aripiprazole	£24,483	2.597	£27.15	0.004	£6,231
First-line olanzapine	£24,456	2.593			

- the acute hospital cost per day used in the model appeared to be based on the national average unit cost for HRG code PA53B (Eating Disorders with length of stay 8 days or more) rather than the national average unit cost for HRG code PA52. A clarification was requested from the manufacturer (see Addendum to this report) who stated that the incorrect national average unit cost had been used and submitted corrected analyses.
- there is an error in presenting the PSA results. Correct values for total discounted cost and total discounted QALYs for first-line aripiprazole and total discounted QALYs for first-line olanzapine have been included, but total **undiscounted** cost for first-line olanzapine has been included. This error affects all the probabilistic analyses presented in the MS and is discussed (with corrections provided) in section 4.3.4.6 of this report.

4.3.3.2 External consistency

There is limited discussion of the external validity of the model. The MS states that structural assumptions (which appear primarily to be drawn from the model developed for the NICE adult guideline[11]) and data inputs were reviewed by two clinical experts to assess their appropriateness for modelling adolescent schizophrenia. The MS further states that the model concept and structural assumptions were validated, prior to building the model, with a health economic expert with an interest in the field of mental health. There is no further detail on the validation process. The MS does not make any detailed reference to modelling methods adopted in the evaluations of treatment of adult schizophrenia (reviewed in section 6.1 of the MS).

The results from the published evaluations are compared with those from the *de novo* cost effectiveness analysis in section 6.10.1 (p 123 to 124) of the MS. However, the conclusions drawn from this are fairly limited. They state that both the MS and Davies and colleagues[9] analyses suggest that aripiprazole is a cost effective treatment in comparison to olanzapine, and that both the MS model and the model developed for the NICE adult guideline[11] are characterised by high levels of uncertainty.

4.3.4 Assessment of Uncertainty

The MS reports results of the assessment of parameter uncertainty performed via both one-way DSA and PSA. Results of the DSA were reported using a tornado diagram (section 6.7.7, p109 of the MS). Besides the probabilistic mean values obtained for total and incremental costs and QALYs, the PSA results were also reported in scatter plots and CEACs. The probability of being cost effective at a £20,000 per QALY threshold was also reported.

Scenario analyses (explored both deterministically and probabilistically) were conducted for key parameters of the model: RR of relapse, benzodiazepine use as a proxy of the occurrence of EPS, treatment efficacy determined by RRs instead of ORs, and disutility from clozapine.

Methodological and structural uncertainty is partly addressed in the MS by scenario analyses discussed in detail in section 4.3.4.3 of this report. Section 6.6.1 of the MS (p104) refers to discussion of the model structure with an expert in health economics with a specific interest in mental health, but there is no discussion of whether structural assumptions were tested in sensitivity analysis. Structural assumptions that could have been analysed would include the

assumptions that all relapsing patients switch medication or that exclusion of mortality has no impact. It might also be considered appropriate to consider sensitivity to methodological assumptions in the adjusted indirect comparison (for example the method for dealing with zero cell counts).

4.3.4.1 One-way sensitivity analyses

The MS states (section 6.6.2, p104), all variables were included in the DSA, either using the CI (estimated in the adjusted indirect comparison or taken from the original study which was for the base case estimate), or by assigning them upper and lower limits that vary by 30% from the mean value. The parameters whose actual CI were used are the following:

- ORs, RRs and rates of withdrawal (due to adverse events, lack of efficacy and other reasons)
- ORs, RRs and rates of occurrence of weight gain, somnolence and EPS
- annual rate and RR of relapse
- utility value of “stable schizophrenia” and disutility of side effects
- daily cost of aripiprazole, olanzapine, clozapine and benzodiazepines

Parameters included in the DSA using a 30% range from the mean were:

- the cost of switching treatment
- the proportion of patients requiring GP, dietitian, and psychiatrist visits, the number of these visits, their duration and unit costs
- the proportion of patients receiving benzodiazepines and their daily dosage
- the proportion of patients relapsing, the unit cost of acute hospitalisation and community-based care for relapsing patients and the proportion of relapsed patients who receive olanzapine.

No checks have been included in the MS model to ensure values for the DSA remain within their logical limits. Hence some variables appear to be entered with unfeasible values (such as proportions/ percentages greater than 100%).

The ERG consider that the justification provided for the range chosen (± 30%) was not adequate and that in some cases this arbitrary range could be replaced with empirical estimates of a 95% confidence interval. For example, a CI could be estimated for the proportion of patients who relapse at six months on aripiprazole, using a SE derived for the observed proportion

(20%) and the number of aripiprazole-treated patients (444) reported to be included in the analysis by Moeller and colleagues.[20] Additionally, the 95% CI (7.1 to 38.4) on the 22.7 difference in mean fall in hospital admissions between those with and without crisis resolution teams reported by Glover and colleagues[27] could be used to estimate the CI for the proportion of patients hospitalised for relapse.

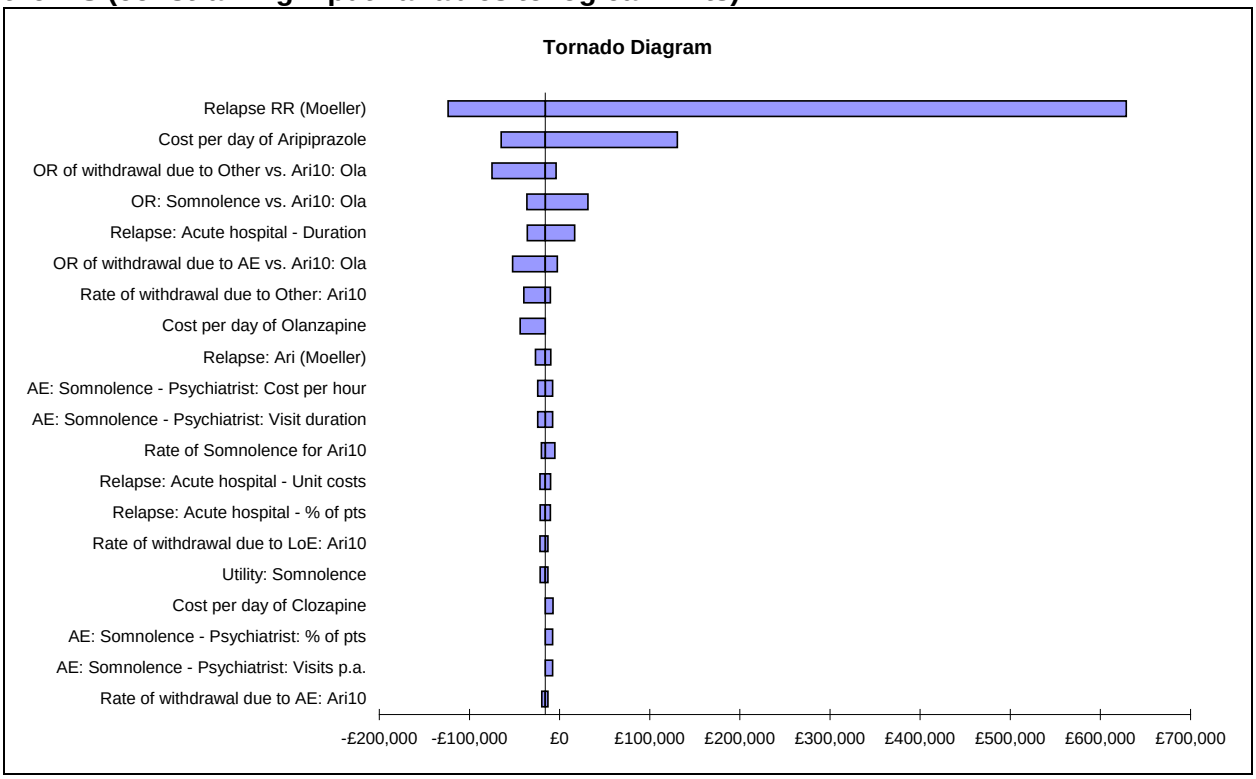
Table 38 (p 90) in the MS provides a summary of values used for discontinuation and adverse events parameters in the model. While the mean values are correct, the CI reported in the table are incorrect. However, correct values are reported in Table 59 (Appendix 14, p164) in the MS and these (correct) values are used in the electronic model.

According to the MS (p109), the model results are most sensitive to changes in the RR of relapse and the daily cost of aripiprazole. The ICER varies between -£123,663 and £628,706 per QALY for a RR of relapse between [redacted] and [redacted] and between -£64,755 and £130,723 per QALY for a range of daily cost of aripiprazole from £2.28 to £6.84. The MS emphasises that the DSA results show dominance of first-line aripiprazole for the majority of the analyses, given that besides the RR of relapse and the daily cost of aripiprazole, only the OR of somnolence was also able to produce an ICER greater than the £20,000 per QALY threshold considered in the analysis when subjected to DSA. Compared to the strategy where olanzapine is the first line treatment, the ICER reaches £31,361 per QALY if the 53,01 upper limit of the OR for somnolence is used.

In section 6.7.10 (p 121) of the MS, regarding the DSA results on the daily cost of aripiprazole, the manufacturer states that the highest ICER is associated with the use of oral solution, and that tablets are far more likely to be used in practice (as confirmed by the ERG clinical advisor). Concerning the OR of somnolence, the MS explains that the highest ICER is achieved with the lowest value of the CI, where the OR of somnolence equals 0.54, which corresponds to olanzapine having a lower rate of somnolence than aripiprazole.

The ERG re-ran the MS sensitivity analyses, after correcting for the errors noted above (percentages exceeding 100%). This has a limited impact on results, reducing the variation in ICER associated with those variables that were being sampled outside their logical limits, see Figure 1.

Figure 1: Tornado plot based on ERG corrected version of sensitivity analysis reported in the MS (constraining input variables to logical limits)



4.3.4.2 ERG deterministic sensitivity analysis

The ERG re-ran the manufacturer's sensitivity analyses for the corrected base case (see section 4.3.3.1 of this report) with updated assumptions regarding the lower and upper limits for a number of variables – alternative assumptions regarding the mean/ base case value for input variables are examined in section 4.3.4.4, reporting the ERG scenario analyses. In the ERG sensitivity analyses:

- The upper limit for all variables estimated as percentages were constrained to be less than or equal to 100%. This affected the upper limits for the proportion of patients with weight gain who see their GP, the proportion of patients with somnolence who see a psychiatrist, the proportion of relapsing patients who are admitted as in-patients and the proportion of relapsing patients who receive higher dose olanzapine during relapse;
- The lower and upper limits for the RR of relapse were set equal to the 95% confidence interval ([redacted] to [redacted]) calculated for the ratio of the crude risks (19.4%/20% [redacted]) based on a standard calculation for the SE of a RR;

