NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Aripiprazole for the treatment and prevention of acute manic episodes in bipolar disorder in children and adolescents [ID305]

Specification for manufacturer/sponsor submission of evidence

January 2013

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Abbreviations

Abbreviation	Definition
ADHD	Attention Deficit Hyperactive Disorder
ADHD-RS-IV	Attention-Deficit Hyperactivity Disorders Rating Scale
AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
BNF	British National Formulary
CD	Conduct Disorder
CDRS-R	Depression Rating Scale-Revised
CGAS	Children's Global Assessment Scale
CGI-BP	Clinical Global Impressions Scale-Bipolar Version
CGI-S	Clinical Global Impressions-Severity of Illness scale
CHMP	Committee for Medicinal Products for Human Use
CHQ-P50	Questionnaire-Parent Form 50
CI	Confidence Interval
CMRS-P	Child Mania Rating Scale-Parent Version
CPN	Community Psychiatric Nurse
CrI	Credibility Interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPS	Extrapyramidal Symptoms
ES	Effect Size
GAS	(Adult) Global Assessment Scale
GBI	General Behaviour Inventory Scale
GP	General Practitioner
HRQoL	Health Related Quality of Life
KADS	Kutcher Adolescent Depression Scale
LOCF	Last Observation Carried Forward
LS	Least Squares
NA	Not Applicable
NHS	National Health Service

NHSC	National Horizon Scanning Centre
NMA	Network Meta-Analysis
NNT	Number Needed to Treat
NR	Not Reported
ODD	Operational Defiant Disorder
OECD	Organisation for Economic Co-operation and Development
ONS	Office of National Statistics
PQ-LES-Q	Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality Adjusted Life Year
QoL	Quality of Life
QW	Once weekly
RCT	Randomised Controlled Trial
RD	Risk Difference
RR	Risk Ratio
SAE	Serious Adverse Event
SD	Standard Deviation
SHO	Senior House Officer
SNAP IV	Swanson, Nolan and Pelham Scale Version IV
TEAE	Treatment Emergent Adverse Event
YMRS	Young Mania Rating Scale

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

- The UK approved name, brand name, marketing status and principal mechanism of action of the proposed technology.
- The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost.
- The indication(s) and any restriction(s).
- The recommended course of treatment.
- The main comparator(s).
- Whether the key clinical evidence in the submission comes from head-to-head randomised controlled trials (RCTs), from an indirect and/or mixed treatment comparison, or from non-randomised studies.
- The main results of the RCTs and any relevant non-RCT evidence.
- In relation to the economic evaluation, details of:
  - the type of economic evaluation and justification for the approach used
  - the pivotal assumptions underlying the model/analysis
  - the mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation.
- Tabulation of the base-case results as follows:

The Technology and Indication

Aripiprazole (Abilify®) is an atypical antipsychotic with partial dopamine D2 and D3 agonistic properties. Positive CHMP opinion was granted for aripiprazole on 14th December 2012 for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

Posology

Aripiprazole is available as tablets, orodispersible tablets or oral solution for the treatment of children and adolescents (see Table 1 for acquisition costs). It is recommended that these patients initiate treatment with the oral solution and then change to tablets. The expected recommended dose of aripiprazole is 10 mg/day, with the option of increasing this up to a maximum of 30 mg/day. For patients who respond to aripiprazole, the expected length of a course of treatment is 12 weeks as stipulated in the licence, with subsequent courses given in cases of relapse of manic symptoms (approximately 15% of patients over 6 months [Section 6.3.5]).

Table 1: Acquisition costs of aripiprazole

Formulation and Strength	Pack size	Cost per pack
5 mg tablet, 10 mg tablet, 15 mg tablet	28 tablets	£95.74
30 mg tablet	28 tablets	£191.47
1 mg/mL oral solution	150 mL	£102.57

Comparators

NICE guidelines state that children and adolescents experiencing acute mania should be treated according to the recommendations for adults with bipolar disorder, with the exception that therapy should be initiated at lower doses.[1] The guidelines also recommend that **an atypical antipsychotic associated with lower weight and non-elevation of prolactin levels should be considered** for maintenance (Section 2.3).[1]

No atypical antipsychotic is currently approved for the treatment of paediatric bipolar disorder in the UK, although risperidone, quetiapine and olanzapine (in addition to aripiprazole) are currently being used off-label in these patients (Section 2.6).[1-4] There is some uncertainty as to which order the atypical antipsychotics are normally used in, and there is likely to be variation in clinical practice. Based on expert opinion,[2-4] the main comparators to aripiprazole are expected to be as follows:

- First-line use: risperidone
- Second-line use after risperidone: quetiapine
- Third-line used after risperidone and quetiapine: olanzapine

The key clinical evidence in this submission comes from a network meta-analysis of the pivotal RCTs for each of the four atypical antipsychotics.

Key Efficacy and Safety Results

Aripiprazole is the only effective therapy that fulfils the requirement for an atypical antipsychotic associated with both low weight gain and low risk of prolactin increase.

Efficacy from the pivotal RCT, NCT00110461 (Section 5.5)

The large and high-quality RCT, NCT00110461, demonstrated that both the 10 mg and 30 mg doses of aripiprazole induced resolution of manic symptoms as measured by YMRS change from baseline from as early as week 1, at week 12 and sustained up to week 30 ([redacted]).[5, 6] Response rates (defined as the percentage of patients achieving a ≥50% reduction from baseline YMRS) were also significantly higher in the 30 mg and 10 mg aripiprazole arms compared to placebo at both the double blind study endpoint at week 4 ($p<0.0001$ and $p=0.0074$, respectively) and at weeks 12 ($p<0.0001$ for both doses) and 30 [redacted].[5, 6]

Safety from the pivotal RCT, NCT00110461 (Section 5.9)

While long-term data lacks for the other antipsychotics, aripiprazole has been demonstrated to have an acceptable long-term safety profile for adolescents aged 13 and over. This is particularly true with respect to adverse events of particular interest in children and adolescents and to which this juvenile population is particularly prone, such as weight gain and increases in serum prolactin levels:

- The incidence of clinically significant weight gain (≥7%) was not significantly different in the 30 mg and 10 mg aripiprazole arms compared to placebo at week 4 and remained low over time in the whole trial population.[5, 7]
- There were also no increases in serum prolactin level, with prolactin levels in all active treatment groups falling over the duration of the 30-week study.[7]

In line with the data available for the other antipsychotics, somnolence and extrapyramidal symptoms occurred more frequently in patients receiving aripiprazole than placebo.[5] However, the vast majority of cases were of mild-to-moderate severity, occurred in the first 4 weeks of the trial and are expected to be manageable.

The CHMP limited the indication for aripiprazole to adolescents aged 13 or over due to safety concerns in younger patients.

Comparative effectiveness (Section 5.7)

A Bayesian network meta-analysis was performed using the pivotal placebo-controlled study for each atypical antipsychotic. There were no statistically significant differences in response rates (measured by YMRS change) at weeks 1-3 between the atypical antipsychotics, although there was a trend for aripiprazole to have greater efficacy versus all others at week 1 and versus quetiapine and olanzapine at week 3.

By week 3/4, aripiprazole was already associated with significantly better outcomes than the other atypical antipsychotics for the adverse events of particular importance in the child and adolescent patient population, weight gain (except compared to risperidone) and prolactin increases:

- Aripiprazole-treated patients were significantly less likely to experience clinically significant weight gain than patients on olanzapine (RR olanzapine vs. aripiprazole: 12.52 [95%CrI 2.31-76.22] and quetiapine (RR quetiapine vs. aripiprazole: 11.1 [95% CrI 1.30-116.1]). This significant result at such an early time point (week 3 or 4) is particularly notable considering that weight gain can develop gradually over time.
- Aripiprazole-treated patients were also significantly less likely to experience a clinically significant increase in prolactin than patients on olanzapine (RR olanzapine vs. aripiprazole: 175.70 [95% CrI 10.86-6414]), risperidone (RR risperidone vs. aripiprazole: 139.80 [95% CrI 5.52-7202]) or quetiapine (RR quetiapine vs. aripiprazole: 31.22 [95% CrI 1.81-1191]).

There were no significant differences between aripiprazole and the other atypical antipsychotics in terms of EPS (RR vs. aripiprazole for risperidone: 0.71 [95% CrI 0.20-2.93]; for quetiapine: 0.72 [95% CrI 0.12-8.38]) or somnolence rates (RR vs. aripiprazole for risperidone: 0.58 [95% CrI 0.23-1.38]; for quetiapine: 0.59 [95% CrI 0.23-1.43]).

Cost-effectiveness

The strong efficacy and safety profile of aripiprazole means that it is a cost-effective therapy compared to usual care at any position in the treatment pathway.

Model structure and assumptions

Aripiprazole was evaluated in the model as a first, second and third line therapy compared to a usual care strategy where no aripiprazole was used, which consisted of risperidone, quetiapine and then olanzapine.

A Markov state transition model was developed to reflect the treatment pathway for adolescents with bipolar I disorder (Section 6.2.3). The model consists of three phases:

1. The **acute** phase where the patient is treated as an inpatient in hospital to manage their acute manic event. Patients who discontinue their atypical antipsychotic or do not respond by week 3 enter acute 2nd or 3rd line treatment. When patients have responded they remain in hospital under observation for a further 5 weeks until they are stabilised. Patients can relapse from this responder observation state and move to acute 2nd or 3rd line treatment.
2. The **maintenance (euthymic)** phase, where patients are discharged from hospital and remain on treatment with an atypical antipsychotic for an average of 4 further weeks before being taken off treatment (giving an average treatment duration of 10-12 weeks). Patients can relapse from these states back into the acute inpatient phase at week 1.
3. The **therapy resistance** phase, where patients have not responded to three lines of atypical antipsychotic therapy. Patients are maintained on lithium only.

The main assumptions underlying the model are as follows:

- Patients will switch treatment if they have not achieved a full YMRS response (≥50% reduction from baseline) by week 3.
- The efficacy and tolerability of aripiprazole is based on pooled evidence for 10 mg and 30 mg dosing. The comparator evidence is also based on pooled doses from clinical trials.
- Response and non-response to a given treatment is independent of when or where it comes in a treatment sequence, including after a recurrent acute manic episode, due to the large absence of data on these aspects.

- Relapse rates in the maintenance phase are based on expert opinion and assumed to be equivalent for all treatments.

Base Case Results (Section 6.7.6)

Aripiprazole used at any stage of the treatment pathway is dominant to usual care, and is therefore a cost-effective option for the NHS (Table 2). Aripiprazole used as second line therapy after risperidone dominates all other strategies.

Table 2: Base-case results – All Strategies vs. Usual Care

Technologies	Total costs (£)	Total QALYs	Incremental costs (£) vs. Usual Care	Incremental QALYs vs. Usual Care	ICER (£) (cost per QALY) vs. Usual Care
Usual care (RIS, QUE, OLA)	£75,066	2.51637			
Aripiprazole 2nd line (RIS, ARI, QUE)	£74,133	2.52466	-£932	0.00830	Dominant
Aripiprazole 1st line (ARI, RIS, QUE)	£74,379	2.52348	-£686	0.00712	Dominant
Aripiprazole 3rd line (RIS, QUE, ARI)	£74,888	2.52297	-£178	0.00660	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; OLA, olanzapine; QALYs, quality-adjusted life years; RIS, risperidone; QUE, quetiapine

It should be noted that generic forms of aripiprazole are due to reach the market in 2014 and therefore aripiprazole will become even more cost-effective in the future.

Sensitivity Analysis Results (Sections 6.7.7- 6.7.11)

The deterministic sensitivity analysis showed that the model is robust and not sensitive to changes in the majority of parameters. The key driver of the cost-effectiveness model was shown to be the response rates at week 3. A higher response rate over the first 3 weeks of treatment results in patients leaving hospital earlier, which has both cost and health-related quality of life (HRQoL) benefits. Given the evidence available, aripiprazole is associated with a favourable response rate at some timepoints in the first three weeks of treatment compared to the comparators, which has health and cost benefits for all aripiprazole strategies in the base case.

The probabilistic sensitivity analysis (PSA) showed that there is some uncertainty surrounding the base case ICERs, which is unsurprising given the lack of statistically significant differences in response rates between the four atypical antipsychotics. For all three aripiprazole strategies the majority of the PSA iterations indicated cost-effectiveness or dominance.

In scenario analysis, the dominance of all three aripiprazole strategies over usual care was stable to changes in the source of utilities and the order of treatment in usual care. Second line aripiprazole remained dominant or cost-effective (ICER <£20,000) versus usual care in all scenarios investigated.

Implications for the NHS

Given the estimated small size of the population (~150 patients aged 13-17 years with bipolar I disorder receiving treatment each year), the recommendation of aripiprazole would be expected to have a budget impact of £30,070 over the next 5 years (Section 7).

This minimal budget impact in addition to the good long-term safety profile of aripiprazole in the indication under appraisal means that the risk surrounding the recommendation decision is expected to be low.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Abilify®

Approved name: aripiprazole

Therapeutic class: atypical antipsychotic

1.2 What is the principal mechanism of action of the technology?

Aripiprazole's efficacy in bipolar I disorder is thought to be mediated through a combination of partial agonism at dopamine D2 and D3 as well as at serotonin 5HT1a receptors, and antagonism of serotonin 5HT2a receptors.[8] Aripiprazole displays high *in vitro* binding affinity for dopamine D2 and D3, and serotonin 5HT1a and 5HT2a receptors, and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors.[8] Aripiprazole also exhibits moderate binding affinity for the serotonin reuptake site.[8] Interaction with receptors other than dopamine and serotonin subtypes is possible and may explain some clinical aspects of aripiprazole.[8]

Aripiprazole's mechanism of action partially differs from the other atypical antipsychotics, which antagonise the D2 receptor.[9-11] This and other differences in

binding affinities may explain the differences in the adverse effect profiles observed between the different atypical antipsychotics.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

New information since original submission of Section A is presented in italics:

Positive CHMP opinion for the indication detailed in this submission was granted on 13th December 2012. [redacted]

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

New information since original submission of Section A is presented in italics:

The CHMP assessment report published on 13th December 2012 discussed the length of treatment, the effectiveness in subgroups with co-morbidities and the safety profile in younger patients:

- *The CHMP concluded that the efficacy of aripiprazole was demonstrated over placebo in bipolar I disorder patients aged 10-17 years old at week 4 as shown by statistically significant improvement on the total YRMS score. This efficacy was maintained through week 30 showing a statistically significant sustained improvement over placebo in both 10 mg and 30 mg. However, given the high number of discontinuations and the lack of statistical significance in observed analysis at week 12, the CHMP concluded that the treatment should not be prolonged longer than 12 weeks.*

- *The CHMP reviewed subgroup data and concluded that the presence of any comorbidity, including ADHD, did not seem to influence the YMRS changes with aripiprazole at weeks 4 and 12. Therefore the indication was not restricted to specific subgroups with or without comorbidities.*

- *The CHMP concluded that the available data to date raised safety concerns regarding mostly weight gain and EPS symptoms, especially in the young bipolar I disorder population aged 10-12 years. The CHMP therefore noted that the safety profile was not favourable for the younger population (10-12 years) and therefore concluded that the benefit –risk balance was only positive in the paediatric bipolar I disorder population aged 13 years and older. More AEs occurred with 30 mg aripiprazole than with 10 mg dose. The CHMP concluded that an increase over 10 mg should only be performed under strict surveillance.*

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

New information since original submission of Section A is presented in italics:

Positive CHMP opinion was granted for aripiprazole on 14th December 2012. Aripiprazole has been recommended for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

Aripiprazole already has a European marketing authorisation for:

- The treatment of moderate to severe manic episodes in bipolar I disorder, and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (adult population only).

- The treatment of schizophrenia in adults and in adolescents 15 years and older.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Thirty-week data from the Otsuka-sponsored pivotal randomised controlled trial (RCT) of aripiprazole for the treatment of manic and mixed episodes of bipolar I disorder in children and adolescents have already been presented at congresses.[6, 12]

Several academic-sponsored studies have been identified on clinicaltrials.gov that are reported to have assessed aripiprazole in the indication under review and have recently been completed.[13-15] However, Bristol-Myers Squibb/Otsuka do not know whether data will be available from these studies within the next 12 months.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Aripiprazole has already been launched in the UK for adult bipolar I disorder and for schizophrenia from 15 years of age.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Aripiprazole has been licensed (either as monotherapy or in combination with lithium or valproate) in the US since 2009 for the treatment and prevention of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in paediatric patients 10 to 17 years of age. Aripiprazole is similarly licensed for paediatric bipolar disorder in Turkey.

Aripiprazole is licensed in the EU and other major markets for the other indications stated in Section 1.5.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Aripiprazole is not subject to any other form of health technology appraisal in the UK at the current time.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A1: Unit costs of technology being appraised

Pharmaceutical formulation	• Tablets (5 mg, 10 mg, 15 mg, 30 mg) • Orodispersible tablets (10 mg, 15 mg) (placed on the tongue and swallowed, or dissolved in water) • Oral solution (1 mg/mL) • Solution for injection (7.5 mg/mL) (there is no experience of use of this formulation in children and adolescents under 18 years of age[8])
Acquisition cost (excluding VAT)	Tablets or orodispersible tablets: • 5 mg (blue), net price 28-tab pack = £95.74 • 10 mg (pink), 28-tab pack = £95.74 • 15 mg (yellow), 28-tab pack = £95.74 • 30 mg (pink), 28-tab pack = £191.47 Oral solution: • 1 mg/mL, net price 150 mL with measuring cup = £102.57 Solution for injection: • 7.5 mg/mL, net price 1.3-mL (9.75-mg) vial = £3.42
Method of administration	• Tablets: swallowed • Orodispersible tablets: placed on the tongue and allowed to dissolve, or dispersed in water and swallowed • Oral solution: swallowed • Solution for injection: injected intra-muscularly
Doses and	The exact dosing of aripiprazole in paediatric bipolar I disorder

dosing frequency	has not yet been determined. Therefore it is assumed that the dosing for adolescents aged 13 and over with manic episodes on bipolar I disorder will be the same as that for schizophrenia patients aged 15 or older. The expected recommended dose of aripiprazole for adolescents aged 13 years or older (for manic episodes of bipolar I disorder) is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases can be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg. The CHMP concluded that an increase over 10 mg should only be performed under strict surveillance.
Average length of a course of treatment	12 weeks, as per licence
Average cost of a course of treatment	For a course of 12 weeks (84 days), the 10 mg dose would cost £287.22. This would be the same for a 15 mg dose. A course of 30 mg dose would cost £574.41
Anticipated average interval between courses of treatments	There is uncertainty around the anticipated interval between courses. Some patients may not experience a relapse, but others may relapse within a few months.
Anticipated number of repeat courses of treatments	As above, there is uncertainty around the average number of courses of treatment required. Due to the frequent relapsing nature of paediatric bipolar I disorder (see Section 2.1), many patients would be expected to require subsequent courses of

	treatment after the first course.
Dose adjustments	No dose adjustment is needed for renal or hepatic impairment, although the maximum daily dose of 30 mg aripiprazole should be used with caution in patients with severe hepatic impairment.[8]

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable; aripiprazole is not a device.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Usual clinical practice for the treatment of manic episodes associated with paediatric bipolar I disorder involves the use of the atypical antipsychotics risperidone, quetiapine and olanzapine, as well as aripiprazole;[1-4] all of these medications are currently being used off-label (see Section 2.6). The frequency of monitoring for aripiprazole is not expected to be greater than for the other atypical antipsychotics, and may even be less due to the lower need for monitoring of prolactin and weight gain with aripiprazole.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

There are no therapies that need to be taken concomitantly with aripiprazole.

As per treatment with other atypical antipsychotics, mood stabilisers such as lithium and valproate can be added to aripiprazole if symptoms persist. Lithium is currently the only medication with a marketing authorisation for the treatment of manic

episodes associated with bipolar I disorder in children and adolescents. Sedation medication (benzodiazepine) can also be added if necessary.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Bipolar I disorder

Bipolar disorder is a disease in which a patient's mood and energy levels can oscillate, affecting their ability to perform everyday tasks such as attending school or socialising with their peers.[16] Bipolar I disorder is characterised by at least one manic episode, with periods of major depression.[17] If manic and depressive phases overlap and a patient experiences manic and depressive symptoms simultaneously or in close succession, this is defined as a mixed state.[16]

In children and adolescents, bipolar disorder is considerably less well-characterised and less understood than in adults, as epidemiological data provides a mixed assessment of the disease.[18, 19] It is generally agreed by UK experts that bipolar I disorder can be diagnosed in children and adolescents, but there is much uncertainty surrounding the validity of diagnosing the other less severe bipolar subtypes (bipolar II disorder, bipolar otherwise not specified) in children.[1, 18] The NICE Clinical Guideline 38 recommends that when diagnosing bipolar I disorder in children or adolescents, the following criteria should be used:[1]

- mania must be present
- euphoria must be present most days and for most of the time (for a period of 7 days)

Irritability is not a core diagnostic criterion for prepubescent children or for adolescents, but for the latter it can be helpful in making a diagnosis if it is episodic, severe, results in impaired function and is out of keeping or not in character.[1]

Symptoms of mania

The main symptoms experienced during manic episodes are outlined in Table A2. It should be noted that the symptoms experienced by pre-pubescent children can be different from those experienced by adolescents, as they tend to frequently manifest

as euphoria and grandiosity rather than irritability or aggression, which are more common symptoms in adolescents.[1, 18]

Table A2: The main symptoms of manic episodes in bipolar I disorder in children and adolescents[1, 16, 20]

Manic Phase Symptoms
• Poor concentration • Little need for sleep • Poor temper control • Reckless behaviour and lack of self control • Euphoria/very elevated mood • Grandiosity • Irritability • Psychosis (loss of contact with reality)

Children and adolescents with bipolar I disorder have a high comorbidity rate

As discussed previously, children and adolescents with bipolar disorder commonly present with other psychiatric disorders, such as attention deficit-hyperactivity disorder (ADHD; estimates of rate of comorbidity with bipolar disorder vary between 11% and 75%), oppositional defiant disorder (46.4%-75%), conduct disorder (5.6%-37%) and anxiety disorders (12.5%-56%).[20] Additionally, the prevalence of comorbid substance abuse in paediatric bipolar disorder is thought to range from 0% to 40%.[18]

Interestingly, the prevalence of comorbidities is thought to vary with age. Children with bipolar disorder are more commonly affected by co-occurring ADHD, whereas the rate of substance abuse in adolescent-onset bipolar disorder is thought to be much greater.[20]

Issues with the diagnosis of bipolar I disorder in the UK

Paediatric bipolar disorder is often missed as a diagnosis in the UK and recognition of the disease can be difficult.[18, 21] One of the reasons bipolar disorder in children and adolescents may be missed is the significant symptomatic overlap with several common psychiatric childhood diseases (particularly ADHD, conduct disorder and anxiety disorders).[22] Therefore recognition of bipolar disorder in children requires specific differentiation from these other diseases that may co-occur.[22] A delay in diagnosis may lead to lack of appropriate treatment, which could result in severe

impairment in social development (eg. schooling and thus later potentially the ability to find qualified work) and quality of life (QoL) in these patients.[23] Initiation of treatment in the early phases of paediatric bipolar disorder is expected to improve the overall prognosis.[23]

Children and adolescents have a more severe course of bipolar I disorder than adults

Compared to adult-onset bipolar disorder, children and adolescents often experience more severe manifestations, which may lead to worse outcomes in the long term.[24] The severity of the bipolar disorder is often more pronounced in children and adolescents, as they appear to undergo more rapid changes in disease states, which are thought to be more heightened than in adults.[25] The majority of sufferers appear to recover from the dysfunction associated with the initial episode and reach a euthymic state,[26] but relapse is common.[27] Additionally, the risk of psychosis and illness recurrence are increased in paediatric bipolar, compared to adult onset disease.[24] Earlier onset is also associated with greater rates of suicide attempts and violence.[28]

Furthermore, the diagnosis and management of bipolar disorder in children and adolescents is complicated by the cognitive and emotional developmental stage of the patients.[25] Due to the young age of onset of paediatric bipolar disorder, the normal psychosocial development of children is impaired and therefore they are at greater risk of developing academic, social and legal problems.[19] The long-term consequences of bipolar disorder have a negative impact on the ability of children to carry out normal daily functions, particularly affecting school performance.[6]

Children and adolescents are more prone to adverse events than adults

Children and adolescents have been found to be more prone than adults to some adverse events associated with antipsychotic therapy, such as weight gain, somnolence, extrapyramidal symptoms and side effects associated with prolactin increases, which include sexual dysfunctions and bone mass loss.[29-31] For children and adolescents, weight gain is particularly associated with additional long-term health risks and personal issues about body image.[32, 33] Additionally, the social stigma associated with bipolar disorder can be greatly heightened by unwanted adverse drug effects such as weight gain and sexual dysfunctions.

Due to these issues, the NICE Clinical Guidelines recommend an atypical antipsychotic that is associated with low weight gain and non-elevation of prolactin levels (which can lead to sexual dysfunction and low bone mass) as the first-line prophylactic agent for prevention of mania relapse in children and adolescents.[1]

Quality of life is severely affected by paediatric bipolar I disorder

Research in a cohort of patients aged 8-18 in a specialty clinical setting has shown that the QoL experienced by children and adolescents with bipolar disorder is severely reduced.[34] This study has suggested that the QoL may be lower than that of patients of the same age suffering from other chronic conditions such as asthma, atopic dermatitis, obesity, arthritis, oxygen dependence, depression and behaviour disorders.[34] Another study has reported that an earlier age of onset of bipolar disorder is associated with a lower QoL over the long term, indicating that the occurrence of bipolar disorder in childhood has worse outcomes later in life.[35]

Of the many QoL domains that are affected by bipolar I disorder mania, psychosocial aspects are particularly impaired, including social and family well-being.[36] It has been reported that the only measure of Health Related QoL (HRQoL) that is not significantly different to the general population at baseline is physical functioning.[36] Several studies have demonstrated that following pharmacological treatment, HRQoL improves in children with bipolar disorder, due to improvement in the ability to get along with others, the management of their behaviours and family functioning.[36, 37] Further to patient quality of life, studies have shown that greater objective and subjective caregiver burden is associated with fewer 'well patient days' over a given time period.[38]

2.2 How many patients are assumed to be eligible? How is this figure derived?

The only UK estimate from an epidemiological study on the number of eligible patients comes from a study on the prevalence of paediatric bipolar disorder that reported a 0% prevalence in a cohort of 5-15 year olds.[39] However, the true prevalence of children and adolescents with bipolar I disorder eligible for aripiprazole treatment in the UK is unlikely to be 0%, for the following reasons:

- The cohort did not include 15-18 year olds, which is the adolescent age-group likely to be most diagnosed with bipolar disorder in the UK.

- It is recognised by the British Association for Psychopharmacology that paediatric bipolar has most likely been missed or misdiagnosed in the UK in the past.[18] Therefore, it is expected that the rate of diagnosis, or at least of symptomatic treatment, would have increased in the UK over the last 9 years since the epidemiological study was conducted.
- Retrospective studies have suggested that as many as 10-20% of adults with bipolar disorder experienced the onset of symptoms when they were younger than 10 years old and 60% when they were less than 20 years old.[20]
- Further evidence suggests that the prescribing prevalence in the UK for antipsychotics for patients 7 to 12 years of age almost tripled between 1992 (0.23 users per 1000 patient-years) and 2005 (0.61 users per 1000 patient-years).[40] Although not all of these antipsychotics would be prescribed for bipolar disorder, this does indicate that the diagnosis and treatment rates of psychiatric conditions in children and adolescents in the UK are increasing over time.

The most appropriate estimate of the prevalence of paediatric bipolar I disorder in the UK is 136 patients hospitalised per year. This is derived from a UK retrospective study of a clinical cohort of patients at the Maudsley and Bethlem Royal Hospital Child and Adolescent Department (a specialist centre for psychiatric illness) between 1974 and 1996, where 38 adolescent (aged 11-18) cases of bipolar disorder were diagnosed within 22 years, providing an estimate of 1.7 cases per year for a specialist centre for psychiatric illness.[39] Given that there are approximately 80 child and adolescent mental health inpatient units in England and Wales,[41] this produces an estimate of 136 hospitalised cases seen per year. The majority of these patients are likely to be diagnosed with bipolar I disorder, given the difficulty in diagnosing the other subtypes of bipolar in children and adolescents, and therefore all would be likely to be eligible for aripiprazole treatment. This number is actually likely to have risen since 1996, due to the increase in diagnosis rates as previously discussed.

There were no other more appropriate epidemiological or clinical studies identified that could give a more accurate estimate of prevalence or incidence for the UK (see Appendix 1a for a list of the studies identified). The estimate above is in line with a study conducted in a comparable country, Ireland, which would estimate about 114 patients diagnosed with bipolar I disorder every year in the UK. This Irish study does have it limitations, however, in that it also included adults and only looked at cases of psychosis. Therefore it is recognised that there is some uncertainty surrounding the

number of eligible children and adolescents in the UK that are diagnosed with bipolar I disorder mania.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

The NICE Clinical Guideline 38, published in 2006, provides recommendations for the management of bipolar disorder in adults, children and young people, in primary and secondary care.[1] The guidance recognises the fact that there are significant limitations to the evidence base for under 18s as the current diagnostic criteria developed for adults have restrictions when applied to children and young people. In addition, pharmacological-based evidence at the time of guidelines development for the treatment of bipolar disorder in children was also limited.

General management principles for the drug treatment of bipolar disorder in children and adolescents include starting at lower doses than in adults and close monitoring, as this population may be more susceptible to adverse events, such as sedation, obesity, extrapyramidal symptoms, metabolic changes and raised prolactin.[1]

NICE guidelines state that children and adolescents experiencing acute mania should be treated according to the recommendations for adults with bipolar disorder, with the exception that therapy should be initiated at lower doses. The following factors should also be considered:[1]

- Height and weight should be checked and monitored regularly.
- Prolactin levels should be monitored.
- The risk of increased prolactin levels with risperidone and weight gain with olanzapine should be considered.
- Following an inadequate response to antipsychotics, adding lithium or valproate should be considered. Valproate should normally be avoided in girls and young women because of teratogenicity risks during pregnancy and risk of polycystic ovary syndrome.

The long-term management of children and adolescents with bipolar is also considered in the NICE guidelines. The recommendations state that treatment should

normally be regulated by specialist clinicians and management should be the same as for adults, with the exception that:[1]

- Atypical antipsychotics that are associated with lower weight gain and non-elevation of prolactin levels should be the first line prophylactic agent.
- In female patients, lithium should be considered as the second-line prophylactic agent. In males, lithium or valproate should be considered.

Additionally, guidelines for inpatient services for children and adolescents are also discussed. The recommendations state that admission as an inpatient or day patient, or more intensive community treatment, should be considered for children and adolescents at risk of suicide or other serious harm. Such care should be provided in specialist units, designed specifically for children and adolescents and able to support their educational, social and personal needs.[1]

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

As discussed by the NICE Clinical Guideline 38, the only drug licensed for use in children and adolescents with bipolar disorder it lithium, which is limited to patients over the age of 12 and should only be used as an adjunct to atypical antipsychotics for acute treatment or as second-line for prophylaxis.[1] However, The Royal College of Paediatrics and Child Health recommend that unlicensed medications may be prescribed where there are no suitable alternatives and where the use is accepted by a professional opinion.[1] As mentioned by the NICE guidelines and discussed in Section 2.3, paediatric subjects may be more susceptible to antipsychotic adverse events compared to adults and therefore careful treatment selection, monitoring and management is essential in this group of patients.[1, 27] In addition to the published guidance, the opinions of clinical experts were attained (Section 9.14, Appendix 14). Expert opinion agreed that off-label use of atypical antipsychotics is standard practice

for the treatment of children and adolescents with manic episodes of bipolar I disorder.[2-4]

None of the three clinical experts interviewed used lithium or divalproex monotherapy as first- or second-line therapy for the treatment of paediatric bipolar I disorder mania, which differs to the NICE guideline.[2-4] They preferred a different atypical antipsychotic as second and third line therapy, and one expert said that they would consider adding a mood stabiliser to an atypical antipsychotic as a third-line option.[2] The same three clinical experts agreed that paediatric patients experiencing an acute manic episode of bipolar disorder would be hospitalised, and that they would remain hospitalised for up to two months under observation.[2-4] This estimate is in agreement with a European study on the length of hospitalisation of adolescents for acute mania, which found a mean duration of 10 weeks.[42]

Taking all evidence into account, a recommendation for aripiprazole will not be expected to change the clinical pathway, but would only be expected to change the choice of atypical antipsychotic to one with minimal perturbation of metabolic parameters and prolactin, as well as reduced monitoring.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Only lithium is currently licensed for use in children and adolescents who present with manic episodes of bipolar I disorder.[1] Other mood stabilisers and antipsychotics are recommended for off-label use by the NICE Clinical Guideline 38, but the previous lack of a licensed atypical antipsychotic means that best practice is unclear and may differ between institutes, as indicated by the expert panel interviewed (see Section 2.6).[2-4]

2.6 Please identify the main comparator(s) and justify their selection.

Lithium is currently the only pharmacotherapy that has a licence for the treatment of children and adolescents who present with manic episodes of bipolar I disorder.[1] However, mood stabilisers such as lithium are not generally used as monotherapy treatment for children with bipolar disorder. Clinical opinion is that if used at all, they are used as adjuncts to atypical antipsychotics.[2]

The atypical antipsychotics quetiapine, risperidone and olanzapine, as well as aripiprazole, are known to be used off-label for paediatric bipolar disorder in the UK.[1-4] There is some uncertainty as to which order the atypical antipsychotics are normally used in, and there is likely to be variation in clinical practice. The choice in clinical practice in the UK is presumably based on perceived efficacy, safety, cost and previous experience. Aripiprazole is frequently cited as the atypical antipsychotic with least risk of causing weight gain or prolactin increases in both adults and children, whereas olanzapine and risperidone are associated with higher risks.[43,44, 45] Risperidone has been available as a generic for many years, meaning that it has been cheaper than other atypical antipsychotics and physicians may be accustomed to using it.

As mentioned previously, clinical experts were asked to provide their opinion on the current treatment pathways utilised in paediatric bipolar (Section 9.14, Appendix 14). The responses from the three clinical experts in terms of positioning of each of the atypical antipsychotics were as follows:

- One of the clinical experts used risperidone as first line therapy, followed by quetiapine and then would add a mood stabiliser to an antipsychotic as third line. This expert stated that aripiprazole would replace quetiapine as second-line therapy.[2]
- Another expert stated to already use aripiprazole as first-line therapy, followed by quetiapine and then olanzapine.[3]
- The third expert would not give a usual treatment order, but stated that the choice of risperidone, aripiprazole and olanzapine was based on the individual case.[4]

Based on this expert opinion, the main comparators to aripiprazole are expected to be as follows:

- First-line use: risperidone
- Second-line use after risperidone: quetiapine
- Third-line used after risperidone and quetiapine: olanzapine

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The main adverse events associated with atypical antipsychotics that can be managed are extrapyramidal symptoms (EPS), weight gain and somnolence. Nausea can also occur.

- EPS are managed with temporary dose reduction, or benzodiazepine and anticholinergic medication.
- Aripiprazole has been found to have a lower incidence of weight gain in children and adolescents compared to other antipsychotics,[44, 46] and therefore is expected to require less intervention for weight gain. The use of drugs to prevent weight gain is rare.
- Somnolence is often managed by changing the time of administration or dose reduction, rather than pharmacological intervention.
- Nausea is often managed by temporary dose reduction and the prescription of anti-emetics.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Table A3 below displays the expected resource use of aripiprazole across location of care, administration costs, monitoring/testing and staff usage. It is important to note that these resource use estimates would apply to all atypical antipsychotics (unless otherwise specified), and aripiprazole use is not expected to increase the resources required to treat adolescents who experience a manic episode of bipolar disorder above the levels currently seen in clinical practice.

Table A3: Resource use associated with aripiprazole use

Resource	Estimated use
Location of care	Initially patients would be treated as hospital inpatients for up for 2 months to allow close observation of the symptoms and treatment emergent adverse effects suffered by the child or adolescent (expert opinion).[2-4] Euthymic patients would then be discharged and would only be seen as hospital outpatients or in specialist psychiatric centres, unless they experience another acute episode that requires re-hospitalisation.
Administration costs	None
Monitoring and testing	Close monitoring of children and adolescents with bipolar I disorder taking pharmacotherapy is advised, in order to adjust treatment doses as necessary and to identify adverse events.[1] Once discharged from hospital, patients would be expected to attend hospital outpatient clinics, GP visits and be visited by community psychiatric nurses (CPNs) in order to monitor their symptoms and adverse events. The following parameters should be monitored annually: • Thyroid function • Blood pressure • Smoking/alcohol use Weight should be regularly monitored,[32] monthly for the first 6 months of treatment and then every 6 months.[1] The following tests should be performed when taking atypical antipsychotics: • Blood glucose test: at start of treatment and then at 3 months (and at 1 month if taking olanzapine); more often if evidence of elevated levels[1] • Test for elevated prolactin levels: for patients taking risperidone only, at start and if symptoms of raised prolactin develop[1]
Staff	Inpatients and outpatients would be seen by specialist psychiatric consultants. Whilst in hospital, patients would also be expected to be attended by hospital staff such as nurses. As outpatients, patients would also be expected to visit their GP and would also be attended by CPNs. The rates of staff usage for children would be expected to exceed the following estimates made for adults with bipolar disorder by the National Collaborating Centre for Mental Health[47] to inform the NICE guidelines: • **Contact with psychiatric consultants and senior house officer (SHO):** At weeks 1, 2, 4, 6, 10, 14, 22 and every 3 months thereafter; first four visits and one visit at the end of the year with a psychiatric consultant; remaining contact with an SHO. Duration 20 min per visit, with the exception of the first and second visit, lasting 45 and 30 min respectively.

	• **Contact with GPs:** At weeks 2, 4, 6 and every 6 weeks thereafter; duration 10 min per visit, with the exception of the first two visits, lasting 20 min each. • **Contact with CPNs:** Home visits at weeks 1, 2, 4 and every 4 weeks thereafter; duration 30 min per visit.

2.9 Does the technology require additional infrastructure to be put in place?

As aripiprazole is not expected to change the structure of the current care pathway or to increase the need for monitoring compared to other currently used treatments, no additional infrastructure is expected to be required.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

Currently, off-label use of atypical antipsychotics is recommended by guidelines (NICE Clinical Guideline 38[1]) as there are no licensed alternatives. However, this may mean that there are differences in practice across physicians, resulting in some children and adolescents being offered antipsychotics while others are not,

depending on whether the physician is comfortable prescribing off-label medication. Therefore the current situation could promote inequality, and a licensed and recommended treatment is required to allow universal access to medication.

The Royal College of Paediatrics and Child Health recommend that physicians may legally prescribe unlicensed medications where there are no suitable alternatives and where the use is accepted by a professional opinion.[47] However, when aripiprazole receives its license for the treatment of children and adolescents with bipolar I disorder, the use of other, non-licensed atypical antipsychotics in first intention would no longer be considered legal by the Royal College of Paediatrics and Child Health, as aripiprazole would represent a fully licensed alternative. It is unclear how NICE intends to deal with recommendations of aripiprazole compared to unlicensed comparators. Bristol-Myers Squibb/Otsuka feel that it may not be best practice to recommend off-label use of medications outside of their marketing authorisation over the use of licensed medications that have been approved for use on the basis of appropriate and validated scientific evidence.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

There are no specific equity or equality issues relating to the use of aripiprazole under its licence.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

Aripiprazole will be compared to unlicensed antipsychotics in the indirect comparison and cost-effectiveness analyses, as these are used by physicians in clinical practice.[2-4] Bristol-Myers Squibb/Otsuka understand that the technology under appraisal should be compared to other medications that are routinely used in clinical practice. However, as previously stated, it is unclear how NICE intends to deal with recommendations of aripiprazole compared to unlicensed comparators. Bristol-Myers Squibb/Otsuka suggest that it is not best practice to recommend off-label use of medications outside of their marketing authorisation over the use of licensed medications.

4 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Children and adolescents with acute manic or mixed episodes associated with bipolar I disorder	Clinical effectiveness and economic evidence will be presented for adolescents with acute manic episodes associated with bipolar I disorder	N/A
Intervention	Aripiprazole for the treatment of children and adolescents with acute manic or mixed episodes associated with bipolar I disorder	Clinical effectiveness and economic evidence for aripiprazole will be presented for the treatment of adolescents with bipolar I disorder mania	N/A
Comparator(s)	• Antipsychotics (such as olanzapine, quetiapine or risperidone) • Valproate • Lithium • Combination treatment with any of the above	• The atypical antipsychotics (olanzapine, quetiapine or risperidone) • Combination treatment of any atypical antipsychotic with either valproate or lithium	Mood stabilisers such as lithium and valproate are not generally used as monotherapy treatment for children with bipolar disorder (expert opinion).[2-4] Clinical opinion is that if used at all, they are used as adjuncts to atypical antipsychotics.[2]

Outcomes	The outcome measures to be considered include: • response rate • range and severity of symptoms of mania and depression • recurrence of manic episodes • body mass index (adjusted for the child's age and gender) • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • response rate • range and severity of symptoms of mania and depression • recurrence of manic episodes • body mass index • adverse effects of treatment • health-related quality of life.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The cost-effectiveness will be expressed in terms of incremental cost per quality-adjusted life year. The time horizon will cover the period of adolescence, which will be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The time horizon will not include treatment of bipolar disorder into adulthood, as this is a different indication and is appraised separately by NICE.	

Subgroups to be considered	If evidence allows, the effectiveness of aripiprazole in pre-pubescent children compared with post-pubescent children will be assessed. If evidence allows the effectiveness of aripiprazole alone or in combination with lithium or valproate will be assessed.	The feasibility of performing subgroup analyses based on age in the pivotal aripiprazole RCT is currently under assessment.	There is no evidence for aripiprazole in combination with either lithium or valproate in children or adolescents with bipolar I disorder, and therefore this cannot be considered in the submission.
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation.	The atypical antipsychotics risperidone, quetiapine and olanzapine will be used as comparators in the economic model, even though they do not have marketing authorisations for the acute or maintenance treatment of children or adolescents with bipolar I disorder. Bristol-Myers Squibb/ Otsuka request that NICE applies the same principles of issuing acute and maintenance guidance within marketing authorisations across all comparators.	

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)		

5 Clinical evidence

Summary of Clinical Evidence

Efficacy

- The large and high-quality trial NCT00110461 demonstrated that both doses of aripiprazole induced resolution of manic symptoms as measured by YMRS change from baseline as early as week 1 and up to week 30 ([redacted]).
- Response rates (defined as the percentage of patients achieving a ≥50% reduction from baseline YMRS) were also significantly higher in the 10 mg and 30 mg aripiprazole arms compared to placebo at both week 4 (p<0.0001 and p=0.0074, respectively) and week 30 [redacted].

Safety

- In both studies NCT00110461 and NCT00116259, aripiprazole demonstrated an acceptable safety profile in children aged 13 or older. This is particularly true with respect to adverse events of particular interest in children and adolescents and to which this juvenile population is particularly prone, such as weight gain and increases in serum prolactin levels.

Comparative Efficacy and Safety

- A network meta-analysis was performed to compare the efficacy and safety of the atypical antipsychotics.
- There were no statistically significant differences in YMRS response rates at weeks 1-3 between the atypical antipsychotics, although there was a trend for aripiprazole to have greater efficacy compared to all others at week 1 and quetiapine and olanzapine at week 3.
- Aripiprazole-treated patients were significantly less likely to experience clinically significant weight gain than patients on olanzapine (RR olanzapine vs. aripiprazole: 12.52 [95%CrI 2.31-76.22] and quetiapine (RR quetiapine vs. aripiprazole: 11.1 [95% CrI 1.30-116.1]) at study endpoint. Aripiprazole-treated patients were significantly less likely to experience a clinically significant increase in prolactin than patients on olanzapine (RR olanzapine vs. aripiprazole: 175.70 [95% CrI 10.86-6414]), risperidone (RR risperidone vs. aripiprazole: 139.80 [95% CrI 5.52-7202]) or quetiapine (RR quetiapine vs. aripiprazole: 31.22 [95% CrI 1.81-1191]).

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

5.1 Identification of studies

Summary of Identification of Studies

- A systematic review was performed to identify all relevant clinical information available for the treatment and prevention of acute manic and mixed episodes in bipolar disorder in children and adolescents with aripiprazole.
- A wide range of electronic databases was searched using search terms taken from a previous systematic review commissioned by NICE in 2005, adapted by the addition of filters for children and adolescents.

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

A systematic review was designed to identify all relevant clinical information available for the treatment of acute manic and mixed episodes in bipolar I disorder in children and adolescents with aripiprazole. The review was based on the search and inclusion strategy as a previous systematic review (commissioned by NICE in 2005),[47] which did not identify any RCT or non-RCT evidence for aripiprazole in children and adolescents with bipolar I disorder.

Databases were searched to include studies from 2005-present. A list of databases is provided in Appendix 2. The search terms were taken from a previous systematic review commissioned by NICE in 2005[47] (Appendix 2). The modifications to the previous review were as follows:

- The term “Epidemiologic study characteristics/” was added to the RCT filter in order to also capture non-RCTs.

- Filters for studies examining children and adolescents were added to the RCT and non-RCT filter (terms based on those from Jensen 2007,[48] Zuddas 2011[49] and Fraguas 2011[50]).

The reference lists of all included studies and additional systematic reviews (Jensen 2007,[48] Zuddas 2011,[49] Fraguas 2011,[50] and Liu et al. 2011[51]) were hand-searched. Additional horizon scanning was performed using Google search engine and media reports.

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

The searches for clinical trials were limited to those including participants under the age of 18. The inclusion criteria for RCTs were as follows:

RCT Evidence Inclusion Criteria

- Included patients with manic or mixed episodes of bipolar I disorder
- Included patients aged <18
- Randomised controlled trial
- At least one of the interventions studied must be aripiprazole
- Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed and the study’s data and results must be extractable

Non RCT Evidence Inclusion Criteria

- Included patients with manic or mixed episodes of bipolar I disorder
- Included patients aged <18
- Non-randomised controlled trial that still evaluates the effectiveness of interventions (acceptable study designs: prospective cohort study, retrospective chart/database review)

- At least one of the interventions studied must be aripiprazole
- Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed and the study's data and results must be extractable

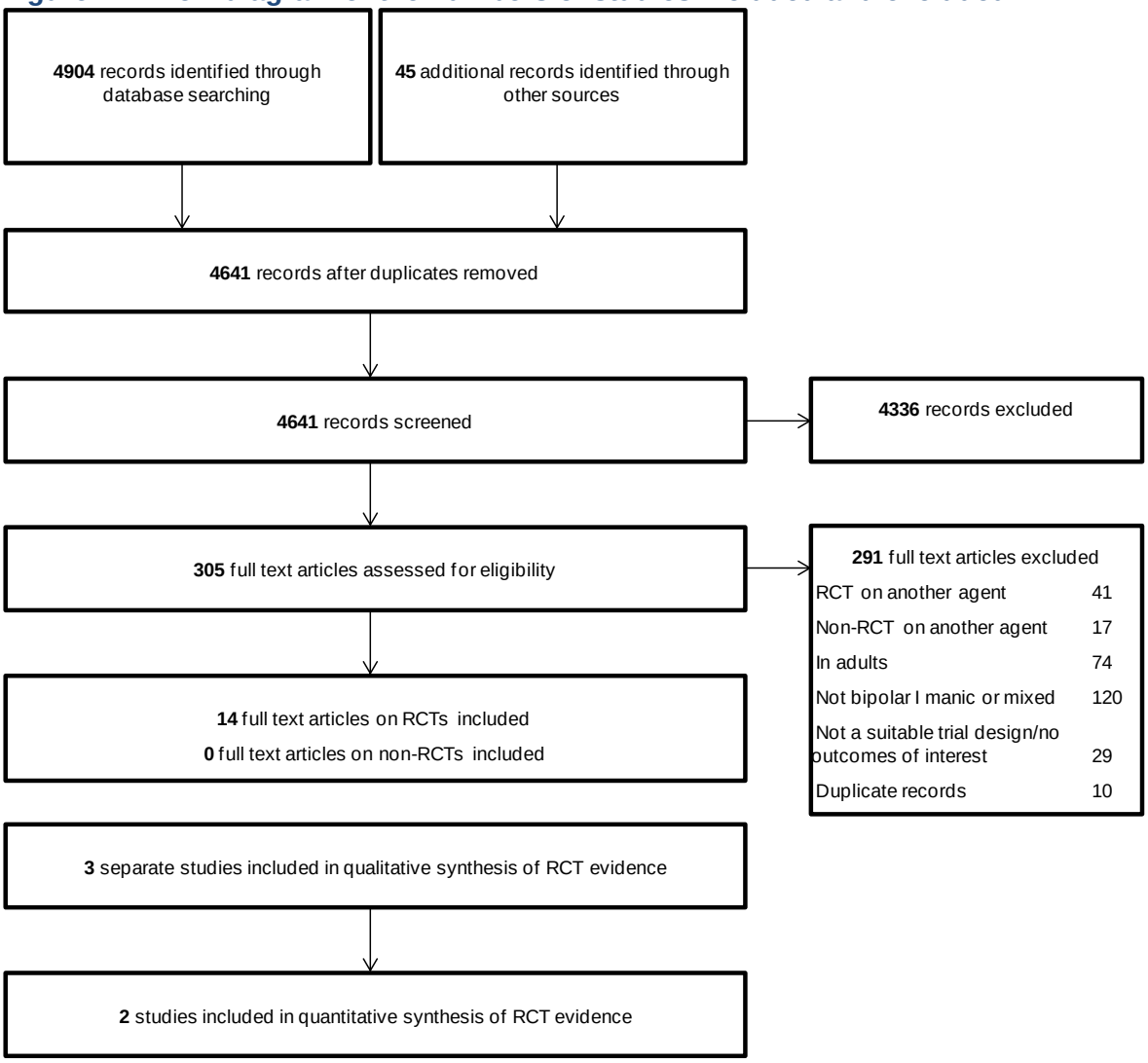
The inclusion criteria for non-RCTs were similar to the RCT criteria, except that studies could be longitudinal cohort studies. Cross-sectional or retrospective studies were excluded, as this level of evidence was deemed poor.

Inclusion of studies was restricted to only those in English.

Results from the searches described in section 5.1.1 were de-duplicated and twice reviewed for the inclusion criteria listed previously: once using the abstracts and then more rigorously, using full texts. Each review was performed independently by two reviewers, who then came to a consensus on the results.

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

Figure B1: Flow diagram of the numbers of studies included and excluded



5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The 15 articles included in the systematic review relate to three aripiprazole RCTs. The articles relating to each trial are listed in Table B1.

Table B1: List of articles relating to each RCT

Trial number	No. articles	Primary reference	Secondary references	Comments
NCT00110461	11	Findling 2009[5]	Correll 2008[7] Findling 2007[6] Forbes 2008[12] Loze 2011a[52] Loze 2011[53]b Mankoski 2011[54] NHSC 2008[55] Pikalov 2009[56] Whitehead 2009a[37] Whitehead 2009b[37]	Pivotal RCT
NCT00116259	2	Tramontina 2009[57]	Tramontina 2007[58]	Includes both bipolar I and II patients. Tramontina 2007 presents long-term efficacy data up to week 12 in terms of change from baseline in YMRS, but only for a population who were allocated to placebo in the double-blind phase of the trial.
NCT00194077	2	Findling 2012[59]	Findling 2011[60]	Investigates maintenance in very young children, therefore not suitable for indirect comparison

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table B2 List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
NCT00110461	Aripiprazole 10 mg or 30 mg once daily for 4 weeks in the acute phase and for an additional 26 weeks in the extension phase	Placebo	296 subjects aged 10-17 years old with a confirmed DSM-IV diagnosis of bipolar I disorder, with current manic or mixed episodes, with or without psychotic features, and a Young Mania Rating Scale total score ≥20 at baseline.	Findling et al. J Clin Psychiatry 2009; 70(10):1441-1451[5]
NCT00116259	Aripiprazole. Starting dose was 5 mg QW for those weighing >50 kg and 2 mg QW for those weighing <50 kg. Doses were increased by 5 mg QW for 6 weeks depending on clinical response and the onset of adverse events, until a maximum of 20 mg/day was attained.	Placebo	43 children & adolescents aged 8-17 years old, diagnosed with DSM-IV bipolar I or II disorder co-morbid with DSM-IV ADHD. Other inclusion criteria were clear reports of ADHD symptom onset preceding any mood symptomatology and an acutely manic or mixed state (defined as Young Mania Rating Scale score ≥20 at baseline).	Tramontina et al. J Clin Psychiatry 2009; 70(5):756-764[57]
NCT00194077	Aripiprazole (started at 0.1 mg/kg/d, increased to maximum of 15 mg per day)	Placebo	96 outpatients aged 4-9 years meeting DSM-IV criteria for bipolar disorder (I, II, not otherwise specified, cyclothymia).	Findling et al. J Clin Psychiatry 2012;73(1):57-63[59]

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

None of the three RCTs compare aripiprazole to another atypical antipsychotic; all are placebo-controlled.[5, 59] Therefore an indirect comparison has been performed (see Section 5.7).

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

NCT00194077 will not be discussed further as the patients population studied did not include children over the age of 10 and therefore does not include a population for which aripiprazole is indicated.[59] The study also included bipolar types other than type I, which are not covered by aripiprazole's licence. The reason for this study's inclusion in the list of relevant RCTs despite these factors was to demonstrate that aripiprazole has been shown to be effective and safe in a young population and for transparency.

NCT00116259 will not be discussed in detail either, owing to it being a small study including only 23 patients receiving aripiprazole.[57] Furthermore, it evaluated the use of aripiprazole in a very specific population of children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder (ADHD). It also included patients with bipolar II disorder as well as those with bipolar I disorder. As it does include some patients expected to be covered in aripiprazole's licence, however, it was included in the meta-analysis for transparency.

List of relevant non-RCTs

5.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be

provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

No relevant non-RCTs were identified in the systematic review.

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Study NCT00110461 consisted of an acute phase and an extension phase.[5, 6, 61] Each subject had the potential to participate in the study for a total of up to 30 weeks of double-blind treatment, including the 4-week acute phase with a 6-month extension phase. In the acute phase, subjects were screened for a period of up to 28 days, and if they met the entrance criteria, were randomised on Day 1 to either 10 mg or 30 mg of aripiprazole, or to placebo. Further details of study NCT00110461 and also of study NCT00116259 are presented in Table B3.

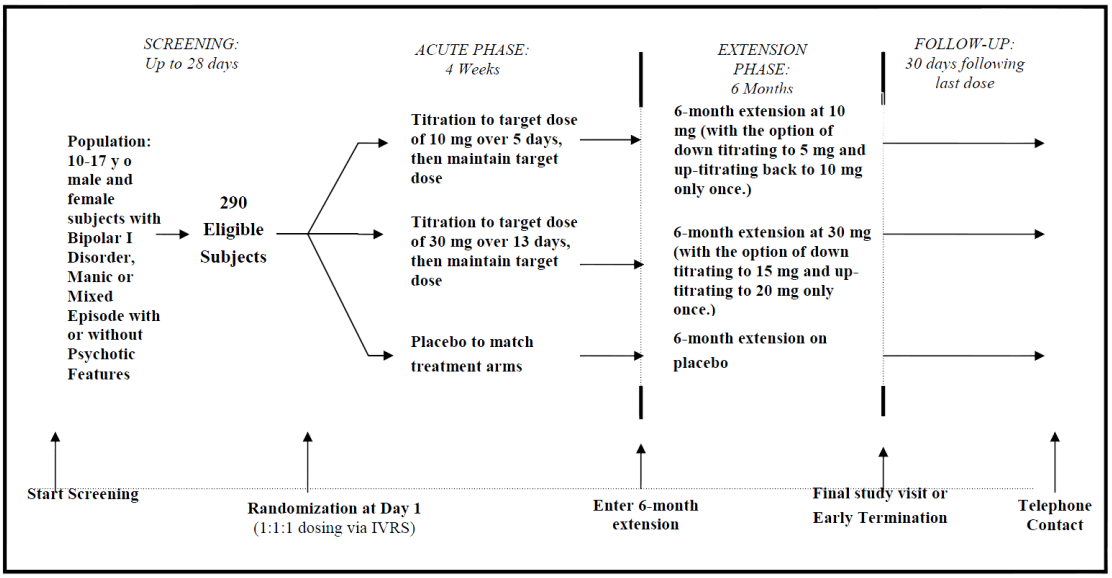
Table B3 Comparative summary of methodology of the RCTs

Trial no. **(acronym)**	**NCT00110461**[5, 6, 61]	**NCT00116259**[57]
Location	59 investigational sites in the United States	Single investigational site in Brazil (Hospital de Clínicas de Porto Alegre, Rio Grande do Sul)
Design	A phase III multicenter, double-blind, randomised, placebo-controlled clinical trial. The study included a 4-week acute phase with a 6-month extension period, [redacted] On Day 1 of the acute phase (baseline), patients were randomised to either placebo, aripiprazole 10 mg/day or aripiprazole 30 mg/day groups. Subjects reached their target dose through a forced titration schedule and proceeded with treatment at their target dose until Week 4. If the subject reached Week 4, he or she continued into the extension phase, beginning at the same dose taken at the end of the acute phase. [redacted] Please see Figure B2 for a diagram of the study design. Subject evaluations took place at Day 1, Day 4 (phone call), and at Weeks 1, 2, 3 and 4 during the acute phase, and [redacted]	Double-blind, randomised, placebo-controlled trial. The study consisted of a 6-week treatment period. Subjects were randomised to either placebo or aripiprazole.
Duration of study	[redacted] the acute phase lasted 4 weeks and the extension phase lasted 26 weeks. The study was conducted between March 2005 and February 2007.	6 weeks
Method of randomisation	Subjects were randomised 1:1:1 in a double-blind fashion following [redacted]	A computer-derived algorithm was used to randomly assign patients to treatment groups. Group allocation was performed by an independent third party.
Method of blinding (care provider, patient and outcome assessor)	Both patient and investigator were blinded. The study medication was provided as weekly (9-day) blister cards. [redacted]	The weekly pill package was provided to each patient by the independent third party. Both aripiprazole and placebo tablets were identical in appearance and had the same taste and smell.

	[redacted]	
Intervention(s) (n =) and comparator(s) (n =)	**Interventions:** • Aripiprazole 10 mg/day (n=98) • Aripiprazole 30 mg/day (n=99) **Comparator:** • Placebo (n=99) The aripiprazole doses were administered according to the following titration schedule: • Aripiprazole 10 mg: 2 mg/day for 2 days, 5 mg/day for 2 days, and 10 mg/day as the target dose starting on day 5. Subjects remained on the 10 mg dose for the remainder of the acute phase period. • Aripiprazole 30 mg: 2 mg/day for 2 days, 5 mg/day for 2 days, 10 mg/day for 2 days, 15 mg/day for 2 days, 20 mg/day for 2 days, 25 mg/day for 2 days and 30 mg/day as the target dose starting on day 13.	**Interventions:** Aripiprazole 20 mg/day (n=18) **Comparator:** Placebo (n=25) The dose of aripiprazole initially administered to patients depended on their weight: subjects weighing ≥50 kg received a 5 mg starting dose; those weighing ≤50 kg received a 2 mg dose. The dose was increased by 5 mg/week following weekly assessments of clinical response and safety. This occurred until a maximum dose of 20 mg/day was reached.
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy outcome was the change from baseline to Week 4 on the Young Mania Rating Scale (YMRS) total score.	The primary efficacy outcomes were change from baseline to endpoint (week 6) in: • The Young Mania Rating Scale (YMRS); • The Swanson, Nolan and Pelham Scale Version IV (SNAP IV); • Weight
Secondary outcomes (including scoring methods and timings of assessments)	Secondary efficacy outcomes were changes from baseline scores in: • Children's Global Assessment Scale (CGAS); • Clinical Global Impressions Scale-Bipolar Version (CGI-BP) severity of mania, depression and overall bipolar illness; • Children's Depression Rating Scale-Revised (CDRS-R) score; • General Behaviour Inventory Scale (GBI) score (consisting of 20-items with 2 subscales assessing symptoms of mania/hypomania and depression, completed by both	Secondary efficacy outcomes were change from baseline to the endpoint in scores of: • Child Mania Rating Scale-Parent Version • Clinical Global Inpressions-Severity of Illness scale (CGI-S) • The Brazilian version of the Children's Depression Rating Scale-Revised (CDRS-R) • Kutcher Adolescent Depression Scale (KADS)

	parents/guardians); • Attention-Deficit Hyperactivity Disorders Rating Scale (ADHD-RS-IV) score Response rate was also measured ('response' being defined as ≥50% reduction from YMRS total score).	
Duration of follow-up	Telephone follow-up occurred 30 days after the last dose of the study medication	

Figure B2: Study design schematic for NCT00110461[61]



Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Table B4 Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
NCT00110461[5, 6, 61]	• Male and female subjects • Age 10 – 17 years • DSM-IV diagnosis of bipolar I disorder with current manic or mixed episodes, with or without psychotic features. Trained clinicians confirmed the primary diagnosis using the Schedule for Affective Disorders and Schizophrenia for School Aged Children: Present and Lifetime Version (K-SADS-PL). • Young Mania Rating Scale total score ≥20 at baseline • Co-morbid diagnoses were permitted including Attention Deficit Disorder (ADHD), Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD) and anxiety disorders	• Bipolar II disorder, bipolar disorder not otherwise specified, a pervasive developmental disorder, schizophrenia, schizoaffective disorder, psychosis due to other medical conditions or concomitant medication. • Mental retardation (documented IQ<70 or clinical/social/school history suggestive of mental retardation) • DSM-IV substance or alcohol use disorder • Positive drug screen for cocaine or other substances of abuse • Sexual activity without contraceptive use • Pregnancy & lactation • Any other medical reason as determined by the investigator • Noncompliance with medication washout • Inability to swallow tablets whole • History of antipsychotic treatment resistance or neuroleptic malignant syndrome • Subjects who had made suicide attempts in the previous 6 months, had a score >3 on the Suicidal Ideation item of the Children's Depression Rating Scale-Revised (CDRS-R), or who were determined by the investigator to be at risk of suicide • Clinically important laboratory test results, vital sign or ECG abnormalities

		• Diabetes mellitus • Abnormally elevated serum glucose levels • Epilepsy • History of severe head trauma • Stroke • Unstable thyroid pathology requiring treatment • Other unstable medical conditions • Prior participation in an aripiprazole study • Allergy or hypersensitivity to aripiprazole • Participation in an investigational drug trial in the past month
NCT00116259[57]	• Age 8 to 17 years • DSM-IV bipolar I or II disorder comorbid with DSM-IV ADHD • Clear reports of ADHD symptom onset preceding any mood symptomatology • Acutely manic or mixed state, defined as a Young Mania Rating Scale score ≥20 at the baseline visit	• Estimated IQ <70, assessed by a trained psychologist using the Wechsler Intelligence Scale for Children, Third Edition • Use of any medication 4 weeks prior to entering the study • Diagnoses of pervasive developmental disorder, schizophrenia, or substance abuse or dependence • Severe suicide/homicide risk contraindicating outpatient treatment • Previous use of aripiprazole • Any other acute or chronic disease that might interfere in the study • Pregnancy
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

Differences in inclusion criteria between the two RCTs include the fact that study NCT00116259 included patients with bipolar I or II disorder comorbid with ADHD, while NCT00110461 excluded patients with bipolar II disorder (although bipolar I patients with comorbid ADHD were permitted to participate). Study NCT00116259 also has a lower inclusion age than NCT00110461 (8 years being the minimum, compared to 10 years).

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Patient characteristics at baseline in the two studies are presented in Table B5. In study NCT00110461 it can be seen that the three patient groups (placebo, aripiprazole 10 mg/day, and aripiprazole 30 mg/day) are similar across all baseline characteristics presented. In study NCT00116259, the mean YMRS total score is slightly higher in the placebo group and there are a greater proportion of males compared to the aripiprazole group.

Table B5 Characteristics of participants in the RCTs across randomised groups

Trial no. (acronym) **Baseline characteristic**	**Placebo**	**Aripiprazole 10 mg**	**Aripiprazole 30 mg**
NCT00110461[5, 6, 61] (n=296)	(n=99)	(n =98)	(n = 99)
Mean age (years) ± SD	13.3 ± 2.1	13.7 ± 2.2	13.3 ± 2.3
Gender (% male)	56.6	53.1	51.5
Mean age at onset (years) ± SD	11.9 ± 3.0	12.5 ± 3.2	12.0 ± 3.0
Mean duration of bipolar disease (years) ± SD	1.4 ± 1.9	1.3 ± 2.2	1.3 ± 2.5
YMRS total score, mean ± SD	30.7 ± 6.8	29.8 ± 6.5	29.5 ± 6.3
Weight, mean ± SD, kg	60.5 ± 17.3	63.8 ± 20.1	60.5 ± 21.5
BMI, mean ± SD, kg/m^2	23.8 ± 5.7	24.2 ± 5.4	23.7 ± 6.7
Trial no. (acronym) **Baseline characteristic**	**Placebo**	**Aripiprazole 20 mg**	-
NCT00116259[57] (n=43)	(n=25)	(n=18)	-
Mean age (years) ± SD	12.16 ± 2.75	11.72 ± 2.71	-
Gender (% male)	56	33.3	-
Mean age at bipolar disorder onset (years) ± SD	8.64 ± 3.54	7 ± 3	-
YMRS total score, mean ± SD	40.56 ± 9.01	35.94 ± 8.55	-
Weight, mean ± SD, kg	51.34 ± 18.92	48.24 ± 17.46	-

N = number of patients; SD = standard deviation; YMRS = Young Mania Rating Scale

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table B6 Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
NCT00110461[5, 6, 61]	Change from baseline to Week 4 on the YMRS total score	The YMRS scale is widely accepted and commonly used for measuring manic symptoms in clinical trials with children and adolescents with juvenile bipolar disorder.[57]	Change from baseline score in Children's Global Assessment Scale (CGAS)	The CGAS was adapted from the Adult Global Assessment Scale (GAS). It is a valid and reliable tool for rating a child's general level of functioning on a health-illness continuum.[62]
			Change from baseline in Clinical Global Impressions Scale-Bipolar Version (CGI-BP) severity of mania, depression and overall bipolar illness	The CGI is commonly used for making global assessments both in clinical trials and in a clinical practice setting.[63]
			Change from baseline in Children's Depression Rating Scale-Revised (CDRS-R) score	The CDRS-R is frequently used in clinical studies to evaluate the treatment of juvenile depression.[64, 65]
			Change from baseline in General Behaviour Inventory (GBI) score	The GBI is a reliable and valid instrument to screen for bipolar disorder.[66]
			Change from baseline in Attention-Deficit Hyperactivity Disorders Rating Scale (ADHD-RS-IV) score	The ADHD-RS-IV is a validated instrument for assessing symptoms of ADHD.[67, 68]
			YRMS response rate	Although not commonly used in clinical practice, clinical experts agreed that this was the most appropriate measure of response for demonstration of efficacy and for decision making.[2-4]

NCT00116259[57]	Changes from baseline to endpoint in the YMRS	The YMRS scale is widely accepted and is commonly used for measuring manic symptoms in clinical trials with children and adolescents with juvenile bipolar disorder.[57]	Change in score from baseline to endpoint in Child Mania Rating Scale-Parent Version (CMRS-P)	The internal consistency and test-retest reliability of the CMRS-P are high, each scoring 0.96.[57]
	Changes from baseline to endpoint in the Swanson, Nolan and Pelham Scale Version IV	The SNAP-IV is frequently used in ADHD investigations, with internal consistency varying from good to excellent.[57]	Change in score from baseline to endpoint in Clinical Global Impressions-Severity of Illness scale (CGI-S)	The CGI is commonly used for making global assessments both in clinical trials and in a clinical practice setting.[63]
	Changes from baseline to endpoint in weight	Weight gain is a common adverse event associated with antipsychotic therapy.[29, 30, 31] In children and adolescents particularly, weight gain is associated with further long-term health risks.[33]	Change in score from baseline to endpoint in the Brazilian version of the Children's Depression Rating Scale-Revised (CDRS-R)	The CDRS-R is frequently used in clinical studies to evaluate the treatment of juvenile depression.[64, 65] The Brazilian version has been validated.[69]
			Change in score from baseline to endpoint in the Kutcher Adolescent Depression Scale (KADS)	The mean correlation with clinician-administered depression rating scales is 0.69.[57]

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table B7 Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT00110461[5, 61]	Null hypothesis: that there is no difference between the aripiprazole and placebo arms in YMRS total score from baseline to week 4. Alternative hypothesis: that there is a difference between aripiprazole and placebo YMRS total score from baseline to week 4.	**Primary endpoint:** An overall F-test for mean change from baseline in YMRS total score was performed at significance level 0.05 (two-tailed) for the aripiprazole 10 mg, aripiprazole 30 mg and placebo groups. The null hypothesis was rejected, and so differences between groups were then investigated: aripiprazole 10 mg vs. placebo and aripiprazole 30 mg vs. placebo were tested at a 2-tailed 0.05 significance level. Change in scores from baseline were analysed using ANCOVA with treatment as a factor and baseline score as a covariate at each timepoint. Least squares (LS) means were used for the treatment comparisons. Two-tailed Student t tests were used to test differences between the LS means within the ANCOVA model. The proportion of responders was analysed using chi-squared tests. The proportion of patients with clinically significant weight gain (≥7% increase from baseline) was tested using the Fisher exact test.	The study was designed to have 85% power to detect a difference between aripiprazole and placebo of a -5.1 point change from baseline YMRS total score at week 4.	Analyses of safety and tolerability included data from all randomised subjects who had taken at least 1 dose of study medication (safety sample). The efficacy sample included all patients in the safety sample who had at least 1 post-baseline efficacy assessment. All analyses were conducted in the last-observation-carried-forward (LOCF) dataset.
NCT00116259[57]	Patients would show a better response in manic and ADHD symptoms with aripiprazole than with placebo	Changes between baseline and endpoint scores in primary outcome measures were analysed using ANCOVA models.	The computation of sample size was based on the expectation of at least a moderate effect size (ES) for aripiprazole. ES of 0.7 was	Patients with baseline and at least one post-baseline measurement were included in the analysis using last observation carried forward

	Aripiprazole would not be associated with clinically significant weight gain.		stipulated, an expected between-group difference of 30% in the change from baseline to endpoint in YMRS scores, with SDs in both groups of half the size of the change from baseline to endpoint. A sample size of 50 subjects was estimated based on this computation.	(LOCF). Other missing data in the middle of the protocol were extrapolated from curve estimation.

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

For the pivotal study NCT00110461, post-hoc subgroup analyses were carried out on:

- Age subgroups (10-12, 13-17 years). This was due to the concern that the safety profile might differ between age groups.
- The presence of current comorbid ADHD. Subjects were defined as having current comorbid ADHD if they either had current diagnosis of ADHD or if they discontinued medication for ADHD in the run-in phase. This subgroup analysis was performed to investigate whether aripiprazole had effects on ADHD symptoms that could affect the conclusions on its efficacy for bipolar I disorder symptoms.

Participant flow

5.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

The CONSORT flow chart for study NCT00110461 is presented in Figure B3. Participant flow in both the acute and extension phases ('continuation phase') of the study is included.

At week 12, approximately half of the subjects receiving aripiprazole remained in the double-blind study, compared with about one quarter of subjects receiving placebo. Of the 77 subjects on placebo who left the double-blind study by week 12, over half of them (n = 42, 54.5%) left because of lack of efficacy. In contrast, of the 103 subjects receiving aripiprazole who discontinued by week 12, only 23 (22.3%) left because of lack of efficacy. (source: EPAR)

The corresponding CONSORT flow chart for study NCT00116259 is presented in Figure B4.

Figure B3: NCT00110461 flow diagram for participant flow[61]

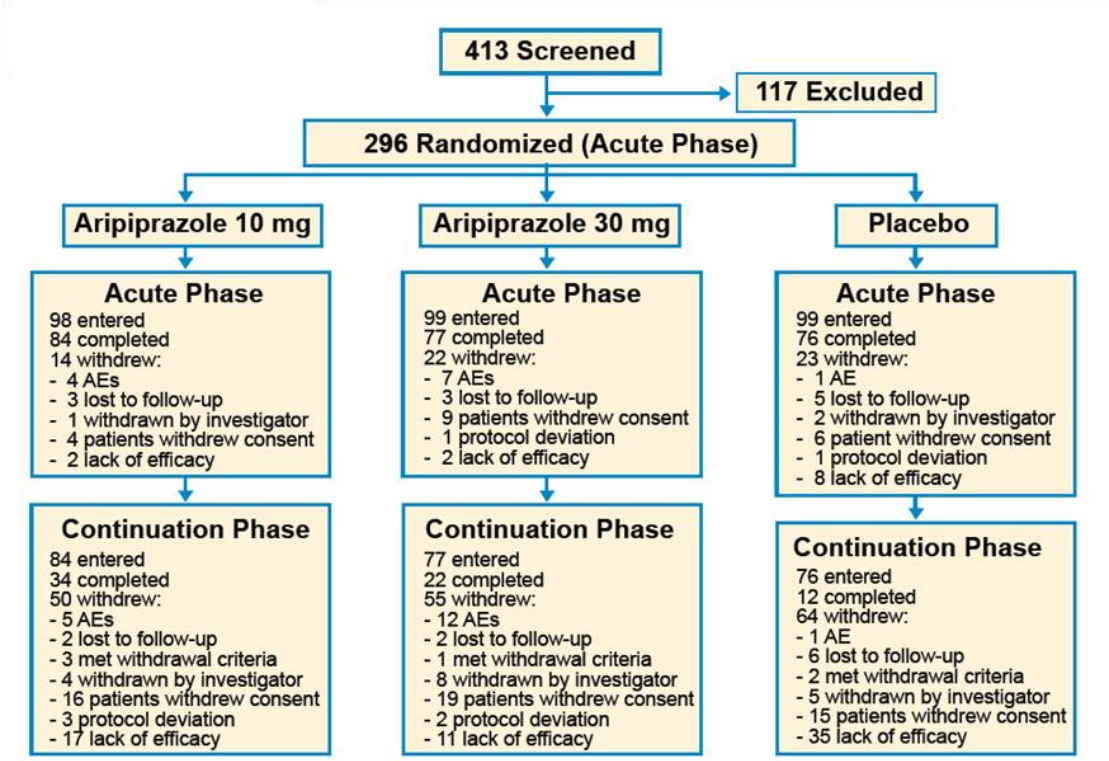
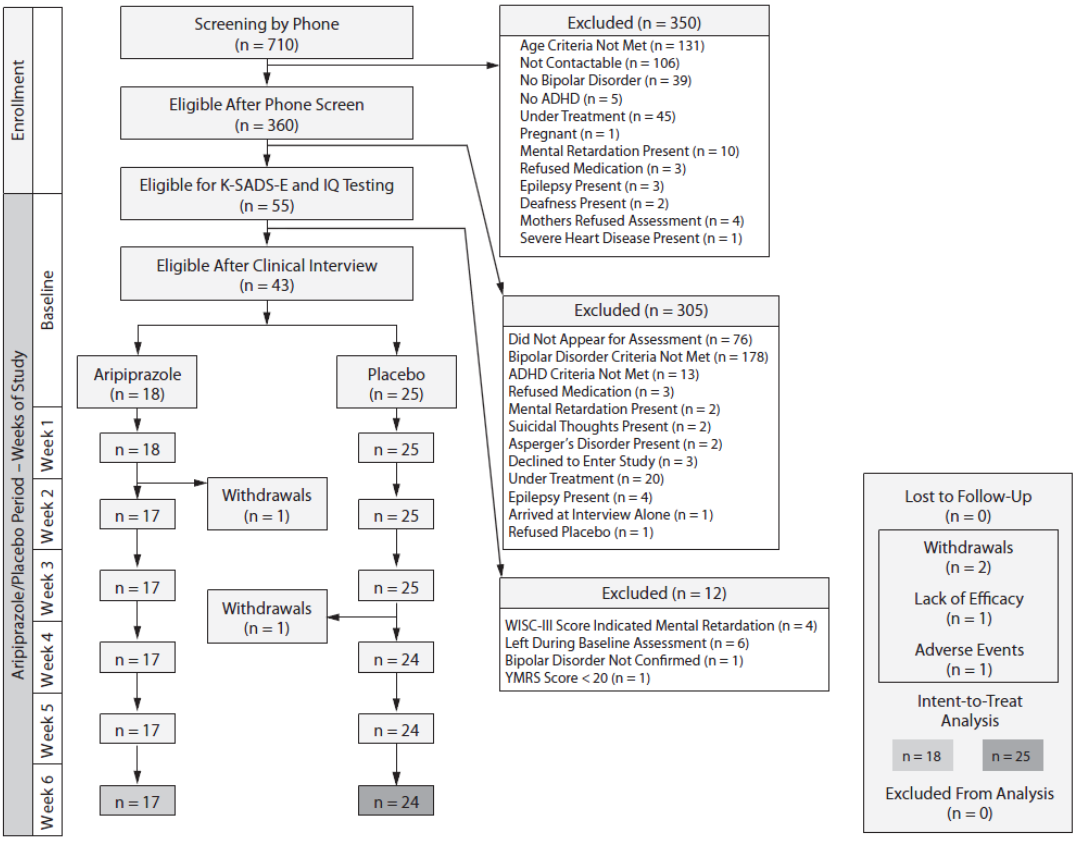


Figure B4: NCT00116259 flow diagram for participant flow[57]



5.4 *Critical appraisal of relevant RCTs*

Summary of critical appraisal of relevant RCTs

- Both studies NCT00110461 and NCT00116259 had adequate randomisation, allocation concealment and blinding throughout. The treatment groups were similar at baseline, and patient numbers across groups remained balanced for the study duration. Missing data was accounted for using last-observation-carried-forward methods.