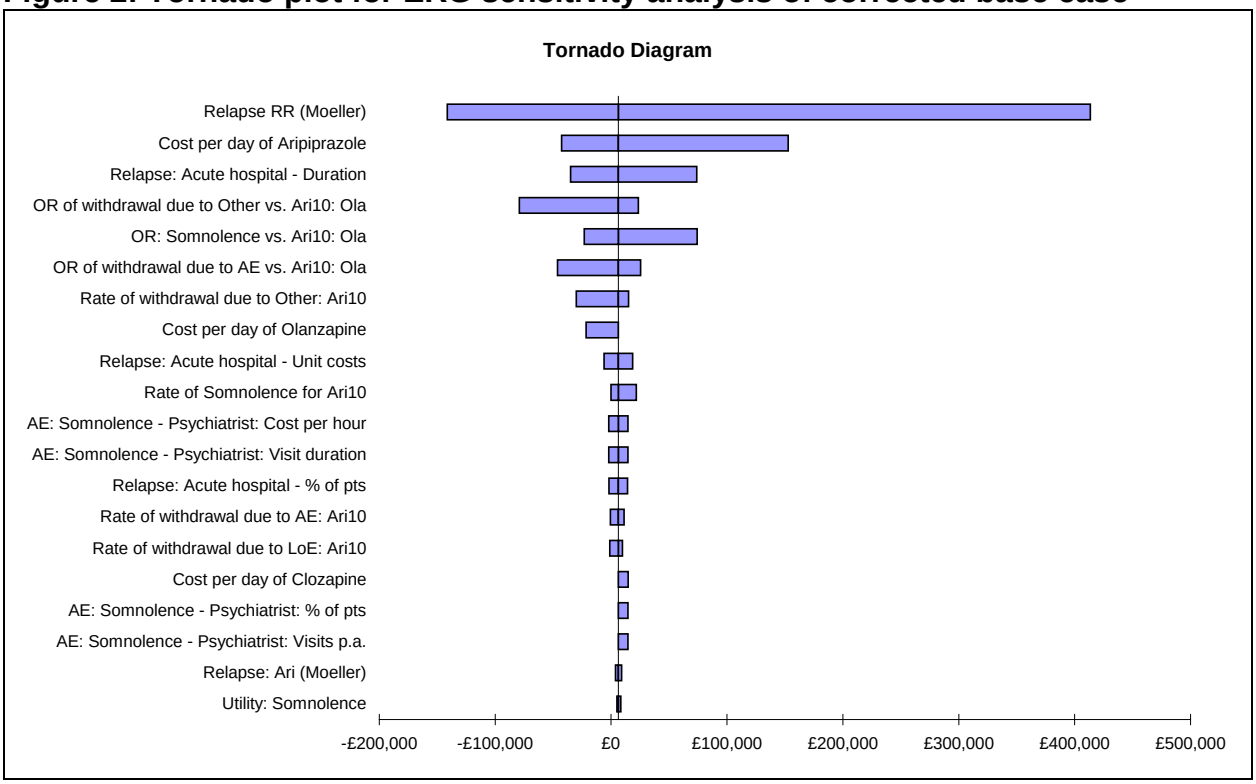
- The lower and upper limits for incidence of relapse on aripiprazole were based on the 95% confidence interval for an observed proportion of 20% in a sample of 444 patients (19.31% to 20.81%);
- The lower and upper limits for the proportion of relapsing patients who were admitted as in-patients was based on the 95% confidence interval reported by Glover and colleagues[27] (0.616 to 0.929).

The tornado plot for the ERG sensitivity analyses (see Figure 2) looks similar to that for the ERG's corrected version of the manufacturer's sensitivity analysis (see Figure 1) except that the change in scale of the x-axis indicates that the range associated with the RR of relapse is lower (£554,850, ranging from £413,440 to £-141,410) than in the ERG's corrected version of the manufacturer's sensitivity analysis (£752,369, ranging from £628,706 to £-123,663). The order of influential variables is largely unchanged in the ERG sensitivity analyses (except that risk of relapse on aripiprazole has dropped from nine to nineteenth place). A larger number of variables are associated with potentially high value ICERs at one of the extreme values, in the ERG sensitivity analysis compared with the manufacturer's sensitivity analysis:

- RR of relapse (ICER up to £413,440)
- Cost per day of aripiprazole (ICER up to £152,836)
- Acute hospital stay for relapsing patients (ICER up to £73,880)
- OR withdrawal due to other causes (ICER up to £23,568)
- OR somnolence (ICER up to £74,174, at lower limit)
- OR withdrawal due to adverse events (ICER up to £25,496)

It should also be noted that the central point on the plot (crossing the x-axis at the base case ICER) is above zero in the ERG analysis, reflecting the base case ICER of £6,231 in the corrected base case analysis, compared with £-15,882 in the manufacturer's analysis.

Figure 2: Tornado plot for ERG sensitivity analysis of corrected base case



4.3.4.3 Scenario Analysis

The MS presents four scenario analyses in section 6.7.9 (p 112) of the MS. Three of these are intended to test structural assumptions of the model concerning:

1. the use of adult RR of relapse
2. the exclusion of EPS
3. the disutility from treatment with clozapine

The remaining scenario analysis addresses:

4. the methodological decision of electing to use ORs of the trial outcomes instead of RRs.

Given the uncertainty of the assumption that adult estimates apply to adolescents and the high sensitivity of the model results to the RR of relapse, the first scenario analysis presented in the MS tests the impact of using estimates of annual probabilities of relapse from a MTC conducted for the NICE guideline for adults with schizophrenia.[11] As the MTC did not include clozapine, the estimate for the RR of relapse of clozapine versus olanzapine was sourced from Davies and colleagues[9] for this scenario analysis.

The second scenario analysis, called “benzodiazepines”, addressed the inclusion of EPS, one of the adverse events which most impact upon the HRQoL of patients with schizophrenia. Since the proportion of patients experiencing EPS was not reported for both included trials,[2,1] the proportion of patients who received benzodiazepines was used as a proxy, although the manufacturer recognise the limitations of this measure. The associated costs of a psychiatrist visit and prescription of benzodiazepines were also used in this scenario, as well as the disutility associated with EPS reported by Briggs and colleagues.[23]

The third scenario analysis was carried out to account for the decrement in utility associated with the use of clozapine, due to patients’ awareness of its potential serious adverse events (p 120). As stated in the MS, this “disutility with clozapine” analysis was performed by applying the highest and the lowest utility decrements used for other adverse events in the model (0.01 for somnolence and 0.2 for EPS).

The fourth scenario analysis (p 118) uses treatment efficacy estimates based on the RRs (estimated in the adjusted indirect comparison) for the withdrawal and adverse events reported in the trials instead of the ORs used in the base case.

Overall, the ERG considers the choice to include the RR of relapse and treatment efficacy in the scenario analyses is appropriate. However, the approach used in the first scenario to assess uncertainty is questionable. Given that alternative adult estimates were used, uncertainty over the use of adult data for an adolescent population was not clarified by the MS.

The results presented in the MS (pages 113 to 114) for the scenario analysis performed on the RR of relapse are provided below in Table 26. These are plotted on a cost-effectiveness plane on page 114 of the MS, where the high uncertainty of these estimates can clearly be seen. The MS points to the discrepancy in the deterministic results of this scenario compared with those in the base case analysis in the MS, highlighting the high level of uncertainty that characterises the results of the MTC of efficacy data derived from NICE adult schizophrenia guideline.[11]

Table 26: Deterministic and PSA results of the relapse scenario analysis (MS tables 47 and 48)

Analysis	Treatment strategy	Total Cost (£)	Total QALYs	Incremental Cost	Incremental QALY	ICER (£/QALY)

Deterministic	First-line aripiprazole	17,040	2.611	904.22	0.003	276,514
	First-line olanzapine	16,136	2.608			
PSA	First-line aripiprazole	16,388	2.611	-16	0.008	Dominant
	First-line olanzapine	16,404	2.603			

The results presented in the MS for the “benzodiazepines” scenario analysis are shown below in Table 27. The ERG detected an error in the MS interpretation of the PSA results, where it was suggested that first-line aripiprazole was dominant (which is not the case as both incremental costs and QALYs are negative). The ERG estimated an ICER of £1,006,000 per QALY for the incremental costs and QALYs located in the south-west quadrant of the CE plane presented in Figure 16 (page 118) of the MS. The deterministic results conflict with the probabilistic ones. While the first-line aripiprazole strategy is found non cost-effective according to the deterministic analysis, the PSA results show it as the dominant strategy. However, this is due to an error in deriving the PSA results, referred to in section 4.3.3.1 and covered in detail in section 4.3.4.5.

The adequacy of benzodiazepines as a surrogate for EPS occurrence in order to estimate the impact of the inclusion of this adverse event is questionable. It may be overestimating the proportion of patients with EPS, since antipsychotics can be combined with benzodiazepines for other reasons, such as behavioural control or for the treatment of secondary psychiatric problems (e.g. depression and anxiety).[11] On the other hand, the costs related to EPS may be underestimated, given that treatment of EPS frequently implies the use of other drugs, for example anticholinergics.[1,11]

Table 27: Deterministic and PSA results of the benzodiazepines scenario analysis (MS tables 49 and 50)

Analysis	Treatment strategy	Total Cost (£)	Total QALYs	Incremental Cost	Incremental QALY	ICER (£/QALY)
Deterministic	First-line aripiprazole	24,552	2.445	10.13	-0.010	Dominated
	First-line olanzapine	24,542	2.455			
PSA	First-line aripiprazole	24,570	2.441	-1,006	-0.001	Dominant
	First-line olanzapine	25,576	2.442			

The deterministic results of the treatment efficacy scenario analysis were presented in detail in the MS as shown in Table 28. For the PSA analysis only incremental cost (£978) and incremental QALYs (0.017) are provided, along with a plot on the cost effecteiveness plane which shows that first-line aripiprazole is dominant in the majority of simulations. Additionally, a CEAC showing the probability of 94% of aripiprazole being cost effective is included on page 119 of the MS.

Table 28: Deterministic results of the treatment efficacy scenario analysis (MS table 51)

Analysis	Treatment strategy	Total Cost (£)	Total QALYs	Incremental Cost	Incremental QALY	ICER (£/QALY)
Deterministic	First-line aripiprazole	23,799	2.596	-106.24	0.005	Dominant
	First-line olanzapine	23,905	2.591			

The deterministic and probabilistic ICERs obtained in the “disutility with clozapine” scenario were also plotted on CE planes. Both scatterplots, one obtained using the lowest disutility value (0.01) and the other using the highest one (0.2), presented on pages 120 and 121 of the MS, show the dominance of the strategy with aripiprazole as first line (both deterministic and probabilistic ICER mean values below ICER threshold). The MS states as well that the CEACs showed the high probability of aripiprazole being cost-effective at the £20,000 per QALY threshold using both disutility values (95.76% with 0.01 and 96.01% with 0.2).

No discussion on the conflicting results between deterministic and probabilistic sensitivity analyses is provided in the MS. The conclusions on the scenario analyses presented in the MS (page 122) tend to give more relevance to PSA results compared to the deterministic ones without discussion. The MS concludes that overall PSA results of the first two scenario analyses conducted show aripiprazole as more cost-effective first line therapy than olanzapine, and that using RR instead of OR and accounting for disutility from clozapine did not have much influence on cost-effectiveness results. However, as noted in section 4.3.3.1 of this report, an error in the model means that the PSA results were based on undiscounted, rather than discounted, costs for first-line olanzapine leading to an over-estimation of the cost effectiveness of first-line aripiprazole compared with first-line olanzapine.

The ERG considers that the deterministic scenario analysis results better reflect the impact of parameter variation on the cost-effectiveness of a strategy. Considering the deterministic results presented above, the scenario analyses show that the strategy with aripiprazole as first line

treatment becomes non cost-effective if different estimates for relapse risk are used and if EPS is modelled as an adverse event.