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- 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)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?

- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

See Section 9.3, appendix 3 for full details of quality assessment for studies NCT00110461 and NCT00116259.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Summaries of the quality assessment results for each study are presented in Table B8.

Table B8 Quality assessment results for RCTs

Trial no. (acronym)	NCT00110461[5, 61]	NCT00116259[57]
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	Yes

5.5 *Results of the relevant RCTs*

Summary of the results from relevant RCTs

- The large and high-quality trial NCT00110461 demonstrated that both doses of aripiprazole induced resolution of manic symptoms as measured by YMRS change from baseline as early as week 1, at week 12 and up to week 30 ([redacted]).
- Response rates (defined as the percentage of patients achieving a ≥50% reduction from baseline YMRS) were also significantly higher in the 10 mg and 30 mg aripiprazole arms compared to placebo at week 4 ($p<0.0001$ and $p=0.0074$, respectively), week 12 ($p<0.0001$ for both doses) and week 30 [redacted].
- There was a trend for improved quality of life in both aripiprazole arms compared to placebo at weeks 4 and 30, as measured by the PQ-LES(Q).
- The small RCT NCT00116259 similarly demonstrated aripiprazole to be efficacious in paediatric bipolar disorder with ADHD.

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

See Section 5.5.3.

5.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

See Section 5.5.3.

5.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

NCT00110461

In study NCT00110461, aripiprazole 10 mg and 30 mg were found to be effective in the treatment of bipolar I disorder, manic or mixed episode with or without psychotic features in children and adolescents.[5] This conclusion was justified based on the attainment of both the primary and the majority of secondary efficacy endpoints. Data for the acute phase is presented in full in Table B9, while data for the extension phase is presented in Table B96 in Appendix 18. All analyses were conducted in the LOCF dataset.

Primary Efficacy Analysis

With respect to the primary efficacy endpoint, both aripiprazole doses demonstrated statistically significant improvements over placebo in the YMRS total score at week 4, with treatment differences from placebo of -5.99 (95% CI: -8.49 to -3.50; $p<0.0001$) for the aripiprazole 10 mg arm, and -8.26 (95% CI: -10.7 to -5.77; $p<0.0001$) for the aripiprazole 30 mg arm. From a clinical perspective this signifies the resolution of manic symptoms, as demonstrated by the reduction in scores at week 4 compared to baseline on a standardised rating scale.

Secondary Efficacy Analyses

Statistically significant improvements in YMRS total score were demonstrated as early as week 1 for both aripiprazole doses, and were maintained until week 30 (up to week 30, $p<0.0001$ at all visits; Figure B5). At week 30, the treatment difference in YMRS total score from placebo for the aripiprazole 10 mg dose was -5.89 (95% CI: -8.70 to -3.08), and for the aripiprazole 30 mg dose was -6.73 (95% CI: -9.53 to -3.94; Table B95, Appendix 18). From a clinical perspective this signifies that the resolution of manic symptoms occurred as early as week 1 in both aripiprazole groups, and superiority over placebo was maintained for the remainder of the study up to week 30.

A post-hoc analysis of study NCT00110461 found that aripiprazole specifically and significantly improved the following core markers of manic symptoms measured by the YMRS: elevated mood, increased motor activity/energy, need for sleep, irritability, speech, language/thought disorder, abnormal thought content and disruptive/aggressive behaviour.[52]

Both aripiprazole doses were also statistically significant at week 4 in the following secondary endpoints: response rate (defined as the percentage of patients achieving

a 50% or higher reduction from baseline in YMRS total score; Table B9; Figure B6), and mean changes from baseline in CGAS score (Table B9; Figure B7), CGI-BP Severity scores for Mania (Table B9; Figure B8) and Overall Bipolar Illness (Table B9; Figure B9), GBI-Parent/Guardian Version and Subject Version Mania Total score (Table B9), and the ADHD-RS-IV Total score (Table B9; Figure B10). From a clinical perspective, improvement in the CGAS score for patients receiving aripiprazole represents an improvement in psychological, social and school functioning; improvement in the CGI-BP indicates improvement in severity of illness for mania and overall bipolar illness; while improvement in the GBI-Parent/Guardian Version and Subject Version score signifies that both patients and their parents reported improvements in mood-related behaviour.

Efficacy was maintained through to week 30 in LOCF analysis, with both aripiprazole doses showing statistically significant sustained improvements over placebo with respect to response rate (Figure B6), and mean changes from baseline in CGAS score (Figure B7), CGI-BP Severity scores for Mania (Figure B8) and Overall Bipolar Illness (Figure B9), GBI Parent Version Mania Total score (Figure B11) and ADHD-RS-IV Total score (Figure B10). Aripiprazole 30 mg also demonstrated statistically significant improvement over placebo at week 30 for the GBI Subject Version Mania Total score (Figure B11). Clinically, this means that the improvements in psychological, social and school functioning seen with aripiprazole at week 4 as well as the improvements in behaviour, severity of illness overall and severity of illness for mania were maintained in the long-term.

The CHMP assessment report stated that observed case analysis failed to show statistical significance for aripiprazole over placebo for both doses on all analysed efficacy endpoints at week 12. Coupled with the high discontinuation rate, this was the reason that the CHMP restricted treatment length with aripiprazole to 12 weeks.

Table B9 Mean changes from baseline in the acute phase of study NCT00110461[5, 61]

		Placebo		Aripiprazole 10 mg/day			Aripiprazole 30 mg/day			p value vs. placebo
		N	Mean change from baseline	N	Mean change from baseline	Treatment difference (95% CI)	N	Mean change from baseline	Treatment difference (95% CI)	
YMRS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 4	92	-8.2	96	-14.2*	-5.99 (-8.49 to -3.50)	99	-16.5*	-8.26 (-10.7 to -5.77)	*p<0.0001
CGI-BP severity	Mania – week 4	92	-0.8	96	-1.6*	-0.81 (-1.15 to -0.48)	99	-2.1*	-1.26 (-1.59 to -0.93)	*p<0.0001
	Depression – week 4	92	-0.6	96	-0.9*	-0.25 (-0.54 to 0.04)	99	-0.9**	-0.26 (-0.55 to 0.03)	*p=0.0878 **p=0.0752
	Overall – week 4	92	-0.8	96	-1.6*	-0.83 (-1.16 to -0.51)	99	-2.0*	-1.18 (-1.51 to -0.86)	* p<0.0001
CGAS score	Week 4	92	5.8	96	15.1*	9.30 (5.77 to 12.84)	99	17.3*	11.51 (7.99 to 15.03)	*p<0.0001
GBI total scores	Parent/guardian (mania) – week 4	91	-4.0	95	-9.9*	-5.88 (-8.02 to -3.73)	96	-9.5*	-5.46 (-7.60 to -3.32)	*p<0.0001
	Parent/guardian (depression) – week 4	91	-3.8	95	-5.9*	-2.13 (-4.20 to -0.07)	96	-4.1**	-0.31 (-2.37 to 1.76)	*p=0.0430 **p=0.7696
	Patient (mania) – week 4	91	-4.6	96	-6.4*	-1.85 (-3.67 to -0.03)	96	-6.6**	-2.03 (-3.85 to -0.20)	*p=0.0468 **p=0.0296
	Patient (depression) – week 4	91	-3.4	96	-3.4*	0.07 (-1.73 to 1.86)	96	-3.3**	0.19 (-1.61 to 1.98)	*p=0.9418 **p=0.8377
ADHD-RS-IV total score	Week 4	90	-3.7	95	-12.5*	-8.86 (-12.3 to -5.43)	97	-11.9*	-8.23 (-11.6 to -4.83)	*p<0.0001
CDRS-R	Week 4	85	-4.9	91	-7.2*	-2.28 (-4.81 to 0.25)	94	-6.1**	-1.19 (-3.69 to 1.32)	*p=0.0767 **p=0.3515

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

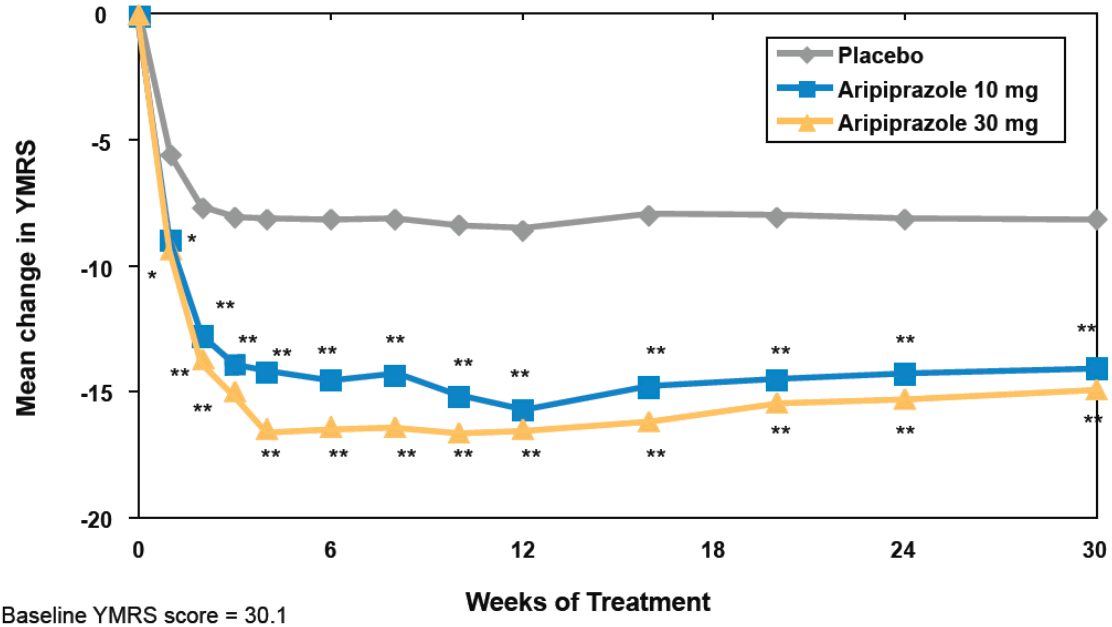
N = number of subjects, with the variation reflecting that all rating scales were not completed for all subjects; NR = not reported
Positive change of the CGAS and P-QLES-Q scores signifies improvement; for all other scales, negative change signifies improvement

Table B10 Responders and patients achieving remission in the acute phase of study NCT00110461[5, 61]

		Placebo			Aripiprazole 10 mg/day			Aripiprazole 30 mg/day			p value, aripiprazole 10 mg vs. placebo	Aripiprazole 10 mg: 95% CI for difference (%)	p value, aripiprazole 30 mg vs. placebo	Aripiprazole 30 mg: 95% CI for difference (%)	Relative risk (risk difference)	
		N	n	%	N	n	%	N	n	%					Aripiprazole 10 mg	Aripiprazole 30 mg
% patients who were responders (defined as ≥50% reduction from baseline YMRS total score)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 4	92	24	26.1	96	43	44.8	99	63	63.6	0.0074	[redacted]	<0.0001	[redacted]	1.72 (18.70)	2.44 (37.5)
% patients who were in remission (defined as YMRS total score ≤12 and CGI-BP severity score for mania ≤2)	Week 4	N.R.	N.R.	5.4	N.R.	N.R.	25.0*	N.R.	N.R.	47.5**	p=0.0002	N.R.	<0.0001	N.R.	4.63 (19.60)	8.80 (42.1)

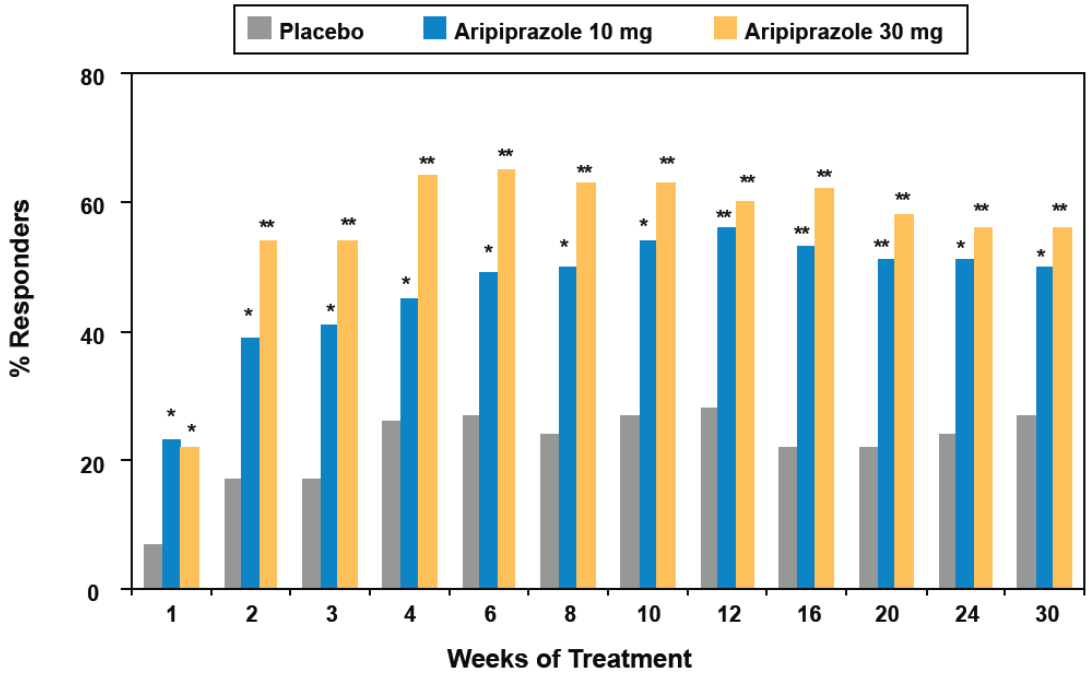
N = number of randomised subjects with both baseline and at least one post-baseline value; n = number of responders; NR = not reported

Figure B5 Mean change from baseline in YMRS total score across the acute and extension phases of study NCT00110461[6]



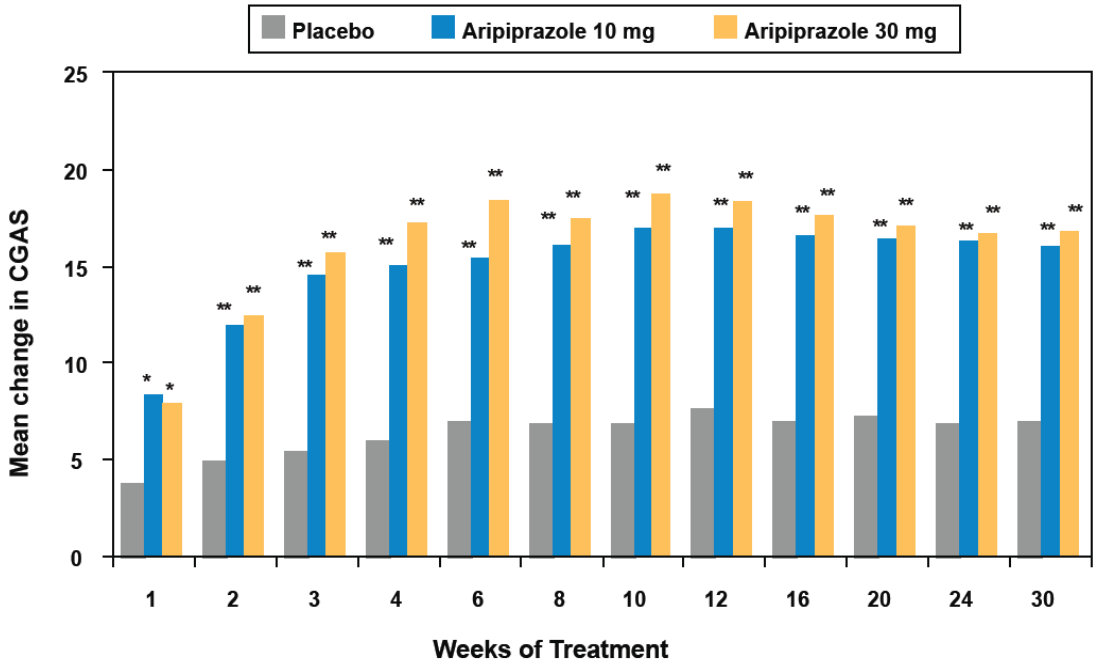
Baseline YMRS score = 30.1
*P<0.05, **P<0.0001

Figure B6 Patient response rate across the acute and extension phases of study NCT00110461[6]



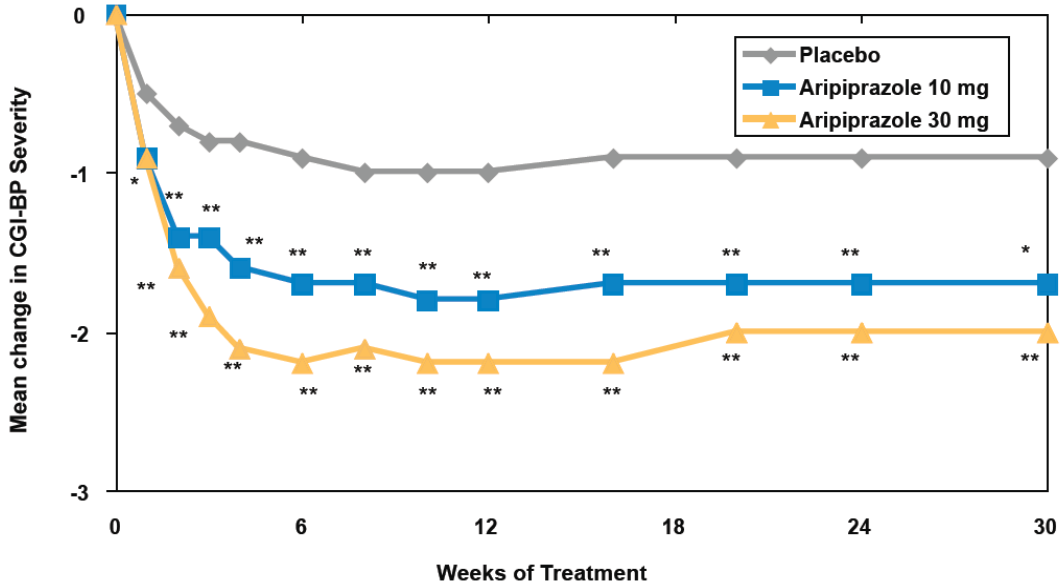
Response defined as ≥ 50% reduction from baseline in YMRS
*P<0.05, **P<0.0001

Figure B7 Mean change in CGAS across the acute and extension phases of study NCT00110461[6]



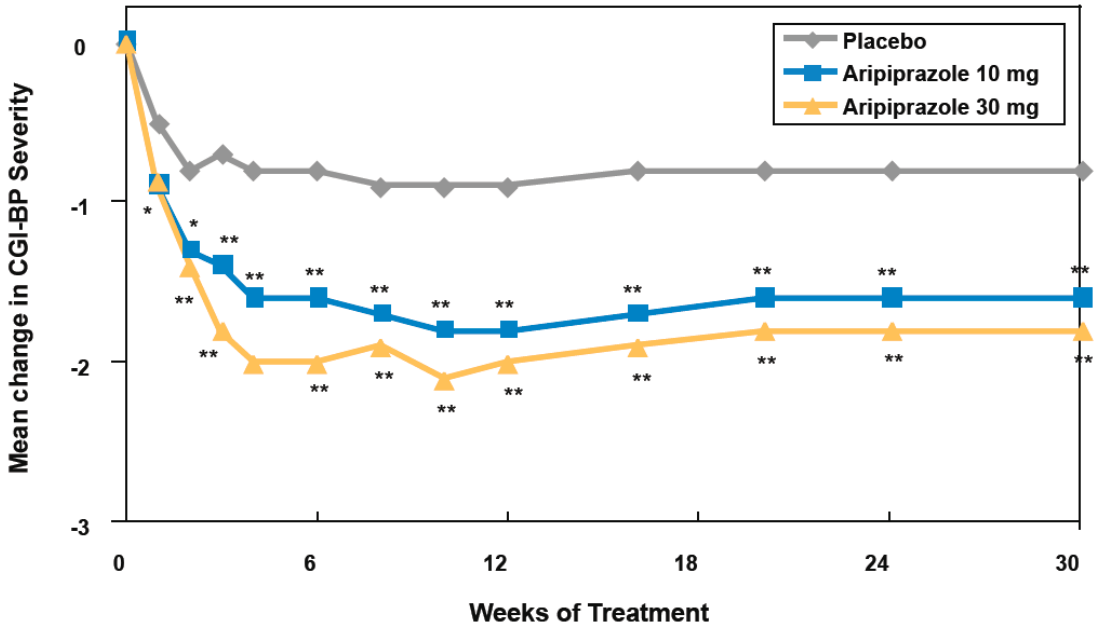
Mean baseline CGAS= 46.6
*$P \leq 0.001$; **$P \leq .0001$

Figure B8 Mean change in CGI-BP Severity score for Mania across the acute and extension phases of study NCT00110461[6]



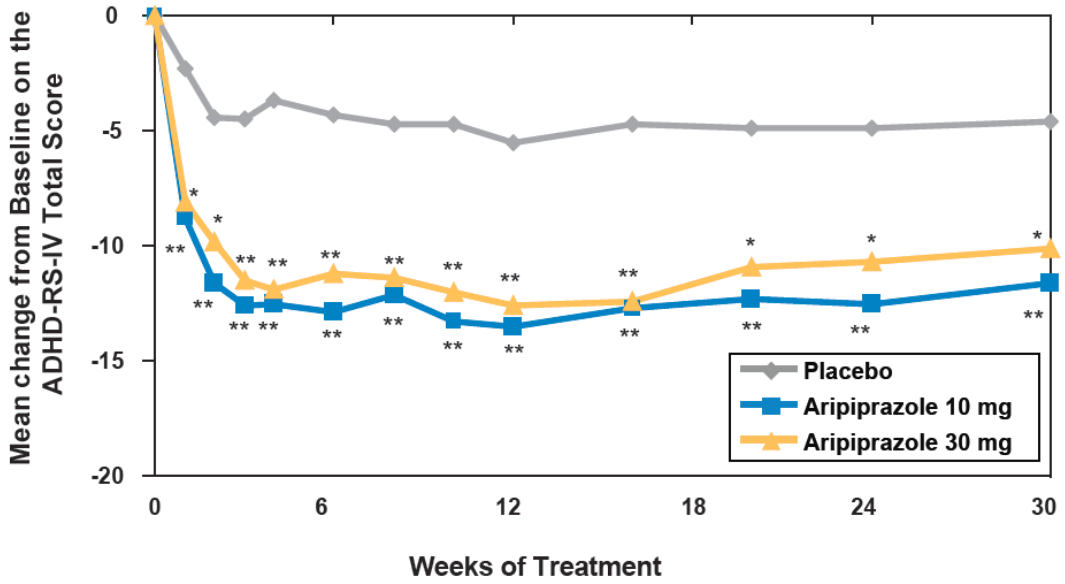
Baseline CGI-BP Severity score (Mania) = 4.73
*$P<0.05$; **$P \leq 0.0001$

Figure B9 Mean change in CGI-BP Severity score for Overall Bipolar Illness across the acute and extension phases of study NCT00110461[6]



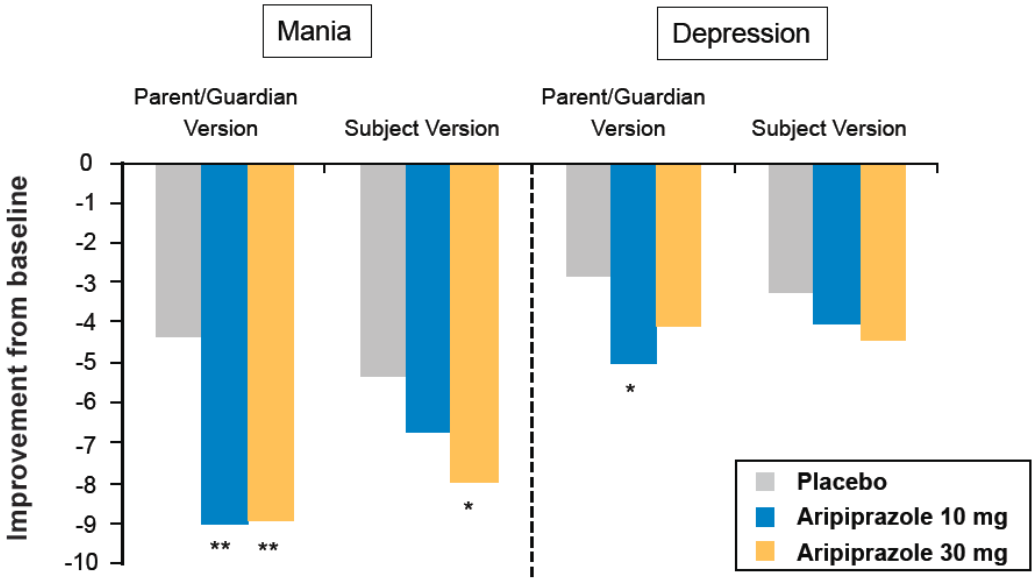
Mean baseline CGI-BP Severity score (Overall Bipolar Illness) = 4.7
*P<0.05, **P≤0.0001

Figure B10 Mean change in ADHD-RS-IV total score across the acute and extension phases of study NCT00110461[6]



Mean baseline ADHD-RS-IV = 33.1
*P<0.002; **P<.0001

Figure B11 Mean change from baseline on the GBI Parent/Guardian and Subject Versions at week 30 in study NCT00110461[6]



Baseline GBI Mania: P/G = 18.1; Subject = 14.9
Baseline GBI Depression: P/G = 13.1; Subject = 11.3
*$P<0.01$; **$P<0.0001$

[redacted] From a clinical perspective, this implies that the relapse rate for these patients (on active drug and placebo) is low, at least up to week 30.

Table B11 Incidence of hospitalizations for worsening bipolar disorder during the acute phase, and across the entire study duration (acute and extension phase)[a]

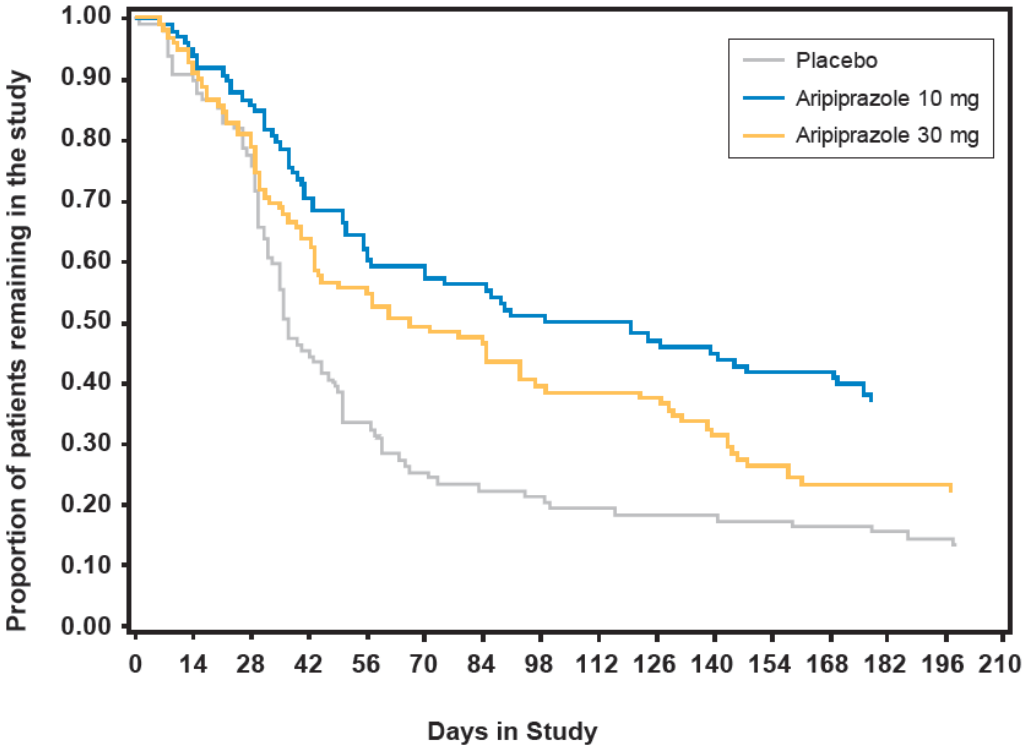
Hospitalisation status at the beginning of the acute phase	Type of hospitalisation at the end of the phase	Aripiprazole 10 mg (N=98)		Aripiprazole 30 mg (N=99)		Placebo (N=99)	
		n	%	n	%	n	%
Acute phase							
Inpatient	Inpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Outpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Outpatient	Inpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Outpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute + extension phase							
Inpatient	Inpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Outpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Outpatient	Inpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Outpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]Subjects had at least one hospitalisation due to worsening bipolar disorder during the study period

Time to Discontinuation

No statistically significant differences were observed between the aripiprazole 10 mg arm and placebo or the aripiprazole 30 mg arm and placebo with respect to time to discontinuation due to all reasons, during the Acute Phase (up to week 4).[61] For the entire study period, statistically significant differences in time to discontinuation due to all reasons were found between both the aripiprazole 10 mg arm compared to placebo ($p<0.0001$) and the 30 mg arm compared to placebo ($p=0.0124$). Both aripiprazole doses showed significantly superior retention profiles over the 30-week duration of the study compared to placebo (Figure B12). Possible reasons why patients receiving aripiprazole were more likely to remain in the study could include the fact that they experienced a resolution of their symptoms, and may not have experienced adverse events to a degree which would cause them to discontinue.

Figure B12 Kaplan-Meier plot of time to discontinuation for all reasons through to week 30 of study NCT00110461[6]



Aripiprazole-10 mg vs Placebo: $P \leq 0.0001$
Aripiprazole-30 mg vs Placebo: $P = 0.0124$

Quality of Life

Quality of life as measured by the PQ-LES-Q was also assessed throughout study NCT00110461.[37] On both the PQ-LES-Q total (T) and overall (O) measures, while the differences to the placebo arm did not reach statistical significance, both aripiprazole arms demonstrated a trend for improvement relative to placebo. Using observed case analysis, a correlation at week 4 and week 30 between percent change in PQ-LES-Q(T) and percent change in YMRS was demonstrated ($r = -0.18$ and -0.29, respectively; $p < 0.03$). The percent change in PQ-LES-Q(T) by category of percent change in YMRS is reported in Table B12, which also indicates that an improvement in bipolar I disorder mania symptoms in children and adolescents is significantly associated with an increase in quality of life. This further supports the premise that aripiprazole therapy resolves manic symptoms and correlates with an improvement in quality of life rating scales in this age group.

Table B12 Association of quality of life and YMRS clinical improvement in the acute and extension phase of study NCT00110461[37]

		YMRS categories				P value from trend analysis	P value from regression analysis
		20%;	20-30%;	30-50%;	>50%		
% change in mean PQ-LES-Q(T)	Week 4	1.7	2.3	12.5	10.4	0.007	0.01
	Week 30	3.3	NA	-2.6	16.6	0.02	0.02

Subgroup analysis – by age

Table B13 to Table B15 below show that aripiprazole was efficacious compared to placebo in all age subgroups.

Table B13 Mean change from baseline in YMRS score from baseline by age group

Visit/week	10 – 12 years						13 – 17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
OC												
Baseline	31	31.5	40	28.4	36	29.9	65	29.0	59	30.3	58	31.9
Week 4	25	-16.0**	30	-15.5**	26	-5.8	53	-14.9*	45	-17.9*	41	-11.1
Week 12	17	-20.4	17	-20.6	7	-15.8	34	-21.4	25	-20.5	13	-21.5
LOCF												
Baseline	31	31.5	40	28.4	36	29.9	65	29.0	59	30.3	58	31.9
Week 4	31	-15.6**	40	-15.5**	34	-4.7	65	-13.9*	59	-16.8**	58	-10.1
Week 12	31	-16.2**	40	-15.9**	36	-6.9	65	-15.6*	59	-16.8**	58	-9.7

*p < 0.05, **p < 0.001 vs. Placebo
[a] a negative mean indicates improvement
LS = Least Squares

Table B14 Mean change from baseline in CGI-BP severity score for mania by age group

Visit/week	10 – 12 years						13 – 17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
OC												
Baseline	31	4.8	40	4.6	36	4.7	65	4.6	59	4.6	58	4.9
Week 4	25	-1.6*	30	-2.0**	26	-0.7	53	-1.9*	45	-2.2**	41	-1.1
Week 12	17	-2.1	17	-2.8	7	-2.2	34	-2.7	25	-2.8	13	-2.5
LOCF												
Baseline	31	4.8	40	4.6	36	4.7	65	4.6	59	4.6	58	4.9
Week 4	31	-1.6*	40	-2.0**	34	-0.5	65	-1.7*	59	-2.1**	58	-1.0
Week 12	31	-1.6*	40	-2.2**	36	-0.9	65	-1.9*	59	-2.2**	58	-1.1

*p < 0.05, **p < 0.001 vs. Placebo
[a] a negative mean indicates improvement

Table B15 Mean change from baseline in CDRS-R score by age group

Visit/week	10 – 12 years						13 – 17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
OC												
Baseline	31	33.5	38	33.1	31	33.1	60	36.1	56	34.8	55	34.2
Week 4	25	-7.3	29	-7.3	23	-5.0	50	-8.2	42	-6.3	40	-6.7
Week 12	17	-9.1	16	-5.4	6	-14.3	31	-11.0	23	-8.9	13	-12.9
LOCF												
Baseline	31	33.5	38	33.1	31	33.1	60	36.1	56	34.8	55	34.2
Week 4	31	-7.3	38	-5.4	30	-4.1	60	-7.8	56	-6.4	55	-5.0
Week 12	31	-7.6	38	-5.0	31	-5.4	60	-8.1	56	-5.6	55	-4.8

*p < 0.05, **p < 0.001 vs. Placebo
[a] a negative mean indicates improvement

Subgroup analysis – by ADHD comorbidity

Table B16 presents the number of patients with and without current comorbid ADHD by age subgroup. As can be seen from

Table B17, ADHD status did not change the aripiprazole treatment effect significantly, particularly at week 12, where the use of ADHD medication was also permitted.

Table B16 Number of patients with or without current comorbid ADHD separated by age group

	10 - 12 years	13 - 14 years	15 - 17 years	Total (10 - 17 years)
Patients with current comorbid ADHD	67	33	39	139
Patients without current comorbid ADHD	22	30	40	92

Table B17 Patients with and without current ADHD: mean change from baseline by age group 10-12. 13-14 and 15-17 for YMRS total score (LOCF)

Visit/ Week	10 – 12 years (N=89)						13 – 14 years (N=63)						15 – 17 years (N=79)					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
Current ADHD																		
Week 4	21	-15.32**	25	-15.51**	20	-2.28	7	-12.63	11	-17.57*	15	-9.43	16	-16.14	12	-15.15	11	-9.46
Week 12	21	-13.95*	25	-16.27**	21	-5.48	7	-15.61	11	-18.39*	15	-7.50	16	-17.55	12	-16.15	11	-9.13
No ADHD																		
Week 4	6	-14.96	8	-15.11*	8	-7.42	15	-12.55	7	-12.84	8	-9.74	16	-12.34	15	-14.80	9	-12.17
Week 12	6	-16.67*	8	-16.23*	8	-8.64	15	-14.98	7	-13.00	8	-8.16	16	-15.84	15	-12.32	9	-12.86

* $p < 0.05$, ** $p < 0.001$ vs. Placebo

NCT00116259

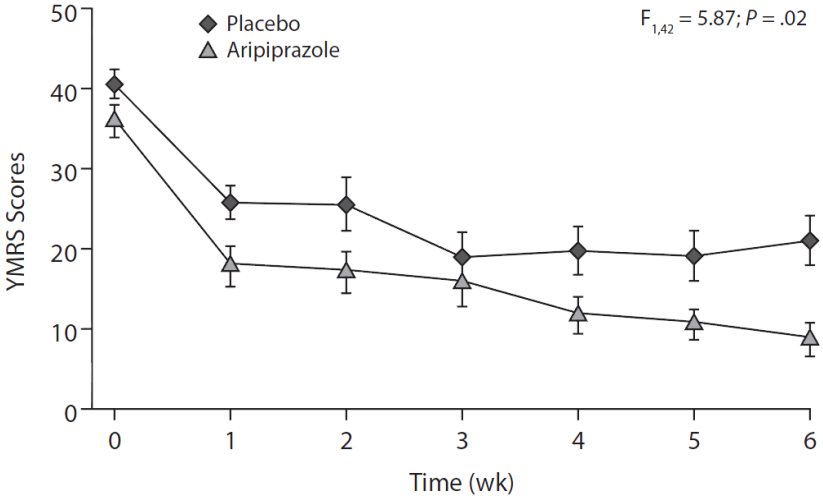
Results from study NCT00116259, which included only paediatric patients with comorbid ADHD, are presented in Table B18. Patients receiving aripiprazole showed a significantly larger reduction in YMRS total scores from baseline to week 6 than patients on placebo (-27.22 vs. -19.52, p=0.02; Figure B13). A greater proportion of patients on aripiprazole compared to patients on placebo were also responders (88.9% vs. 52%, p=0.02; NNT=2.70) and achieved remission (72% vs. 32%, p=0.01; NNT = 2.50). This demonstrates that aripiprazole is effective in reducing symptoms in children and adolescents with bipolar disorder who also have a diagnosis of ADHD.

Table B18 Relevant outcomes from study NCT00116259[57, 70]

		Placebo		Aripiprazole 5 - 20 mg			p value vs. placebo	Relative risk (risk difference)
		N	Value	N	Value	Treatment difference (95% CI)		
YMRS	Mean change from baseline at week 6	25	-19.52	18	-27.22	0.80 (0.15 – 1.41)	0.02	N.A.
Response rate ('response' defined as ≥50% reduction from baseline YMRS total score)	% patients who were responders at week 1[70]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.73 (23.50)
	% patients who were responders at week 2[70]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.39 (17.10)
	% patients who were responders at week 3[70]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.93 (-4.50)
	% patients who were responders at week 4[70]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.49 (27.30)
	% patients who were responders at week 6	25	52.0	18	88.9	N.R.	0.02	1.71 (36.90)
Remission rate (defined as YMRS total score ≤12)	% patients who were in remission at week 6	25	32.0	18	72.0	N.R.	0.01	2.25 (40)

YMRS = Young Mania Rating Scale; N = number of patients; CI = confidence interval; N.R. = not reported; N.A. = not applicable
All data taken from Tramontina et al (2009)[57] unless otherwise stated

Figure B13 Changes in YMRS total scores during study NCT00116259[57]



5.6 *Meta-analysis*

Summary of Meta-analysis

- A meta-analysis of NCT00110461 (pooled 10-30 mg dose) and NCT00116259 (20 mg dose aripiprazole) was performed for completeness.
- The meta-analysis found aripiprazole to still be statistically significantly superior to placebo in inducing symptomatic response (as measured by >50% change in YMRS score) at weeks 1, 2 and 4, but not at week 3.
- The meta-analysis found aripiprazole to be associated with a statistically significant higher rate of EPS than placebo, but not of somnolence.
- However, the small size of study NCT00116259 and the different patient population from the pivotal aripiprazole study (includes bipolar II disorders and restricted to patients with ADHD) means that the results are of limited use.

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

5.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).

- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

A meta-analysis was performed to combine results from NCT00110461[5] (pooled 10-30 mg dose) and NCT00116259[57] (20 mg dose aripiprazole). As NCT00116259 is a very small study, this meta-analysis was performed in order to be as transparent as possible, rather than to provide meaningful results; the small sample size of Tramontina 2009 actually increases the uncertainty of the meta-analysis results compared to the results from the NCT00110461, the large pivotal clinical trial. NCT00116259 also included patients with bipolar II disorder, which are outside of aripiprazole's expected licence, and was limited to a subgroup of patients with comorbid ADHD. Therefore the additional information that this study provides in relation to the decision problem is limited and the meta-analysis results, which are presented in full in Appendix 17 (Section 9.17) only, should be treated with caution.

The main results were:

- There was a significantly greater chance of achieving YMRS response at weeks 1, 2 and 4 with aripiprazole than with placebo.
- There was a greater chance of achieving YMRS response at week 3 with aripiprazole than with placebo, but the difference between treatments was not significant.
- There were fewer patients discontinuing treatment at week 3 with aripiprazole than with placebo, but not significantly so.
- There was a significantly greater chance of experiencing EPS with aripiprazole than with placebo.
- Patients taking aripiprazole are more likely to experience somnolence than patients on placebo, but the difference was not significant.

5.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should

summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable

5.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

NCT00194077 was not included in the meta-analysis as it only included children under the age of 10, which are not covered by aripiprazole's licence, which is restricted to children aged 13 or over.[59]

Summary of Network Meta-analysis

- A Bayesian network meta-analysis was performed using the pivotal placebo-controlled study for each atypical antipsychotic.
- There were no statistically significant differences in YMRS response rates at weeks 1-3 between the atypical antipsychotics, although there was a trend for aripiprazole to have greater efficacy compared to all others at week 1 and quetiapine and olanzapine at week 3.
- Aripiprazole-treated patients were significantly less likely to experience clinically significant weight gain than patients on olanzapine (RR olanzapine vs. aripiprazole: 12.52 [95%CrI 2.31-76.22] and quetiapine (RR quetiapine vs. aripiprazole: 11.1 [95% CrI 1.30-116.1]) at study endpoint. This significant result at such an early time point (week 3 or 4) is particularly notable considering that weight gain can develop gradually over time.
- Aripiprazole-treated patients were significantly less likely to experience a clinically significant increase in prolactin than patients on olanzapine (RR olanzapine vs. aripiprazole: 175.70 [95% CrI 10.86-6414]), risperidone (RR risperidone vs. aripiprazole: 139.80 [95% CrI 5.52-7202]) or quetiapine (RR quetiapine vs. aripiprazole: 31.22 [95% CrI 1.81-1191]).
- There were no significant differences between aripiprazole and the other atypical antipsychotics where data were available in terms of EPS (RR vs. aripiprazole for risperidone: 0.71 [95% CrI 0.20-2.93]; for quetiapine: 0.72 [95% CrI 0.12-8.38]) and somnolence rates (RR vs. aripiprazole for risperidone: 0.58 [95% CrI 0.23-1.38]; for quetiapine: 0.59 [95% CrI 0.23-1.43]).

5.7 Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should

be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

5.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

A systematic review was designed to identify all relevant clinical information available for the treatment and prevention of acute manic and mixed episodes in bipolar disorder in children and adolescents with the following comparators:

- Risperidone
- Quetiapine
- Olanzapine
- Combination of any of the above with lithium or valproate

The review was based on the same search and inclusion strategy as a previous systematic review (commissioned by NICE in 2005),[47] which did not identify any RCT or non-RCT evidence for aripiprazole in children and adolescents with bipolar I disorder. In the previous systematic review, three randomised controlled trials were identified that examined the use of antipsychotics in the treatment of mania in children and adolescents. However, only the results from one trial (DelBello 2002[71]) were included in this update. Of the two other excluded studies, one was an open label trial with some bipolar II patients (Pavuluri 2004[72]), and one was a semi-randomised controlled trial which also included bipolar II patients (Biederman 2005[73]). For the long term management of children and adolescents with bipolar disorder, the only study identified by the previous systematic review was excluded not only because it examined lithium, but also because it included a mixture of bipolar I and II patients (Findling 2005[74]).

Databases were searched to include studies from 2005-present. A list of databases is provided in Appendix 2. The search terms were taken from a previous systematic

review commissioned by NICE in 2005 [47] (Appendix 2). The modifications to the previous review were as follows:

- The term "Epidemiologic study characteristics/" was added to the RCT filter in order to also capture non-RCTs.
- Filters for studies examining children and adolescents were added to the RCT and non-RCT filter (terms based on those from Jensen 2007,[48] Zuddas 2011[49] and Fraguas 2011[50]).

The reference lists of all included studies and additional systematic reviews (Jensen 2007,[48] Zuddas 2011,[49] Fraguas 2011,[50] and Liu et al. 2011[51]) were hand-searched. Additional horizon scanning was performed using Google search engine and media reports.

5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Identification and selection of trials

The searches for clinical trials were limited to those including participants under the age of 18. The inclusion criteria for RCTs were as follows:

RCT Evidence Inclusion Criteria

- Patients with manic or mixed episodes of bipolar I disorder only
- All patients aged ≤18
- Randomised controlled trial
- At least one of the interventions studied must be an atypical antipsychotic (risperidone, quetiapine or olanzapine) other than aripiprazole
- Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed and the study's data and results must be extractable

Non RCT Evidence Inclusion Criteria

- Patients with manic or mixed episodes of bipolar I disorder only
- All patients aged ≤18
- Non-randomised controlled trial that still evaluates the effectiveness of interventions (acceptable study designs: prospective cohort study, retrospective chart/database review)
- At least one of the interventions studied must be an atypical antipsychotic (risperidone, quetiapine or olanzapine) other than aripiprazole
- Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed and the study's data and results must be extractable

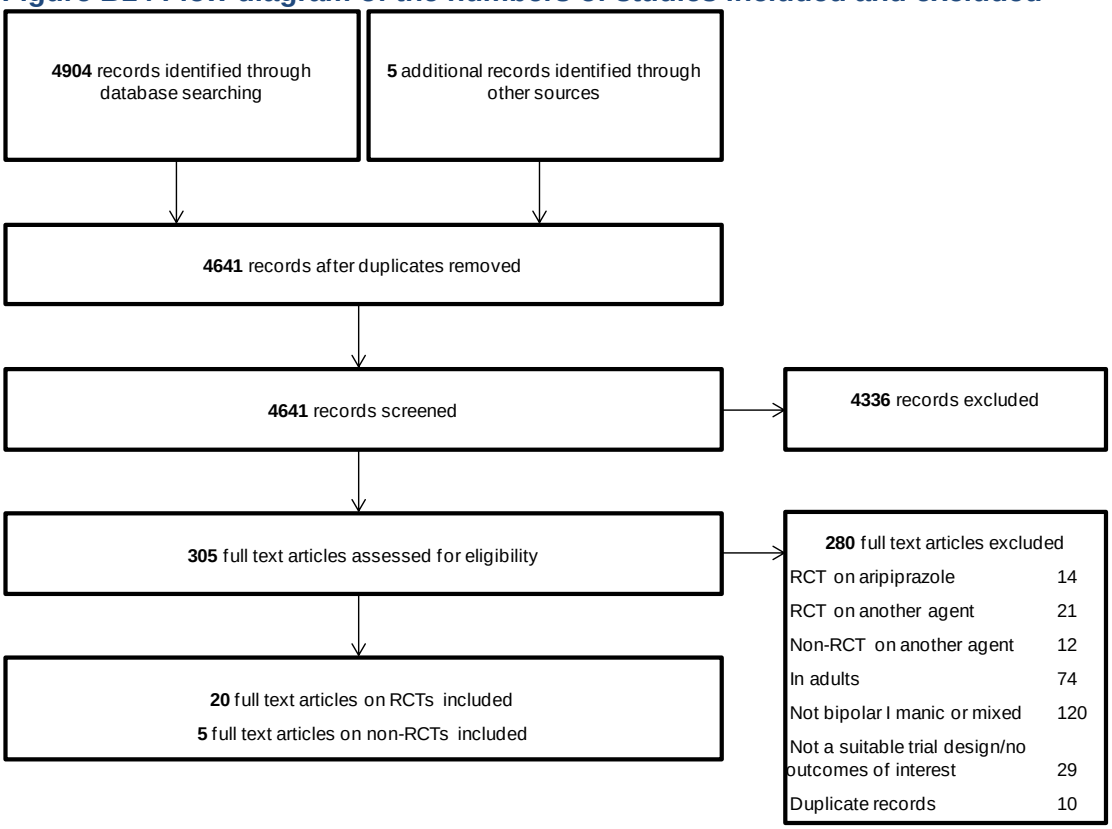
The inclusion criteria for non-RCTs were similar to the RCT criteria, except that studies could be longitudinal cohort studies. Cross-sectional or retrospective studies were excluded, as this level of evidence was deemed poor.

Inclusion of studies was restricted to only those in English.

Results from the searches described in section 5.7.1 were de-duplicated and twice reviewed for the inclusion criteria listed previously: first using the abstracts and then more rigorously, using full texts. Each review was performed independently by two reviewers, who then came to a consensus on the results.

Figure B14 presents the inclusion and exclusion of studies. Twenty articles on RCTs were included and 5 articles on non-RCTs were included. The non-RCTs are described in more detail in Section 5.8.

Figure B14 Flow diagram of the numbers of studies included and excluded



Methodology of the included trials

Twenty articles on RCTs were found, which discussed seven separate RCTs (four for risperidone, two for quetiapine and one for olanzapine).

Two studies included in the systematic review did not report any useful outcomes and therefore have not been included in the indirect comparison.[24, 75] As a result they will not be described any further. Summaries of the methodologies of five additional studies included in the systematic review that did report useful outcomes are presented in Table B19.[19, 29, 76-78] Participant characteristics for these studies are presented in Table B20.

Table B19 Comparative summary of methodology of the included RCTs

Trial no. (acronym)	Haas 2009[19]	Study 149[76]	Tohen 2007[29]	Pavaluri 2010[77]	Geller 2012[78]
Location	21 sites in United States.	United States: 41 centres, 31 centres randomised patients.	24 sites in the United States and 2 sites in Puerto Rico. Study settings included university medical centres, outpatient clinics and private practices	Not explicitly stated but likely to be a single site in the United States	5 sites in the United States
Design	Randomised, double-blind placebo-controlled, 3-arm study.	Multicenter, randomised, double-blind, placebo-controlled, parallel group study.	Multicenter, parallel, double-blind randomised placebo-controlled trial. Subjects were randomised to receive either olanzapine 2.5-20 mg/day or placebo.	Double-blind, randomised outpatient trial of risperidone plus placebo vs. divalproex plus placebo	Controlled, randomised, no-patient-choice parallel comparison of lithium, divalproex sodium or risperidone.
Duration of study	21 days	21 days	**Period I:** screening/washout period lasting 2-14 days. **Period II:** 3-week, double-blind treatment with olanzapine or placebo. **Period III:** 26-week open-label olanzapine treatment (results not presented in this study).	6 weeks plus a 1-week washout period prior to study entry	8 weeks
Method of randomisation	1:1:1. Unclear method	1:1:1. Unclear method	NR	NR	Randomisation was stratified by age group (6-12 years vs.13-15 years) and by the presence or absence of mixed mania, psychosis and daily rapid cycling. Statistical software (SAS version 8.1) was used to generate random lists of the 3 medications for each combination of the stratifying variables at each site. For each patient the randomised

					medication was determined by selecting the next available entry in the list corresponding to the subjects stratifying variables and site.
Method of blinding (care provider, patient and outcome assessor)	Double blind; unclear method.	Double blind; unclear method.	NR	Investigational staff involved in rating efficacy and safety measures, parents, caregivers and subjects were blind to the medication administered. Patients receiving risperidone plus placebo received a placebo capsule that resembled divalproex while patients receiving divalproex plus placebo received a placebo capsule resembling risperidone.	Patients, family members, treating clinicians and staff performing the weekly assessments were not blinded to the treatment. However, independent evaluators performing the baseline and endpoint assessments were blinded.
Intervention(s) (n =) and comparator(s) (n =)	Placebo (n=58), risperidone 0.5-2.5 mg/day (n=50), or risperidone 3-6 mg/day (n=61).	Quetiapine IR fixed doses 400 mg/day (n=95) or 600 mg/day (bid or tid) (n=98) or placebo (n=91).	**Interventions:** Olanzapine 2.5-20.0 mg/day (n=107) **Comparator:** Placebo (n=54)	**Interventions:** Risperidone 0.5-2.0 mg/day plus placebo (n=33) **Comparator:** Divalproex 15 mg/kg/day plus placebo (n=33)	**Interventions:** Risperidone (n=89) **Comparators:** Lithium (n=90) Divalproex sodium (n=100) Risperidone was titrated to a maximum dose of 4-6 mg/day. Lithium was titrated to a maximum daily dose of 1.1-1.3 mEq/L. Divalproex sodium was titrated to a maximum daily dose of 111-125 µg/mL.
Primary outcomes	Change in YMRS total score from baseline to endpoint	Mean change from baseline to Day 21 in total YMRS	Mean change from baseline to endpoint (week 3 in period	YMRS	Clinical Global Impressions for Bipolar Illness

(including scoring methods and timings of assessments)	(day 21).	score.	II) in the YMRS total score		Improvement-Mania (CGI-BP-IM) at endpoint (week 8). Ratings of 1 or 2 (very much or much improved respectively) were counted as response.
Secondary outcomes (including scoring methods and timings of assessments)	Change in YMRS total score between baseline and days 7 and 14. Number of subjects (%) who responded: ≥50% reduction in YMRS from baseline to end point. Onset of sustained YMRS response (achieved for at least 2 consecutive measurements and for remainder of treatment phase). Change from baseline in CGI-BP score at each time point. Change from baseline in BPRS-C total score and BPRS-C depression factor score at each time point. Safety assessments included AE monitoring and scores on EPS rating scales.	YMRS response (%), defined as ≥50% reduction from baseline in YMRS total score YMRS remission (%), defined as YMRS total score ≤ 12. CGI-BP severity of illness (LS mean change from baseline) CGI-BP Global Improvement (% of patients "much improved" or "very much improved") CGAS total score (LS mean change from baseline).	Baseline to endpoint (week 3) changes of: • YMRS individual items • Clinical Global Impressions-Bipolar Version overall, severity of mania or depression subscales • Children's Depression Ratings Scale-Revised • ADHD Rating Scale-IV-parent version • Overt Aggression Scale • Rates of response (≥50% decrease in the YMRS total score from baseline to endpoint) • Rates of remission (YMRS total score ≤12 at week 3) • Incidence of switch to depression (Clinical Global Impressions depression score ≤3 at baseline and ≥4 at any time during the double-blind phase)	• Children's Depression Ratings Scale-Revised • Clinical Global Impressions Scale for Bipolar Disorder • The Overt Aggression Scale • Brief Psychiatric Rating Scale for Children • Child Mania Rating Scale (completed by parents)	• KSADS Mania Rating Scale (KMRS) at endpoint (week 8) • Modified Side Effects Form for Children and Adolescents and Modified Abnormal Involuntary Movement Scale (AIMS) at all time points
Details of study population	Included children and adolescents (10-17 years, inclusive) diagnosed using	Included children and adolescents (10 to 17 years, inclusive) with mania.	The study enrolled male and female patients aged 13-17 years. All subjects met	Inclusion criteria included: • A DSM-IV diagnosis of bipolar disorder Type I	Participants were outpatients aged 6.0-15.11 years old with a DSM-IV diagnosis of

(summary of inclusion and exclusion criteria)	DSM-IV criteria for bipolar I disorder, current episode manic or mixed (confirmed by K-SADS-PL). Patients with co-occurring ADHD or DBD were also included Patients must have had a total score of ≥20 YMRS at screening and baseline.		diagnostic criteria for manic or mixed bipolar episodes (with or without psychotic features) according to the DSM-IV. Subjects could be inpatients or outpatients with a total score of ≥20 on the Adolescent Structured YMRS. Exclusion criteria included: • Prior nonresponse to olanzapine • Treatment within the previous 30 days with an experimental medication not available for clinical use • Serious suicidal risk • Clinically significant abnormal laboratory values at baseline • DSM-IV substance dependence within the past 30 days • Treatment with a long-lasting neuroleptic within 14 days prior to randomisation	(mixed or manic) • 8-18 years old • ADHD was included in present Exclusion criteria included: • Active substance abuse based on DSM-IV criteria • Serious medical problems • History of allergy to risperidone or divalproex • Presence of autism, nonaffective psychotic disorders or any other psychiatric disorder requiring pharmacotherapy	bipolar I disorder manic or mixed episode for at least 4 consecutive weeks immediately preceding baseline. They also had a CGAS score of 60 or less at baseline and were in good physical health. Co-morbid ADHD, ODD and conduct disorders were allowed. Exclusion criteria included: • IQ of less than 70 • Lifetime history of schizophrenia, pervasive developmental disorder or major medical or neurological disease • Substance use dependency
Duration of follow-up			The open-label period after the double-blind period lasted 26 weeks	6 weeks	8 weeks

NR = not reported

Table B20 Characteristics of participants in the included RCTs across randomised groups

Haas 2009[19] **Baseline characteristic**	**Placebo**	**Risperidone 0.5-2.5mg daily**	**Risperidone 3-6 mg daily**	**p-value**
n	N=58			
Median age (years) ± SD	13.0 (10-17)	13.0 (10-17)	13.0 (10-17)	
Gender (% male)	48	56	43	
Mean age at onset (years) ± SD				
Mean duration of bipolar disease (years) ± SD				
YMRS total score, mean ± SD	31.0 (7.5)	31.1 (6.0)	30.5 (6.9)	
Weight, mean ± SD, kg				
BMI, mean ± SD, kg/m^2				
Study 149[76] **Baseline characteristic**	**Placebo**	**Quetiapine 400 mg**	**Quetiapine 600 mg**	**p-value**
n	N=89	N=93	N=95	
Mean age (years) ± SD	13.11 (2.16)	13.15 (2.18)	13.31 (2.14)	
Gender (% male)	50.5%	57.9%	60.7%	
Mean age at onset (years) ± SD				
Mean duration of bipolar disease (years) ± SD				
YMRS total score, mean ± SD	31.3 (7.1)	30.6 (6.04)	31.7 (5.59)	
Weight, mean ± SD, kg	59.71 (18.08)	60.08 (17.83)	62.48 (19.42)	
BMI, mean ± SD, kg/m^2	23.5 (5.31)	23.38 (4.77)	24.14 (5.67)	
Tohen 2007[29] **Baseline characteristic**	**Placebo**	**Olanzapine 2.5-20.0 mg/day**		**p-value**
n	54	107		-
Mean age (years) ± SD	15.4±1.2	15.1±1.3		0.250
Gender (% male)	44.4	57.0		0.13
Mean age at onset (years) ± SD	11.5±3.1	10.9±3.3		0.331
Mean duration of bipolar disease	NR	NR		NR

(years) ± SD				
YMRS total score, mean ± SD	NR	NR		NR
Weight, mean ± SD, kg	NR	NR		NR
BMI, mean ± SD, kg/m^2	NR	NR		NR
Pavaluri 2010[77] **Baseline characteristic**	**Divalproex 15 mg/kg/day plus placebo**	**Risperidone 0.5-2.0 mg/day plus placebo**		**p-value**
n	33	32		-
Mean age (years) ± SD	11.23±3.50	10.47±3.18		NR
Gender (% male)	57.6%	62.5%		NR
Mean age at onset (years) ± SD	NR	NR		NR
Mean duration of bipolar disease (years) ± SD	NR	NR		NR
YMRS total score, mean ± SD	NR	NR		NR
Weight at baseline Normal, n (%) Overweight, n (%)	 29 (87.9%) 30 (93.8%)	 4 (12.1%) 2 (6.3%)		NR
BMI, mean ± SD, kg/m^2	NR	NR		NR
Geller 2012[78] **Baseline characteristic**	**Risperidone 4-6 mg/day**	**Lithium 1.1-1.3 mEq/l/day**	**Divalproex sodium 111-125 µg/ml/day**	**p-value**
n	89	90	100	-
Mean age (years) ± SD	11.0 (3.0)	9.7 (2.7)	9.7 (2.4)	NR
Gender (% male)	47.2%	58.9%	44.0%	NR
Mean age at mania episode onset (years) ± SD	5.8 (2.9)	5.0 (2.7)	5.0 (2.2)	NR
Mean duration of bipolar disease (years) ± SD	NR	NR	NR	NR
YMRS total score, mean ± SD	NR	NR	NR	NR
Weight, mean ± SD, kg	40.7 (18.4)	40.2 (17.2)	38.5 (14.9)	NR
BMI, mean ± SD, kg/m^2	19.1 (4.5)	19.6 (4.3)	19.4 (3.8)	NR

Quality Assessment

As Pavaluri 2010 was a small study and Geller 2012 was not placebo-controlled, these studies were not included in the meta-analysis as they were found to increase uncertainty and did not add any further significant information (also see Section 5.7.8). For transparency, a summary of the quality and results of these studies is presented in Section 9.19, Appendix 19. A summary of the quality assessment of the three remaining comparator studies are presented in Table B21 and the full quality assessments can be found in Section 9.5, Appendix 5).

Table B21 Quality assessment results for RCTs

Trial no. (acronym)	Haas 2009[19]	Study 149[76]	Tohen 2007[29]
Was randomisation carried out appropriately?	Not clear	Not clear	Not clear
Was the concealment of treatment allocation adequate?	Not clear	Not clear	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Not clear	Not clear	Not clear
Were there any unexpected imbalances in drop-outs between groups?	Yes	Yes	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Yes	No
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.	Yes.	Yes

Results

Results from the three studies included in the network meta-analysis are presented in Table B22.

Table B22 Relevant outcomes from Haas 2009,[19] Study 149,[76] and Tohen 2007[29]

Haas 2009[19]		Placebo		Risperidone 0.5-2.5 mg daily			Risperidone 3-6 mg daily			p value vs. placebo
		N	Value	N	Value	Treatment difference (95% CI)	N	Value	Treatment difference (95% CI)	
YMRS response (≥50% reduction from baseline in total YMRS)	% at Week 1	58	8.8	50	29.2		61	20.3		
	% at Week 2	58	26.3	50	57.1		61	61.7		
	% at Week 3	58	26.3	50	59.2		61	63.3		Risperidone 0.5-2.5 mg: p=0.002 Risperidone 3-6 mg: p<0.001
Discontinuation rate	n (%) at Week 3	58	12 (20.7)	50	5 (10.0)		61	15 (24.6)		
Extrapyramidal symptoms	% at Week 3	58	5	50	8		61	25		
Somnolence	n (%) at Week 3	58	11 (19)	50	21 (42)		61	34 (56)		
Clinically significant weight gain	% at Week 3	58	5.3	50	14.3		61	10		
Clinically significant increase in prolactin	% at Week 3	Males: 26 Females: 27	Males: 0 Females: 0	Males: 24 Females: 21	Males: 0 Females: 23.8		Males: 20 Females: 33	Males: 5 Females: 36.4		
Study 149[76]		**Placebo**		**Quetiapine 400 mg**			**Quetiapine 600 mg**			**p value vs. placebo**
		N	**Value**	**N**	**Value**	**Treatment difference (95% CI)**	**N**	**Value**	**Treatment difference (95% CI)**	
YMRS response	n (%) at Week 1									
	n (%) at Week 2									

	n (%) at Week 3	89	37	93	64		95	58		Quetiapine 400 mg: p=0.001 Quetiapine 600 mg: p=0.005
Discontinuation rate	n (%) at Week 3	90	25 (27.5)	95	19 (20.0)		98	18 (18.4)		
Extrapyramidal symptoms	n (%) at Week 3	90	1 (1.1)	193	7 (3.6) – quetiapine 400 mg and 600 mg pooled results					
Somnolence	n (%) at Week 3	165	14 (8.5)	340	100 (29.4)					
Clinically significant weight gain	n (%) at Week 3		0		12 - quetiapine 400 mg and 600 mg pooled results					
Clinically significant increase in prolactin	n (%) at Week 3		Males: 4 Females: 0		Males: 13.4 Females: 8.7					
Tohen 2007[29]		**Placebo**		**Olanzapine 2.5-20.0 mg/day**						**p value vs. placebo**
		N	**Value**	**N**	**Value**	**Treatment difference (95% CI)**				
YMRS response	n (%) at Week 1	54	11.6%	105	27.1%	NR	-	-	-	<0.05
	n (%) at Week 2	54	16.8%	105	47.0%	NR	-	-	-	<0.05
	n (%) at Week 3	54	22.2%	105	48.6%	NR	-	-	-	0.002
Discontinuation rate	n (%)	54	35.2%	107	20.6%	NR	-	-	-	NR

Any extrapyramidal symptom event	n (%) at Week 3	54	NR	107	NR	NR	-	-	-	NR
Somnolence	n (%) at Week 3	54	NR	107	NR	NR	-	-	-	NR
Clinically significant weight gain (≥7%)	n (%) at Week 3	54	1.9%	107	41.9%	NR	-	-	-	NR
Clinically significant increase in prolactin	n (%) at Week 3	54	2.2%	107	46.7%	NR	-	-	-	NR

5.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Table B23 Summary of the trials used to conduct the main indirect comparison (doses are per day. If two doses are given, this indicates two different arms of the trial)

No. trials	References of trials	Placebo	Aripiprazole	Risperidone	Quetiapine	Olanzapine
1	NCT00110461 (Findling 2009[5])	✓	✓ 10 mg, 30 mg			
1	Haas 2009[19]	✓		✓ 0.5-2.5 mg, 3-6 mg		
1	Study 149[76]	✓			✓ 400 mg, 600 mg	
1	Tohen 2007[29]	✓				✓ Up to 20 mg
Adapted from Caldwell et al. (2005) Simultaneous comparison of multiple treatments combining direct and indirect evidence. BMJ 331: 897–900						

Table B24 Summary of the trials used to conduct the indirect comparison presented as sensitivity analysis (Appendix 15)

No. trials	References of trials	Placebo	Valproate	Aripiprazole	Risperidone	Quetiapine	Olanzapine
1	NCT00110461 (Findling 2009[5])	✓		✓ 10 mg, 30 mg			
1	Haas 2009[19]	✓			✓ 0.5-2.5 mg, 3-6 mg		
1	Study 149[76]	✓				✓ 400 mg, 600 mg	
1	Tohen 2007[29]	✓					✓ Up to 20 mg
1	Tramontina 2009[57]	✓		✓ 20 mg			
2	Pavaluri 2010[77]		✓ 60-120 µg		✓ 0.5-2.5 mg		
	Geller 2012[78]		✓ 111-125 µg		✓ 4-6 mg		
Adapted from Caldwell et al. (2005) Simultaneous comparison of multiple treatments combining direct and indirect evidence. BMJ 331: 897–900							

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

The table below shows which studies are included in the analysis for each outcome, as complete data are not available for all of them.

Table B25 Summary of data used in the analysis

	YMRS week1	YMRS week2	YMRS week3	Discont. week 3	Extrapyr. symptoms	Weight gain	Prolactin increase	Somnolence
Pivotal RCTs								
Findling 2009[5]	✓	✓	✓	✓	✓	✓	✓	✓
Tohen 2007[29]	✓	✓	✓	✓		✓	✓	
Haas 2009[19]	✓	✓	✓	✓	✓	✓	✓	✓
Study 149[76]			✓	✓	✓	✓	✓*	✓*
Other RCTs								
Tramontina 2009[57]	✓	✓	✓	✓	✓			✓
Pavaluri 2010[77]				✓	✓			
Geller 2012[78]								✓

*The rate for quetiapine was taken from a pooled estimate between Study 149 and a paediatric schizophrenia study

The main analyses were run on the four pivotal studies shown in the first part of the table. Evidence on all comparators was not available for every outcome. Data from the three other studies have been included in additional sensitivity analyses only, which are presented in Appendix 15. This is due to the fact that these small studies increased the uncertainty in the analysis and were deemed not to add any further significant information (also see Section 5.7.8).

The efficacy outcomes that were analysed in the network meta-analysis were as follows:

- YMRS response (defined as ≥50% reduction in YMRS total score from baseline) at week 1
- YMRS response at week 2
- YMRS response at week 3
- Discontinuation at week 3 (all discontinuations were included, not just those for lack of efficacy)

The safety outcomes that were analysed in the network meta-analysis were as follows:

- Extrapyramidal symptoms (as defined by each study)
- Clinically significant weight gain (increase of >7% of baseline weight)

- Clinically significant prolactin increase (as defined by each study)
- Somnolence (as defined by each study)

For the rates of adverse events, no adjustment was made for drug exposure time, as the difference between the study durations was relatively small. For the main analysis using only the four pivotal RCTs, the safety outcomes for aripiprazole at 4 weeks were compared to other comparator rates at 3 weeks, which may disadvantage aripiprazole.

The age subgroup of 13-17 year olds was not used from aripiprazole study NCT00110461 due to the non-availability of YMRS response data for this subgroup.

5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

The objective of this analysis was to assess the efficacy and safety of aripiprazole versus placebo and three comparators. A network analysis is a type of analysis that allows for all the evidence on a network of treatments to be analysed at once. The situation here is perfectly suited to this with the network of treatments being aripiprazole, olanzapine, risperidone, quetiapine and placebo.

Approach

The approach chosen for this analysis was a Bayesian model.

Both fixed-effect and random-effect models were considered for the analysis. With a fixed effect model it is assumed that differences in true relative treatment effects are only caused by the difference in treatments and no other factors. Each study estimates the same true treatment effect and differences between studies are only due to chance. With a random-effect approach, it is assumed that differences between studies are also caused by heterogeneity between studies. The variation observed in individual study results is hence caused not only by sampling error (as with the fixed-effect approach) but also by the variation in the true underlying effects in each study, which is called the random-effects variance. The use of the random-effects model is generally advocated if there is heterogeneity between study results, caused for example by different study populations across studies or methodological differences.

However, data are available in very few studies for this analysis, and each study compares a different pair of treatments. There is therefore not enough evidence to support the estimation of a random-effects model.

The fixed-effect model implemented in this analysis can be written as follows:

$n_{ib(i)} \sim Bin(p_{ib(i)}, N_{ib(i)})$
$n_{it(i)} \sim Bin(p_{it(i)}, N_{it(i)})$
$logit(p_{ib(i)}) = \lambda_i$
$logit(p_{it(i)}) = \lambda_i + \theta_{i,b(i),t(i)}$

Where:

- i represents the study.
- b(i) the baseline treatment in that study
- t(i) the comparator in that study
- $n_{ib(i)}$ (resp. $n_{it(i)}$) the number of events observed in the baseline (resp. treatment) arm of study i
- $N_{ib(i)}$ (resp. $N_{it(i)}$) the total number of patients in that arm.
- λ_i the baseline effect (log-odds) of treatment b(i) in study i
- $\theta_{i,b(i),t(i)}$ the log odds-ratio of treatment t(i) relative to treatment b(i) in study i.

Vague non-informative normal priors were given to all parameters.

Implementation

These models were implemented in WinBugs, version 1.4.3.

Three Markov chains with different initial values were used. For each analysis, an initial 30,000 iterations were run, allowing the simulations to converge. Results were based on a further 50,000 iterations.

Reporting and interpretation of results

For each outcome, results are reported as:

- Median RR of each treatment versus placebo and associated 95% credible interval.
- Median RR of each treatment versus aripiprazole and associated 95% credible interval.
- Median probability of experiencing the event with each treatment and associated 95% credible interval.
- Probability of each treatment being the best

A 95% credible interval can be interpreted as the range of values within which the parameter has a 95% probability of falling. The conclusions in terms of significance are similar to the ones drawn from confidence intervals. If the credible interval does not include 1, then the two treatments can be considered significantly different.

Conversely, if the credible interval includes 1 then it cannot be concluded that there is a higher risk or chance of experiencing the outcome with one treatment or the other.

The probability of each treatment being the best for each outcome is calculated as the proportion of simulations in which this treatment is ranked 'best' in terms of relative efficacy/safety.

The Winbugs code is shown in Appendix 16.

5.7.6 Please present the results of the analysis.

The relative risks using placebo and aripiprazole as references derived from the analyses on the pivotal studies are presented here. The primary dose of interest is the pooled aripiprazole dose, but results for the 10 mg and 30 mg doses are also shown.

For each comparator, if there were two active arms of the trial then these were pooled. This is justified because all doses of the comparators investigated in the trials are licensed for use within the adult indications, and therefore could be also be used in children in clinical practice.

The probabilities of achieving each outcome with each treatment used in the economic modelling, and the probability of each treatment being the best can be found in Appendix 15.

Efficacy outcomes

<u>YMRS response at week 1</u>

Aripiprazole was found to be significantly better than placebo at achieving YMRS response at week 1. It was also numerically better than olanzapine and risperidone at both doses examined, but the differences were not statistically significant (Table B26).

Table B26 Risk ratios versus placebo and aripiprazole for YMRS response at week 1

	Aripiprazole pooled dose		Aripiprazole 10mg		Aripiprazole 30mg	
	median	**95% CrI**	median	95% CrI	median	95% CrI

RR versus Placebo						
Placebo	**1.00**	**-**	1.00	-	1.00	-
Aripiprazole	**3.47**	**1.77, 7.31***	3.50	1.69, 7.54*	3.40	1.63, 7.37*
Olanzapine	**2.59**	**1.20, 5.93***	2.59	1.19, 5.94*	2.59	1.20, 5.94*
Risperidone	**2.95**	**1.32, 7.07***	2.95	1.33, 7.08*	2.94	1.32, 7.11*
RR versus Aripiprazole						
Placebo	**0.29**	**0.14, 0.57**	0.29	0.13, 0.59	0.29	0.14, 0.61
Aripiprazole	**1.00**	**-**	1.00	-	1.00	-
Olanzapine	**0.74**	**0.27, 2.01**	0.74	0.27, 2.08	0.76	0.27, 2.16
Risperidone	**0.85**	**0.31, 2.34**	0.84	0.30, 2.43	0.87	0.31, 2.51

*Statistically significant result

YMRS response at week 2

Aripiprazole was found to be significantly better than placebo at achieving YMRS response at week 2. All treatments performed in a very similar way for this outcome (Table B27).

Table B27 Risk ratios versus placebo and aripiprazole for YMRS response at week 2

	Aripiprazole pooled dose		Aripiprazole 10 mg		Aripiprazole 30 mg	
	median	**95% CrI**	median	95% CrI	median	95% CrI
RR versus Placebo						
Placebo	**1.00**	**-**	1.00	-	1.00	-
Aripiprazole	**2.63**	**1.83, 3.83***	2.26	1.45, 3.43*	2.98	2.07, 4.30*
Olanzapine	**2.68**	**1.66, 4.32***	2.68	1.66, 4.30*	2.68	1.65, 4.30*
Risperidone	**2.62**	**1.72, 3.93***	2.61	1.71, 3.94*	2.61	1.71, 3.93*
RR versus Aripiprazole						
Placebo	**0.38**	**0.26, 0.55**	0.44	0.29, 0.69	0.34	0.23, 0.48
Aripiprazole	**1.00**	**-**	1.00	-	1.00	-
Olanzapine	**1.02**	**0.61, 1.67**	1.19	0.68, 2.09	0.90	0.55, 1.46
Risperidone	**0.99**	**0.62, 1.57**	1.16	0.69, 1.96	0.87	0.55, 1.37

*Statistically significant result

YMRS response at week 3

Aripiprazole was found to be significantly better than placebo at achieving YMRS response at week 3. It was also better than olanzapine and quetiapine, however the differences were not statistically significant (Table B28). Aripiprazole and risperidone perform in a very similar way for this outcome (Table B28).

Table B28 Risk ratios versus placebo and aripiprazole for YMRS response at week 3

	Aripiprazole pooled dose		Aripiprazole 10 mg		Aripiprazole 30 mg	
	median	**95% CrI**	median	95% CrI	median	95% CrI
RR versus Placebo						
Placebo	**1.00**	**-**	1.00	-	1.00	-
Aripiprazole	**2.39**	**1.76, 3.24***	2.13	1.45, 2.99*	2.63	1.94, 3.53*
Olanzapine	**2.12**	**1.39, 3.11***	2.12	1.39, 3.12*	2.12	1.39, 3.12*
Risperidone	**2.44**	**1.70, 3.37***	2.43	1.71, 3.37*	2.44	1.71, 3.37*
Quetiapine	**1.90**	**1.38, 2.54***	1.90	1.38, 2.55*	1.90	1.39, 2.54*
RR versus Aripiprazole						
Placebo	**0.42**	**0.31, 0.57**	0.47	0.33, 0.69	0.38	0.28, 0.52
Aripiprazole	**1.00**	**-**	1.00	-	1.00	-
Olanzapine	**0.89**	**0.56, 1.35**	1.00	0.61, 1.62	0.81	0.52, 1.22
Risperidone	**1.02**	**0.69, 1.47**	1.15	0.75, 1.77	0.93	0.63, 1.33
Quetiapine	**0.79**	**0.54, 1.15**	0.89	0.59, 1.38	0.72	0.50, 1.04

*Statistically significant result

Discontinuation at week 3

Patients on aripiprazole were less likely to discontinue treatment at week 3 than patients on placebo and risperidone, but more likely to discontinue than patients on olanzapine and quetiapine (a result driven by the 30 mg aripiprazole arm) (Table B29). None of these differences were significant (Table B29).