4.3.4.4 ERG scenario analysis

The ERG ran a number of scenario analyses using the corrected model (see section 4.3.3.1) applying alternative estimates for parameter inputs in the base case analysis and also examining some alternative structural assumptions as well as issues arising from the methods of the adjusted indirect comparison used to derive effectiveness estimates used in the model. Specific scenarios examined in the ERG scenario analyses are:

- Removing the apparent double-counting where relapsed patients accrue the full cycle cost of medication in the cycle in which they relapse and the full cycle costs of their next available line of medication in the following cycle, while also attracting the full cycle cost for management of relapse. The potential impact of this was explored by subtracting half the cycle cost for patients' current medication in the cycle in which they experience relapse and also half the cycle cost of their next available line of medication in the cycle following relapse;
- Applying the RR of relapse reported by Moeller and colleagues[20] rather than the assumed value of [redacted] derived by the manufacturer, as the ratio of the crude risks;
- Assuming that fewer adolescents who experience relapse would be admitted as in-patients. Clinical advice to the ERG suggested that this proportion may be lower in children and adolescents, than in adults (see section 4.3.2.4 of this report);
- The manufacturer's base case assumes a length of stay for relapsed patients who are admitted as in-patients of 42 days (1 cycle) without justifying this assumption. Clinical advice to the ERG suggested this length of stay may be too low. As discussed in section 4.3.2.4 of this report, current HES data reports an average length of stay of 107.7 days for admitted patients with a primary diagnosis of schizophrenia (note these data are not reported for the adolescent age group alone);
- The manufacturer's base case assumes a length of stay for relapsed patients who are managed in the community of 42 days (1 cycle) without justifying this assumption. An alternative scenario is examined using the duration of community-based treatment used in the NICE adult schizophrenia guideline;[11]
- The manufacturer assumed, without discussion, that the utility for relapse (0.604) could be applied to patients discontinuing due to adverse events, lack of efficacy or other

reasons. These patients are not modelled as having a relapse and the utility reduction (approximately 34%) is greater than for all of the side effects of treatment included in the rating exercise reported by Briggs and colleagues.[23] Three alternative scenarios were examined – no utility reduction for the first treatment cycle (this is unrealistic, but is included as an extreme value for comparison with the base case and the remaining scenario analyses), a reduction of 10% (equivalent to the reduction associated with weight gain estimated by Briggs and colleagues[23]), and a reduction of 20% (equivalent to the reduction associated with EPS estimated by Briggs and colleagues[23]);

- The manufacturer assumed that weight gain occurs only in the first cycle with each line of treatment. This may be a reasonable assumption, but the model only applies a disutility for the first cycle of weight loss – implicitly assuming that the weight gain resolves within one cycle or that patients adjust and experience no quality of life reduction due to weight gain beyond the first cycle. This is likely to under-estimate the impact of weight gain. The model was adjusted to include the utility effect of weight gain over a longer duration – in this scenario analysis it is assumed that patients who experience weight gain in the first cycle with each line of treatment continue to experience disutility while they remain on that line of treatment;
- Clinical advice to the ERG suggested that the impact of weight gain may be greater for adolescents than for adults. Hence, the utility weights elicited by Briggs and colleagues[23], in an adult population, may underestimate the utility impact for adolescents. In the scenario analysis the proportionate decrease in utility is increased from 10% to 20% (equivalent to EPS). An additional scenario analysis is included to combine the assumption of longer term effects (beyond first cycle with each line of treatment) with the assumption of greater utility impact of weight gain;
- Finally, two scenarios address the methodological assumption in the adjusted indirect comparison, where all 2x2 tables with zero value cell counts were adjusted by the addition of 0.5 to each cell. In other contexts the adjustment may use a value of 1 rather than 0.5 (see section 4.3.2.2 of this report). For withdrawal due to adverse events the OR changes from favouring aripiprazole (1.57) to favouring olanzapine (0.86) whereas in the case of weight gain the OR in both cases favours olanzapine, but is very close to unity (0.91 rather than 0.51) when an adjustment of 1, rather than 0.5, is applied.

Table 29 reports the results of the ERG scenario analyses. Scenarios including parameters associated with relapse lead to the most dramatic alterations in the estimated ICER. Applying

the RR of relapse reported by Moeller and colleagues[20] or a longer duration of in-patient stay lead to a dramatic increase in ICER (to £57,152 and £70,644, respectively), while reducing the proportion of patients admitted as in-patients reduces the cost of first-line aripiprazole, relative to first-line olanzapine, leading to first-line aripiprazole being dominant. Adjusting treatment costs for patients experiencing relapse (by reducing medication costs in the cycle in which relapse occurs and in the cycle following relapse) has the effect of reducing total costs for first-line aripiprazole by approximately £160, while total costs for first-line olanzapine reduce by approximately £200, resulting in an increase in the incremental cost and an increase in the ICER, to £13,763.

Adjusting the estimated utility in patients discontinuing in the first cycle of treatment and scenarios for disutility associated with weight gain reduce the QALY gain for first line aripiprazole, but have comparatively little impact on the ICER. Applying an alternative adjustment for zero valued cell counts has little effect when applied to the estimated OR for significant weight gain, but leads to first line aripiprazole being cost saving when applied to estimating the OR for withdrawal due to adverse events.

Table 29: ERG scenario analyses

		Total		Incremental		ICER (£ per QALY gained)
		Cost (£)	QALYs	Cost (£)	QALYs	
Corrected base case	First line aripiprazole	24,483	2.597	27	0.004	6,231
	First line olanzapine	24,456	2.593			
1) Adjust medication costs for patients who experience relapse	First line aripiprazole	24,322	2.597	60	0.004	13,763
	First line olanzapine	24,262	2.593			
2) RR relapse = 0.92	First line aripiprazole	23,977	2.598	229	0.004	57,152
	First line olanzapine	23,748	2.594			
3) 50% of relapsed patients are admitted as in-patients	First line aripiprazole	17,838	2.597	-34	0.004	-7,785
	First line olanzapine	17,872	2.593			
4) Length of stay for relapsed patients admitted	First line aripiprazole	55,019	2.597	308	0.004	70,644

as in-patients = 107.7 days	First line olanzapine	54,711	2.593			
5) Duration of community-based care for relapsed patients = 56 days	First line aripiprazole	24,552	2.597	28	0.004	6,377
	First line olanzapine	24,524	2.593			
6) Utility for patients discontinuing in the first treatment cycle is same as for stable schizophrenia	First line aripiprazole	24,483	2.605	27	0.001	19,594
	First line olanzapine	24,456	2.603			
7) Utility for patients discontinuing in the first treatment cycle is 10% lower than for stable schizophrenia	First line aripiprazole	24,483	2.602	27	0.002	12,053
	First line olanzapine	24,456	2.600			
8) Utility for patients discontinuing in the first treatment cycle is 20% lower than for stable schizophrenia	First line aripiprazole	24,483	2.600	27	0.003	8,703
	First line olanzapine	24,456	2.597			
9) Disutility associated with weight gain continues while patients remain on a given treatment	First line aripiprazole	24,483	2.588	27	0.004	7,091
	First line olanzapine	24,456	2.584			
10) Greater disutility for weight gain (20%)	First line aripiprazole	24,483	2.596	27	0.004	6,293
	First line olanzapine	24,456	2.592			
11) Greater disutility for weight gain (20%) and continue disutility while patients remain on a given treatment	First line aripiprazole	24,483	2.578	27	0.003	8,275
	First line olanzapine	24,456	2.575			
12) Alternative adjustment for zero cell counts in calculating OR withdrawal due to adverse events	First line aripiprazole	24,486	2.598	-13	0.003	-4,166
	First line olanzapine	24,498	2.594			
13) Alternative adjustment for zero cell counts in calculating OR significant weight gain	First line aripiprazole	24,484	2.597	27	0.004	6,045
	First line olanzapine	24,457	2.593			

Table 30 reports the cost effectiveness results for combinations of scenarios included in the analyses in Table 29. As in the previous analysis, adjusting medication costs for patients who experience relapse approximately doubles incremental costs, without affecting incremental QALYs, leading to an approximate doubling in the ICER. Including disutility from weight gain

while patients remain on a given medication has comparatively little impact on the ICER (rising from £13,763 to £15,663) while reducing disutility for patients discontinuing due to adverse events, lack of efficacy or other reasons in the first treatment cycle has a larger effect (ICER increases from £15,663 to £23,144 when this assumption is applied in addition to those already considered). Reducing the proportion of relapsed patients who are admitted as in-patients leads to first line aripiprazole being dominant. However, if the length of stay for those patients who are admitted is increased to 107.7 days, the ICER increases markedly (to £56,972) and further increases (to £218,853) if the RR of relapse reported by Moeller and colleagues[20] is used.

Table 30: Scenario analysis with cumulative changes to base case assumptions

		Total		Incremental		ICER (£ per QALY gained)
		Cost (£)	QALYs	Cost (£)	QALYs	
Corrected base case	First line aripiprazole	24,483	2.597	27	0.004	6,231
	First line olanzapine	24,456	2.593			
Adjust medication costs for patients who experience relapse (1)	First line aripiprazole	24,322	2.597	60	0.004	13,763
	First line olanzapine	24,262	2.593			
As above plus: disutility associated with weight gain continues while patients remain on a given treatment (9)	First line aripiprazole	24,322	2.588	60	0.004	15,663
	First line olanzapine	24,262	2.584			
As above plus: utility for patients discontinuing in the first treatment cycle is 20% lower than for stable schizophrenia (8)	First line aripiprazole	24,322	2.591	60	0.003	23,144
	First line olanzapine	24,262	2.588			
As above plus: 50% of relapsed patients are admitted as in-patients (3)	First line aripiprazole	17,677	2.591	-1	0.003	Dominant
	First line olanzapine	17,678	2.588			
As above plus: Length of stay for relapsed patients admitted as in-patients = 107.7 days (4)	First line aripiprazole	37,429	2.591	180	0.003	69,638
	First line olanzapine	37,248	2.588			
As above plus: RR relapse = 0.92 (2)	First line aripiprazole	36,593	2.592	514	0.002	232,981
	First line olanzapine	36,079	2.590			

Notes:
The figure in brackets, following the text describing the additional scenario applied in each row, refers to the number of the scenario analysis in the previous table (Table 29)

4.3.4.5 Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis can be run by clicking on the 'Simulation' button on the '*Simulations*' worksheet in the Excel model. The number of simulations to be run in the PSA can be set in cell D4 of the '*Simulations*' worksheet. The '*Data & References*' worksheet contains a table of input values for all model parameters, which lists the point estimate used in the deterministic base case analysis (labelled "default value") along with a lower and upper value for each input. The lower and upper values listed are the limits used in the deterministic sensitivity analyses, discussed above, and are based on 95% confidence intervals (where such data are available) or on an assumed variation of ± 30%. Irrespective of whether the range from lower to upper value was based on observed data the model uses these values to estimate a SE as the basis for parameterising distributions in the PSA, except for utilities which use the SEs reported by Briggs and colleagues[23].

The PSA takes about 20 minutes to run (on a computer with 1.86 GHz dual core processor and 2 Gb memory) for 10,000 simulations. The MS reports the results of probabilistic evaluations of the base case and of the four scenario analyses (RR of relapse, use of benzodiazepines, treatment efficacy and disutility with clozapine). Results for the probabilistic base case are presented in Table 45, page 110, of the MS which reports the probabilistic mean (but no measures of dispersion, such as percentile-based 95% confidence interval) for total costs and total QALYs for each treatment strategy, as well as the incremental cost and incremental QALYs for first-line aripiprazole compared with first-line olanzapine. These are shown in Table 15 (page 45) of this report. A scatter-plot of the base case cost effectiveness results and a CEAC are also presented in the MS (Figures 13 and 14, p 110 to 112). There is no discussion in the MS on the discrepancy in the estimated incremental cost between the deterministic and probabilistic evaluations of the model (in the base case the estimated incremental costs differ by approximately £1,000, ranging from -£69.21 in the deterministic evaluation to -£1,016 in the probabilistic evaluation; this is discussed in more detail later in the ERG report).

Results for the probabilistic evaluation of the scenario analyses are reported on page 114 of the MS (for RR of relapse), pages 116 to 118 (for use of benzodiazepines), pages 118 to 119 (for treatment efficacy) and pages 120 to 121 (for disutility with clozapine).

The PSA includes all variables in the model, but there is limited discussion in the MS to justify the distributions chosen or of appropriate ranges for the data. In particular, there is no discussion over the appropriateness of the ± 30% assumed for those variables where no variance data were available. Details of variables included in the PSA, their deterministic base case value, lower and upper values and the assumed distribution are included in Table 59 (p 163 to 167) of the MS. The distributions chosen for variables in the model, and their parameterisation, are generally appropriate (see summary below).