Table B29 Risk ratios versus placebo and aripiprazole for discontinuation at week 3

	Aripiprazole pooled dose		Aripiprazole 10 mg		Aripiprazole 30 mg	
	median	**95% CrI**	median	95% CrI	median	95% CrI
RR versus Placebo						
Placebo	**1.00**	**-**	1.00	-	1.00	-
Aripiprazole	**0.73**	**0.41, 1.24**	0.55	0.24, 1.10	0.89	0.47, 1.55
Olanzapine	**0.54**	**0.28, 0.99**	0.54	0.28, 0.99	0.54	0.28, 0.99
Risperidone	**0.88**	**0.46, 1.61**	0.88	0.46, 1.62	0.88	0.46, 1.60
Quetiapine	**0.70**	**0.43, 1.11**	0.70	0.43, 1.11	0.70	0.43, 1.11
RR versus Aripiprazole						
Placebo	**1.37**	**0.80, 2.43**	1.82	0.91, 4.12	1.13	0.64, 2.13
Aripiprazole	**1.00**	**-**	1.00	-	1.00	-
Olanzapine	**0.75**	**0.32, 1.72**	1.00	0.38, 2.76	0.61	0.26, 1.49
Risperidone	**1.21**	**0.52, 2.78**	1.61	0.61, 4.48	0.99	0.42, 2.39
Quetiapine	**0.96**	**0.46, 2.01**	1.28	0.54, 3.27	0.79	0.37, 1.74

Safety outcomes

Summary of the probabilities of events occurring for all adverse events (as used in the economic model).

Table B30 Median probability of adverse events occurring

	EPS		Weight gain		Prolactin increase		Somnolence	
	median	95% CrI	median	95% CrI	median	95% CrI	median	95% CrI
Placebo	0.030	0.01, 0.06	0.016	0.004, 0.038	0.012	0.003, 0.029	0.078	0.045, 0.12
Aripiprazole (pooled dose)	0.158	0.053, 0.328	0.034	0.007, 0.119	0.002	0, 0.025	0.463	0.271, 0.711
Olanzapine	NR		0.450	0.123, 0.896	0.416	0.106, 0.883	NR	
Risperidone	0.112	0.033, 0.305	0.041	0.008, 0.159	0.321	0.062, 0.95	0.266	0.145, 0.432
Quetiapine	0.116	0.028, 0.528	0.403	0.092, 0.964	0.070	0.014, 0.29	0.273	0.15, 0.441

Extrapyramidal symptoms

Patients on aripiprazole were found to be significantly more likely to experience extrapyramidal symptoms than patients on placebo. They were also more likely to experience them than patients on risperidone and quetiapine (a result driven by the 30 mg aripiprazole arm), but these differences were not significant (Table B31).

Table B31 Risk ratios versus placebo and aripiprazole for extrapyramidal symptoms

	Aripiprazole pooled dose		Aripiprazole 10 mg		Aripiprazole 30 mg	
	median	**95% CrI**	median	95% CrI	median	95% CrI
RR versus Placebo						
Placebo	**1.00**	**-**	1.00	-	1.00	-
Aripiprazole	**5.28**	**2.65, 11.74***	3.71	1.66, 8.87*	6.99	3.43, 15.51*
Risperidone	**3.73**	**1.28, 13.84***	3.73	1.27, 13.84*	3.72	1.28, 13.78*
Quetiapine	**3.79**	**0.67, 44.77**	3.80	0.66, 44.12	3.80	0.67, 43.82
RR versus Aripiprazole						
Placebo	**0.19**	**0.09, 0.38**	0.27	0.11, 0.60	0.14	0.06, 0.29
Aripiprazole	**1.00**	**-**	1.00	-	1.00	-
Risperidone	**0.71**	**0.20, 2.93**	1.01	0.26, 4.47	0.53	0.15, 2.18
Quetiapine	**0.72**	**0.12, 8.38**	1.04	0.15, 12.47	0.54	0.09, 6.00

*Statistically significant result

Clinically significant weight gain

There was no significant difference between aripiprazole and placebo in the risk of experiencing a clinically significant increase in weight.

Aripiprazole (pooled dose) was, however, significantly less likely to induce clinically significant weight gain than olanzapine and quetiapine (Table B32). The estimations of the effects of olanzapine and quetiapine are very imprecise due to the small number of events observed in the placebo arms of these studies (1/54 in the olanzapine study, 0/90 in the quetiapine one). The comparison between aripiprazole and risperidone also favoured aripiprazole, but the difference is not significant (Table B32).

Table B32 Risk ratios versus placebo and aripiprazole for clinically significant weight gain

	Aripiprazole pooled dose		Aripiprazole 10 mg		Aripiprazole 30 mg	
	median	**95% CrI**	median	95% CrI	median	95% CrI
RR versus Placebo						
Placebo	**1.00**	**-**	1.00	-	1.00	-
Aripiprazole	**2.13**	**0.76, 7.20**	0.98	0.22, 4.24	3.22	1.1, 10.91
Olanzapine	**26.44**	**7.46, 130.3***	26.30	7.49, 127.6*	26.35	7.49, 128.4*
Risperidone	**2.54**	**0.78, 10.78**	2.53	0.78, 10.74	2.55	0.78, 10.62
Quetiapine	**23.54**	**3.92, 217.9***	22.67	3.8, 195.6*	22.32	3.79, 196.8*
RR versus Aripiprazole						
Placebo	**0.47**	**0.14, 1.32**	1.02	0.24, 4.55	0.31	0.09, 0.91
Aripiprazole	**1.00**	**-**	1.00	-	1.00	-
Olanzapine	**12.52**	**2.31, 76.22***	27.57	4.12, 216.2*	8.24	1.53, 50.23*
Risperidone	**1.19**	**0.22, 6.94**	2.65	0.39, 20.21	0.79	0.15, 4.61
Quetiapine	**11.1**	**1.30, 116.1***	23.99	2.34, 297.00*	6.98	0.84, 72.47

*Statistically significant result

Clinically significant increase in prolactin

Patients on aripiprazole are less likely to experience a clinically significant increase in prolactin than patients on placebo, but not significantly so. Patients on aripiprazole are, however, significantly less likely to experience this than patients on olanzapine, risperidone and quetiapine (Table B33).

Table B33 Risk ratios versus placebo and aripiprazole for clinically significant increase in prolactin

	Aripiprazole pooled dose		Aripiprazole 10 mg		Aripiprazole 30 mg	
	median	**95% CrI**	median	95% CrI	median	95% CrI
RR versus Placebo						
Placebo	**1.00**	**-**	1.00	-	1.00	-
Aripiprazole	**0.20**	**0.01, 2.43**	0.11	0, 1.93	0.40	0.01, 4.81
Olanzapine	**33.83**	**9.15, 186.1***	32.82	9.06, 169.8*	33.47	9.09, 185.2*
Risperidone	**25.88**	**3.82, 291.8***	24.84	3.78, 261*	25.81	3.8, 308.1*
Quetiapine	**5.97**	**1.72, 32.14***	5.97	1.72, 31.87*	5.97	1.72, 32.36*
RR versus Aripiprazole						
Placebo	**4.89**	**0.41, 140.3**	8.74	0.52, 2179	2.47	0.21, 72.42
Aripiprazole	**1.00**	**-**	1.00	-	1.00	-
Olanzapine	**175.70**	**10.86, 6414***	310.70	12.84, 85630*	88.75	5.48, 3267*
Risperidone	**139.80**	**5.52, 7202***	251.20	6.82, 82530*	71.13	2.84, 3736*
Quetiapine	**31.22**	**1.81, 1191***	57.86	2.33, 16060*	15.85	0.93, 618.5*

*Statistically significant result

Somnolence

Patients on aripiprazole were significantly more likely to experience somnolence than patients on placebo. They are also more likely to experience somnolence than patients on risperidone and quetiapine, but these differences were not significant (Table B34).

Table B34 Risk ratios versus placebo and aripiprazole for somnolence

	Aripiprazole pooled dose		Aripiprazole 10 mg		Aripiprazole 30 mg	
	median	**95% CrI**	median	95% CrI	median	95% CrI
RR versus Placebo						
Placebo	**1.00**	**-**	1.00	-	1.00	-
Aripiprazole	**5.85**	**2.75, 14.10***	5.21	2.21, 13.27*	6.41	3.02, 14.87*
Risperidone	**3.39**	**1.87, 6.27***	3.40	1.88, 6.25*	3.40	1.88, 6.24*
Quetiapine	**3.47**	**1.90, 6.69***	3.49	1.91, 6.76*	3.48	1.89, 6.73*
RR versus Aripiprazole						
Placebo	**0.17**	**0.07, 0.36**	0.19	0.08, 0.45	0.16	0.07, 0.33
Aripiprazole	**1.00**	**-**	1.00	-	1.00	-
Risperidone	**0.58**	**0.23, 1.38**	0.65	0.24, 1.68	0.53	0.21, 1.24
Quetiapine	**0.59**	**0.23, 1.43**	0.67	0.25, 1.76	0.54	0.22, 1.29

*Statistically significant result

5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Not applicable.

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

The four pivotal trials included in the main analyses are relevant, so no exclusion has been performed. However, sensitivity analyses were run including the additional studies detailed in section 5.7.4. Analyses were conducted first by including only the studies comparing risperidone to valproate. As a second step, study NCT00116259 was also added. This study was added as a separate analysis due to the fact that it also included patients with bipolar II disorder, who are outside of aripiprazole's expected licence. The study was also limited to a subgroup of bipolar I patients with ADHD and therefore is less comparable in terms of patient population than the other studies included.

The results of these sensitivity analyses are consistent with those of the main analyses shown in section 5.7.6 and the conclusions in terms of significance of the treatment effects remain the same. In most cases the new data added in the sensitivity analyses are weak, as very few events are observed or the total population is very small. Therefore these analyses do not add significantly to the evidence already presented and the results are shown in Appendix 15 only.

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

The only direct evidence available in this analysis was the effect of each treatment compared to placebo, presented in section 5.5. The results of the network meta-analysis are consistent with those of the direct comparisons, and the conclusions in terms of significance are the same. Both sets of results derived from the analyses on

the pivotal studies only are summarised below (Table B35) for the pooled aripiprazole dose, which is the main treatment of interest.

Table B35 Comparison of the direct and network meta-analysis results for aripiprazole versus placebo

Aripiprazole pooled dose versus Placebo	Direct meta-analysis RR (95% CI)	Network meta-analysis RR (95% CrI)
YMRS response at week1	3.54 (1.56, 8.00)	3.47 (1.77, 7.31)
YMRS response at week 2	2.74 (1.71, 4.39)	2.63 (1.83, 3.83)
YMRS response at week 3	2.77 (1.73, 4.44)	2.39 (1.76, 3.24)
Discontinuation at week 3	0.71 (0.40, 1.26)	0.73 (0.41, 1.24)
Extrapyramidal symptoms	4.36 (2.08, 9.17)	5.28 (2.65, 11.74)
Clinically significant weight gain	1.97 (0.68, 5.73)	2.13 (0.76, 7.20)
Clinically significant increase in prolactin	0.25 (0.02, 2.68)	0.20 (0.01, 2.43)
Somnolence	7.39 (2.36, 23.17)	5.85 (2.75, 14.10)

5.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

No relevant non-RCTs for aripiprazole were identified in the systematic review.

Non-RCTs in children/adolescents suffering from bipolar I disorder were identified from the systematic review (see Section 5.7.2) for the other atypical antipsychotics, risperidone and olanzapine. Four non-RCTs were identified that investigated risperidone. Of these, two looked at risperidone for the treatment of ADHD symptoms in bipolar children and adolescents,[79, 80] one only reported MRI outcomes,[81] and the final study investigated risperidone as an add-on to lithium in lithium non-responders.[82] The olanzapine non-RCT was a 4-week MRI study.[83] None of these reported any outcomes that would be suitable for use in an indirect comparison or in the economic modelling.

5.9 *Adverse Events*

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

Summary of Adverse Events

- In both studies NCT00110461 and NCT00116259, aripiprazole demonstrated an acceptable safety profile in children aged 13 or older. This is particularly true with respect to adverse events of particular interest in children and adolescents and to which this juvenile population is particularly prone, such as weight gain and increases in serum prolactin levels.
- Study NCT00110461 demonstrated that the incidence of clinically significant weight gain (≥7%) was not significantly different in the 30 mg and 10 mg aripiprazole arms compared to placebo at week 4 and remained low over time.
- There were also no increases in serum prolactin level, with prolactin levels in all treatment groups falling over the duration of the 30-week study.
- In contrast, somnolence and extrapyramidal symptoms occurred more frequently in patients receiving aripiprazole than placebo. However, the vast majority of cases occurred in the first four weeks of the study, were of mild-to-moderate severity and were expected to be manageable.
- Study NCT00116259 established the same safety profile for aripiprazole as study NCT00110461, with no significant differences in weight gain or BMI between treatment groups, and increases in somnolence and extrapyramidal symptoms in the aripiprazole arms compared to placebo.
- The CHMP limited the indication for aripiprazole to adolescents aged 13 or over due to safety concerns in younger patients.

5.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

Safety assessment was not the primary objective of the RCTs outlined in Section 5.3.

5.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

NCT00110461

In study NCT00110461, daily doses of both aripiprazole 10 mg and 30 mg were generally safe and well-tolerated in children and adolescents with bipolar I disorder. In both treatment arms the majority of treatment-emergent adverse events (TEAEs) were mild or moderate in severity. There were no deaths or suicides during the study. Adverse events occurring in ≥5% of any group in the acute phase of the study are presented in Table B36, [redacted]

[redacted]

Differences between the treatment groups in the incidence of clinically significant weight gain (≥7% weight gain compared to baseline) and change from baseline in BMI were not statistically significant at week 4 (Table B37). [redacted] such changes were overall not clinically relevant based on z-scores and shift tables.[7] Weight z-score describes how similar a subject is to same age and same gender peers by measuring the number of standard deviations from the expected weight. Overall, the mean changes in weight z-scores and BMI z-scores for each visit were within 0.5 standard deviations of the population for all three treatment arms (Table B37 and Table B39), showing that patients remained within normal limits for this population.[7]

There were no increases in serum prolactin level, with prolactin levels in all treatment groups falling over the 30-week duration of the study (Table B37 and Table B39).[7] This decrease in prolactin levels across all groups is likely due to the fact that a substantial proportion of the patient population had previously been treated with other antipsychotics (57.4%) and therefore may have had an elevated prolactin level at baseline.[5] In contrast, somnolence and extrapyramidal symptoms occurred more frequently in patients receiving aripiprazole than placebo. These adverse events were reported at a higher rate in patients receiving the higher, 30 mg dose of aripiprazole. However, the vast majority of cases were of mild to moderate severity, and are expected to be manageable.[56, 61]

Adverse events from study NCT00110461

Table B36 Adverse events across the acute phase of study NCT00110461[5, 61]

System organ/ class/adverse events	Time period 1: Acute phase (up to week 4)						
	Aripiprazole 10 mg: N (%) of patients (n = 98)	Aripiprazole 30 mg: N (%) of patients (n = 99)	Placebo: N (%) of patients (n = 97)	Relative risk for aripiprazole 10 mg (95% CI)	Risk difference for aripiprazole 10 mg	Relative risk for aripiprazole 30 mg (95% CI)	Risk difference for aripiprazole 30 mg
Mortality							
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	N.A.	0.00	N.A.	0.00
Suicide	0 (0.0)	0 (0.0)	0 (0.0)	N.A.	0.00	N.A.	0.00
Adverse events							
Total AEs	72 (73.5)	75 (75.8)	57 (58.8)	1.25 (1.02 – 1.53)	14.70	1.29 (1.06 – 1.58)	17.00
Total SAEs	5 (5.1)	2 (2.0)	5 (5.2)	0.98 (0.29 – 3.27)	-0.10	0.38 (0.08 – 1.94)	-3.20
Extrapyramidal disorder	12 (12.2)	27 (27.3)	3 (3.1)	3.94 (1.15 – 13.50)	9.10	8.81 (2.77 – 28.04)	24.20
Somnolence	19 (19.4)	26 (26.3)	3 (3.1)	6.26 (1.92 – 20.44)	16.30	8.48 (2.66 – 27.08)	23.20
Fatigue	13 (13.3)	9 (9.1)	4 (4.1)	3.24 (1.09 – 20.44)	9.20	2.22 (0.71 – 6.98)	5.00
Headache	17 (17.3)	19 (19.2)	16 (16.5)	1.05 (0.56 – 1.95)	0.80	1.16 (0.64 – 2.13)	2.70
Akathisia	8 (8.2)	11 (11.1)	2 (2.1)	3.90 (0.86 – 17.71)	6.10	5.29 (1.22 – 22.96)	9.00
Nausea	9 (9.2)	12 (12.1)	4 (4.1)	2.24 (0.71 – 7.06)	5.10	2.95 (0.98 – 8.86)	8.00
Vomiting	8 (8.2)	7 (7.1)	9 (9.3)	0.88 (0.36 – 2.19)	-1.10	0.76 (0.30 – 1.97)	-2.20
Blurred vision	8 (8.2)	8 (8.1)	0 (0.0)	N.A.	8.20	N.A.	8.10
Salivary hypersecretion	3 (3.1)	8 (8.1)	0 (0.0)	N.A.	3.10	N.A.	8.10
Decreased appetite	6 (6.1)	3 (3.0)	3 (3.1)	1.97 (0.51 – 7.64)	3.00	0.97 (0.20 – 4.69)	-0.10
Dizziness	5 (5.1)	5 (5.1)	1 (1.0)	5.10 (0.59 – 44.07)	4.10	5.10 (0.59 – 43.99)	4.10
Increased appetite	2 (2.0)	5 (5.1)	3 (3.1)	0.65 (0.11 – 3.82)	-1.10	1.65 (0.41 – 6.67)	2.00
Upper abdominal pain	4 (4.1)	5 (5.1)	3 (3.1)	1.32 (0.30 – 5.74)	1.00	1.65 (0.41 – 6.67)	2.00

Dystonia	0 (0.0)	5 (5.1)	0 (0.0)	N.A.	0.00	N.A.	5.10
Exacerbation of bipolar disorder	0 (0.0)	3 (3.0)	5 (5.2)	N.A.	-5.20	0.58 (0.14 – 2.35)	-2.20
Extrapyramidal symptom categories							
Dystonic event (dystonia and muscle spasms)	0 (0.0)	7 (7.0)	2 (2.0)	N.A.	-2.00	3.50 (0.73 – 16.78)	5.00
Parkinsonism event (extrapyramidal disorder, bradykinesia and tremor)	14 (14.2)	29 (29.2)	4 (4.1)	3.46 (1.18 – 10.18)	10.10	7.12 (2.59 – 19.56)	25.10
Dyskinetic event	2 (2.0)	0 (0.0)	0 (0.0)	N.A.	2.00	N.A.	0.00
Residual event (muscle twitching)	1 (1.0)	1 (1.0)	0 (0.0)	N.A.	1.00	N.A.	1.00
Akathisia event (akathisia and psychomotor activation)	8 (8.1)	12 (12.1)	2 (2.0)	4.05 (0.86 – 19.98)	6.10	6.05 (1.36 – 26.87)	10.10
Any extrapyramidal symptom event	23 (23.5)	39 (39.4)	7 (7.2)	3.26 (1.47 – 7.26)	16.30	5.47 (2.57 – 11.64)	32.20

CI = confidence interval; N.A. = not available

Dystonic event: dystonia, emprosthotonos, muscle contractions involuntary, muscle rigidity, muscle spasms, muscle spasticity, myotonia, nuchal rigidity, oculogyration, opisthotonos, pleurothotonus, risus sardonicus, torticollis, trismus

Parkinsonism event: akinesia, asterixis, athetosis, bradykinesia, cogwheel rigidity, essential tremor, extrapyramidal disorder, freezing phenomenon, hypertonia, hypokinesia, hypokinesia neonatal, intention tremor, masked facies, Parkinson's disease, parkinsonian crisis, parkinsonian gait, parkinsonian rest tremor, parkinsonism, tremor, tremor neonatal

Akathisia event: akathisia, hyperkinesias, psychomotor hyperactivity, hyperkinesias neonatal

Dyskinetic event: ballismus, buccoglossal syndrome, choreoathetosis, clumsiness, dyskinesia, dyskinesia neonatal, dyskinesia esophageal, fumbling, on-and-off phenomena, tardive dyskinesia, head titubation

Residual event: chorea, Huntington's chorea, muscle twitching, myoclonus, clonus

Subjects with multiple adverse event terms within the same category counted only once toward the total. Subjects with extrapyramidal symptom events within multiple categories counted only once toward the total.

Adapted from European Public Assessment Reports published by the European Medicines Agency

Table B37 Changes in baseline metabolic parameters in the acute phase of study NCT00110461[5, 61]

		Placebo		Aripiprazole 10 mg/day		Aripiprazole 30 mg/day		p value vs. placebo
		N	Value	N	Value	N	Value	
BMI	Change from baseline to week 4, mean (SD), kg/m^2	65	0.1 (0.8)	75	0.2 (0.8)*	72	0.3 (1.1)*	*N.S.
	Subjects with BMI >95th percentile for age and gender, n (%)							
	Baseline	97	30 (30.9)	98	27 (27.6)	99	27 (27.3)	
	Week 4	65	18 (27.7)	75	22 (29.3)	72	24 (33.3)	
	Subjects with BMI change from normal at baseline to abnormal (>95th percentile) at week 4, n (%)	46	2 (4.3)	53	1 (1.9)	48	0	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Body weight	Change from baseline to week 4, mean (SD), kg	65	0.56 (2.14)	75	0.82 (1.69)*	73	1.08 (2.27)*	*N.S.
	Incidence of potentially clinically significant weight gain at week 4 (≥7%), n (%)	65	3 (4.6)	75	3 (4.0)*	73	9 (12.3)*	*N.S.
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Prolactin level	Mean (SD), ng/mL							
	Males – baseline	54	6.65 (5.70)	52	5.42 (3.39)	51	5.92 (3.89)	
	Males – change at week 4	37	-0.11 (6.35)	37	-3.35 (3.49)	31	-4.23 (4.47)	
	Females – baseline	43	10.6 (11.3)	46	12.2 (12.9)	48	7.7 (4.0)	
	Females – change at week 4	26	-2.69 (12.58)	31	-5.74 (13.78)	37	-1.59 (5.21)	

Table B38 Adverse events across the acute and extension phases of study NCT00110461[61]

System organ/ class/adverse events	Time period 2: Acute + extension phases (up to week 30)						
	Aripiprazole 10 mg: % of patients (n = 98)	Aripiprazole 30 mg: % of patients (n = 99)	Placebo: % of patients (n = 97)	Relative risk for aripiprazole 10 mg (95% CI)	Risk difference for aripiprazole 10 mg	Relative risk for aripiprazole 30 mg (95% CI)	Risk difference for aripiprazole 30 mg
Mortality							
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suicide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events							
Total AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total SAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extrapyramidal disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Akathisia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blurred vision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Salivary hypersecretion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Upper abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dystonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation of bipolar disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperinsulinemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertriglyceridemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extrapyramidal symptom categories							
Dystonic event (dystonia and muscle spasms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parkinsonism event (extrapyramidal disorder, bradykinesia and tremor)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyskinetic event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Residual event (muscle twitching)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Akathisia event (akathisia and psychomotor activation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; N.A. = not available

Dystonic event: dystonia, emprosthotonos, muscle contractions involuntary, muscle rigidity, muscle spasms, muscle spasticity, myotonia, nuchal rigidity, oculogyration, opisthotonos, pleurothotonus, risus sardonicus, torticollis, trismus

Parkinsonism event: akinesia, asterixis, athetosis, bradykinesia, cogwheel rigidity, essential tremor, extrapyramidal disorder, freezing phenomenon, hypertonia, hypokinesia, hypokinesia neonatal, intention tremor, masked facies, Parkinson's disease, parkinsonian crisis, parkinsonian gait, parkinsonian rest tremor, parkinsonism, tremor, tremor neonatal

Akathisia event: akathisia, hyperkinesias, psychomotor hyperactivity, hyperkinesias neonatal

Dyskinetic event: ballismus, buccoglossal syndrome, choreoathetosis, clumsiness, dyskinesia, dyskinesia neonatal, dyskinesia esophageal, fumbling, on-and-off phenomena, tardive dyskinesia, head titubation

Residual event: chorea, Huntington's chorea, muscle twitching, myoclonus, clonus

Subjects with multiple adverse event terms within the same category counted only once toward the total. Subjects with extrapyramidal symptom events within multiple

categories counted only once toward the total.

Adapted from European Public Assessment Reports published by the European Medicines Agency

Table B39 Changes in baseline metabolic parameters in the extension phase of study NCT00110461[61]

		Placebo		Aripiprazole 10 mg/day		Aripiprazole 30 mg/day		p value vs. placebo
		N	Value	N	Value	N	Value	
BMI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Body weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Prolactin level, mean (SD), ng/mL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Safety subgroup analysis by age at week 12

Post-hoc analyses were performed to assess the safety profile across the age groups of 10-12 and 13-17 year olds. These subgroup analyses were performed at week 12 to match the 12-week treatment period stated in the licence. The overall AE profile is presented in Table B40. EPS-SAS (SAS: Simpson Angus Scale) and EPS-AIMS (AIM:Abnormal Involuntary Movement Scale Scale) mean changes are presented for 10-12 years and 13-17 years groups in Table B41 and Table B42. Mean change from baseline in weight gain and BMI by age subgroups are presented in Table B43 and Table B44. These data are the basis of the CHMP's decision to limit the indication for aripiprazole in paediatric bipolar I disorder to adolescents aged 13 and over.

Table B40 TEAEs ≥5% in subjects 10-12 years versus 13-17 years (week 12)

	10-12 years			13-17 years		
MedDRA Term	**Arip 10 mg N= 32 n (%)**	**Arip 30 mg N= 40 n (%)**	**Placebo N= 39 n (%)**	**Arip 10 mg N= 66 n (%)**	**Arip 30 mg N= 59 n (%)**	**Placebo N= 58 n (%)**
Vision blurred	2 (6.3)	4 (10.0)	0	7 (10.6)	4 (6.8)	0
Abodominal Pain upper	2 (6.3)	3 (7.5)	1 (2.6)	6 (9.1)	2 (3.4)	2 (3.4)
Diarrhoea	0	2 (5.0)	0	4 (6.1)	3 (5.1)	0
Nausea	5 (15.6)	6 (15.0)	0	8 (12.1)	8 (13.6)	5 (8.6)
Salivary Hypersecretion	1 (3.1)	3 (7.5)	0	2 (3.0)	5 (8.5)	0
Stomach discomfort	1 (3.1)	2 (5.0)	2 (5.1)	1 (1.5)	4 (6.8)	0
Vomiting	5 (15.6)	4 (10.0)	3 (7.7)	7 (10.6)	4 (6.8)	6 (10.3)
Fatigue	4 (12.5)	3 (7.5)	2 (5.1)	12 (18.2)	8 (13.6)	2 (3.4)
Pyrexia	2 (6.3)	2 (5.0)	0	-	-	-
Gastroenteritis viral	0	1 (2.5)	2 (5.1)	1 (1.5)	3 (5.1)	0
Influenza	0	0	2 (5.1)	-	-	-
Nasopharyngitis	4 (12.5)	1 (2.5)	1 (2.6)	-	-	-
Upper respiratory tract infection	2 (6.3)	2 (5.0)	1 (2.6)	3 (4.5)	1 (1.7)	2 (3.4)
Blood creatinine phosphokinase increased	-	-	-	1 (1.5)	4 (6.8)	0
Weight increased	2 (6.3)	3 (7.5)	0	5 (7.6)	2 (3.4)	1 (1.7)
Decreased appetite	1 (3.1)	3 (7.5)	0	6 (9.1)	1 (1.7)	3 (5.2)
Increased appetite	2 (6.3)	4 (10.0)	1 (2.6)	3 (4.5)	3 (5.1)	2 (3.4)
Arthralgia	1 (3.1)	2 (5.0)	0	-	-	-
Neck pain	2 (6.3)	0	0	-	-	-
Pain in extremity	0	2 (5.0)	0	-	-	-
Akathisia	-	-	-	8 (12.1)	12 (20.3)	1 (1.7)
Dizziness	-	-	-	7 (10.6)	4 (6.8)	1 (1.7)
Dystonia	-	-	-	1 (1.5)	5 (8.5)	0
Extrapyramidal disorder	6 (18.8)	10 (25.0)	2 (5.1)	6 (9.1)	17 (28.8)	1 (1.7)
Headache	5 (15.6)	9 (22.5)	4 (10.3)	14 (21.2)	13 (22.0)	14 (24.1)
Lethargy	1 (3.1)	2 (5.0)	0	-	-	-
Sedation	2 (6.3)	0	0	-	-	-
Somnolence	5 (15.6)	11 (27.5)	0	19 (28.8)	16 (27.1)	3 (5.2)

Table B41 EPS-AIMS, mean changes from baseline by age group (week 12)

Visit/week	10-12 years						13-17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
OC												
Baseline	31	0.0	40	0.1	36	0.1	65	0.1	59	0.0	58	0.2
Week 4	25	-0.1	30	-0.1	26	-0.1	53	-0.0	45	0.1	41	-0.0
Week 12	17	0.0	17	0.0	7	0.0	34	-0.1	25	-0.1	13	-0.1
LOCF												
Baseline	31	0.0	40	0.1	36	0.1	65	0.1	59	0.0	58	0.2
Week 4	31	-0.1	40	-0.1	34	0.1	65	-0.0	59	0.1	58	0.0
Week 12	31	-0.1	40	-0.1	36	0.0	65	-0.1*	59	-0.1	58	0.0
* p < 0.05, ** p < 0.001 vs. Placebo												

[a] a negative mean indicates improvement

Table B42 EPS-SAS, mean changes from baseline by age group (week 12)

Visit/week	10-12 years						13-17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
OC												
Baseline	30	10.1	40	10.3	36	10.2	65	10.2	59	10.3	58	10.2
Week 4	24	1.0	30	1.8*	26	-0.2	53	0.3	45	1.0*	41	-0.0
Week 12	16	-0.3	17	0.6	7	-0.2	34	0.2	25	0.3	13	-0.1
LOCF												
Baseline	30	10.1	40	10.3	36	10.2	65	10.2	59	10.3	58	10.2
Week 4	30	1.3	40	1.6*	34	-0.1	65	0.2	59	0.9**	58	-0.1
Week 12	30	0.1	40	1.1*	36	-0.0	65	0.2	59	0.7*	58	-0.1
* p < 0.05, ** p < 0.001 vs. Placebo												

[a] a negative mean indicates improvement

Table B43 Mean weight change (in kg) from baseline by age group (week 12)

Visit/week	10-12 years						13-17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
OC												
Baseline	32		40		39		66		59		58	
Week 4	26	1.2	31	1.4*	26	0.4	49	0.6	42	0.9	39	0.7
Week 12	16	2.8	16	4.0*	7	0.8	33	2.6*	25	2.1	14	0.2
LOCF												
Baseline	32		40		39		66		59		58	
Week 4	30	0.9	39	1.2	37	0.3	65	0.4	57	0.7	55	0.7
Week 12	30	2.2*	39	2.6**	37	0.4	65	1.6*	57	1.3	55	0.5
* p < 0.05, ** p < 0.001 vs. Placebo (Aripiprazole 10 mg and Aripiprazole 30 mg treatment group)												

Table B44 Body mass index (kg/m^2), mean changes from baseline by age group (week 12)

Visit/week	10-12 years						13-17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
OC												
Baseline	32		40		39		66		59		58	
Week 4	26	0.5	30	0.5*	26	0.0	49	0.1	42	0.2	39	0.2
Week 12	16	0.9	16	1.4*	7	0.0	33	0.8*	25	0.4	14	0.0
LOCF												
Baseline	32		40		39		66		59		58	
Week 4	30	0.3	38	0.5*	37	-0.0	65	0.0	57	0.1	55	0.2
Week 12	30	0.7*	38	0.9**	37	0.0	65	0.4	57	0.3	55	0.1
* $p < 0.05$, ** $p < 0.001$ vs. Placebo (Aripiprazole 10 mg, and Aripiprazole 30 mg treatment group)												

NCT00116259[57]

Similarly to study NCT00110461, study NCT00116259 reported that aripiprazole had an acceptable safety profile.[57] It was also reported that somnolence and extrapyramidal symptoms were increased in the aripiprazole group relative to placebo (Figure B15). In contrast, weight gain and BMI changes were not significantly different between the aripiprazole and placebo groups between baseline and week 6 (Table B45).

The incidence of adverse events in both treatment groups is illustrated in Figure B15, while changes from baseline in BMI and weight gain are presented in Table B45.

Figure B15 The incidence of treatment-emergent adverse events at any time in study NCT00116259[57]

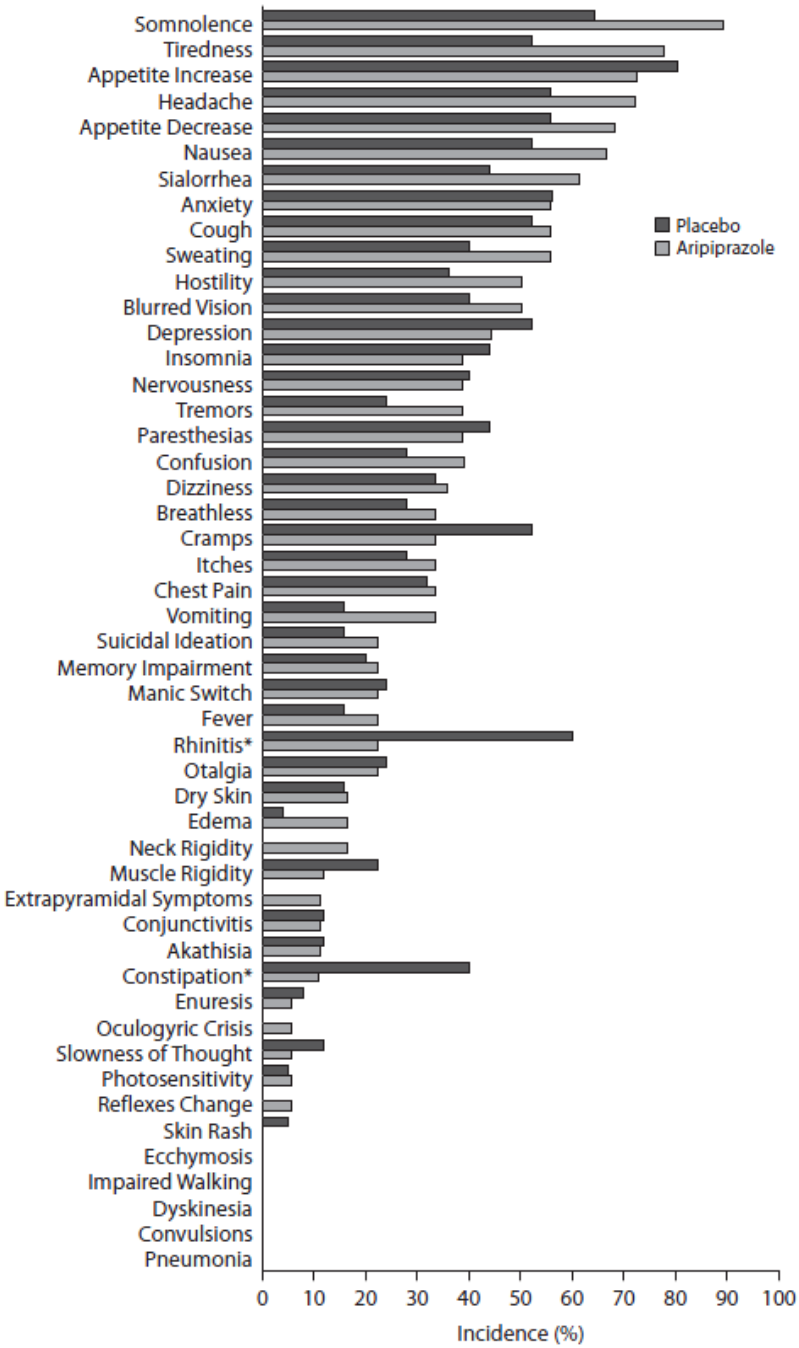


Table B45 Changes in baseline metabolic parameters in study NCT00116259[57, 70]

		Placebo		Aripiprazole 5-20 mg/day		Effect size	95% Confidence Intervals	p value vs. placebo
		N	Value	N	Value			
BMI	[redacted]		[redacted]		[redacted]			
	Change from baseline in BMI at week 3, mean (SD)	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	p=0.49
Body weight	[redacted]	N.R.	[redacted]	N.R.	[redacted]	N.R.	N.R.	N.R.
	Change from baseline to week 6, mean (SD), kg	N.R.	0.72		1.2	0.35	0.26 to 0.96	p=0.25
	[redacted]		[redacted]		[redacted]			

All data was from Tramontina et al (2009)[57] unless otherwise indicated

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

It has been demonstrated in the large, pivotal RCT NCT00110461 and the small RCT NCT00116259 that aripiprazole has an acceptable safety profile.[5, 57] With regards to certain adverse events such as weight gain and prolactin levels, it has also been established that the safety profile is favourable compared to that of both placebo and other atypical antipsychotic agents. For example, in the 30 mg and 10 mg aripiprazole arms compared to placebo, study NCT00110461 demonstrated that the incidence of clinically significant weight gain (≥7%) was not significantly different in the 30 mg and 10 mg aripiprazole arms compared to placebo (12.3% and 4.6% vs. 4.0%, respectively).[5] Prolactin levels also did not increase over the duration of the study, and fell in all treatment groups. The indirect comparison established that aripiprazole was superior to both olanzapine and quetiapine in terms of weight gain, and was also superior to the other atypical antipsychotics regarding prolactin levels (specifically olanzapine, risperidone and quetiapine).

The improved performance of aripiprazole in these respects compared with other agents is particularly significant due to the fact that children and adolescents are more prone than adults to weight gain and side effects associated with prolactin increases (see Section 2.1).[29-31] Weight gain in children and adolescents is also associated with additional long-term health risks and personal issues regarding body image.

While in both studies somnolence and extrapyramidal symptoms occurred more frequently in patients receiving aripiprazole than placebo, there were no significant differences compared to other atypical antipsychotics for these two outcomes. In addition, the large majority of cases in study NCT00110461 tended to be mild-to-moderate, and were expected to be manageable.

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The efficacy of aripiprazole in the treatment of manic or mixed episodes of bipolar I disorder in children and adolescents has been established in a large, well-designed RCT (study NCT00110461).[5, 61] Daily doses of 10 mg and 30 mg aripiprazole both proved significantly more efficacious than placebo in affecting a resolution of manic symptoms as measured by YMRS total score as early as week 1 and continuing through to week 30. Response rates (the proportion of patients experiencing a ≥50% reduction in manic symptoms from baseline YMRS) were also significantly higher in the groups receiving daily doses of aripiprazole 10 mg and 30 mg compared to placebo during both the acute and extension phases.[5, 6, 61]

As well as significant improvements in the resolution of manic symptoms, aripiprazole also effected significant improvements in psychological, social and school functioning as measured by the CGAS, severity of illness for mania and overall bipolar illness as measured by the CGI-BP, and mood-related behaviours as reported by both patients and their parents using the GBI (see Section 5.5.3).