Summary of assumptions for the manufacturer's PSA:

- "Clinical effectiveness" variables
  - ORs (or RRs) for discontinuation or adverse events for olanzapine relative to ariprazole were sampled as normal distributions, with the mean equal to the natural logarithm of the deterministic input value and SE recovered from the 95% CI calculated in the adjusted indirect comparison (see section 5.7.6, p 55). The sampled values were then exponentiated to give parameter inputs on the normal, rather than the log, scale;
  - Probabilities of discontinuation or adverse events for aripiprazole were sampled as beta distributions, parameterised using the number of events (α) and non-events (β) (events were reported in Table 21, p 53);
  - RR of relapse was sampled as a normal distribution, with the mean equal to the natural log of the deterministic input value and SE derived from a range estimated as ± 30% of the mean. The sampled value was then exponentiated to give parameter inputs on the normal, rather than the log, scale;
  - Probability of relapse on aripiprazole was sampled as a beta distribution, parameterised using the method of moments,[28] using the proportion of relapsers reported by Moeller and colleagues,[20] assuming a 95% confidence interval around the mean based on variation of ± 30% (Moeller and colleagues[20] do not report 95% CI for proportions). This CI is far greater than the 95% CI estimated based on 89 events in a population of 444 persons (calculated in section 6.3.2, p 87) – where 95% CI is 0.1931 to 0.2081;

- Quality of life
  - Utility for the stable schizophrenia state was sampled as a beta distribution, parameterised using the methods of moments[28] using the mean and SE reported by Briggs and colleagues;[23]
  - Utility for other states is estimated as percentage disutility from the stable schizophrenia state and sampled as a beta distribution, parameterised using the method of moments.[28] Mean percentage disutility is estimated by subtracting the state-specific utility from the value for stable schizophrenia (e.g. for relapse state the percentage disutility is (0.919 - 0.604)/0.919 = 34.28%) and the SE for state-specific utility (e.g. 0.042 for relapse) is used. This approach ensures that the health state utilities estimated for relapse and for treatment-related side effects are lower than that for stable schizophrenia in all simulations, but it does not ensure that the rank order of the relapse and side effects disutilities is maintained (i.e. there is nothing to ensure that relapse, EPS, weight gain and somnolence remain in this order, from greatest to least disutility). In practice, the relatively large differences between the utility estimates for relapse and each of the side effects means that this order is preserved in the majority of simulations.
- Resource use
  - Drug costs are sampled using a gamma distribution, parameterised using the methods of moments.[28] The mean of the distribution is the cost per day used in the base case analysis (drug dosages taken from the SPC and costed for the most commonly prescribed brand and packaging, see section 4.3.2.4 of this report for more details) with the SE derived from the range between the lowest and highest cost formulations and packaging for each drug. This approach to sampling drug costs does not explicitly take into account variation in dosage of individual medications, but only captures variation in unit cost.
  - Resource use associated with relapse involved sampling values for five different variables:
    - The proportion of patients admitted for in-patient care and the proportion of relapsed patients treated with olanzapine were sampled as gamma distributions, parameterised using the method of moments.[28] The mean of the distribution was based on assumptions adopted for the NICE adult schizophrenia guideline[11] and SEs were derived from a range estimated as ± 30% of the mean. Use of gamma distributions for these variables does not appear appropriate as this will permit

unfeasible values (proportions greater than 1) to be sampled. Indeed, the upper limit used in the base case for both variables is greater than 1. Use of a beta distribution would have ensured that values outside the logical limits for this variable would not be sampled. As discussed in section 4.3.4.1 of this report, values for the 95% confidence interval reported by Glover and colleagues[27] could have been used for the proportion of relapsed patients admitted for in-patient care rather the arbitrary range of ± 30%.

- The duration of in-patient care, community-based care and olanzapine-treatment for relapsing patients were sampled as gamma distributions, parameterised using the method of moments,[28] with a mean of 42 days (1 cycle) and lower limit of zero. The upper limits were set to be the base case values adopted for the model reported in the NICE adult schizophrenia guideline[11] (111 days for in-patient care and olanzapine treatment and 56 days for community-based care). The MS contains no discussion or justification for these ranges.

o Resource use associated with adverse events involved sampling values for nineteen different variables (see section 4.3.2.4 for details of variables involved in estimating resource use associated with each type of adverse event):

- The proportion of patients seeing their GP for weight gain, seeing a psychiatrist for somnolence or for EPS and the proportion of patients with EPS who are prescribed lorazepam were sampled as gamma distributions, parameterised using the methods of moments,[28] with the mean equal to the deterministic input value and the SE derived from a range estimated as ± 30% of the mean. As stated above, the use of gamma distributions for these variables does not appear appropriate as this will permit unfeasible values (proportions greater than 1) to be sampled. The upper limit used in the base case for all these proportions was greater than 1.
- The proportion of patients seeing a dietitian for weight gain was sampled as a beta distribution, parameterised using the methods of moments,[28] with the mean equal to the deterministic input value and SE derived from a range estimated as ± 30% of the mean. It appears that a beta distribution was used in this case, rather than the gamma distribution used for other proportions, because the base case value was 0.2 (rather than 1, which was base case value for other proportions), which would permit estimation of the parameters (α and β) of a beta distribution using standard methods.[28]

    - The number of visits patients made to their GP and to the dietitian for weight gain, to the psychiatrist for somnolence or for EPS were sampled as gamma distributions, parameterised using the method of moments,[28] with the mean equal to the deterministic input value and SE derived from a range estimated as ± 30% of the mean.
    - The duration of visits patients made to their GP, to the dietitian for weight gain, and to the psychiatrist for somnolence or for EPS were sampled as gamma distributions, parameterised using the method of moments,[28] with the mean equal to the deterministic input value and SE derived from a range estimated as ± 30% of the mean.
- Unit cost
    - Relapse - unit costs for in-patient care and community-based care (cost per day) were sampled as gamma distributions, parameterised using the method of moments,[28] with the mean equal to the deterministic input value and SE derived from a range estimated as ± 30% of the mean.
    - Adverse events - unit costs for GP, psychiatrist and dietitian time (cost per hour) and cost of lorazepam for patients experiencing EPS were sampled as gamma distributions, parameterised using the methods of moments,[28] with the mean equal to the deterministic input value and SE derived from a range estimated as ± 30% of the mean.

In summary, the approach to sampling ORs and RRs for discontinuation, probability of discontinuation and adverse events for aripiprazole and utilities appears to be appropriate in the PSA. However, the approach to sampling proportions and the estimated variation for RR of relapse (olanzapine versus aripiprazole), relapse on aripiprazole, length of in-patient stay and duration of community-based care is less appropriate (considered further in section 4.3.4.6 of this report). It appears that the reason for using gamma distributions to sample a number of variables that are expressed as proportions is because the base case value for these proportions is 1. The standard method for estimating the parameters (α and β) of a beta distribution[28] would fail for mean values of 1. However, as noted above, adopting a gamma distribution leads to unfeasible values being sampled.

As noted earlier in this report (section 4.3.3.1), there is an error in the PSA results in the electronic model (and hence in the MS), where the total undiscounted (rather than discounted)

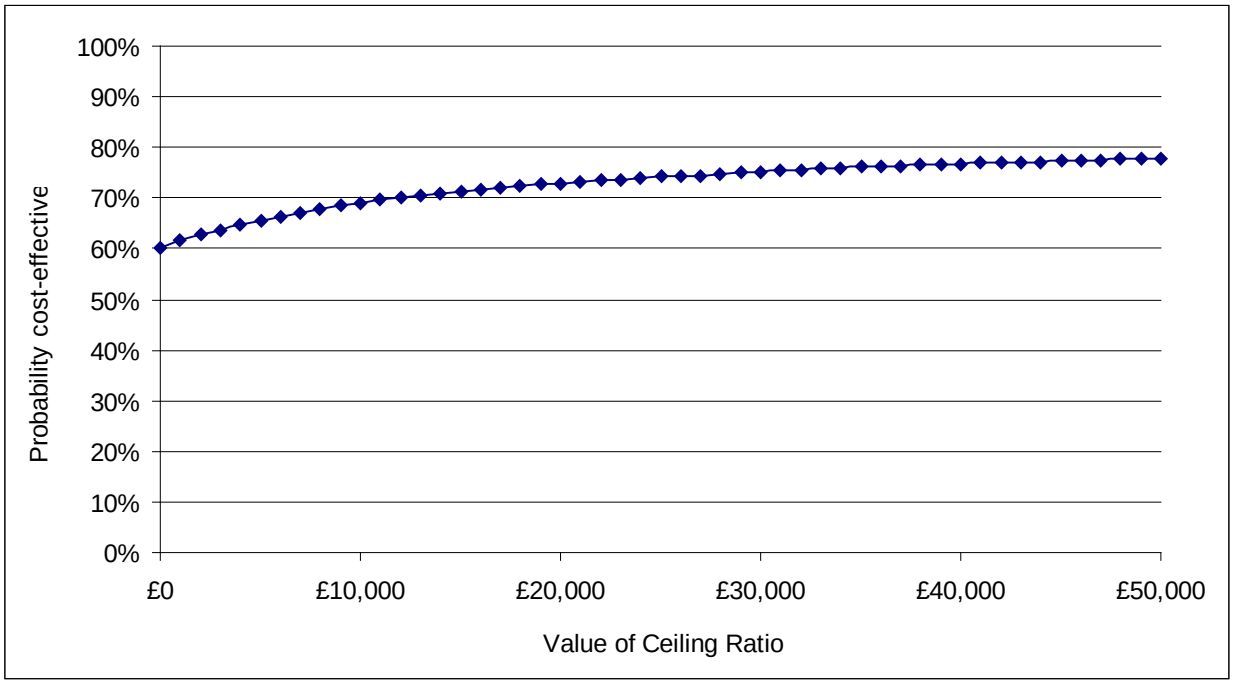
cost for first-line olanzapine strategy has been included. Table 31 presents the results of the probabilistic evaluation of the base case after correcting the model, which yields results which are more consistent with the deterministic base case than those presented in the MS.

Table 31: Results of probabilistic evaluation of model correcting for error in copying value

Treatment strategy	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£ per QALY gained)
First-line aripiprazole	£23,976 (7,082 to 60,710)	2.596 (2.457 to 2.703)	-£37.78 (-1,064 to 1,359)	0.008 (-0.004 to 0.028)	First-line aripiprazole dominates
First-line olanzapine	£24,014 (7,250 to 61,042)	2.588 (2.449 to 2.697)			

Figure 3 presents the CEAC for the PSA after correcting for the error in copying costs for first-line olanzapine strategy, which estimates a lower probability of first-line aripiprazole being cost effective at all willingness to pay threshold values, compared with the CEAC presented in the MS. The probability of first-line aripiprazole being cost effective at a willingness to pay threshold of £20,000 per QALY gained is 73%. The equivalent value at a willingness to pay threshold of £30,000 per QALY gained is 75%.

Figure 3: CEAC for manufacturer's PSA after correcting for error in copying costs for first-line olanzapine strategy



4.3.4.6 ERG Probabilistic Sensitivity Analysis

The ERG re-ran the PSAs for the corrected model. In addition to the corrections applied in the deterministic model (i.e. including costs of managing relapse for patients who remain on their first line treatment in cycle 1, but relapse in cycle 2 and adjusting medication costs for patients who experience relapse), corrections to the parameterisation of distributions for variables expressed as percentages, alternative estimates for variation in RR of relapse (olanzapine versus aripiprazole) and in risk of relapse on aripiprazole (based on 95% CIs rather than an arbitrary range) were also applied.

Table 32 and Table 33 present the mean total and incremental cost and QALYs (with percentile-based 95% CIs) derived in additional PSAs undertaken by the ERG. Table 32 reports the results of the PSA conducted on the corrected base case and with additional changes to the manufacturer's model to correct errors in sampling (such as proportions sampled using inappropriate distributions which may return unfeasible values). Table 33 repeats the analysis reported in Table 32, except that the RR of relapse (olanzapine versus aripiprazole) is estimated using the values reported by Moeller and colleagues[20] rather than the value assumed by the manufacturer. In both analyses, the mean cost with first line aripiprazole is greater than first line olanzapine, with the difference in costs increasing when the RR of relapse reported by Moeller and colleagues[20] is used, while the incremental QALYs remain largely unchanged. The incremental cost effectiveness ratios, evaluated at the mean cost and QALYs are £22,182 per QALY gained for the analysis reported in Table 32 and £47,103 per QALY gained for the analysis reported in Table 33.