The indirect comparison described in Section 5.7 determined that the acute efficacy of aripiprazole in terms of YMRS response rate is comparable to that of other atypical antipsychotics at week 2 (specifically olanzapine and risperidone). There may additionally be a trend for improved efficacy of aripiprazole compared to certain agents at weeks 1 and 3 (week 1: olanzapine and risperidone; week 3: olanzapine and quetiapine), although there was no significant difference. As a result, in terms of efficacy, aripiprazole is at least equivalent to the other atypical antipsychotics.

A trend was additionally seen with regards to improvements in quality of life in both aripiprazole arms on the PQ-LES-Q(T) and (O) scales across the acute and extension phases of the trial (see Section 5.5).[37, 61]

As well as proven efficacy, aripiprazole has demonstrated an acceptable safety profile for patient aged 13-17, with low weight gain and no increase in serum prolactin levels, which is particularly useful for treating adolescents.

Between baseline and week 4, mean weight change from baseline was not significantly different between the two aripiprazole groups and placebo.[5] Mean change from baseline in BMI at weeks 4 and 30 and the incidence of clinically significant weight gain were also not significantly different between groups.[5, 6, 61] The indirect comparison established that aripiprazole was superior to both olanzapine and quetiapine in terms of weight gain, and was also superior to the other atypical antipsychotics regarding prolactin levels (specifically olanzapine, risperidone and quetiapine).

The favourable safety profile of aripiprazole with respect to these adverse events is particularly significant because children and adolescents are more prone than adults to weight gain and side effects associated with prolactin increases as a result of antipsychotic therapy (see Section 2.1).[29-31] Weight gain in children and adolescents is associated with both personal issues regarding body image and long-term health risks, such as increased risk for diabetes and heart disease, which impact the health care system. Prolactin elevations also have numerous physiologic manifestations including amenorrhea, abnormal bone resorption, delayed puberty and short stature. All of these adverse events, which are more common in other atypical antipsychotics than in aripiprazole, could reduce medication compliance, potentially leading to relapse.

In contrast, somnolence and extrapyramidal symptoms occurred more frequently in patients receiving aripiprazole than placebo.[5] These adverse events were reported particularly in patients receiving the higher 30 mg daily dose of aripiprazole. As the highest recommended adult dose of 30 mg rarely needs to be prescribed beyond the acute phase, even within the adult population, it is expected that the optimal efficacy and safety profile for children and adolescents will be derived from an aripiprazole dose lower than this. In the long-term extension of NCT00110461, the average maintenance dose was 15.9-16.8 mg.[7] It was also the case that the rate of many adverse events, such as extrapyramidal symptoms and somnolence, declined over time, with the majority of events occurring in the first four weeks of the study as opposed to in the long-term extension phase.

The cases of somnolence and sedation that occurred in study NCT00110461 tended to be mild to moderate, transient and tolerable, and in most cases did not lead to treatment discontinuation.[56, 61] Extrapyramidal symptoms similarly tended to be mild or moderate in nature, and are expected to be easily managed with the help of prescription medication if required.[61]

To conclude, aripiprazole offers a licensed treatment with proven efficacy and an acceptable safety profile in patients aged 13-17 in both the short and the long-term. The safety profile of aripiprazole in the short-term compares favourably to that of the other atypical antipsychotics in several important respects, whilst aripiprazole is the only atypical antipsychotic for which long-term safety data exists. In addition, aripiprazole supports the quality of life of children and adolescents suffering from this debilitating, chronic condition which endangers their development at a crucial stage of their lives.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths of the clinical evidence base

The major strength of the clinical evidence base for aripiprazole under consideration in this submission is the availability of data from a well-designed, large pivotal RCT in the population of interest (NCT00110461).[5] Furthermore, it presents the only long term RCT safety data published to date for any atypical antipsychotic in children and adolescents with bipolar disorder.

Limitations of the clinical evidence base

The main clinical evidence base is limited to one large RCT (NCT00110461), as the other RCT identified (NCT00116259) was a small trial with only 18 patients receiving aripiprazole.[57] Although included in the meta-analysis, this study does not contribute substantially to the evidence base.

The pivotal RCT NCT00110461 included patients aged 10 to 12, which are outside of the licence for aripiprazole. This therefore meant that subgroup analyses had to be conducted on the trial population to demonstrate efficacy in the age group 13-17.

One further limitation is that neither study NCT00110461 nor NCT00116259 are UK-specific, NCT00110461 being conducted exclusively in the US, and NCT00116259 being conducted in Brazil.[5, 57] The generalisability of results obtained in the US to a UK population is considered in Section 5.10.4.

For informing the decision problem, the major limitation of the study design is that patients continued treatment to week 30 and therefore there are no data on relapse rates when patients stop treatment at week 12 as per the licence.

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The inclusion criteria of study NCT00110461 allowed the participation of patients with co-morbidities such as ADHD (153 patients, 51.7%) and ODD (93 patients, 31.4%),[5] which is likely to reflect the population seen in clinical practice (see Section 2.1).[20]

In addition, the outcomes reported in study NCT00110461 are highly relevant to patients in clinical practice and are therefore relevant to the decision problem. As described in Section 1.3.5, many of the outcome measures have been validated and found to demonstrate high internal consistency and test-retest reliability. Although the YMRS total score is not expected to be used directly by practicing clinicians, it is widely accepted as an appropriate instrument for measuring treatment response in clinical trials. Furthermore, results reported for the CGI-BP, which is commonly used by practicing clinicians,[63] illustrated the same improvement attributable to aripiprazole as seen with the YMRS (Table B9 and Table B95). The YMRS measures a wide range of symptoms applicable to bipolar disorder, the improvement of which are directly relevant to clinical benefits experienced by patients. Aripiprazole has been shown to specifically and significantly improve the following symptoms measured by the YMRS: elevated mood, increased motor activity/energy, need for sleep, irritability, speech, language/thought disorder, abnormal thought content and disruptive/aggressive behaviour.[52] In addition, experts agreed that the YMRS is the best available measure of clinical response, which can then inform treatment decisions in clinical practice (Appendix 14).[2-4]

As well as measuring relevant efficacy outcomes, outcomes measured included important adverse events such as weight gain and prolactin increases. These adverse events were less likely to occur with aripiprazole than with other atypical antipsychotics. In addition, quality of life was measured, and a trend for improvement with aripiprazole identified.

In contrast, caregiver outcomes, such as caregiver quality of life, were not measured in the study.

5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the

technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Conduct of the trials

Study NCT00110461 investigated dosing schedules of aripiprazole that would be administered in clinical practice. Patients were also allowed to receive benzodiazepine and anticholinergic therapy for the treatment of extrapyramidal symptoms,[5] as would be expected to occur in clinical practice.

Some differences in clinical practice between the US and the UK mean that most patients in the trial were out-patients, seen once a week for out-patient visits. Only [redacted].[61] In contrast, all children experiencing a manic episode in the UK would be expected to be hospitalised. An inpatient setting is likely to give rise to increased monitoring, resulting in better management of response to adverse events through daily dose adjustment and prescribing of other medication. Patients in the UK would therefore be expected to have improved outcomes compared to US patients included in the trial, although there is no evidence to support this claim.

Inclusion and exclusion criteria

Certain inclusion and exclusion criteria utilised in study NCT00110461 were necessary in order to enrol a homogenous population in which treatment effects could be observed. However, such criteria may have reduced the external validity of the trial population. For example, patients were only allowed to have failed one previous antipsychotic treatment of adequate dose and duration; such patients would not be excluded from receiving aripiprazole in clinical practice. In addition, patients were excluded if they had an inability to swallow tablets whole; however, orodispersible tablets and an oral solution are now available for aripiprazole. The inclusion of these latter patients would not be expected to influence any efficacy conclusions.

The fact that the included participants of study NCT00110461 were not UK-based may be a limiting factor with regards to external validity, as the diagnosis of bipolar disorder in adolescents can be different in the US compared to the UK.[21]

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

A systematic review was designed to identify all relevant cost-effectiveness information available for the treatment of acute manic and mixed episodes in bipolar I disorder in children and adolescents. The review was based on the search and inclusion strategy of a previous systematic review (commissioned by NICE in 2005),[47] to identify more recent cost-effectiveness studies in bipolar disorder.

The previous review identified six studies.[47] However, five were in adults (Tohen 1999[84], Zajecka 2002[85], Tohen 2002[86], Revicki 2005[87] and Keck 1996[88]). Bridle 2004 did include one study in children in their de novo economic model;[89] however, as the majority of included studies were in adults, the economic evaluation does not report any useful results pertinent to this submission. Therefore, none of these studies met the inclusion criteria for the current systematic review and were not included.

Databases were searched to include studies published from 2005 to present. A list of databases is provided in Appendix 10. The search terms were taken from a previous systematic review commissioned by NICE in 2005 (Appendix 10).[47] Whilst the searches were performed to identify data in children, the economic evidence for bipolar disorder in children and adolescents may be scarce. Therefore the search terms were not limited to children and studies in adults were captured separately during the review process.

The inclusion criteria were as follows:

- Patients with manic or mixed episodes of bipolar disorder.

- Includes patients aged <18 (studies including patients ≥18 were collected separately).
- Full economic evaluation (including cost-consequence, cost-minimisation, cost-effectiveness, cost-utility and cost-benefit evaluations) that compares two or more interventions.
- At least one of the interventions studied must be a pharmacological agent.
- Study must be from an OECD country, as the aim of the review is to identify economic information transferable to the UK context.
- Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed and the study's data and results must be extractable.

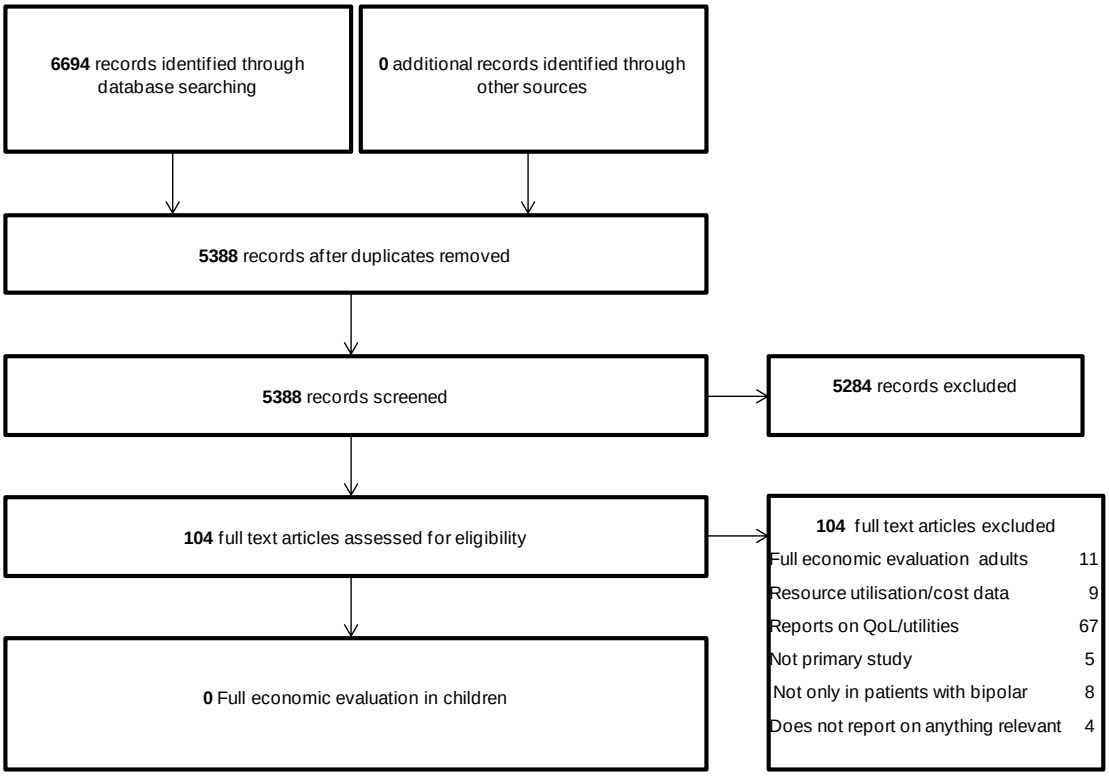
Results from the searches described above were de-duplicated and reviewed twice: once using the abstracts and then more rigorously using full texts for the inclusion criteria listed previously.

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

No published cost-effectiveness analyses in children with bipolar I disorder were identified (Table B46). Eleven studies which described full economic evaluations in adults with bipolar disorder were identified; however, they did not provide any further information to inform the de novo economic model that had been previously identified from other sources.

Table B46 Number of economic evaluations included and excluded



6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated

instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

No full economic evaluations were identified for interventions for bipolar disorder in children or adolescents.

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The patient population considered in this economic evaluation is children and adolescents with manic episodes of bipolar I disorder between the ages of 13 and 17 years, reflecting the licence for which aripiprazole has received positive CHMP opinion (Section 1.5). The age of onset implemented in the model is 15 years, which is the expected average age of a cohort of 13 to 17 year olds.

The efficacy data used in the model for aripiprazole was derived from the whole study NCT00110461 population, which was aged 10-17 and therefore included patients aged 10-12 who are outside of the licence for aripiprazole. The justification for using the efficacy data from the whole population is fourfold:

1. The full population is a larger dataset and therefore the analysis is more highly powered.

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[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

2. The efficacy of aripiprazole was consistent across age groups (Table B13 to Table B15), and therefore the efficacy data from the whole population can be used to represent the 13-17 subgroup.

3. The age subgroup of 13-17 years was a post-hoc rather than pre-specified subgroup.

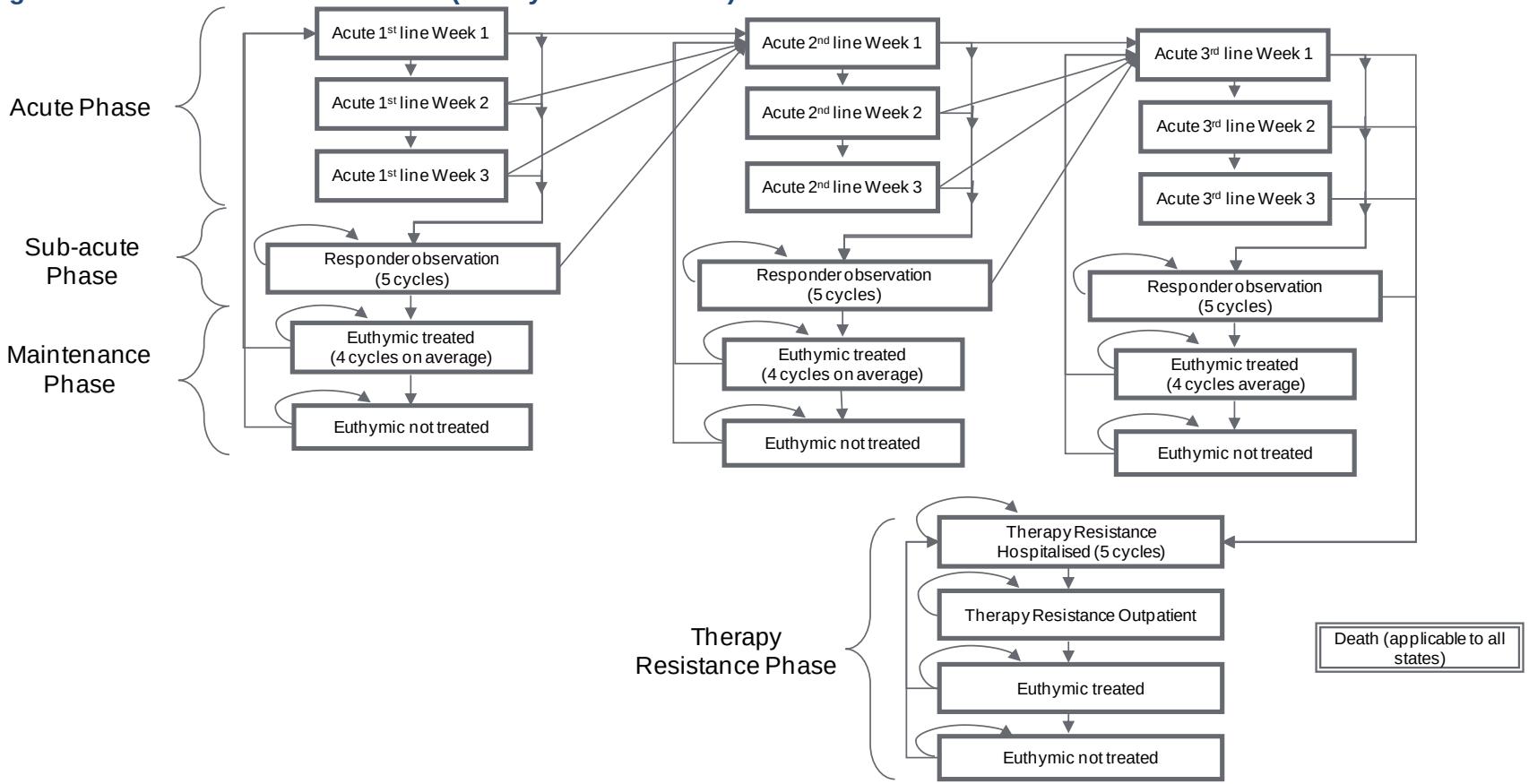
4. Analysis on YMRS response was not performed by age subgroup and therefore the age subgroup of 13-17 could not be used in NMA and compared to the other atypical antipsychotics.

The safety data was also taken from the whole population, rather than the age subgroup of 13-17 due to the fact that the age subgroup data became available too late in the submission process for it to be used in the NMA and therefore the model. The use of the whole population safety outcomes in the model is a conservative approach for aripiprazole, as the CHMP have concluded that safety outcomes such as EPS and weight gain are more pronounced in the age subgroup of 10-12, who are excluded from the licence.

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

Figure B16 Markov Model Schematic (one cycle = one week)



6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The chosen structure of the economic model is a Markov state transition model considering 23 different health states, including death. A Markov model was chosen as it was considered the most appropriate model to reflect the complicated therapy pathway, which includes 3 lines of therapy, as well as the change in states from acute mania to response to euthymia.

The model is comprised of three distinct phases which reflect the treatment pattern for children and adolescents with bipolar I disorder:

4. The **acute** phase where the patient is treated as an inpatient in hospital to manage their acute manic event. Patients who do not respond by week 3 enter acute second or third line week 1. When patients have responded they remain in hospital under observation until they are stabilised. Patients can relapse from this state into acute treatment second or third line week 1.
5. The **maintenance (euthymic)** phase, where patients are discharged from hospital and remain on treatment for an average of 4 further weeks (giving a maximum treatment length on one therapy of 12 weeks) before being taken off treatment. Patients can relapse from these states back into the acute inpatient phase at week 1.
6. The **therapy resistance** phase, where patients have not responded to three lines of therapy. Patients are maintained on lithium only. Patients cannot move back into earlier states in the model from therapy resistance.

Acute phase

Patients enter the model while they are experiencing an acute manic episode and are hospitalised for treatment. The 3 week inpatient acute mania phase reflects the length of treatment in the comparator pivotal clinical trials. Patients initially receive first line therapy for a one week cycle; if they respond to treatment (defined as a 50% change in the YMRS score) at the end of week 1 they move to the responder observation phase. If they do not respond at week 1, patients can receive a further 2 weeks of therapy, and if they respond to treatment at the end of week 2 or week 3 they move into the responder observation phase. If the patient fails first line therapy (i.e. dropped out of first-line treatment), at week 1, 2 or 3, or has not responded by

the third week they are switched to a second line of therapy, beginning again at week 1.

Patients who respond to therapy in the first 3 weeks of the acute phase then enter the ‘responder observation’ state. In this state, patients are still in hospital, but they have responded to therapy and are under observation to ensure that their response is maintained and their condition is stabilised before discharge. Based on expert opinion (Section 9.14, Appendix 14), children and adolescents are modelled to remain in this state for 5 weeks until being discharged from hospital and into the post-acute phase (modelled through tunnel states). Therefore first line responders are hospitalised for 6, 7 or 8 weeks, depending on whether they responded at week 1, 2 or 3, respectively.

Second line therapy and third line therapy follow the same pattern described above. Patients who do not respond to third line therapy move to the “therapy resistance” phase.

Maintenance (euthymic) phase

In the maintenance (euthymic) phase, patients who have responded to therapy are discharged from hospital and re-enter the community.

Patients initially enter the euthymic treated state where they remain on treatment for an average of 4 further cycles, giving a total treatment period of 10-12 weeks.

From the euthymic treated state, patients may either relapse into the acute manic state, or move into the euthymic not treated state, where patients are no longer on antipsychotic treatment. Patients will either remain in this state, or may relapse to the acute mania state. Depressive relapses are not modelled, as the atypical antipsychotics including aripiprazole are not specifically licensed for the treatment of these in bipolar I disorder.

Patients who relapse are assumed to receive the treatment to which they initially responded, irrespective of whether they relapse from the euthymic treated or non-treated states. It is likely that dose elevation and close monitoring of treatment compliance when back in hospital would re-initiate the response to that medication.

Therapy resistance phase

Patients in the therapy resistance state have not responded to any of the three drugs in the acute phase. Expert opinion suggests that the number of patients who are deemed as “therapy resistant” is very small and that these patients are comparatively rare in clinical practice in the UK (Appendix 14). This is likely due to the fact that patients are kept hospitalised for an average of 2 months in order to facilitate close monitoring, which would result in lower discontinuation rates and possibly better responses than seen in clinical trials where the majority of patients are not hospitalised.

Patients are modelled as being maintained on lithium in the therapy resistant state, as lithium has a licence for treatment of this patient population and clinical expert opinion was that symptomatic patients would not go un-treated even if they did not fully respond to standard therapy (Appendix 14). Although lithium monotherapy use may be relatively rare in clinical practice, patients in the model were not maintained on their third line therapy due to the fact that a significant proportion of patients (approximately 25% by the end of the model) reach therapy resistance. This is a product of using a dichotomous response criterion to predict failure of treatment and using discontinuation rates from the trials, and therefore does not reflect clinical practice. Therefore maintenance on third line therapy would unfairly disadvantage that treatment and would not provide a clinically meaningful comparison of treatments.

From the therapy resistant outpatient state, patients can spontaneously respond and move to the euthymic treated and then the not treated states (if they do not experience a relapse). This was incorporated into the model based on the clinical trial data, where a small proportion of placebo patients experienced a response, demonstrating that spontaneous resolution of symptoms can occur.

As patients have failed all the therapies in the model, they cannot return to any of the other treatment phases once they have entered the therapy failure phase.

Death

Patients can die in any state. Bipolar-specific mortality rates are applied to the model in an age-dependent manner (see Section 6.3.3, Table B53).

6.2.4 Please define what the health states in the model are meant to capture.

The health states in the model relate to the treatment and hospitalisation status of the patient; whether they are on or off treatment, and whether they are in- or out-patients.

Acute manic states

The acute manic phase is designed to capture the following:

- The existence of manic symptoms, which is reflected in the utility applied to the acute manic states (see Section 6.4.9).
- Inpatient status, which is reflected in both the utility applied to acute manic states (see Section 6.4.9) and the costs of inpatient stay (see Section 6.5.6).
- Risk of adverse events, including EPS, somnolence and weight gain. This is reflected by adjusting the utility applied to these states for each treatment by the relative incidences of the adverse events for each treatment (see Sections 6.3.1, 6.4.8 and 6.4.9).

Subacute state (responder observation)

The subacute, responder observation state is designed to capture the following aspects:

- Response to treatment and therefore the resolution of manic symptoms, which is reflected in the utility applied to this state (see Section 6.4.9)
- Inpatient status, which is important as the risks of relapse and adverse events are high soon after initial response and therefore close monitoring and dose adjustment is required. Inpatients status is reflected in both utilities and costs (see Sections 6.4.9 and 6.5.6).
- Risk of adverse events, including EPS, somnolence and weight gain. This is reflected by adjusting the utility applied to this state for each treatment by the

relative incidences of the adverse events for each treatment (see Sections 6.3.1, 6.4.8 and 6.4.9).

Euthymic treated state

The euthymic state where patients are still on treatment is designed to capture the following:

- Lack of severe manic symptoms, but not reached the level of HRQoL of the general population due to having to take medication and the risk of minor or major symptom relapses. This is reflected in the utility applied to this state (Section 6.4.9).
- Outpatient care, which is reflected in the resource use and costs for this state, such as outpatient consultant visits (Section 6.5.6).
- Risk of weight gain. This is reflected by adjusting the utility applied to this state for each treatment by the relative incidences of weight gain for each treatment (Sections 6.3.1, 6.4.8 and 6.4.9).

Euthymic not-treated state

The euthymic state where patients are no longer treated is designed to capture the following:

- Lack of severe manic symptoms, but not reached the level of HRQoL of the general population due to the risk of minor or major symptom relapses. This is reflected in the utility applied to this state (Section 6.4.9).
- Outpatient care, which is reflected in the resource use and costs for this state, such as outpatient consultant visits (Section 6.5.6).
- No risk of adverse events.
- A higher risk of relapse of acute symptoms than for the euthymic treated state (Section 6.3.5).

Therapy resistance phase

The therapy resistance phase captures all patients who do not respond to three lines of atypical antipsychotic therapy, and is designed to incorporate the following aspects:

- Residual manic symptoms. There may be some improvement from baseline in symptoms, but patients have not achieved a sufficient symptomatic change to be classed as responders. This is reflected in the utility applied to the therapy resistant states (see Section 6.4.9).
- There is both an inpatient and outpatient state within the therapy resistance phase, where utilities and costs are changed accordingly.

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The main characteristics of the condition are described in Section 2.1. This model structure represents the acute phase, where the short cycle length reflects the rapid changes in disease states that can occur in children and adolescents. As discussed in Section 2.1, patients with bipolar I disorder who have had a manic episode can recover from this episode and reach a euthymic state which is represented in the maintenance phase of the model. However, relapse is common and is modelled using an ongoing probability of relapse back into the acute mania phase. As also discussed in Section 2.1, children and adolescents may be more prone to adverse events than adults, particularly the long-term health risks associated with weight gain, and therefore the model takes into account side effects associated with treatment where possible.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table B47 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	3 years	The time horizon used in the model is 3 years, which follows patients entering the model at aged 15 until adulthood, where treatment management options will differ as stated in the NICE clinical guidelines for bipolar disorder. Therefore this time horizon is deemed to sufficiently capture the important cost and health benefit differences between the technologies for the adolescent population. Additionally, due to the limited long-term data available for this indication a lifetime time horizon was not deemed to be appropriate, as extrapolation of short term results over a longer time horizon may introduce significant bias and uncertainty into the model.	NICE CG38 clinical guideline[1] NICE methods guide 2008
Cycle length	1 week	This short cycle length reflects the frequency of assessments in the acute phase of the clinical trials. The main outcome of YMRS response is reported weekly and drives the transition probabilities between the states in the first 3 weeks of the acute treatment phase.	Clinical trials[5, 19, 29, 76]
Half-cycle correction	None	Half-cycle correction was not applied in the base case. It can be applied in the economic model by selecting this option in the Index sheet.	Not applicable
Were health effects measured in QALYs; if not, what was used?	QALY	As discussed in the decision problem	NICE methods guide
Discount of 3.5% for utilities and costs	3.5%	As discussed in the decision problem	NICE methods guide
Perspective (NHS/PSS)	NHS/PSS	As discussed in the decision problem	NICE methods guide
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Three treatment strategies including aripiprazole (as a first, second and third line therapy) are compared to a strategy that does not include aripiprazole. The treatments strategies are listed below in Table B48. An alternative order of olanzapine and quetiapine is investigated in the scenario analysis (Section 6.7.9).

Table B48 Treatment strategies compared in the model

Strategy no.	1st line	2nd line	3rd line
1 (usual care)	Risperidone	Quetiapine	Olanzapine
2	Risperidone	Aripiprazole	Quetiapine
3	Aripiprazole	Risperidone	Quetiapine
4	Risperidone	Quetiapine	Aripiprazole

Currently, the only licensed therapy for adolescents with bipolar I disorder is lithium, which is licensed for those aged 12 years and older.[1] However, guidelines from the Royal College of Paediatrics and Child Health (2000) stated that other, unlicensed medications could be prescribed for children and adolescents if there are no suitable alternatives and if the use of the medication is justified by a responsible body of professional opinion. [90]

Based on the above recommendations, the list of relevant comparators to be used in the model is expanded to include atypical antipsychotics. Furthermore, through expert consultation, the main comparators to aripiprazole are expected to be risperidone, quetiapine and olanzapine (see Section 2.6). Whilst the use of these therapies is technically outsides their licenses, it is accepted that the use of atypical antipsychotics (including aripiprazole) for paediatric bipolar I disorder is widespread in the UK. Including these unlicensed comparators in the model increases the relevance of the economic model to clinical practice within the NHS.

Aripiprazole is expected to be licensed at a dose of 10 mg per day, which can be increased with strict monitoring. Dosing can be varied throughout the patient's

treatment course to reach the optimal balance between maximising response and minimising adverse events. However, modelling dosing change would further complicate the current model and would not significantly increase the accuracy of the resulting analysis. Therefore, for the base case analysis, the efficacy and safety results of the 10 mg and 30 mg aripiprazole arms were pooled. The costs for these two doses were also averaged. The un-pooled results and costs for the 10 mg dose are investigated in a scenario analysis.

Although the pooled dose may be a good approximation of the average dose (and therefore of the average efficacy and safety) in the acute manic phase, it is likely that patients in the sub-acute and maintenance phases would on average receive a lower dose than this. Therefore the base case of the model may overestimate aripiprazole costs associated with the sub-acute and maintenance phases.

Where comparator trials reported data from multiple doses, results and costs were also pooled for the base case analysis. The dose ranges of these comparators assessed in their respective RCTs were all within the range licensed for their use in adults.

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the ‘response’ criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.

- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

No continuation rule has been assumed in the model.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

Treatment effects implemented in the model were derived from the network meta-analysis of RCTs (Section 5.7). Treatment discontinuation and response were analysed separately. Discontinuation and YMRS response were estimated at weeks 1, 2 and 3. These estimates were combined and implemented in the economic model using the methods described below.

Treatment response/no response:

Response to treatment is determined in the economic analysis by a 50% reduction in YMRS score. This is in line with the outcomes obtained from the clinical trials. Probabilities of response derived from the network meta-analyses at weeks 1, 2 and 3 (Section 5.7.6) are used for all drugs evaluated in the model. Median point estimates of cumulative response at each time point (presented in Table B49) were used in the base case deterministic analysis. Methods used to preserve correlated outputs from the NMAs conducted at each time point are described in greater detail in section 5.7.5. These were transformed into transition probabilities using methods outlined in section 6.3.2.

Table B49 Cumulative probabilities of response during treatment of acute mania

	Cumulative probability of responding		
Drug	**Week 1**	**Week 2**	**Week 3**
Placebo (a)	0.080	0.192	0.246
Aripiprazole	0.281	0.507	0.591
Risperidone	0.239	0.504	0.601
Quetiapine (b)	0.222	0.401	0.467
Olanzapine	0.209	0.517	0.523

(a) placebo was not used in the model, but is presented here for reference
(b) in the absence of week 1 or 2 response data for QTP, treatment effect compared to ARI at week 3 assumed to be same at weeks 1 and 2

Hypothetical patients responding at each time point - week 1, 2 or 3 - move into a sub-acute, observation health state ('responder observation'). Patients that do not respond by week 3 are assigned to the next treatment in the sequence where a similar process follows.

Treatment effects are assumed to be independent; that is response and non-response to a given treatment is independent of when or where it comes in a treatment sequence, including after a recurrent acute manic episode. This assumption is necessary due to the lack of sequence specific data. It is not clear whether patients who had not responded to one atypical antipsychotic would be less likely to respond to another; if this is the case, the model would over-estimate treatment effects for second and third line therapies.

Discontinuation

Probabilities of treatment discontinuation at week 3 were also derived from the network meta-analysis (5.7). Median point estimates of cumulative discontinuation at week 3 (presented in Table B50) were used in the base case deterministic analysis. Methods used to preserve correlated outputs from the NMA are described in greater detail in section 5.7.5. These were transformed into transition probabilities using methods outlined in section 6.3.2.

Due to lack of evidence on the discontinuation at week 1 and 2 for all comparators, the analysis uses data from the pivotal aripiprazole trial (NCT00110461) to determine

the relationship between discontinuation at weeks 1 and 2 compared to week 3 (see Table B51). In the pivotal aripiprazole RCT, results showed that of all patients discontinuing by week 3, 60.23% had done so by week 2.[61] Similarly, the results showed that of all patients who discontinued by week 2, 19.42% had done so by the end of week 1. These proportions were thus applied to the week 3 probabilities of discontinuation for risperidone, quetiapine and olanzapine from the network meta-analysis in order to derive discontinuation rates at weeks 1 and 2 for all drugs.

Table B50 Cumulative discontinuation for all drugs based on results of NMA

Drug	RR vs placebo (a)	Prob disc wk 3	Prob disc 2 (RR vs wk 3 = 0.602) (b)	Prob disc 1 (RR vs wk 2 = 0.194) (c)
Placebo	1	0.241	0.145	0.028
ARI	0.730	0.176	0.106	0.021
RIS	0.878	0.212	0.128	0.025
QTP	0.698	0.168	0.102	0.020
OLA	0.544	0.131	0.079	0.015

Disc = discontinuation
(a) Outputs from NMA of discontinuation at week 3
(b) Derived by multiplying week 3 probability by aripiprazole-derived RR for week 2 vs week 3 responders from Table B51 .
(c) Derived by multiplying week 2 probability by aripiprazole-derived RR for week 1 vs week 2 responders from Table B51.

Table B51 Cumulative discontinuation from placebo observed in NCT00110461

Week of treatment	Cumulative discontinuation	Responders wk T / responders wk T-1
Week 1	0.020	
Week 2	0.103	0.194
Week 3	0.171	0.602

Source: Clinical Study Report Aripiprazole pivotal RCT[61]

Hypothetical patients discontinuing treatment at each time point - week 1, 2 or 3 - move on to the next treatment in the sequence where a similar process follows.

Relapse

Recurrent acute episode (i.e. relapse) could occur at any point after initial response. The relapse risks during the sub-acute and euthymic phases were based on expert opinion (see Section 6.3.5 and Appendix 14 for further details):

- 5% while on treatment: 0.57% weekly during responder observation and euthymic treated states (based on 9 weeks in total across responder observation and euthymic treated)
- 15% during the 6 months following coming off treatment: 0.67% weekly during euthymic not-treated state

Patients who relapse during the responder observation sub-acute state are assumed to move on to the next drug in the treatment sequence. Patients who relapse following a period of euthymia on or off treatment are assumed to resume the same treatment as that to which they previously responded.

Adverse events

Adverse events included in the model were based on data observed from the clinical trials for EPS, weight gain, and somnolence. The weekly incidence of each AE and the relative differences across treatments was estimated from a network meta-analysis in a similar way as for the efficacy parameters (see Section 5.7.6, Table B30). In the network meta-analysis, the 4-week incidence of AEs for aripiprazole was compared to the 3-week incidence of AEs for the other atypical antipsychotics without adjustment. This may disadvantage aripiprazole.

The olanzapine RCT did not report the incidence of EPS or somnolence,[29] so in the model this was set equal to the lowest other estimate for each AE, which was risperidone in both cases.

The incidence of these adverse events was used to weight average costs and utilities according to treatment and health state.

Mortality risk

Mortality risk of patients included in the model is assumed to be greater than the mortality risk of the general population (Section 6.3.3) and is applied to weekly transitions. The pivotal aripiprazole RCT reported no deaths over the 30-week

course of the study,[66] and none of the other atypical antipsychotic RCTs reported on the risk of mortality or suicide, so no mortality difference between treatments could justifiably be included in the model.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Acute mania

Cumulative probabilities for response and discontinuation (presented in Table B50and Table B51) from the network meta-analyses were transformed into conditional weekly transition probabilities. The probability of responding or discontinuing during week 2 is calculated as the cumulative probability of responding or discontinuing at week 2 conditional upon having not responded or discontinued at week 1.

For example, the transition probability of discontinuing treatment during week 2, is estimated as follows:

$$\frac{(cumulative_pDisc_wk2 - cumulative_pDisc_wk1)}{(1 - cumulative_pResp_wk1 - cumulative_pDisc_wk1)}$$

Similarly, the transition probabilities of responding or discontinuing during week 3 were conditional upon having not responded or discontinued during weeks 1 or 2.

Base case transition probabilities during the acute mania stage calculated in this way are presented for all drugs in Table B52.

Table B52 Transition probabilities during acute mania

Drug	Transition probabilities acute								
	Week 1			Week 2			Week 3		
	pResp	pDisc	pCont	pResp	pDisc	pCont	pResp	pDisc	pCont
Aripiprazole	0.281	0.021	0.698	0.323	0.122	0.554	0.217	0.181	0.602
Risperidone	0.239	0.025	0.736	0.360	0.140	0.500	0.263	0.229	0.508

Quetiapine	0.222	0.020	0.758	0.236	0.108	0.657	0.133	0.135	0.732
Olanzapine	0.209	0.015	0.775	0.397	0.082	0.520	0.015	0.129	0.856
pResp: probability of response; pDisc: probability of discontinuation; pCont: probability of continuation									

Sub-acute state (responder observation)

Patients responding to treatment during the acute mania phase are assumed to stay in hospital and continue treatment during a 5-week sub-acute phase. During this time, they may relapse to acute mania. Based on expert opinion, 5% of patients entering this sub-acute phase will relapse over the 5 weeks in this state and the 4 weeks in the euthymic treated state (Appendix 14). If the true transition rate is assumed to be constant over the corresponding time period, then the probability P_j can be estimated by:

$$P_j = 1 - \left[1 - P_{(t_0, t_j)}\right]^{\frac{1}{j}}$$

where *p* is the probability and j represents a number of equal time intervals (i.e. weeks). The weekly probability of relapse is estimated to be 0.57%. Patients who relapse move to the acute state week 1 of the next therapy in the sequence. No data was available to differentiate this risk between drugs; therefore, the same value was applied for all drugs.

Patients who do not relapse to acute mania during this 5-week sub-acute period are assumed to reach a euthymic state and be discharged from hospital. Tunnel states have been used to implement these time-in-state dependent transitions.

Euthymic treated

Patients who have reached the stable, euthymic phase continue treatment and continue to face a risk of recurrent acute mania. Using the same assumptions and formula as above, the weekly probability of relapse during this phase is estimated to be 0.57%.

Patients in the stable, treated state will also stop treatment and remain euthymic after some time. It is assumed that on average, euthymic patients will discontinue treatment after 4 weeks, to reach a total treatment period of between 10 and 12

weeks on one therapy. Using the same assumptions and formula as above, the weekly probability of discontinuing treatment and maintaining euthymia is estimated to be 15.9%. No data was available to differentiate this risk between drugs; therefore, the same value was applied for all drugs.