Table 32: Corrected base case (corrected ranges)

	Cost (£)		QALYs	
	Mean	(95% CI)	Mean	(95% CI)
First line aripiprazole	24,594	(7,295 to 62,957)	2.596	(2.455 to 2.707)
First line olanzapine	24,385	(7,364 to 63,120)	2.589	(2.446 to 2.702)
Incremental	208	(-993 to 1,834)	0.008	(-0.003 to 0.027)

Table 33: Corrected base case (RR relapse = 0.92)

	Cost (£)		QALYs	
	Mean	(95% CI)	Mean	(95% CI)
First line aripiprazole	23,812	(6,882 to 61,853)	2.596	(2.456 to 2.702)
First line olanzapine	23,452	(7,007 to 60,778)	2.588	(2.445 to 2.697)
Incremental	360	(-924 to 2,238)	0.008	(-0.004 to 0.028)

Table 34 reports the probability of first line aripiprazole being cost effective, relative to first line olanzapine, for a range of willingness to pay threshold values from the PSAs reported in Table 32 and Table 33.

Table 34: Probability of cost effectiveness for range of WTP threshold values

	Probability of being cost effective at given willingness to pay threshold		
	£20,000	£30,000	£50,000
Corrected base case	52.5%	59.1%	68.5%
Corrected base case (RR relapse = 0.92)	42.6%	48.9%	58.8%

Figure 4 presents the CEACs for the analyses reported above. The shape of the CEACs reflects the fact that there is a large proportion of simulations where first-line aripiprazole dominates (30% and 26% for the analyses reported in Table 32 and Table 33 respectively) but also a proportion where first-line aripiprazole is dominated (8% and 12% for the analyses reported in Table 32 and Table 33 respectively) – scatterplots of the incremental cost and incremental QALYs (with 95% confidence ellipses are shown in Figure 5 and Figure 6). This reflects the large degree of uncertainty in the model, particularly around the estimated RR of relapse (which has a mean of [redacted] (95% CI from [redacted] to [redacted] in the corrected base case analysis and mean of 0.92 (95% CI from 0.67 to 1.26) for the analysis using values reported by Moeller and colleagues[20]). The scatterplots (Figure 5 and Figure 6) reflect the parameter uncertainty included in the PSA, but interpretation of these results also needs to be informed by consideration of additional uncertainty relating to the applicability of adult data used in the model to adolescent populations.

Figure 4: CEACs derived from ERG probabilistic sensitivity analysis

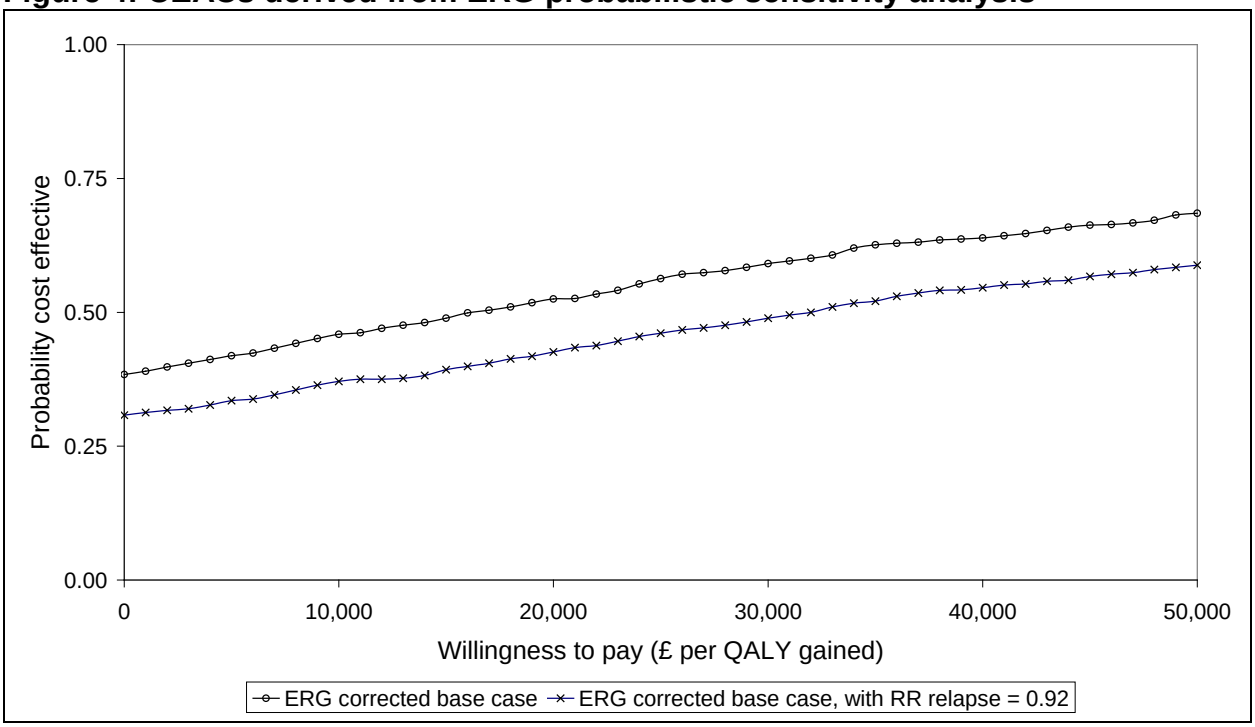


Figure 5: Scatterplot for corrected base case

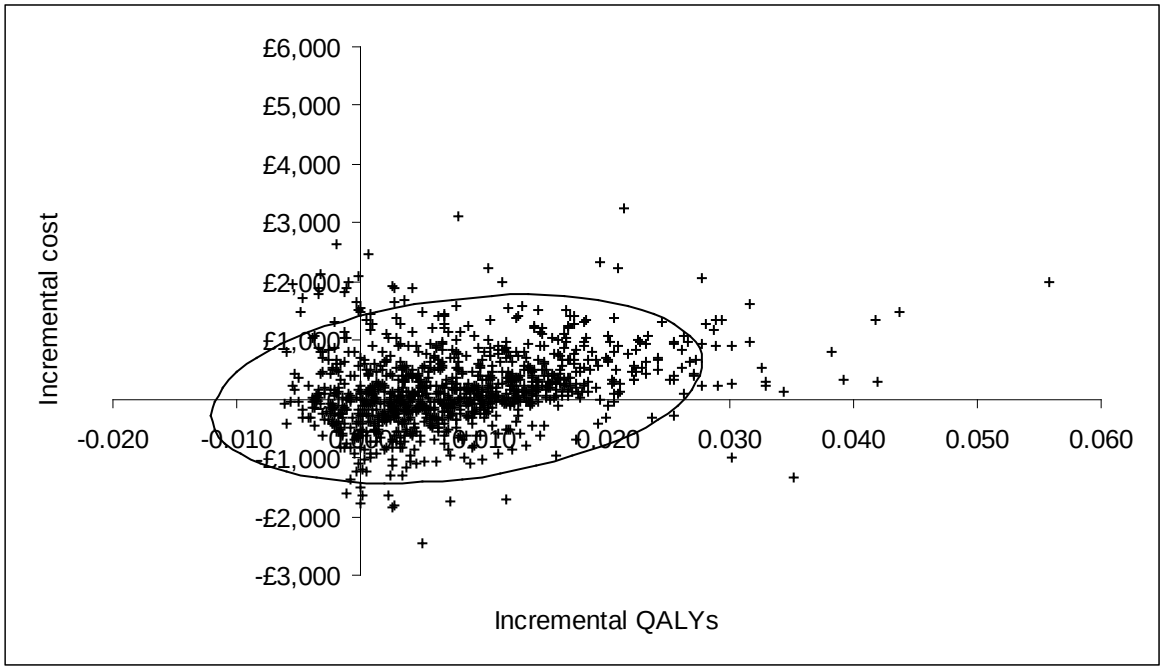
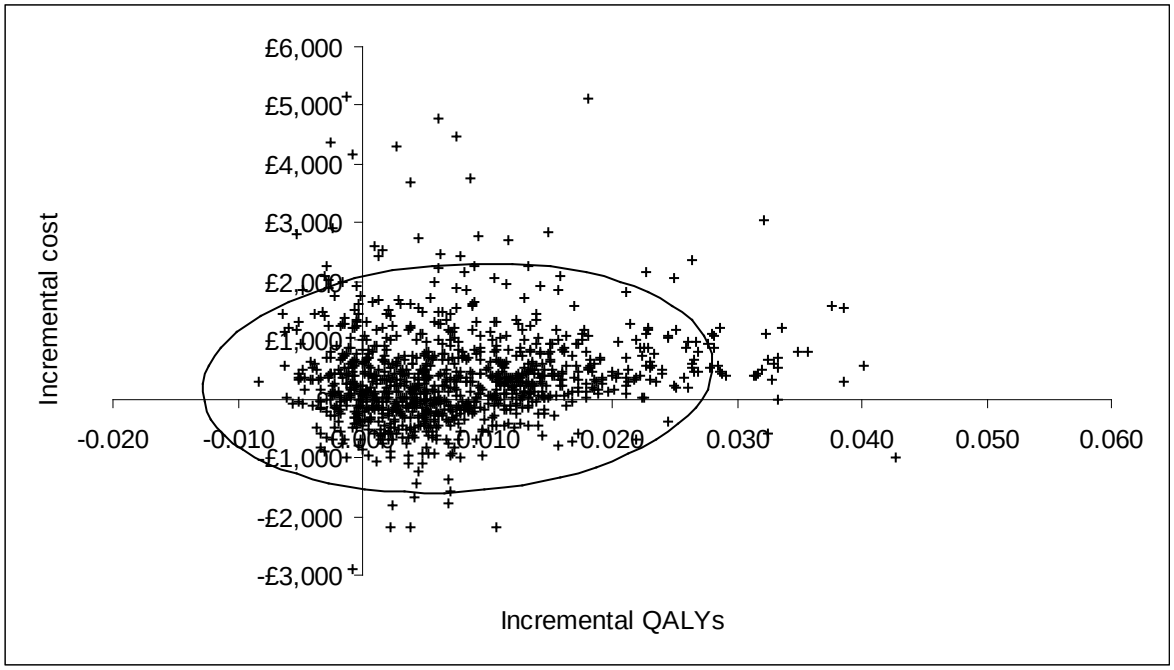


Figure 6: Scatterplot for corrected base case (RR relapse = 0.92)



4.3.5 Comment on validity of results presented with reference to methodology used

The structure adopted for the economic model is reasonable, and consistent with previous economic evaluations. However, separating the model into a decision tree, for the first two cycles, and a Markov model for the remaining cycles has introduced unnecessary complexity and appears to have led to an error being introduced into the model calculations (see section 4.3.3.1 of this report for full details). This separation has also resulted in the electronic model being difficult to understand – this is not helped by poor layout in which model calculations are widely distributed across the worksheets containing the decision tree and Markov models for each treatment strategy.

The methods used to derive input data for the economic model are generally appropriate. The use of an adjusted indirect comparison to estimate withdrawals (due to adverse events, lack of efficacy and other causes) and treatment-related side effects is reasonable and the analysis appears to have been conducted appropriately although the MS contains no interpretation, discussion or critical assessment of the results of the analysis. In particular, the MS contains no discussion of the sensitivity of the results of the adjusted indirect comparison to the approach taken to dealing with zero value cell counts in 2x2 tables.

The methods used to transform six-month relapse risks (taken from a published study on adult populations[20]) to six-week risks (the length of cycles in the model) appear appropriate and have been correctly implemented in the model. However the MS has not used the RR of relapse reported in the original publication, but uses a re-estimated value based on crude risks reported in the paper. The appropriateness of adopting a RR based on the crude risks appears questionable given the baseline differences in populations reported in the paper (discussed in section 4.3.2.2 of this report). The MS does not report the method used to identify this reference or whether targeted searches were undertaken to identify studies of relapse in patients with schizophrenia treated with atypical antipsychotics. There is no critical appraisal of this study or any discussion of the generalisability of evidence from treatment of adults with schizophrenia in the United States to the UK context.

Population of the model was generally hampered by a lack of data specific to adolescents. As a result, data on relapse, health state utility, disutility associated with treatment-related side effects and resource use assumptions are all derived from studies of adult rather than adolescent populations. This approach can be justified, in the absence of data specific to the population in the scope of this appraisal, but needs to be acknowledged as a limitation and source of uncertainty when interpreting the results of the economic evaluation. It is less easy to accept the justification in the MS for excluding clozapine from the systematic review of clinical evidence and the stated assumption (without reference to published evidence or expert opinion) that, in the absence of other data, risks derived for aripiprazole can be applied to clozapine-treated patients.