Euthymic not treated

Patients who have discontinued treatment following a period of stable euthymia face a risk of recurrent acute mania. Based on expert opinion, their risk off-treatment is assumed to be slightly higher than on-treatment (15% over 6 months) (Appendix 14). Using the same assumptions and formula as above, the weekly probability of relapse is estimated to be 0.67%.

Treatment resistance

Patients who have exhausted all three drugs in a given sequence are classified as treatment resistant. Patients reaching this stage are assumed to receive lithium and remain in hospital for 5 weeks. After 5 weeks, they are discharged and are assumed to be managed on an outpatient basis. A small proportion of these patients are expected to reach spontaneous euthymia following outpatient management. According to Findling 2007,[6] approximately 24.4% of placebo patients are expected to reach euthymia over 6 months. This rate of spontaneous resolution, derived from placebo-treated patients, is assumed in the model to be appropriate for therapy resistant patients. Also assuming this transition occurs at a constant rate, this translates to a weekly probability of 1.07%. Following a period of euthymia on treatment (lithium), patients may discontinue treatment and maintain euthymia.

Patients may relapse to acute mania from any of these outpatient states and return to hospital. The probabilities of relapsing from these states are the same as those outlined in the preceding sections.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Effectiveness over time

Discontinuation rates would be expected to vary considerably over time in the acute phase, as this is the period when patients are switched to different treatments due to adverse events or non-response. Data was not available for week 1 or 2 discontinuation rates for risperidone, quetiapine or olanzapine; therefore, the ratio of discontinuation rate for week 3 vs 2 and week 2 vs 1 were taken from the aripiprazole data and applied across all comparators (Section 6.3.1).

Response rates would also be expected to change over the first few weeks and then level off (as demonstrated by the long term aripiprazole clinical data, see Figure B6).[5] Therefore, where data was available, comparative estimates of response rate for each comparator were applied for week 1, 2 and 3. Where data at weeks 1 and 2 were not available (for quetiapine only), the week 3 RR of quetiapine vs aripiprazole was applied to the week 1 and 2 aripiprazole response rates. It was assumed that no-one would respond beyond week 3, based on the aripiprazole clinical data and also the lack of comparative RCT data for risperidone, quetiapine and olanzapine beyond week 3. No extrapolation of clinical trial data was necessary.

Expert opinion suggested that the risk of relapse may vary as a function of time and whether the patient is on or off ongoing maintenance treatment (Appendix 14). The weekly risk of relapse to acute mania is slightly higher if the patient discontinues maintenance treatment. There are no published RCT data for risperidone, quetiapine or olanzapine beyond week 3 and therefore it was assumed that all atypical antipsychotics would have equal effectiveness in terms of relapse rate. This assumption is justified because there were no statistically significant differences in response rate in the short term, indicating comparative effectiveness between atypical antipsychotics. Data from adult bipolar disorder also indicates that aripiprazole and olanzapine are similar in terms of long term prevention of relapse.[91] Finally, the assumption of equal risk of relapse for all comparators in the model ensures that the differences in acute phase effectiveness drive the model results, making it better reflect a comparison of acute treatment.

Adverse event probabilities over time

Somnolence often occurs only in the short-term after treatment initiation, and both somnolence and EPS are expected to be manageable. If they are not managed through dose attenuation, then the patient switches therapy (expert opinion) (Appendix 14); this switching in therapy has been captured in the model using the total discontinuation rates for the first 3 weeks of the clinical trials for all comparators. Therefore experts believed that somnolence and EPS would not develop beyond the acute phase (Appendix 14). This is also supported by the aripiprazole trial data, where most instances of EPS and somnolence occurred in the first 4 weeks of the trial (Section 5.9.2). In the model, this has been incorporated by only applying utility weightings for EPS and somnolence to the acute inpatient phase of the model. Costs for the management of EPS and somnolence were assumed to be captured within costs for hospitalisation.

Expert opinion was that weight gain is a longer term adverse event (Appendix 14), and therefore the probability of experiencing clinically significant weight gain was applied to the whole period on treatment.

Mortality over time

Mortality rates will vary over time as the patient cohort ages. In the model, age-specific mortality rates are applied for each successive year. UK age and gender specific mortality rates of the general population were taken from the Office of National Statistics[92] and adjusted to bipolar-specific mortality rates through multiplying by the ratios provided by Laursen et al 2007.[93] Laursen et al 2007 reported that males and females with bipolar disorder under the age of 24 had a 10.09 and 24.93 times higher mortality rate, respectively, than the general population.[93] Overall mortality rates were then calculated for each year of the model based on a starting age in the model of 15 and 53.7% male (latter based on the NCT00110461 baseline population). The mortality rates applied in the model are displayed below in Table B53.

Table B53 Mortality rates applied in the model

Age in model	Annual mortality rate
15	0.0030
16	0.0036
17	0.0043

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Intermediate outcome measures were not used in this model. The main outcome measure considered was the response rate based on a 50% change from baseline in YMRS score, which is a validated instrument for assessing the clinical symptoms of bipolar I disorder. Clinical experts validated that the use of the YMRS scale to measure response was the most appropriate approach to use (Appendix 14).

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Due to the limited published data on children and adolescents in this indication, clinical experts were asked to assess the applicability of several model inputs. Initially, 23 experts in the field of child and adolescent psychiatry in the UK were

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

approached via email, including 22 consultant psychiatrists and 1 psychiatric nurse consultant, of which 10 replied to initial contact. Of those who replied, 3 experts, who had no potential conflicts of interest and were available for a telephone interview, were able to take part in the validation exercise, all of whom were Consultant Child and Adolescent Psychiatrists. Each expert was sent a briefing document which outlined the basic model structure, the aims of the clinical validation and a list of the questions that would be discussed during the telephone interview. These questions covered the model structure, resource use inputs and utility inputs. Opinions on these questions were obtained during a 60 minute telephone interview, where answers to each question were recorded for each advisor. Full details of the questions asked and responses from each expert are provided in Appendix 14.

The responses from the experts regarding utilities, resource utilisation and adverse events are discussed elsewhere in this section (6.4.10, 6.5.4 and 6.5.7 respectively). Of particular relevance to this section are the questions posed to the experts regarding the model structure. The detailed responses from the experts are summarised in Appendix 14.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table B54 List of all variables included in the cost-effectiveness analysis

Parameter	Summary statistics		Sampling Distribution	Distribution parameters		Assumptions/Notes/ Source
	Median	SE		Lognormal: Mean / Beta: alpha / Gamma: alpha	Lognormal: SE / Beta: beta / Gamma: beta	
Discontinuation (Section 6.3.2)						
RR vs placebo at week 3 (RR_wk3_disc)						
ARP	0.7301		Coda			NMA of discontinuation at week 3
RIS	0.8787		Coda			
QTP	0.6977		Coda			
OLA	0.5442		Coda			
Proportion of wk 3 disc occurring by wk 2 (RRwk2_vs_wk3_disc)						
All drugs	0.6023	0.1205	Beta	9.34	6.17	Assume SE = 20%; Source: CSR - Aripiprazole pivotal RCT
Proportion of wk 2 disc occurring by wk 1 (RRwk1_vs_wk2_disc)						
All drugs	0.1942	0.0388	Beta	19.95	82.80	Assume SE = 20%; Source: CSR - Aripiprazole pivotal RCT
Probability of discontinuation at week 3 (pDisc_wk3)						
Placebo	0.2414		Coda			NMA of discontinuation at week 3
ARP	0.1762		Generated			=pDisc_wk3_placebo * RR_wk3_disc
RIS	0.2121		Generated			
QTP	0.1684		Generated			
OLA	0.1314		Generated			
Probability of discontinuation at week 2 (pDisc_wk2)						
Placebo	0.1454		Generated			=pDisc_wk3 * RRwk2_vs_wk3_disc
ARP	0.1062		Generated			
RIS	0.1278		Generated			
QTP	0.1014		Generated			
OLA	0.0791		Generated			
Probability of discontinuation at week 1 (pDisc_wk1)						
Placebo	0.0282		Generated			=pDisc_wk2 * RRwk1_vs_wk2_disc
ARP	0.0206		Generated			
RIS	0.0248		Generated			
QTP	0.0197		Generated			
OLA	0.0154		Generated			
YMRS response (Section 6.3.2)						
Probability of response at week 3 (pResp_wk3)						
Placebo	0.2456		Coda			Source: NMA of YMRS response at week 3
ARP	0.5908		Coda			
RIS	0.6007		Coda			
QTP	0.467		Coda			

OLA	0.5234		Coda			
Proportion of wk 3 responders responding by wk 2 (RRwk2_vs_wk3_resp) (a)						
Placebo	0.7818	0.1564	Beta	4.67	1.30	Assume SE = 20%
ARP	0.8579	0.1716	Beta	2.70	0.45	Assume SE = 20%
RIS	0.8386	0.1677	Beta	3.20	0.62	Assume SE = 20%
QTP	0.8579	0.1716				In the absence of data at weeks 1 and 2, assumed to be equal to ARI
OLA	0.9885	0.0198	Beta	27.69	0.32	Assume SE = 2%
Probability of response at week 2 (pResp_wk2)						
Placebo	0.1920		Generated			=pResp_wk3 * RRwk2_vs_wk3_resp
ARP	0.5068		Generated			
RIS	0.5037		Generated			
QTP	0.4006		Generated			
OLA	0.5174		Generated			
Proportion of wk 2 responders responding by wk 1 (RRwk1_vs_wk2_resp) (b)						
Placebo	0.4167	0.0833	Beta	14.17	19.83	Assume SE = 20%
ARP	0.5542	0.1108	Beta	10.59	8.52	Assume SE = 20%
RIS	0.4742	0.0948	Beta	12.67	14.05	Assume SE = 20%
QTP	0.5542	0.1108				In the absence of data at weeks 1 and 2, assumed to be equal to ARI
OLA	0.4043	0.0809	Beta	14.49	21.35	Assume SE = 20%
Probability of response at week 1 (pResp_wk1)						
Placebo	0.0800		Generated			=pResp_wk2 * RRwk1_vs_wk2_resp
ARP	0.2809		Generated			
RIS	0.2389		Generated			
QTP	0.2220		Generated			
OLA	0.2092		Generated			

Adverse events (Section 6.3.1)						
EPS						
ARP	0.1578		Coda			NMA of incidence of EPS; in the absence of data for OLA, assumed to be equal to RIS
RIS	0.1117		Coda			
QTP	0.1162		Coda			
OLA	0.1117		Coda			
Weight gain						
ARP	0.03403		Coda			NMA of incidence of weight gain
RIS	0.04083		Coda			
QTP	0.4032		Coda			
OLA	0.4501		Coda			
Somnolence						
ARP	0.4631		Coda			NMA of incidence of somnolence; in the absence of data for OLA, assumed to be equal to RIS
RIS	0.2660		Coda			
QTP	0.2732		Coda			
OLA	0.2660		Coda			
Parameter	**Summary statistics**	**Sampling Distribution**	**Distribution parameters**	**Assumptions/Notes / Source**	**Parameter**	**Summary statistics**
	Mean	**SE**				
Recurrent acute mania (all drugs) (Section 6.3.1) (mean)						
9-wk risk of relapse (sub-acute)	0.05	0.015	Beta	10.51	199.61	Expert opinion
6 month risk of relapse (euthymic not treated)	0.15	0.045	Beta	9.29	52.67	Expert opinion
Treatment Resistant (Section 6.3.2)						
6m prob spontaneous euthymia	0.2440	0.0732	Beta	8.16	25.27	Assume SE = 30%; Source: Kindling 2007
Utility - health state (Section 6.4.9)						
Acute Mania (Life mania score 4)	0.69		Generated (=u_SubAcute*(0.69/0.85))			Source: Hayhurst 2006[94]; assumed to be adjusted for hospitalisation
Sub-acute mania (Life mania score 1)	0.85	0.030	Beta	119.57	21.10	Source: Hayhurst 2006[94]; assumed to be adjusted for hospitalisation
Euthymic treated (Life mania score 1)						Assumed equal to sub-acute mania without hospitalisation adjustment

Euthymic not treated (Life mania score 1)						Assumed equal to sub-acute mania without hospitalisation adjustment
Therapy resistant (Life mania score 3)	0.72		Generated (=u_SubAcute*(0.72/0.85))			Source: Hayhurst 2006[94]; assumed to be adjusted for hospitalisation
Therapy resistant (Life mania score 3)						Assumed equal to Therapy resistant inpatient without hospitalisation adjustment
Decrement associated with Hospitalisation	0.07	0.021	Normal	0.07	0.021	Assumed SE = 30% of mean; source: Mental Health Research Review 2000[95]
Utility – AE (Section 6.4.9)						
Extrapyramidal symptoms	0.722	0.023	Beta	273.22	105.20	Assume SE = 30% of Mean; Source: Briggs 2008[96] (schizophrenia)
Weight gain	0.865	0.004	Beta	6290.25	981.71	Assume mean of 0.89 and 0.84 and SE derived using method http://www.burtonsys.com/climate/composite_standard_deviations.html; Source: Boyle 2010[97]
Somnolence multiplier	0.905	0.0184	Beta	228.91	24.03	Assume SE = 30% of Mean; Source: Heeg 2008[98] (schizophrenia)-
Mental health services costs (Section 6.5.6 and 6.5.7)						
Inpatient day	602.10	0.30	Normal	602.10	0.30	Source: NHS Reference Costs 2010-11: MHIPC1
Initial consultant visit: outpatient setting	419.00	0.59	Normal	419.00	0.59	Source: NHS Reference Costs 2010-11: MHOPFAC2
Follow-up consultant visit: outpatient setting	229.00	0.10	Normal	229.00	0.10	Source: NHS Reference Costs 2010-11: MHOPFUC2
Psychologist visit	135.00	-	-	-	-	Unit Costs of Health and Social Care[99]
CPN visit	60.00	-	-	-	-	Unit Costs of Health and Social Care[99]
Dietician visit	35.00	-	-	-	-	Unit Costs of Health and Social Care[99]
Treatment costs per day (Section 6.5.5)						
Aripiprazole	£5.13	-	-	-	-	BNF (December 2012)
Risperidone	£0.06	-	-	-	-	BNF (December 2012)

Quetiapine	£4.04	-	-	-	-	BNF (December 2012)
Olanzapine	£1.32	-	-	-	-	BNF (December 2012)
Lithium	£0.04					NHS Drug Tariff
Lithium monitoring costs:						
Thyroid monitoring	£17.82 per test	-	-	-	-	Soares-Weiser 2007[100], uprated with NHS Pay & Prices Index 2011[99]
Renal function test	£2.42 per test	-	-	-	-	Soares-Weiser 2007[100], uprated with NHS Pay & Prices Index 2011[99]
Serum lithium level test	£3.12 per test	-	-	-	-	Soares-Weiser 2007[100], uprated with NHS Pay & Prices Index 2011[99]
Resource use per month (Section 6.5.4)						
Consultant psychiatrist visit - euthymic treated	1	-	-	-	-	Expert opinion (Appendix 14)
Consultant psychiatrist visit - euthymic not treated	0.6667	-	-	-	-	Expert opinion (Appendix 14)
Consultant psychiatrist visit - therapy resistant outpatients	2	-	-	-	-	Expert opinion (Appendix 14)
Psychologist visit - euthymic treated	0.5	-	-	-	-	Expert opinion (Appendix 14)
Psychologist visit - therapy resistant outpatients	1	-	-	-	-	Expert opinion (Appendix 14)
Lithium thyroid monitoring	0.167	-	-	-	-	NICE CG38[1]
Lithium renal test	0.167	-	-	-	-	NICE CG38[1]
Lithium serum test	0.333	-	-	-	-	NICE CG38[1]
Weight gain (Section 6.5.7)						
Community psychiatric nurse visit	1 visit per month	-	-	-	-	Expert opinion (Appendix 14)
Dietician	2 additional visits	-	-	-	-	Expert opinion (Appendix 14)

a) derived through a comparison of median responses from NMA of week 3 responders vs NMA of week 2 responders for each drug

b) derived through a comparison of median responses from NMA of week 2 responders vs NMA of week 1 responders for each drug

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

No extrapolation beyond the trial follow-up periods was performed. Long term relapse rates were based on expert opinion due to the lack of trial data (Appendix 14). The aripiprazole clinical trial did not report relapse rate after 12 weeks of treatment, as patients continued on treatment for up to 30 weeks in the trial. For relapse rates on treatment, the clinical definition of what constitutes relapse and requires hospitalisation is likely to change between the US (where the aripiprazole clinical trial was conducted) and the UK. Therefore UK expert opinion was considered to be the most appropriate source.

Long term relapse prevention was assumed to be equal for all atypical antipsychotics (see Section 6.3.3 for further details).

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table B55: Assumptions on clinical parameters and model structure

Assumption	Justification, or reference to section of submission where justification is given
Discontinuation rates from the trials were assumed to reflect the rates of switching to 2nd or 3rd line treatment in weeks 1 and 2.	No data from UK clinical practice are available on discontinuation rates of the atypical antipsychotics in the indication under review.
It was assumed that if the patient had not responded by week 3, the patient would switch treatment.	Expert opinion was that 3 weeks would be long enough to evaluate response or non-response (Section 9.14, Appendix 14).[2-4]
Treatment effects are assumed to be independent; that is response and non-response to a given treatment is independent of when or where it comes in a treatment sequence, including after a recurrent acute manic episode.	No data are available on the response rates of atypical antipsychotics taken as second line agents following a prior atypical antipsychotic.
Efficacy and tolerability of aripiprazole is based on pooled evidence for 10 mg and 30 mg dosing. Sensitivity analysis explores efficacy, tolerability and resource use of 10 mg dosing only. Efficacy and tolerability of the comparators was also based on pooled evidence from different dosage arms of the respective trials.	See Section 6.2.7
Discontinuation of treatment effects for all drugs compared to placebo observed at week 3 are assumed to hold for discontinuation at weeks 1 and 2.	No data are available on the discontinuation rates of risperidone, quetiapine and olanzapine at weeks 1 and 2.
In the absence of data on response at weeks 1 and 2 for QTP, the treatment effect compared to aripiprazole observed at week 3 is assumed to hold for response at weeks 1 and 2.	No other data to inform the model.

The calculation of conditional probabilities is based on the assumption that response and discontinuation are mutually exclusive outcomes. That is, patients who are counted as having discontinued cannot also be counted as having responded and vice versa.	This ensures that the model reflects real-life, where patients cannot both discontinue and respond simultaneously.
Patients cannot enter a euthymic health state before spending at least 5 weeks in the sub-acute responder observation health state.	Based on expert opinion (Appendix 14, Section 9.14)
Patients are maintained on the treatment to which they most recently responded during the acute phases.	Based on expert opinion (Appendix 14, Section 9.14)
Patients who relapse to acute mania during a period of responder observation (sub-acute state) are assumed to move on to the next treatment in the sequence. Patients who relapse from euthymia, on or off treatment, are assumed to receive the treatment to which they most recently responded.	Section 6.2.3
Relapse rate is assumed equal for all atypical antipsychotics.	No data to support otherwise. Section 6.3.3
The relapse rate would be 5% over the 9 weeks responder observation and euthymic treated states and 15% over 6 months in the euthymic not-treated state	Based on expert opinion (Appendix 14,Section 9.14)
Patients who have exhausted all three lines of treatment in the sequence are assumed to receive lithium and are managed for 5 weeks in hospital after which they are managed on an outpatient basis. Patients receiving lithium and being managed on an outpatient	Section 6.2.3

basis have a small probability of spontaneously achieving euthymia.	
The incidence of EPS and somnolence for olanzapine was set equal to the lowest other estimate for each AE, which was risperidone in both cases.	The olanzapine RCT did not report the incidence of EPS or somnolence,[29], so a conservative estimate for olanzapine was made. Section 6.3.1
Bipolar disorder was assumed to increase the mortality risk above that of the general population	Bipolar-specific mortality risk was based on evidence from Laursen 2007[93] Section 6.3.3
No mortality difference was assumed between the different treatments	No data to support otherwise

Table B56: Assumptions on measurement and valuation of health effects

Justification	Justification, or reference to section of submission where justification is given
Health state utilities are estimated based on response to treatment and weighted by incidence of adverse events including EPS, somnolence and weight gain.	Based on the literature reporting utilities for adults with bipolar disorder. Section 6.4.9
Drug-related adverse events including EPS and somnolence are assumed to impact quality of life only during the acute and sub-acute phases, but not maintenance phases of the model.	Based on expert opinion (Appendix 14, Section 9.14) and aripiprazole clinical trial evidence[61] Section 6.3.3
Weight gain is assumed to impact quality of life for the duration of time on a given treatment.	Based on expert opinion (Appendix 14, Section 9.14) Section 6.3.3
Health state utilities follow a rank order (best to worst): Euthymic off treatment (0.91) Euthymic on treatment (0.91) - impacted by AEs	Based on the literature reporting utilities for adults with bipolar disorder, and on the logical ranking of each state. Section 6.4.9

Sub-acute responder observation (0.84) Treatment resistant outpatient (0.77) treatment resistant inpatient (0.71) Acute mania (0.68)	

Table B57: Assumptions on measurement and valuation of costs

Assumption	Justification, or reference to section of submission where justification is given
The cost for aripiprazole during the first week of treatment for acute mania is assumed to be based on an increasing dose of oral solution. Thereafter, oral tablets are used.	Based on the Summary of Product Characteristics for aripiprazole dosing in schizophrenia adolescents.[8] This is expected to be the same for bipolar children and adolescents. Section 6.5.5
Monitoring tests whilst in hospital are assumed to be captured within the hospital costs	The differences between AAs according to the monitoring recommended by NICE would be minimal. Excluding these costs disadvantages aripiprazole
The cost of a consultant psychiatrist (£254) is assumed to be a weighted average of NHS reference cost HRGs for initial visit (£419) and follow-up (£229) visit in an outpatient setting, with weights based on reported activity.	Weights were based on reported activity in the NHS reference costs as no other estimates of the relative activity were available.
Assumptions on resource use are conservative and based on expert opinion.	No other data on resource use specific to children or adolescents with bipolar disorder in the UK available.
Adverse events including EPS, somnolence and weight gain are assumed to accrue no additional costs during acute, inpatient management as these will be covered by the cost of inpatient care.	Section 6.5.7

Weight gain is assumed to incur incremental costs during maintenance treatment (outpatient) for the duration of time on a given treatment.	Based on expert opinion (Appendix 14, Section 9.14) Section 6.5.7

Table B58: Assumptions in exploring uncertainty

Assumption	Justification, or reference to section of submission where justification is given
Due to a lack of data, in PSA, some distribution parameters are assumed based on expert opinion or a reasonable range around the mean.	Lack of data to support otherwise
In the PSA, correlations observed between treatment effects in NMA of response at week 3 are assumed to hold for treatment effects at weeks 1 and 2.	This was implemented to avoid illogical results where more patients respond at week 2 than at week 3. Section 6.6.3

6.4 *Measurement and valuation of health effects*

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

The aspects of the condition deemed most likely to affect the patient are as follows:

- Severity of bipolar symptoms, and the impact these have on daily functioning and social interaction (Section 2.1).[34]
- Hospitalisation, as this would be expected to negatively affect the child or adolescent's quality of life.
- Adverse events, such as somnolence, extrapyramidal symptoms, weight gain and those caused by an increase in prolactin (eg. sexual dysfunctions and reduced bone mass).

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

During a manic episode, the patient would experience a severe decrease in HRQoL. This would likely be partly driven by the negative impact of hospitalisation.

Once treatment is initiated, patients would be expected to have improved symptoms and therefore experience some increase in HRQoL. [36, 37] However, they remain hospitalised until they are stable, which would continue to negatively affect their quality of life. After discharge from hospital, patients are expected to experience an

improvement in HRQoL, but not quite reach the level of the general population.[101] When patients are on treatment, they may experience adverse events, which would further decrease their HRQoL.[87]

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

Of all the studies on atypical antipsychotics identified in Section 5, only the aripiprazole RCT (NCT00110461) reported to have measured quality of life.

HRQoL measurement in study NCT00110461

HRQoL was measured using the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) in study NCT00110461.[37] The PQ-LES-Q is made up of 14 items that assess HRQoL with a total score and a one item overall assessment.[37]

<u>Consistency with reference case and appropriateness for cost-effectiveness analysis</u>

EQ-5D, as stipulated in the reference case, was not employed in the pivotal aripiprazole study. The child-specific HRQoL measurement tool used, PQ-LES-Q, was not designed to generate utility values. A literature search identified only one study that had attempted to map PQ-LES-Q values to utilities; the authors used a rudimentary method and described the analysis as exploratory.[102] Therefore it was deemed that there was no validated method for mapping PQ-LES-Q to utilities. Therefore the use of these HRQoL values for the cost-effectiveness analysis is not possible.

Results

On both the PQ-LES-Q total and overall measures, while the differences to placebo did not reach statistical significance in most cases, both aripiprazole arms demonstrated a trend for improvement relative to placebo (Table B59).[37]

Table B59 Least squares (LS) mean change from baseline in total and overall PQ-LES-Q scores (LOCF analysis)[61]

Across the whole trial population, it was shown that improvement in bipolar I disorder mania symptoms in children and adolescents was significantly associated with an increase in HRQoL (week 4 $r = -0.18$; week 30 $r = -0.29$; $p < 0.03$).[37] This supports the statements made in Sections 6.4.1 and 6.4.2, that mania symptoms negatively affect HRQoL and therefore that an increase in HRQoL would be expected during efficacious treatment.

HRQoL measurement in Delbello 2006[36]

HRQoL was reported from the Delbello 2006 RCT, which compared quetiapine with valproate in the treatment of manic episodes in children and adolescents with bipolar I disorder.[36] Significant improvements in HRQoL, as measured by the Child Health Questionnaire-Parent Form 50 (CHQ-P50) scale, were seen in both treatment arms after 28 days.[36] There is no validated method for mapping CHQ-P50 to utilities.

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

The HRQoL values from studies NCT00110461[103] and DelBello 2006[36] were not mapped to utilities due to the lack of validated mapping techniques.

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

A systematic review was designed to identify all relevant HRQoL information available for the treatment of acute manic and mixed episodes in bipolar I disorder in children and adolescents. The review was based on the same search and inclusion strategy of a previous systematic review (commissioned by NICE in 2005), to identify more recent data on quality of life/utilities data for patients with bipolar disorder.

Databases were searched to include studies from 2005-present. A list of databases is provided in Appendix 12. The search terms were taken from a previous systematic review commissioned by NICE in 2005 [47] (Appendix 12). As the quality of life/utility evidence for bipolar disorder in children and adolescents may be scarce, the search terms were not limited to children and studies in adults were captured separately during the review process.

The inclusion criteria were as follows:

- Patients with manic or mixed episodes of bipolar disorder.

- Includes patients aged <18 (studies including patients ≥18 were collected separately).
- Reports quality of life or utility data.
- Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed and the study's data and results must be extractable.

Results from the searches described above were de-duplicated and reviewed twice: once using the abstracts and then more rigorously using full texts for the inclusion criteria listed previously.

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Table B60 Number of HRQoL/utility studies included and excluded

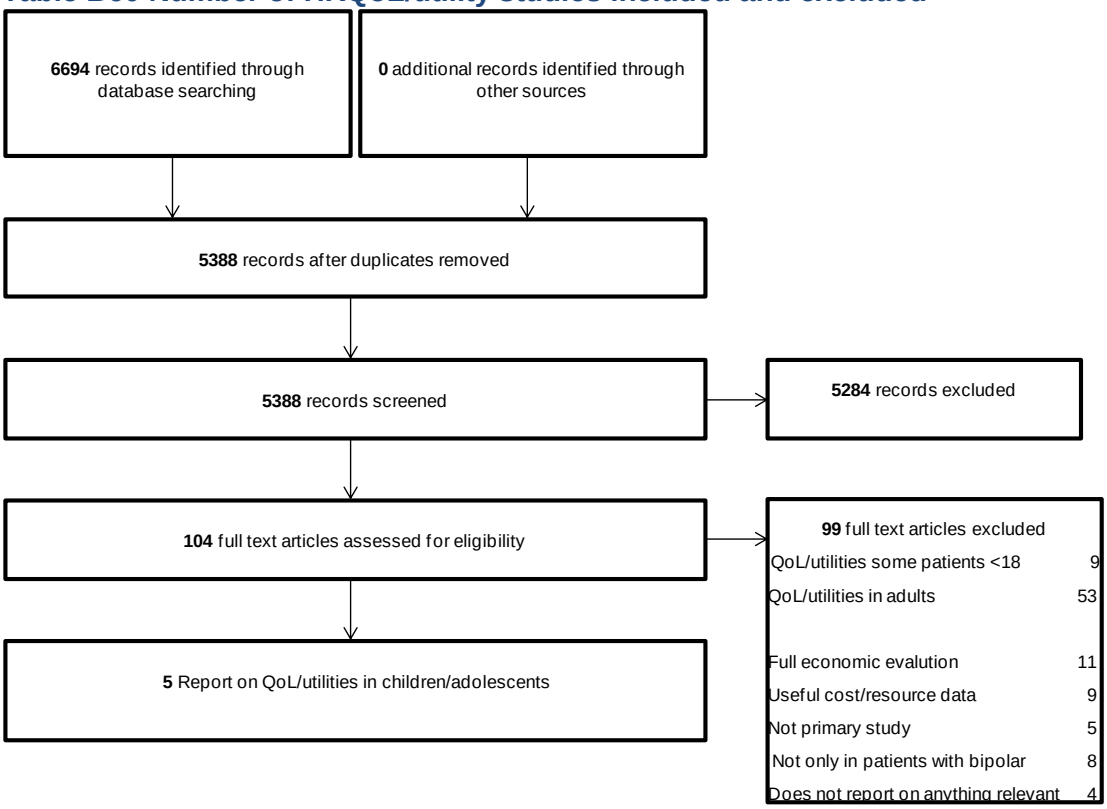


Table B61 List of the HRQoL studies in children and adolescents

	Clayton 2009[104]	Endicott 2009[103]	Freeman 2009[105]	Rademacher 2007[36]	Whitehead 2009[37]
Population	9-18 years with juvenile bipolar disorder	Adolescents with schizophrenia and bipolar	Patients aged 8-18, 17% received bipolar diagnoses	Adolescents with bipolar I, currently manic or mixed	Patients aged 10-17 with bipolar disorder
Information on recruitment	The Bipolar Programme specialist clinic, Australia.	Post hoc analysis of aripiprazole study (NCT00110461[5]).	Recruited from both an urban community health centre (n=402) and an academic medical centre (n=127).	Data collected from later subset of subjects who participated in a clinical trial investigating the efficacy of divalproex vs. quetiapine (DelBello 2006).	Post hoc analysis of aripiprazole study (NCT00110461[5]).
Interventions and comparators	Not applicable	Aripiprazole vs. placebo	Not applicable	Divalproex (n=11) vs. quetiapine (n=12)	Aripiprazole vs. placebo
Sample size	N=16	Schizophrenia N=302, Bipolar N=296	529 youth and caregiver pairs (89 with bipolar disorder)	N=23	N=296
Response rates	100%	NR	65% of patients approached agreed to participate at community site.	23 patients assigned to treatment originally. 18 subjects remained. 5 individuals did not have complete sets of data so could not be used in all of the analyses.	NR
Description of health states	Bipolar disorder in patients at a specialist clinic (NR if inpatient or outpatient)	Largely outpatient bipolar I disorder after treatment for a manic or mixed episode.[5]	Outpatient bipolar disorder	Bipolar I disorder after treatment for a manic or mixed episode. (NR if inpatient or outpatient)	Largely outpatient bipolar I disorder after treatment for a manic or mixed episode.[5]
Adverse events	HRQoL specifically due to adverse events not reported	HRQoL specifically due to adverse events not reported	HRQoL specifically due to adverse events not reported	HRQoL specifically due to adverse events not reported	HRQoL specifically due to adverse events not reported
Appropriateness of health states given condition and	Not specific to manic/mixed episodes, nor bipolar I disorder	Health states are appropriate to the treatment pathway in the model	Not specific to manic/mixed episodes, nor bipolar I disorder	Health states are appropriate to the treatment pathway in the model	Health states are appropriate to the treatment pathway in the model

treatment pathway					
Method of elicitation	PQ-LES-Q	PQ-LES-Q	KINDL-R	CHQ-PF50	PQ-LES-Q
Method of valuation	Utility values were not measured	Utility values were not measured	Utility values were not measured	Utility values were not measured	Utility values were not measured
Mapping	No mapping was performed	No mapping was performed	No mapping was performed	No mapping was performed	No mapping was performed
Uncertainty around values	Small sample size.		Sample not drawn from general paediatric infrastructure. Data derived from parent report, not child report.	Small sample size. Pilot study – did not elect to correct for multiple comparisons. HRQoL measured by parent's ratings.	
Consistency with reference case	None	None	None	None	None
Results with confidence intervals	HRQoL was not significantly negatively related to parent and clinician ratings of mania.	Total score did not reach statistical significance at endpoint. Differences in PQ-LES-Q individual items between schizophrenia and bipolar population. Some items reached significance in 30 mg group.	Youths with bipolar disorder (mean 52.58) had significantly lower HRQOL scores that youths with asthma (73.78*), atopic dermatitis (74.41*), obesity (68.93), arthritis 72.13*), oxygen dependence (63.71*), heart surgery during infancy (76.6*), depression, behaviour disorders and non-mood and non-behaviour psychiatric diagnoses.	Shows significant improvement in most HRQoL subscales following treatment Adolescents with BP have lower than normal HRQoL	Both aripiprazole arms showed improvement on PQ-LES-Q; however they did not reach statistical significance. There was a positive correlation between patient assessed HRQoL and clinician based assessment (trend analysis YMRS p=0.007; CGI-BP p<0.05)
Appropriateness of the study for cost-effectiveness analysis	No utilities suitable for cost-effectiveness analysis	No utilities suitable for cost-effectiveness analysis	No utilities suitable for cost-effectiveness analysis	No utilities suitable for cost-effectiveness analysis	No utilities suitable for cost-effectiveness analysis

Utility results

No studies identified by the systematic review reported utility values for children or adolescents with bipolar disorder. Therefore, the adult papers identified were reviewed. Hayhurst 2006[94] and Revicki 2005[87] were found to report utility values appropriate for the bipolar health states in the model.

In addition, further literature searching identified a UK cohort study that assessed utilities in overweight children.[97] Briggs 2008[96] and Heeg 2008[98] were found to report utilities associated with adverse events in schizophrenia patients.

The choice between these studies is justified in Section 6.4.9.

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The utilities from both Hayhurst et al 2006[94] and Revicki et al 2005[87] demonstrate the same trend as seen from the PQ-LES-Q HRQoL results from study NCT00110461, that HRQoL is associated with bipolar manic symptoms and that improvement of symptoms leads to an increase in HRQoL. This justifies the application of the adult utilities to children and adolescents in the model.

Clinical experts were asked whether they would consider HRQoL in children and adolescents with bipolar I disorder to be greater or less than adults with the same condition. The two experts gave conflicting views, as one stated it would be greater because children/adolescents tend to have a supportive family network, whereas the other expert claimed it would be less because bipolar disorder would affect adolescents' ability to build friendships, which would severely detract from their HRQoL (Appendix 14). On balance, use of adult utilities would seem to be appropriate for children and adolescents. Furthermore, the difference between the general population utility in adults and that in children is taken into account in the model using a multiplicative utility method (please refer to Section 6.4.9 for details).

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

All AEs will negatively affect HRQoL. The AEs most likely to affect HRQoL are EPS, somnolence, weight gain and side-effects associated with prolactin increases. Due to

the lack of data on side-effects associated with prolactin increases for the different comparators, this could not be modelled.

EPS, somnolence and weight gain are expected to affect HRQoL for the following reasons:

- EPS can cause impairment of day-to-day functioning (for short-term duration until the dose of the treatment is optimised)
- Somnolence also affects day-to-day functioning (short-term duration until the dose of the treatment is optimised)
- Weight gain affects self-esteem and social functioning. Weight gain could also lead to other health problems, but the HRQoL impact of these are difficult to quantify and therefore model.

Clinical experts were asked to rank these three adverse events in order of their impact on HRQoL (see Appendix 14 for further details). All three experts independently ranked weight gain as having the most detrimental impact on HRQoL, followed by somnolence and EPS. However, it is believed that the experts factored in the short duration and manageability of somnolence and EPS into this exercise. The literature actually indicates that EPS would be associated with the highest utility decrement, followed by somnolence and then weight gain.[96, 98] The values from the literature have been used in the model, but the utility affects of EPS and somnolence have only been applied to the inpatient acute phase of the model to reflect the experts' views.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

Justification for choice of utility data

Due to the unavailability of published utility data for children or adolescents with bipolar disorder, utility data from adult studies had to be used. Hayhurst 2006 was chosen as the source of utilities for the base case of the model, as the utilities were derived from a UK population using EQ-5D.[94] The main limitation of Hayhurst 2006

was that very few patients with mania were actually included in the study and therefore the reported utilities for manic states are associated with some uncertainty.[94] Therefore, the utilities from Revicki 2005[87], which included 92 manic bipolar patients (from the USA), have been investigated in a scenario analysis.

The selection of utilities from Hayhurst 2006 for the different health states in the model are justified in Table B62.

The impact on utility of hospitalisation was taken from Glennie 1997 (from the Mental Health Research Review 2000[95]), which obtained health state utilities for hospitalised and non-hospitalised Canadian schizophrenia patients using the standard gamble technique.

For weight gain, Boyle 2010[97] was chosen as the source of the utility weighting as this included a UK population aged 11-15 years old, 176 of whom were classified as overweight. Furthermore, this study used the EQ-5D, which is in accordance with the NICE reference case. Revicki 2005 also reported a disutility for weight gain; although this study has the advantage that it included bipolar disorder patients, they were adults from the US and standard gamble techniques were used. The use of the disutility reported for weight gain by Revicki 2005 has been investigated in a sensitivity analysis (Section 6.7.9). The disutility reported in Heeg 2008 for weight gain in adults with schizophrenia was also deemed to be less appropriate for the population being modelled compared to Boyle 2010.

For somnolence, the only reference found to report utilities relating to a similar symptom in a psychiatric patients population was Heeg 2008, which applied a utility weighting for sedation to a UK model.[98] However, the original source of this weighting was not obtainable.

Briggs 2008,[96] a study on UK schizophrenia patients, was used as the source for the utility associated with EPS. Heeg 2008[98] also reported a utility for EPS in schizophrenia patients, but this was from a US population and, unlike Briggs 2008, did not use EQ-5D to value the health state.

Multiplicative utility model and adjustment for age and sex

A multiplicative utility model, rather than an additive one, was employed, which means that when a patient experiences a particular health state (eg. an adverse

event) a utility multiplier (φ) is applied to their base utility value, rather than a decrement. All multipliers, and the data from which they are derived, are listed in Table B62.