The methods of analysis are generally appropriate and conform to NICE methodological guidelines.[18] However, some analytical errors were detected in the electronic model developed for this submission. These have been documented in this report along with corrected results, where this is possible. In all cases, the ERG has attempted to estimate the extent to which such errors may have systematically biased the results presented in the MS and have concentrated on those errors or uncertainties which appear most likely to have introduced bias or which have greatest influence on the model results. The input data in the model are generally in accordance with those listed in the MS and appendices. Notwithstanding this, we cannot guarantee that there are no remaining errors in the MS or the model.

4.3.6 Summary of uncertainties and issues

- The model developed for the submission compares sequential treatment strategies (covering three lines of medication) rather than individual drug regimens. This is consistent with the approach adopted in previous economic evaluations of drug treatment for schizophrenia (in particular the model developed the NICE guideline for schizophrenia in adults[11]), but requires information on the breakdown of cost and effect by line of treatment, and the relevance of each complete treatment strategy to current clinical practice to be interpreted properly;
- The model compares first-line aripiprazole to first-line olanzapine for treatment of adolescent schizophrenia. This is a more limited comparison than that outlined in the scope developed by NICE. The MS justifies the exclusion of other comparators due to the lack of data in adolescents, but does not discuss the relevance of the comparator (or each component line of the first-line aripiprazole strategy) to clinical practice in England and Wales. Clinical advice to the ERG suggested that risperidone would be the most common first line treatment for schizophrenia in adolescent populations;
- Clinical outcomes in the model are based on withdrawal from first and second line treatment and on relapse. The model takes account of the QoL impact of side effects, but does not consider any other aspects of QoL. The model includes a homogeneous, stable schizophrenia health state and does not take account of symptomatology, other than that which will be associated with relapse;
- There is uncertainty over the appropriateness of applying relapse risks observed in adult populations to adolescents. If adults risks are assumed to be applicable to adolescent populations there remains uncertainty whether the single study identified by the manufacturer is relevant to the current context and whether it was appropriate for the manufacturer to assume that a RR of relapse estimated from crude risks should be used rather than the value reported in the study publication;
- There are methodological uncertainties arising from the method of dealing with zero value cell counts in 2x2 tables that were used in the adjusted indirect comparison. The results of the cost effectiveness analysis appear reasonably robust to this uncertainty for one of the input variables, but more sensitive for another;
- Some potentially relevant side effects of treatment have not been included in the model, or could only be included using proxy values. The model does not include sexual dysfunction (clinical advice to the ERG suggested this may be important side effect for some adolescents with schizophrenia) and EPS could only be included by considering

the use of benzodiazepines as a proxy measure (due to the lack of reporting EPS in one of the included trials);

- The MS acknowledges uncertainty over the applicability of utility estimates derived in adult populations to adolescents. The values adopted in the MS appear to have been derived using appropriate methods, but it is unclear whether these values accurately reflect the impact of disease or treatment-related side effects on adolescents with schizophrenia. Clinical advice to the ERG suggested that weight gain may be a more significant factor in adolescents than in adults.

5 Discussion

5.1 Summary of clinical effectiveness issues

The MS includes evidence on the efficacy of aripiprazole relative to placebo from one RCT, and also includes data on adverse events from two non-RCTs. The MS also compares a restricted set of outcomes for aripiprazole with a comparator treatment, olanzapine. Overall the MS contains an unbiased estimate of the efficacy of aripiprazole at six weeks and shows that adverse events are mostly moderate. The estimates of the effectiveness of aripiprazole in relation to other comparator interventions used in this population is however uncertain.

5.2 Summary of cost effectiveness issues

The model structure and methods adopted for the economic evaluation are reasonable and are generally appropriate. The model structure is consistent with previous economic evaluations. However, separating the model into a decision tree followed by a Markov model introduced unnecessary complexity, making the electronic model difficult to understand and appears to have led to an error being introduced into the model calculations.

The economic evaluation is based on a more limited comparison than outlined in the scope developed by NICE. The MS justifies the exclusion of other comparators due to the lack of data in adolescents (in particular a lack of placebo-controlled RCTs, which were required for inclusion in the adjusted indirect comparison), but does not discuss the relevance of the comparator (or each component line of the first-line aripiprazole strategy) to clinical practice in England and Wales. Population of the model was generally hampered by a lack of data specific to adolescents. As a result, input values for a number of model parameters were derived from

studies of adult rather than adolescent populations. This approach can be justified, in the absence data specific to the population in the scope of this appraisal, but needs to be acknowledged as a limitation and source of uncertainty when interpreting the results of the economic evaluation. Pre-model analyses used to estimate parameter inputs and transformations used to prepare data for use in the model appear to be appropriate, although there is limited discussion or critical assessment of the pre-model analyses. Other than the RCTs included in the clinical effectiveness review there is limited discussion or critical assessment of the data sources used to populate the model and in many cases no evidence of systematic targeted searches.

Some analytical errors were detected in the electronic model developed for this, which have been documented in this report. Where possible, corrected analyses have been presented by the ERG. In all cases the ERG has attempted to estimate the extent to which such errors may have systematically biased the results presented in the MS.

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7 Addendum

Section A: Clarification of effectiveness data

Evidence

A1. In order to verify that the clinical data reported in your submission has been correctly presented, could you please provide copies of the Clinical Study Reports cited in your submission?

These are provided.

Literature searches

A2. Please could you confirm which clinical trials registries (e.g. controlled-trials.com, UKCRN clinicaltrials.gov) and conference abstracts were searched?

No clinical trial registries or conference abstracts were searched.

A3. Please could you provide clarification of the approach used, and the content of, the hand-searching?

Based on initial, general keyword searching through PubMed (Medline), two reviews were initially identified: Madaan et al (2008) (1) and Kumra et al (2008) (2). These review articles and their respective bibliographies were used to inform the design of the search strategies. Interrogation of the articles also served to identify poster and abstract articles for inclusion in the search results (3, 4).

A4. The ERG has identified an additional publication of an analysis from the Findling et al RCT (Robb, et al, 2010, Journal of Child and Adolescent Psychopharmacology; 20(1): 33-38). Could you please comment on the relevance of this study to your submission?

This study was a *post hoc* analysis of a specific subset of scores (Hostility) from the Positive and Negative Syndrome Scale PANSS. The PANSS is made up of five psychopathological symptom domains of schizophrenia (Positive, Negative, Depression/Anxiety, Cognitive, Hostility).

The study is not of major relevance to our submission because:

(a) it is *post hoc* analysis conducted outwith the primary outcome measure of the PANSS Total score, and so must be considered less robust than a protocolled analysis;

(b) while it is encouraging that the data suggest that (compared with placebo) individual PANSS Hostility, Uncooperativeness and Poor Impulse Control Items can be significantly improved with aripiprazole 30mg/day, aripiprazole's proven effects on the PANSS Total score are of more relevance to our submission.

Thus, while of interest, we feel the data from Robb et al (2010) do not add anything of additional significance to our submission.

Comparators

A5. Could you please provide details of the methodology adopted for assessing studies for inclusion in the indirect comparison and the non-RCT evidence base supporting your submission?

Indirect comparison

As outlined in Section 5.7.1, the search strategies detailed in Section 5.2 were designed to identify trials that could be used in the indirect comparison as well as providing data for the clinical sections of the submission (i.e. RCTs). Sections 5.2.1 and 5.2.2 have outlined the criteria used to identify studies in adolescent patients with schizophrenia.

In section 5.2.2 of the submission we have reported the following.

For the purposes of indirect comparison with comparator interventions, 2/6 studies were eligible for analysis (one study comparing aripiprazole versus placebo and one study comparing olanzapine versus placebo (5, 6) (see also Section 5.7). All the other studies (4/6) were unsuitable for indirect comparison as they either did not include a placebo group (7-9) or they did not contain sufficient data for comparison (e.g. abstract by Haas (2007) (3)).

In addition, to ensure that the trials were appropriate to include in the indirect comparison we have outlined the details of patient characteristics in section 5.7.7. The treatment groups in the aripiprazole study (5, 10) and the olanzapine study (6) were generally well matched for demographic and baseline characteristics. The average age of patients in Findling et al (2008) (5) was 15.4 years in the placebo arm and 15.6 years in the aripiprazole 10 mg arm, compared with an average age of 16.3 years in the placebo arm and 16.1 years in the olanzapine arm in the Kryzhanovskaya et al (2009) study (6). Both studies recorded outcomes at 6 weeks and measured outcomes in a similar way. We have assumed that the similarity of the trials included in the indirect comparison avoids bias in the estimates of the indirect comparison (11).

Non-RCT evidence.

The aim of the search was to identify prospective, non-randomised evidence regarding the efficacy and safety of aripiprazole for the treatment of adolescents with schizophrenia. Of the 152 non-randomised records identified by the Master search, the flow chart below outlines the reasons for exclusion; no study captured by the searches were considered relevant to the decision problem.

After the first round of exclusions (E1), 63 records were interrogated for inclusion of aripiprazole as a study intervention (E2). Of these, 4 studies were identified (as described in section 5.8 of submission document). The first two rounds of exclusion were based on title and abstract; the final round of exclusion was done based on full text.

Flow chart

Number	Reason for exclusion
E1 (n=89)	
19	Non-prospective study (e.g. retrospective, observational)
10	Non-english record
1	Duplicate
24	Non-specified interventions
3	Not schizophrenia (other or mixed diagnosis excluded)
9	Not schizophrenia (other or mixed diagnosis excluded)
23	No relevant outcome data on efficacy or safety of interventions to treat schizophrenia
E2 (n=59)	
59	Studies did not include aripiprazole as an intervention
E3 (n=4)	
3	Included adult patients only
1	No relevant outcome data (phase II tolerability and pharmacokinetic study [see section 5.8 of submission document])

A6. Please provide details of the methodologies for the studies included in the indirect comparison.

Details of the pivotal clinical trial used to support this submission (study 31-03-239) were outlined in Section 5.3 (both the Findling publication (5) and the CSR 31-03-239 (10) were used to inform the summary of the clinical trial). Both the aripiprazole clinical trial and the olanzapine clinical trial were reviewed according to the quality criteria requested in the NICE STA template.

The methodology of the olanzapine clinical trial (6) is summarised in Table 1 below.

Table 1: Summary of methodology of the Kryzhanovskaya et al (2009) study (6)

Location	Multicentre, United States (20 sites) and Russia (5 sites)
Design	Randomised, double-blind, placebo-controlled study
Duration of study	Three periods; a 2- to 14-day screening and washout period; a 6-week double-blind, acute period with olanzapine or placebo; and an optional 26-week open-label period with olanzapine
Inclusion Criteria	• Adolescents aged 13 to 17 years with schizophrenia of the paranoid, disorganised, catatonic, undifferentiated, and residual types • Total score ≥ 35 on the anchored version of the BPRS-C with a score ≥ 3 on at least one of the following BPRS-C items at randomisation; hallucinations, delusions, or peculiar fantasies
Exclusion Criteria	• Previous participation in a clinical trial of oral olanzapine • Treatment within 30 days of the trial with a drug without regulatory approval for any indication • Documented olanzapine allergic reaction • Previous non-response to an adequate dose/duration of olanzapine treatment • Pregnancy, nursing or refusal to practice acceptable contraception • Acute/unstable medical conditions • Current/expected use of any concomitant psychotropic

	medications (except for certain benzodiazepines and anticholinergics) • Clinically significant laboratory abnormalities • DSM-IV-TR substance dependence within 30 days (except nicotine and caffeine) • Current DSM-IV-TR diagnosis of a comorbid psychiatric or developmental disorder
Intervention(s) (n) and comparator(s) (n)	Olanzapine 2.5 or 5.0 mg/day (which could be increased to a maximum of 20.0 mg/day or decreased by an increment of 2.5 or 5.0 mg/day at the investigator's discretion (n = 72) Placebo (n = 35)
Method of randomisation	Patients were randomly assigned in a 2:1 ratio to either olanzapine or placebo nightly. The method of randomisation was not reported
Method of blinding	The study included a 6-week double-blind period – the method of blinding was not reported
Primary outcomes	Mean change from baseline-to-endpoint change in the investigator-rated BPRS-C total score
Secondary outcomes	Baseline-to-endpoint changes on the CGI-S, PANSS, and the Overt Aggression Scale (OAS). Changes on the CGI-I were evaluated at endpoint. A secondary measure was patients' response rate, defined a priori as a 30% or greater reduction in the BPRS-C total score from baseline to endpoint and a CGI-S score of 3 or lower (mildly ill) at the last measurement
Statistical analyses	Data were analysed on an ITT basis, with a two-sided α level of 0.05. An analysis-of-covariance model with the terms country, therapy and baseline was used to evaluate continuous efficacy data. Categorical data were analysed using a Fisher exact test, and a mixed-model repeated-measures analysis of covariance was used to analyse the change in the BPRS-C total score from baseline to each post-baseline visit. Time-to-event analyses were performed using a log-rank test. The LOCF method was used to analyse mean changes from baseline to endpoint

A7. Please provide all of the results from the RCT (Study No. 31-03-239)[1] that was included in the indirect comparison. It is noted that only a table on the quality assessment for this study has been provided in the submission.

Results from the two studies included in the indirect comparison are outlined in Section 5.7.4. All the data for aripiprazole were taken from the CSR but have also been reported in the publication (Findling et al (5)), therefore both the publication and the CSR have been referenced in the indirect comparison section. A quality assessment was carried out for both the included studies (Section 9.3 for the aripiprazole study, and Section 9.5 for the olanzapine study).

[1]Note, the original ERG question was linked to A6 and the request was for details of the Kryzhanovskaya et al trial, however, this was misinterpreted to mean *Study No. 31-03-239* by the technical team.

A8. The submission includes clozapine as a third line treatment in the economic model, despite not being listed as a comparator in the submission. Please could you clarify why a systematic search to identify studies which include data for this treatment was not

undertaken and why the results, methodology and quality assessment of any identified studies were not presented in the submission.

Clozapine is not considered as a comparator in the submission because, according to clinicians, it would not be given first- or second-line, and is therefore not given in place of aripiprazole or olanzapine. Therefore, we did not carry out any clinical searches on clozapine in the first instance.

However, according to expert opinion, clozapine is commonly used as an end-of-line treatment (in treatment resistant patients), and was therefore considered in the economic model in order to include health states that accurately described what treatments patients may receive after two previous second generation antipsychotics have failed.

In terms of outcomes, only relapse rates and adverse events are considered in the model for clozapine. The relapse rates were taken from the same paper as relapse rates for other treatments in the model, Moeller et al, 2006 (12). We assumed that the adverse events for clozapine would be the same as those for aripiprazole (because adverse events while on clozapine are thought to be worse, according to expert opinion, compared with other second generation antipsychotics this was felt to be a conservative assumption). The effect of including additional disutility while on clozapine was tested in sensitivity analysis and found not to affect the results. The costs of clozapine were also considered.

A9. Section 2.6: Please provide further details and justification of whether the conference abstract identified for risperidone had sufficient data for the clinical review, and explain why the data was deemed insufficient for model parameters.

The conference abstract for risperidone only reported the change in PANSS scores as an outcome. The patients' baseline PANSS scores are not reported and no numbers or percentages of patients were reported for withdrawals or adverse events. For example, the abstract outlines which adverse events were most common but does not provide the numbers of patients experiencing the events. Therefore, we consider that the data provided to be insufficient for inclusion in the indirect comparison.

When the results of this trial are fully published in a peer reviewed journal, the results of risperidone can be evaluated and added to the clinical and cost-effectiveness evidence.

Population

A10. Section 3.1.1: Your submission states that 'other areas of mental health disorders such as learning disabilities are not appropriate for this review'. Please could you clarify what is meant by this, and provide your inclusion and exclusion criteria used to identify people with learning difficulties?

As described in the submission, the diagnosis of schizophrenia requires a definitive methodological approach using precise DSM-IV and K-SADS-PL criteria. Thus "inclusion and exclusion criteria used to identify people with learning difficulties" are not relevant – patients are diagnosed as either suffering or not suffering from schizophrenia, using these diagnostic tools.

In this phrase in our submission we attempted to clarify that while some individuals with learning difficulties may exhibit psychoses, unless they fulfil the DSM-IV/K-SADA-PL criteria for schizophrenia they are (by definition) not schizophrenic, and so are not appropriate for inclusion in our submission on aripiprazole in adolescent schizophrenia.

Clinical evidence

A11. Please could you provide information as to why 'head to head studies with less than two arms including the intervention of interest were excluded' from the clinical evidence, and provide a list of these 78 excluded studies, Please also provide a list of all other excluded studies and the reasons for their exclusion from stages e2 and e3 of the screening process.

"Head to head studies with <2 arms including interventions of interest" were excluded from the review (see Section 5.2.1 of the main submission document). "Interventions of interest" included olanzapine, risperidone, quetiapine, placebo, haloperidol, amisulpride, aripiprazole (as per Section 5.2.1 of the main submission document).

Studies including intervention arms with at least two of the "interventions of interest" were included in the review, while studies with less than two arms of interest were excluded. For instance:

- Hertling et al. (Neuropsychobiology 2003;47(1): 37-46) was excluded as it compared risperidone with flupenthixol in a head-to-head fashion (i.e. <2 arms of interest).
- Whereas, Sikich et al. (American Journal of Psychiatry 2008;165(11): 1420-1431) was included as it compared molindone, olanzapine and risperidone (at least two arms of interest).

The rationale for this approach was to identify a relevant data set that would allow indirect comparison with the technology under assessment (i.e. aripiprazole). Without at least 2 arms of interest, an evidence network could not be created.

(See Appendix A for a list of the 78 excluded studies excluded for reasons of being a "head to head study with <2 arms including interventions of interest". See Appendix B for a list of all other excluded studies and the reasons for their exclusion from stages e2 and e3 of the screening process).

A12. Please provide justification for the LOCF approach to data analysis, and provide for each study arm, information on how many observations in each week were carried forward?

The core data set for all efficacy analyses was the intent-to-treat (ITT) dataset that contains data from all randomised subjects regardless of protocol violation. If a subject received a treatment other than the one to which he or she was randomised, this subject was included in the ITT data set on an "as-randomised" basis. In order to handle missing data and restrictions imposed by different types of analyses (e.g. change from baseline analysis), other data sets derived from the ITT data set were used for the efficacy analyses, such as the observed cases (OC) data set and the last observation carried forward (LOCF) datasets.

For change from baseline analysis, only subjects who had both baseline and post-baseline values were included in the OC and LOCF data sets. LOCF data sets were the primary analysis data sets, as is standard practice in schizophrenia clinical trials.

A13. There is inconsistency in the reporting of analyses from the included trial (Study No. 31-03-239), with some outcome data reported for baseline and endpoint only, whereas others are provided for 0,1,2,3,4,5 and 6 weeks. Please could you clarify the reason for this?

All efficacy outcomes are reported for all weeks 0-6, except for those relating to functioning and quality-of-life. The CGAS and PQLES-Q total and overall scores are only measured and reported at baseline and endpoint (i.e. Week 6). Although there was no rationale provided in the CSR, parameters relating to functioning and quality-of-life are unlikely to show changes on a weekly basis, and so measurements at these times would be meaningless. It is therefore more appropriate, and more clinically relevant, to measure the change after 6 weeks of treatment.

A14. Please provide clarification why P-QLES-Q was classed as an 'other' (not primary or secondary) outcome measure in your submission, the definition of 'other' in this context, and what the implications are for interpreting the P-QLES-Q data as presented.

The P-QLES-Q was classified as 'other' in the clinical trial because it cannot be classed as either an efficacy or safety measure. It is a quality-of-life scale (consisting of 14 items pertaining to daily activities and satisfaction, and an overall assessment item) and thus reliant upon subjective responses from the patient depending on "how they feel" at a particular point in time.

A15. For each of the PANSS, GCI, CGAS, and P-QLES-Q, please provide details of what would be a clinically meaningful change or difference in these measures, and whether the sample size used was considered adequate to provide reasonable power to detect this meaningful change or difference.

There are no agreed parameters by which clinically meaningful changes/differences in PANSS, GCI, CGAS and P-QLES-Q can be pre-defined, and how they link with each other. While a certain level of change in symptom score may, by clinical consensus, be considered clinically meaningful, such considerations are very reliant on the clinical judgement, experience and knowledge of the disease area of the assessing clinician, and their evaluation of the expected/likely clinical responses.

Because such a clinical judgement is *a priori* (not requiring a statistical estimation/interpretation of the data), sample size would not be a factor in considering whether the number of patients were adequate to show a clinically meaningful change or difference.

Section B: Clarification of health economic model

B1. Please could you provide more detail of the methods, quality and results of the study that was used to estimate the relative risk of relapse in the economic model. It is noted that the study from which the relative risk was sourced was not reviewed in your submission.

Summaries of the methodology and results of the study by Moeller et al, 2006 (12) are provided in Table 2 and Table 3. These are followed by a qualitative assessment of the study limitations.

Table 2: Methodology of Moeller et al, 2006 (12)

Location	USA
Design	Retrospective cohort study examining psychiatric relapse rates, defined as hospitalisation for a psychiatric event, for persons with schizophrenia who switched antipsychotic agents.
Duration of study	12 months
Inclusion Criteria	• Kansas Medicaid enrolees with a diagnosis code for schizophrenia • Aged ≥ 18 years • Continuously enrolled in Medicaid during the 12-month study period • Switched from any antipsychotic to either aripiprazole (cases) or 1 or the other atypical antipsychotics (comparisons)
Intervention(s) (n) and comparator(s) (n)	Patients were classifed as switchers if they had previously received an antipsychotic agent and had a prescription for a new atypical antipsychotic agent. Switchers were sorted into the following groups; Cases; those switching to aripiprazole Comparisons; those switching to another SGA (clozapine, olanzapine, quetiapine, risperidone, or ziprasidone)
Outcome variable	Hospitalisation for a psychiatric diagnosis within 6 months of the date of switch; occurrence of hospitalisation, time to admission, length of stay
Analyses	Cases and comparisons were compared with respect to basic demographics, concurrent conditions, and prior psychiatric-related health care use in bivariate analyses using descriptive statistics. Time to relapse was modelled using Cox proportional hazards

Table 3: Results of Moeller et al, 2006 (12)

Patient disposition and demographics	• 965 patients met eligibility criteria; 444 aripiprazole (cases) and 521 SGAs comparisons • Aripiprazole patients were younger than patients receiving SGAs (42.6 vs. 47.1 years, respectively; $p < 0.001$). Study populations were comparable with respect to gender and race • Neurotic, personality, and non-psychotic mental disorders; substance abuse; and depression were the most frequent comorbidities in both treatment groups • Patients on aripiprazole were less likely to suffer from depression than patients on SGAs (26.8% vs. 34.4%, respectively; RR = 1.43; 95% CI = 1.08 – 1.88) • The most commonly reported medical comorbidites were cardiovascular diseases, lipid disorders, diabetes and pulmonary diseases. Rates did not differ between groups • Prior to the switch aripiprazole patients were more likely than SGA patients to have tried more antipsychotic medications (2.83 vs. 2.60, respectively; $p < 0.001$). More patients in the aripiprazole group than the SGA group were switched from an atypical antipsychotic (82.8% vs. 73.5%, respectively; RR = 0.58; 95% CI 0.43 – 0.78). Use of other psychotropic medications was comparable • Previous psychiatric hospitalisations and outpatient visits were

	comparable
Relapse/Time to relapse	Based on psychiatric hospitalisations rates of relapse did not differ between groups: • Six months after being switched from their previous antipsychotic regimen 20% of aripiprazole and 19.4% of SGA patients were hospitalised (RR = 0.92; 95% CI = 0.67 - 1.26) Time to relapse was not statistically different between groups: • Mean times to psychiatric hospitalisation were 65.7 days for the aripiprazole group and 73.8 days for the SGA group
Predictors of relapse	Significant variables in the Cox proportional hazards model included other psychiatric diagnoses and past number of psychiatric-related hospitalisations: • Comorbid diagnoses of depression (adjusted hazard ratio [AHR] = 1.44; 95% CI = 1.05 – 1.98), substance abuse (AHR = 1.80; 95% CI = 1.32 -2.74), and neurotic, personality, and non-psychotic mental disorders (AHR = 2.27; 95% CI = 1.58 – 3.26) all increased the risk of psychiatric hospitalisations • Prior psychiatric hospitalisations also increased the risk of post-switch hospitalisation (AHR -= 1.38; 95% CI = 1.22 – 1.55) Use of apripiprazole versus other SGAs had no effect on the risk of hospitalisation (AHR = 1.16; 95% CI = 0.86 – 1.56)

Quality assessment of Moeller et al, 2006 (12)

A large patient population was included in the study. The selection/eligibility criteria were adequately described. There were, however, some differences between the study groups. Patients in aripiprazole group were on average younger than the SGA group (42.6 vs. 47.1 years, respectively) and received more community support visits, case management, and antipsychotic medications. This may suggest that aripiprazole patients had better access to services, or that they had a more severe form of schizophrenia, than those in the SGA group. Also, more patients in the SGA group suffered from comorbid depression than in the aripiprazole group (34.4% vs. 26.8%, respectively). A higher incidence of depression may be associated with a poorer outcomes and higher rates of relapse and rehospitalisation.

The patient population was recruited from a single US state's Medicaid plan and may not be able to be generalised/extrapolated to other populations. In addition, accurate coding of healthcare services and diagnoses had to be assumed.

The comparator group contained a mixture of SGAs, so individual SGAs could not be compared with aripiprazole. The newer agents are typically classified as a group; however their side effect profiles may differ. These effects could impact on relapse rates and efficacy. In addition, the study included patients who may have been receiving multiple antipsychotics after the switch - not monotherapy with either aripiprazole or SGAs. However, the study was designed to represent real-life prescribing practices.

Moellar et al (2006) examine relapse rates in an adult population which is a recognised limitation of the model. The model was based on the best available data in the absence of relapse rates for adolescents.

B2. Please provide more detail of the methods, quality and results of the study used to obtain HRQoL data for your submission.

The details of the study used to source utility values (13) have been described in section 6.4.6. This section outlines the methods and results of the study and comments have been made on the suitability of the study to inform the economic model included in this submission. The details of the study were provided in conjunction with the requirements outlined in the STA template.

It is difficult to review the overall quality of QoL studies and as far as we are aware there is no proforma to carry out such an evaluation. However, in terms of applicability, Briggs et al 2008 (13) carried out their study in a relevant population (patients with schizophrenia I the UK) and collected utilities for relevant health states such as stable schizophrenia and side effects of treatments.

This study is freely available therefore we have therefore attached a link here: http://www.hqlo.com/content/pdf/1477-7525-6-105.pdf

The health states were developed by the authors in such a way as to ensure that they were clinically relevant and meaningful. They did this by: carrying out a literature review to identify initial health states for discussion; carrying out cognitive interviews in patients with schizophrenia to ensure they were meaningful and clear to patients; and by carrying out a cognitive debrief with lay persons, again to ensure the states were clear and meaningful.

Of the 75 laypersons and 50 patients recruited, all but one participant (from the patient group) completed the study. The patient group completed an EQ-5D questionnaire to validate the baseline health state (stable schizophrenia). The mean utility measured by the EQ-5D was 0.86, which is lower than the utility elicited from the patients in the TTO questionnaire, but very similar to the utilities elicited from the lay population.

The utility values for health states used in the model (either in the base case analysis or in sensitivity analysis) were reported for patients and laypersons as shown in Table 4.

Table 4: Utility values as reported in Briggs et al 2008 (13)

Health State	**Mean utility (SE**	
	Patient sample	**Lay sample**
Stable schizophrenia	0.919 (0.023)	0.865 (0.021)
Weight gain	0.825 (0.028)	0.779 (0.024)
Relapse	0.604 (0.042)	0.479 (0.033)
EPS	0.722 (0.037)	0.574 (0.032)

In order to be consistent in the model, the utility values elicited from patients were used. In Briggs et al (2008), there were differences in the utilities observed in the patient group and the layperson group although the direction of results was the same. We have provided results from the model using utilities from the layperson sample as a sensitivity analysis to show the effect of these differences.

Please note, for this sensitivity analysis we used the model with the revised cost according to clarification point B5. In this sensitivity analysis we have considered that the disutility for somnolence is zero (i.e. that the quality-of-life for somnolence is not considered) as this utility

comes from a separate source. We have provided results from deterministic analysis and PSA. In the PSA analysis the disutility for somnolence was varied from 0-100%.

The base case analysis is presented in Table 5 with the sensitivity analysis showing the results of using the alternative utilities in Table 6. The PSA analysis is presented in Table 7 and Figure 1. The PSA results are based on 10,000 simulations.

Table 5: Base case analysis (using revised model as discussed in clarification point B5)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Aripiprazole - olanzapine - clozapine	£22,981	2.597	-£72.63	0.004	Dominant
Olanzapine - aripiprazole - clozapine	£23,054	2.593	-	-	-
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

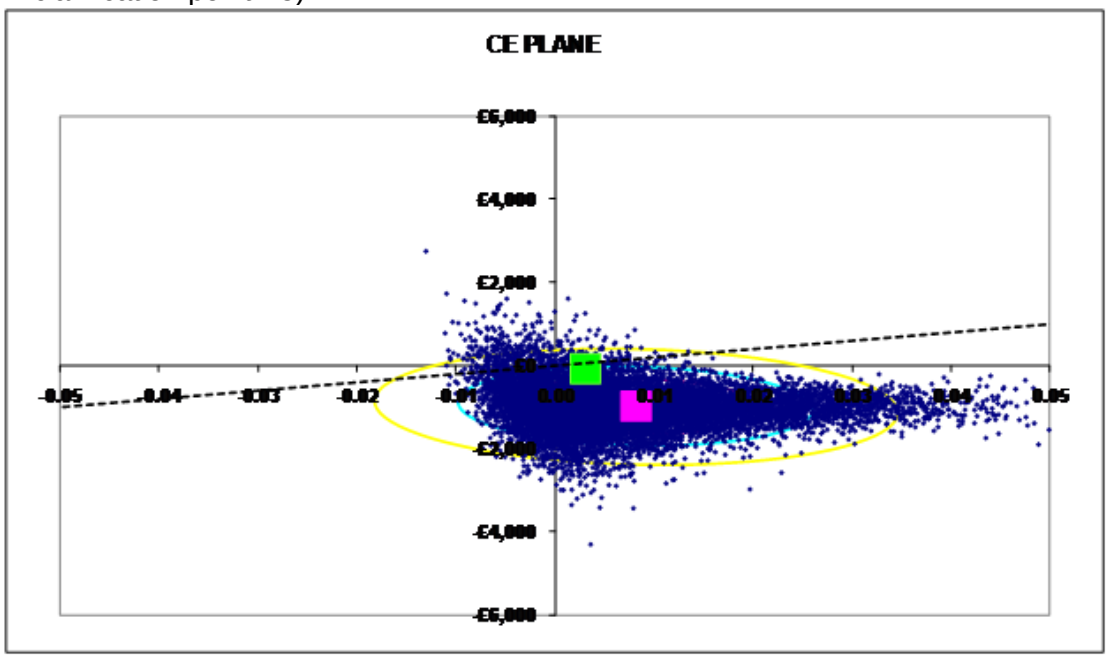
Table 6: Results of additional utility value sensitivity analysis (layperson utility values from Briggs et al 2008 (13)) (using revised model as discussed in clarification point B5)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Aripiprazole - olanzapine – clozapine	£22,981	2.439	-£72.63	0.003	Dominant
Olanzapine - aripiprazole – clozapine	£23,054	2.436	-	-	-
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Table 7: PSA results of additional utility analysis (using revised model as discussed in clarification point B5)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Aripiprazole - olanzapine - clozapine	£23,212	2.437	-£996	0.008	Dominant
Olanzapine - aripiprazole - clozapine	£24,208	2.428	-	-	-
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Figure 1: CE plane - PSA results of additional utility analysis (using revised model as discussed in clarification point B5)



Briggs et al (2008) examined utilities in an adult population which is a recognised limitation of the model. The model was based on the best available data in the absence of utility values for adolescents.

B3. Could you provide more detail on the methods of the prescription cost analysis study described in your submission?

We used the prescription cost analysis data provided at the NHS information centre (http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/prescription-cost-analysis-2008).

We used the number of prescriptions from the PCA and calculated the proportion of each formulation prescribed. The most common formulation was then used as the cost for the treatment. These calculations were also included in the economic model (sheet: prescription cost analysis). The calculations we carried out are shown in column S of this sheet. The highest and lowest costs for the treatments included in the model were used in the PSA.

A recognised limitation of this approach is that the number of adolescent patients cannot be determined from this analysis, therefore the prescription numbers take into account are those for patients of all ages.

B4. It is noted that your submission refers to MIMS online 2010 (no access date given) as the source used for drug acquisition costs, while your electronic model lists the source for drug acquisition costs as BNF No 59, March 2010. Please state which source is correct and provide the date this information was accessed, if using electronic sources. Please not that the technology appraisal process prefers the use of the price quoted in the BNF, where available.

Prices for drugs were taken from MIMS online 2010 (accessed during April 2010). This is because the current version of the BNF does not yet reflect the changes in price according to the PPRS. The model reference is incorrect.

B5. The submission states that the acute hospital cost per day used in the model was based on the national average unit cost for HRG code PA52 (p 99 and 102). The 2008/09 NHS Reference Costs lists the national average unit cost for PA52C (Behavioural Disorders with length of stay 8 days or more) as £23,595. In table 42 you have listed this cost as £24,581 (which is the national average unit cost for PA53B (Eating Disorders with length of stay 8 days or more)). Please clarify which HRG code and cost is correct and the reference you have used.

The correct code is PA52C and the correct cost is £23,595 (taken from 2008/09 NHS Reference Costs). This would mean that the overall cost of relapse per patient is £17,016 rather than £17,700.

We have corrected this error in the model and have presented revised results in Table 9 for the base case scenario (Table 8 shows the original base case results for comparison).

Table 8: Original base case result

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Aripiprazole - olanzapine - clozapine	£23,723	2.597	-£69.21	0.004	Dominant
Olanzapine - aripiprazole - clozapine	£23,792	2.593	-	-	-
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Table 9: Revised base case result (with updated cost)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Aripiprazole - olanzapine - clozapine	£22,981	2.597	-£72.63	0.004	Dominant
Olanzapine - aripiprazole - clozapine	£23,054	2.593	-	-	-
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

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Appendix A

List of 78 records appended with code G exclusion at first round of exclusions.

- Code G: Head to head studies with <2 arms including interventions of interest

1. A double-blind comparison of raclopride and haloperidol in the acute phase of schizophrenia. The British Isles Raclopride Study Group. Acta Psychiatr Scand. [Clinical Trial Comparative Study Randomized Controlled Trial]. 1992 Nov;86(5):391-8.
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Appendix B

Exclusion criteria	Exclusion Code	e2 (n=114)		e3 (n=27)	
		No.	*Ref.*	*No.*	*Ref.*
(Non systematic) review, letter, commentary, case report/series	a	1	(1)	2	(2, 3)
No relevant outcome data on efficacy or safety of interventions to treat schizophrenia	b	1	(4)		
Adult (>17yrs) or child (<13yrs) population	c	103	(5-44)(45-89)(90-107)		
Not schizophrenia (other or mixed diagnosis excluded)	d	1	(108)	2	(109, 110)
Non-english	h	3	(111-113)		
No data on adolescent population (i.e. no subgroup analysis of adolescent pop)	j			17	(114-130)
Systematic review or meta analysis	k			5	(131-135)
Full text unavailable	l	1	(136)		
non-RCT (e.g. non randomised trial, observational, retrospective study)	x	4	(137-140)	1	(141)

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