The advantage of a multiplicative model is that these multipliers can take into account the demographic (age and sex) of the population from which each utility is drawn.[106] This makes the multipliers much more comparable for use in the economic model compared to if an additive model was used. Furthermore, these multipliers are then applied to the general population utility for a cohort of people aged on average 15 years with 53.7% male, and therefore have effectively been adjusted to an adolescent population.[106] For example, at the start of the model, the multiplier (calculated from adult data) for acute mania is 0.775 (Table B62), which is then applied to the general population utility for an adolescent cohort (aged 15 years, 53.7% male) of 0.951, to give a utility value for acute mania in the model of 0.737. This utility is then further adjusted according to hospitalisation status and also according to treatment type, based on the adverse events profile of each treatment. The general population utility to which the multipliers are applied changes with each cycle of the model, as the cohort ages.

The multipliers were derived as follows:

- The mean age and the percentage of males in the population from which the utility was derived were obtained from each source. These were used to estimate the general population utility for a population of that age and sex, using the following formula:[106]
  $U^{\text{general pop (event free)}} = 0.9508566 + 0.0212126 * \text{male} - 0.0002587 * \text{age} - 0.0000332 * \text{age}^2$
- The utility estimate for the health state was extracted from the study (see 'Reported utility for health state' in Table B62 below).
- The utility estimate for the health state was divided by the general population to get the multiplier, φ.
- This effectively adjusts the utility results by the demographic of the populations from which they came.
- In the model, the multipliers are then applied to the general utility of the modelled adolescent population (0.951 at start of model) to give the utility values used for each state. These are not listed in Table B62 as there are

many combinations of health state when hospitalisation and adverse events are included.

Table B62 Summary of quality-of-life values for cost-effectiveness analysis

State	Age of population	Proportion male in population	General population utility for that age and male %	Reported utility for health state, mean (SE)	Utility multiplier (φ)	Reference in submission	Justification
Acute mania	41.5	0.357	0.891	0.690 (0.0408)	0.775	Hayhurst 2006[94]	Assumed to be equivalent to severe mania (LIFE Mania score of 4)
Responder observation	41.5	0.357	0.891	0.850 (0.1075)	0.954	Hayhurst 2006[94]	Assumed to be equivalent to a low mania score (LIFE Mania score of 1). The impacts of hospitalisation and adverse events are then added to this.
Euthymic treated	41.5	0.357	0.891	0.850 (0.1075)	0.954	Hayhurst 2006[94]	Assumed to be equivalent to a low mania score (LIFE Mania score of 1). The impact of adverse events is then added to this.
Euthymic not treated	41.5	0.357	0.891	0.850 (0.1075)	0.954	Hayhurst 2006[94]	Assumed to be equivalent to a low mania score (LIFE Mania score of 1)
Therapy resistance	41.5	0.357	0.891	0.720 (0.0842)	0.809	Hayhurst 2006[94]	Assumed to be equivalent to a medium mania score (LIFE Mania score of 3)

Hospitalisation (multiplier applied to acute mania inpatient phases, responder observation inpatient and to treatment resistant inpatient)	41.5	1.000	0.904	0.834 (0.2502*) (derived from a decrement of 0.07 applied to the general population utility)	0.923	Glennie 1997 (from Mental Health Research Review 2000[95])	See text above
Weight gain	13.2	0.517	0.953	0.865 (0.004)	0.908	Boyle 2010[97]	See text above
EPS	43.5	0.449	0.886	0.722 (0.2166*)	0.815	Briggs 2008[96]	See text above
Somnolence	Multiplier reported in the reference				0.905 (0.0184*)	Heeg 2008[98]	

*SE assumed 30% of mean

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
  - whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Due to the lack of published data on utilities for adolescents with bipolar disorder, three clinical experts were asked to rank the health states according to their opinion on the relative quality of life in each. Further details on the selection of the experts can be found in Section 6.3.5.

Full details of the questions asked and responses from each expert are provided in Appendix 14. Below is a summary of the responses regarding utilities:

- Experts disagreed upon whether the quality of life of children and adolescents with bipolar I disorder would be better or worse than the quality of life of adults with the same disorder. Therefore, on balance, the fairest way to adjust the adult utilities to those applicable to children was to simply adjust according to the difference in the general population utilities between children and adults.

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- All three experts independently ranked weight gain as having the most detrimental impact on HRQoL, followed by somnolence and EPS. However, it is believed that the experts factored in the short duration and manageability of somnolence and EPS into this exercise. The literature actually indicates that EPS would be associated with the highest utility decrement, followed by somnolence and then weight gain.[96, 98]

- The experts disagreed on whether quality of life would increase or decrease when treatment is stopped in the euthymic state. Aside from the increased risk of relapse and the absence of adverse events (which have been modelled), several experts stated that mild symptoms may emerge which would decrease quality of life. However, one expert also stated that coming off treatment would have a positive psychological impact upon the patient. On balance, it was decided to model no change in utility (apart from due to the absence of adverse events) when moving from the euthymic treated to the euthymic not-treated state, especially in the absence of any empirical data.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The differences between what the patient experiences in terms of HRQoL in each state are described in Section 6.4.2.

The HRQoL experienced within each health state is likely to vary slightly from patient to patient due to the following reasons:

- Self-awareness may differ between patients, particularly between pre-pubescent and post-pubescent patients.
- The family and friend support network available to each patient will be different and this could impact on their quality of life.

The utilities applied in the model are thought to represent an average utility for each state, and therefore cover these potential variances. There are no data to support modelling the variances.

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

The main adverse event that has not been included in the cost-effective analysis is clinically important increase in prolactin levels. This was excluded from the analysis because it is an intermediate outcome, which using biochemical measures alone cannot be linked to utility decrements or additional costs. It is, however, known that increased prolactin can cause long-term health problems such as sexual side effects and bone mass loss, which would adversely affect HRQoL.[30, 31] The network meta-analysis demonstrated that aripiprazole-treated patients had a lower risk of clinically significant prolactin increases than the other three atypical antipsychotics (Section 5.7.6).

An adverse event that has been reported to be a problem in adults taking atypical antipsychotics is diabetes. [redacted] Data from adult populations has suggested that aripiprazole may have lower incidence of newly diagnosed diabetes cases than risperidone, olanzapine or quetiapine.[107] However, there are no long-term data on this outcome for the other atypical antipsychotics in children and therefore this adverse event could not be modelled.

The exclusion of prolactin-associated side effects and diabetes from the model is therefore likely to disadvantage aripiprazole compared to the other comparators. Therefore, this is a conservative assumption.

Episodes of depression can detrimentally affect HRQoL in bipolar I patients, but depression was not modelled due to the lack of data on the frequency of episodes between comparators and also the fact that this appraisal is considering aripiprazole for the treatment of manic episodes only. The effect of long-term depressive symptoms on HRQoL may have been captured within the utility measurements for stable bipolar disorder.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The baseline quality of life for a general population of patients aged on average 15 years and 54% male was 0.951. This was derived from the equation discussed in Section 6.4.9. This estimate closely matches the EQ-5D utility obtained from a UK cohort of 1675 children and adolescents aged on average 13.2 years, which was 0.90.[97] The calculated value was used in the model as this relates exactly to the patient characteristics of the trial.

The utility multipliers for each health state were then applied in a multiplicative manner to this baseline utility (please refer to Section 6.4.9 for more details).

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The model captures the expected changes in utility over time that were discussed in Section 6.4.2 in the following way:

- The experience of acute manic symptoms reduces the utility from the baseline value. The utility is then further decreased due to hospitalisation.
- Response to treatment in the model causes patients to move to the responder observation phase, which has a higher utility than acute mania.
- When patients move from the responder observation phase to euthymic treated they leave hospital and therefore the disutility associated with hospitalisation is removed.
- Experience of adverse events (weight gain, EPS, somnolence) is associated with a disutility in the model.

The utility within each health state is assumed to be constant over time. In real clinical practice there would be some transition in HRQoL as patients gradually lose their manic symptoms and respond to treatment. However, the timeframe for this transition is relatively short and would be too complicated to replicate in a model. A constant utility in the euthymic treated and not-treated states is considered a relatively accurately reflection of the real world situation, as stable patients should only experience a change in HRQoL if they experience an adverse event or relapse.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The utility values taken from the literature have been converted into multipliers and adjusted for age and sex of the population from which each was drawn. Please refer to Section 6.4.9 for further details of the methodology.

6.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

As discussed in section 2.8, child and adolescent patients with bipolar disorder are predominantly treated in the primary care setting, with community care as necessary. Feedback from the clinical expert consultation (see 6.3.5 and Appendix 14) suggested that patients presenting with an acute manic episode would be hospitalised and treated until their episode had been controlled and until the consultant was satisfied that they had responded to therapy and were stable. The experts suggested that patients would stay in hospital for up to 2 months. Once patients had been discharged from hospital, it was assumed that if the patient relapsed they would be rehospitalised.

The resource use associated with hospitalisation was taken from the NHS reference costs (code MHIPC1 – Mental Health Services, Children).[108] It was assumed that whilst patients were in hospital, all costs associated with their management (excluding antipsychotic therapy) were covered by this reference cost. This is similar to the approach previously taken in the NICE submission for aripiprazole in children and adolescents with schizophrenia (TA213).[109]

Once discharged from hospital, patients would have follow-up visits with their psychiatrist and potentially other healthcare professionals. These costs are covered by the PSSRU Unit Costs of Health and Social Care and are discussed further in Section 6.5.4.[99]

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS reference costs were incorporated into the model for hospitalisation (as stated in Section 6.5.1) as an accurate cost for in-patient mental health treatment of children was available from reference costs.

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A systematic review was designed to identify all relevant studies on costs and healthcare resource utilisation that do not fulfil the “full economic evaluation” criterion in children and adolescents with bipolar I disorder. The review was based on the

same search and inclusion strategy of a previous systematic review (commissioned by NICE in 2005), to identify more recent studies investigating cost and healthcare resource utilisation data in bipolar disorder.

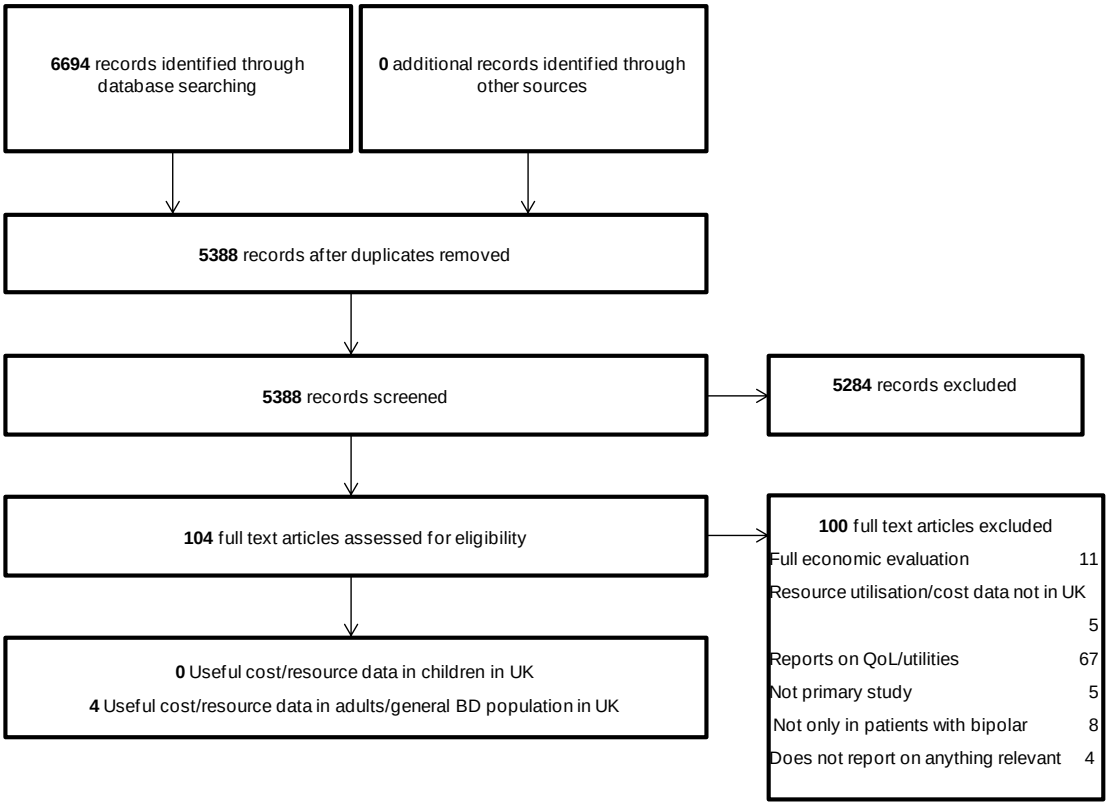
Databases were searched to include studies from 2005-present. A list of databases is provided in Appendix 13. The search terms were taken from a previous systematic review commissioned by NICE in 2005[47] (Appendix 13). Whilst the searches were performed to identify data in children, the costs and healthcare resource utilisation evidence for bipolar disorder in children and adolescents may be scarce. Therefore the search terms were not limited to children and studies in adults were captured separately during the review process.

The inclusion criteria were as follows:

- Patients with manic or mixed episodes of bipolar disorder.
- Includes patients aged <18 (studies including patients ≥18 were collected separately)
- Reports on costs or healthcare resource utilisation from the UK (studies reporting data from outside the UK were collected separately).
- Study must be from an OECD country, as the aim of the review is to identify economic information transferable to the UK context.
- Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed and the study's data and results must be extractable.

Results from the searches described above were de-duplicated and reviewed twice: once using the abstracts and then more rigorously using full texts for the inclusion criteria listed previously.

Table B63 Flow diagram of the numbers of cost/resource use studies included and excluded



While no useful cost/resource utilisation studies in children in the UK were identified, 4 studies were identified that reported on adults/general bipolar disorder population in the UK. A summary of these studies is provided in Table B68.

Table B64 A summary of the studies examining resource utilisation in the UK

Study	Resource utilisation results
Hong 2009[110]	Presents some resource utilisation for two patients groups: those adherent to medication and those non-adherent. However, these were not patient groups that were assessed in the model.
Hong 2010[111]	Presents some resource utilisation for two patients groups: those who relapse and those who do not relapse. The number of outpatient psychiatric visits in the 21 month follow-up for those who relapsed was 19.6 and for those who did not relapse was 13.9. The resource use for those who relapsed and those who did not was not specific to children. As resource use is expected to be different for children than adults, it was decided to use expert opinion to inform resource use in the model (Appendix 14). The resource use in this study is also derived from different sites across Europe. The UK unit costs presented in the paper are also not specific to paediatric services and more up-to-date costs are available from NHS reference costs.
Lam 2005[112]	Study reports resource utilisation in terms of: psychiatric inpatient, general inpatient and community service. Does not present a breakdown of specific resource utilisation data in the three services.
Young 2011[113]	This study aims to examine the economic burden of bipolar disorder in the UK as a whole. Therefore the resources utilisation data presented are taken from national statistics and do not give relevant data for use in the economic model (i.e. per-patient data).

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

As discussed in section 6.3.5 and Appendix 14, an expert consultation was used in the development of the model. From the perspective of resource utilisation in the model, the questions for the experts focused on resource utilisation once patients have been discharged from hospital and also when they experienced adverse events in the outpatient setting. The questions given to the experts and their responses are detailed in full in Appendix 14.

The tables below show the inputs that were used in the model, based on the experts' responses. Table B65 presents the resource utilisation data for patients in the three outpatient states used in the model: euthymic treated, euthymic not treated and therapy resistant outpatients. Table B66 summarises the additional resource utilisation required when patients in the euthymic treated state experience weight gain as an adverse event.

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table B65 Summary of the resource utilisation of patients in the three outpatient states used in the model (expert opinion)

Resource	Visits per month		
	Euthymic treated	Euthymic not treated	Therapy resistant outpatients
Community psychiatric nurse visit	0	0	0
Consultant psychiatrist visit	1	0.6667	2
GP visit	0	0	0
Psychologist visit	0.5	0	1

Table B66 Summary of the additional resource utilisation required by treated euthymic patients when they experience weight gain as an adverse event (expert opinion)

Resource	Weight gain
Community psychiatric nurse visit	1 visit per month
Consultant psychiatrist visit	No additional visit
GP visit	No additional visit
Psychologist visit	No additional visit
Dietician	2 additional visits
Pharmaceutical therapy (please state which therapy)	No pharmaceutical therapy
Diagnostic test (please state which tests)	No additional tests

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

All acquisition costs were taken from the NHS Drugs Tariff, as this was found to be more up-to-date than the British National Formulary (BNF).[114] All treatment costs are listed in Table B67.

There are a number of different formulations of the treatments used in the model available on the market. This reflects the range of doses available to clinicians for treating patients, to ensure a good response but to minimise adverse events.

For aripiprazole, the 28 tablet pack of 10 mg tablets is priced at £95.74 (Section 1.10). The 5 mg and 15 mg packs have the same acquisition cost as the 10 mg pack. The 30 mg pack has an acquisition cost of £191.47 and the 150 mL oral solution (1 mg/mL) has a cost of £102.57.

The SPC for aripiprazole currently states (Section 1.10) that aripiprazole, "should be initiated at 2 mg (using oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg."[8] To incorporate this into the model it was assumed in the first week that aripiprazole patients would use 1 bottle of oral solution based on the above (i.e. the per day cost in the first week was £14.65). For all subsequent weeks on aripiprazole, the cost taken was the mean cost of the 10 mg and 30 mg doses (the two doses investigated in the clinical trials). This cost was £5.15 per day.

For the atypical antipsychotics, the per day cost of therapy was taken as the mean of the costs for the lower and higher doses as used in the clinical trials. The costs were derived from the British National Formulary (BNF).

Lithium is used as a maintenance treatment in the therapy resistance stage. The cost per day for lithium was a mean of the cost for the 250 mg dose and the 400 mg dose (the doses recommended for maintenance). Lithium is also associated with substantial monitoring requirements, as outlined in NICE Clinical Guidance 38.[1] These include: thyroid monitoring and renal function tests every 6 months and serum lithium level monitoring every 3 months. The costs of these tests were thus incorporated into the model for patients receiving lithium in the therapy resistance outpatient state.

The use of antipsychotics is associated with a number of monitoring costs upon treatment initiation. For all antipsychotics, patients' baseline plasma glucose and lipid levels should be measured. The slight differences between the treatments are that for olanzapine, an extra blood glucose test should be performed after 1 month and for risperidone, prolactin levels should also be measured (see Table A3).[1] However, as these monitoring requirements predominantly occur on treatment initiation (when a patient is hospitalised) it is assumed that the costs of these tests are covered by the reference cost for child/adolescent mental health hospitalisation as discussed in 6.5.1. Whilst the NICE clinical guideline does suggest that further monitoring may be required, due to the uncertainty regarding when a patient would receive the tests, and the low cost associated with the tests, these costs were excluded from the

model.[1] As the monitoring requirements are more stringent for olanzapine and risperidone than for aripiprazole, this assumption is a conservative one.

Table B67 Unit costs associated with the technology in the economic model

Agent	Daily dose (mg)	Tablet strength (mg)	Tablets required per day	Tablets/ pack	Cost/pack	Cost/tab	Cost/day	Ref. In submission
Aripiprazole wk 1 (oral solution)	Dose-increase	1 mg/mL		150mL	£102.57	£0.68	£14.65	Section 1.10, BNF (December 2012)
Aripiprazole	10	10	1	28	£95.74	£3.42	£3.42	
Aripiprazole	30	30	1	28	£191.47	£6.84	£6.84	
Average for aripiprazole from wk2							£**5.13**	
Risperidone	2	2	1	60	£1.94	£0.03	£0.03	BNF (December 2012)
Risperidone	6	3	2	60	£2.43	£0.04	£0.08	
Average for risperidone							£**0.06**	
Olanzapine	10	10	1	28	£26.22	£0.94	£0.94	BNF (December 2012)
Olanzapine	20	20	1	28	£47.67	£1.70	£1.70	
Average for olanzapine							£**1.32**	
Quetiapine	300	150	2	60	£96.94	£1.62	£3.21	BNF (December 2012)
Quetiapine	600	300	2	60	£145.71	£2.43	£4.86	
Average for quetiapine							£**4.04**	
Lithium	250	250	1	100	£3.09	£0.0309	£0.03	NHS Drug Tariff[114]
Lithium	400	400	1	100	£4.13	£0.0413	£0.04	
Average for lithium							£**0.04**	
Lithium monitoring costs:								
Thyroid monitoring (1 test every 6 months)					£17.82 per test		£0.11	Soares-Weiser 2007[100], uprated with NHS Pay & Prices Index 2011[99]
Renal function test (1 test every 6 months)					£2.42 per test		£0.01	
Serum lithium level test (1 test every 3 months)					£3.12 per test		£0.04	

Health-state costs

6.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

The costs for the antipsychotics included in the model have already been summarised in 6.5.5 above (Table B67) and the costs associated with adverse events are discussed in 6.5.7; these costs have therefore not been duplicated in Table B68.

Table B68 List of health states and associated costs in the economic model, expressed in per week costs (excluding therapy and monitoring costs)

Health states	Items	Value	Reference in submission
Acute mania	Hospital stay	£4,215	6.5.1; NHS Reference Costs[108]
	Total	**£4,215**	
Responder observation	Hospital stay	£4,215	6.5.1; NHS Reference Costs[108]
	Total	**£4,215**	
Euthymic treated	Consultant psychiatrist	£63.49	Unit Costs of Health and Social Care[99] (per patient-related hour rate adjusted by the resource use in Table B65)
	Consultant psychologist	£16.88	
	Total	**£80.37**	
Euthymic not treated	Consultant psychiatrist	£42.33	Unit Costs of Health and Social Care[99] (per patient-related hour rate adjusted by the resource use in Table B65)
	Total	**£42.33**	
Therapy resistance (hospitalised)	Hospital stay	£4,215	6.5.1; NHS Reference Costs[108]
	Total	**£4,215**	
Therapy resistance outpatient	Consultant psychiatrist	£126.99	Unit Costs of Health and Social Care[99] (per patient-related hour rate adjusted by the resource use in Table B65)
	Consultant psychologist	£33.75	
	Total	**£160.74**	
Death	NA	NA	NA

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

From the perspective of the costs associated with AEs, it was assumed that all costs for the management of AEs in the acute phase of the model were included in the NHS reference cost for in-patient treatment, as used in the acute states. Therefore, no additional costs were added to these states.

Based on expert consultation (see Section 6.3.5 and Appendix 14) and the aripiprazole clinical trial data (see Section 5.9.2), EPS and somnolence are adverse events that occur only in the short-term and are usually resolved through dose reduction or switching therapy, typically before a patient is discharged from hospital. As such, the only adverse event that was included in the maintenance phase of the model was weight gain, which the experts suggested would continue for as long as the patient remained on therapy, but for which they said patients would generally not switch therapy unless weight gain was considered extreme. Therefore, weight gain is the only adverse event included in the model that is associated with additional resource utilisation (and therefore additional costs). The costs associated with the adverse events are summarised in Table B69 and are based on expert consultation.

Table B69 List of adverse events and summary of costs included in the economic model

Adverse events	Items	Value	Reference in submission
Weight Gain	Community psychiatric nurse visit	£60 per month (1 visit per month)	Appendix 14 Unit Costs of Health and Social Care[99]
	Dietician	£70 (2 x hour visits of £35 per hour each)	Appendix 14 Unit Costs of Health and Social Care[99] - cost for a key worker
EPS	NA – these AEs were only included in the acute phase of the model, where all AE costs are included in the NHS reference cost for in-patient treatment.		
Somnolence			

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

No additional costs.

6.6 *Sensitivity analysis*

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The structure of the model reflects the current paradigm for treatment of acute manic episodes in adolescents in line with expert opinion (Section 6.3.5).

Due to the uncertainty surrounding the dosing of aripiprazole that will be used most commonly in clinical practice and the uncertainty of the treatment pathway in this indication, several different scenarios were considered alongside the base case:

- Inclusion of only the 10 mg aripiprazole clinical data.

- Inclusion of data from the NMA sensitivity analysis results that included all identified clinical trials, including the small co-morbid ADHD aripiprazole trial, NCT00116259.
- Use of Revicki 2005 as a source of utilities.
- Alteration of the usual care treatment strategy (strategy 1) to reflect the potential use of olanzapine as second line therapy.

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Details of the sensitivity analyses performed are presented in Table B70 and reflect the variables listed in Section 6.3.6. It was not possible to perform analyses around three variables due lack of primary efficacy data for quetiapine at weeks 1 and 2. Variables altered include the time horizon, discounting rates, discontinuation rates, YMRS response rates at different weeks, treatment resistance, mental health service costs and rates of adverse events. Where appropriate and no other data on variance was available, parameters were varied ±30%.

Table B70: One-way sensitivity analyses

Variable	Base Case	Scenario	Lower Limit	Upper Limit
Time Horizon	3 years	-	1 yr	5 yrs
Discounting Rate Costs	3.5%	-	0%	6%
Discounting Rate QALYs	3.5%	-	0%	6%
Discontinuation				
RR vs placebo at week 3				
ARP	0.7301	±30%	0.51107	0.94913
RIS	0.8787	±30%	0.61509	1
QTP	0.6977	±30%	0.48839	0.90701
OLA	0.5442	±30%	0.38094	0.70746
Proportion of wk 3 disc occurring by wk 2				
All drugs	0.6023	±30%	0.42161	0.78299
Proportion of wk 2 disc occurring by wk 1				
All drugs	0.1942	±30%	0.13594	0.25246
Probability of discontinuation at week 3				
Placebo	0.2414	±30%	0.16898	0.31382
YMRS response				
Probability of response at week 3				
Placebo	0.2456	±30%	0.17192	0.31928
ARP	0.5908	±30%	0.41356	0.76804
RIS	0.6007	±30%	0.42049	0.78091
QTP	0.467	±30%	0.3269	0.6071
OLA	0.5234	±30%	0.36638	0.68042
Proportion of wk 3 responders responding by wk 2 (a)				
Placebo	0.7818	±30%	0.54726	0.95
ARP	0.8579	±30%	0.60053	0.95
RIS	0.8386	±30%	0.58702	0.95
OLA	0.9885	±30%	0.69195	0.99
Probability of response at week 2				
Placebo	0.1920	±30%	0.1344	0.2496
ARP	0.5068	±30%	0.35476	0.56
RIS	0.5037	±30%	0.35259	0.57
OLA	0.5174	±30%	0.36218	0.52
Proportion of wk 2 responders responding by wk 1 (b)				
Placebo	0.4167	±30%	0.29169	0.54171
ARP	0.5542	±30%	0.38794	0.72046
RIS	0.4742	±30%	0.33194	0.61646
OLA	0.4043	±30%	0.28301	0.52559
Probability of response at week 1				
Placebo	0.0800	±30%	0.056	0.104
ARP	0.2809	±30%	0.19663	0.36517
RIS	0.2389	±30%	0.16723	0.31057
OLA	0.2092	±30%	0.14644	0.27196
Recurrent acute mania (all drugs)				

9-wk risk of relapse (responder observation and euthymic Tx)	0.05	±30%	0.035	0.065
6 month risk of relapse (euthymic not Tx)	0.15	±30%	0.105	0.195
Treatment Resistant				
6m prob spontaneous euthymia	0.2440	±30%	0.1708	0.3172
Adverse events				
EPS				
ARP	0.1578	±30%	0.11046	0.20514
RIS	0.1117	±30%	0.07819	0.14521
QTP	0.1162	±30%	0.08134	0.15106
OLA	0.1117	±30%	0.07819	0.14521
Weight gain				
ARP	0.03403	±30%	0.02382	0.04424
RIS	0.04083	±30%	0.02858	0.05308
QTP	0.4032	±30%	0.28224	0.52416
OLA	0.4501	±30%	0.31507	0.58513
Somnolence				
ARP	0.4631	±30%	0.32417	0.60203
RIS	0.2660	±30%	0.1862	0.3458
QTP	0.2732	±30%	0.19124	0.35516
OLA	0.2660	±30%	0.1862	0.3458
Mental health services costs				
Inpatient day	602.10	±30%	421.47	782.73
Haematology	3.36	±30%	2.352	4.368
Initial consultant visit: outpatient setting	419.00	±30%	293.3	544.7
Follow-up consultant visit: outpatient setting	229.00	±30%	160.3	297.7

a) derived through a comparison of median responses from NMA of week 3 responders vs NMA of week 2 responders for each drug
b) derived through a comparison of median responses from NMA of week 2 responders vs NMA of week 1 responders for each drug

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic sensitivity analysis was undertaken to explore how imprecision in model inputs might affect decision uncertainty. Table B54 in Section 6.3.6 presents distributions fitted to all the model parameters and the sources and assumptions for each. All the parameters in Table B54 were sampled in the PSA, apart from the acquisition cost of the treatments, as the price of drugs is fixed in the UK, and the

resource use estimates for the maintenance states, as instead the costs associated with the resource use were sampled.

Inputs derived from network meta-analyses were parameterised using the simulated outputs from the posterior distributions (coda), thus preserving correlation between treatment effects. This was the case for inputs related to response, discontinuation and adverse events.

In the case of response, slight adjustment had to be made to the results in order to capture the time dependency of the outcome in the PSA. Because responses at weeks 1, 2 and 3 were each analysed in a separate network meta-analysis, the simulated outputs from the posterior distributions were only correlated *within* each time point, but not *between or across* the different time points. Furthermore, if responses at each time point were varied independently in the PSA, there was a risk that the sample for cumulative response at week 2 might be greater than the sampled response at week 3, which is illogical.

In order to overcome these problems the model uses the simulated outputs from the posterior distributions from the week 3 NMA, thus preserving correlations between treatment effects at this time point. In order to derive the probability of response at week 2, the median point estimates of response from the week 2 NMA were compared to the median point estimates of response from the week 3 NMA. This produced an estimate for the proportion of responders at week 3 that had responded by week 2. This value was unique to each drug (except QTP, which was assumed to be the same as ARI) and was multiplied by the week 3 simulated value during PSA to derive the probability of response by week 2. The same method was used to calculate the probability of response by week 1, comparing results from the week 1 NMA to the week 2 NMA. Beta distributions were attached to these response ratios using the method of moments and assuming that the standard error was 20% of the mean.

Probabilistic implementation of health state utility values also required some adjustment for sampling in order to avoid illogical values. It was assumed that response would always be better than acute mania and that treatment resistant bipolar disorder would fall somewhere in between. Because the confidence intervals around the individual health state utility weights are overlapping, there is a risk that random sampling could produce estimates that did not fit the assumptions made. Therefore, only the utility for response was sampled. In order to derive the

probabilistic value for acute mania and treatment resistant disease, the mean values for each were compared to the mean value for response to estimate a multiplier. These fixed multipliers were then applied to the sampled value for response. Thus, the relationship between acute mania and response and treatment resistant disease and response was preserved in the probabilistic analysis.

6.7 Results

Summary of Economic Analysis Results

- In the base case it was found that aripiprazole used at any stage of the treatment pathway dominated usual care, where aripiprazole was not used, indicating that it is a cost-effective option for the NHS. Aripiprazole used as second line therapy after risperidone dominated all other strategies.

- It should be noted that generic forms of aripiprazole are due to reach the market in 2014 and therefore aripiprazole will become even more cost-effective in the future.

- The model is robust and not sensitive to changes in the majority of parameters. The key driver of the cost-effectiveness model was shown by deterministic sensitivity analysis to be the response rates at week 3. A higher response rate over the first 3 weeks of treatment results in patients leaving hospital earlier, which has both cost and health-related quality of life (HRQoL) benefits. Given the evidence available, aripiprazole is associated with a favourable response rate at some timepoints in the first three weeks of treatment compared to the comparators, which has health and cost benefits for all aripiprazole strategies in the base case.

- The probabilistic sensitivity analysis (PSA) showed that there is some uncertainty surrounding the base case ICERs, which is unsurprising given the lack of statistically significant differences in response rates between the four atypical antipsychotics. For all three aripiprazole strategies the majority of the PSA iterations indicated cost-effectiveness or dominance.

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The main efficacy and transition data used in the model were taken from an indirect comparison of the pivotal clinical trials for the comparators. The clinical outcomes applied in the model are presented in Section 5.7 and a table of the data inputs used is given in Section 6.3.6. No long-term survival outcomes were available from clinical trials and therefore cannot be compared to the outcomes in the model. The inputs used to inform the transition probabilities in the model are explored further in sensitivity analyses (Section 6.7.7 - 6.7.9)

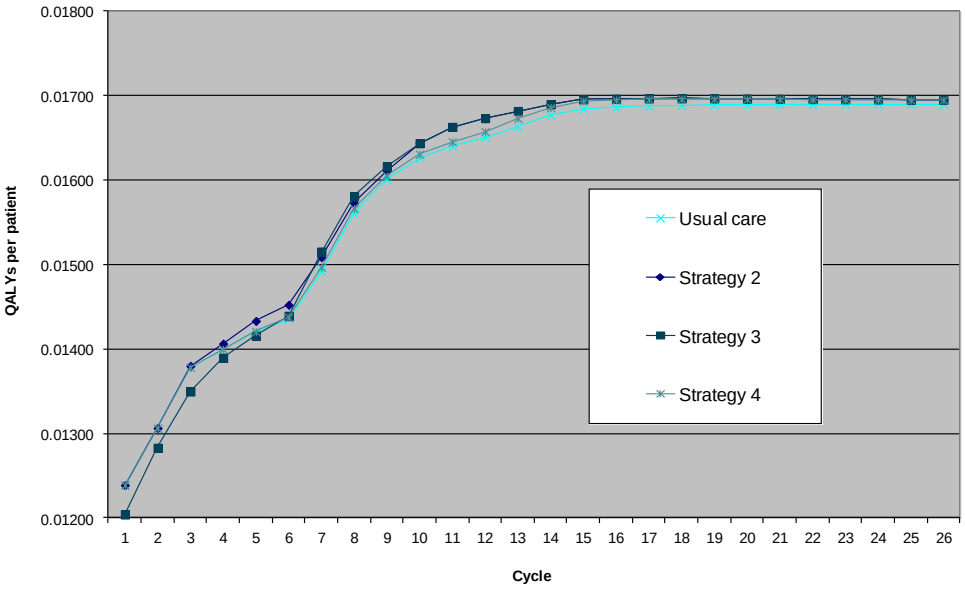
6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The Markov traces for each strategy can be found on the “S1”, “S2, “S3” and “S4” sheets in the provided excel file from cells DA22:EP282.

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

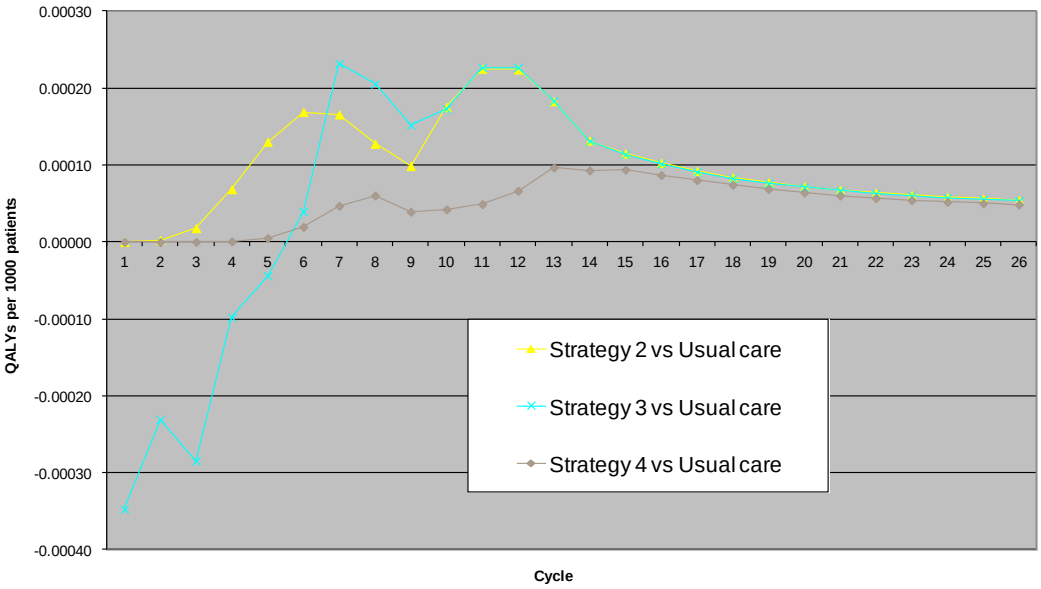
QALY gains are similar across all strategies (Figure B17), with differences between strategies arising primarily during first 15 weeks (Figure B18).

Figure B17 Expected QALYs for first 6 months of evaluation, per 7 day cycle



Usual care: Risperidone, Quetiapine, Olanzapine
Strategy 2: Risperidone, Aripiprazole, Quetiapine
Stretegy 3: Aripiprazole, Risperidone, Quetiapine
Strategy 4: Risperidone, Quetiapine, Aripiprazole

Figure B18 Expected incremental QALYs compared to usual care (strategy 1) for the first 6 months of evaluation, per 7 day cycle



Usual care: Risperidone, Quetiapine, Olanzapine
Strategy 2: Risperidone, Aripiprazole, Quetiapine
Stretegy 3: Aripiprazole, Risperidone, Quetiapine
Strategy 4: Risperidone, Quetiapine, Aripiprazole

6.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

The chosen model structure is not set up to report life years and QALYs for clinical outcomes and therefore they are not presented.

6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table B71, Table B72 and Table B73 present summaries of the undiscounted QALY gains by health state for usual care versus strategies 2, 3 and 4; Table B74, Table B75 and Table B76 present summaries of the undiscounted costs by health state for usual care also versus strategies 2, 3 and 4. Undiscounted QALYs and costs had to be displayed here due to the way the model had been structured.

The chosen model structure is not set up to report resource use by category of cost.

Table B71 Summary of undiscounted QALY gain by health state – Usual care versus Strategy 2

Health state	QALY intervention (Strategy 2)	QALY comparator (Usual Care)	Increment	Absolute increment	% absolute increment
Acute First Line Wk1	1.070	1.070	0.000	0.000	0.00%
Acute First Line Wk 2	0.787	0.787	0.000	0.000	0.00%
Acute First Line Wk 3	0.394	0.394	0.000	0.000	0.00%
Acute First Line Wk 4	0.000	0.000	0.000	0.000	0.00%
Acute Second Line Wk1	0.686	0.616	0.069	0.069	0.24%
Acute Second Line Wk 2	0.478	0.466	0.011	0.011	0.04%
Acute Second Line Wk 3	0.264	0.306	-0.041	0.041	0.14%
Acute Second Line Wk 4	0.000	0.000	0.000	0.000	0.00%
Acute Third Line Wk1	0.400	0.481	-0.081	0.081	0.28%

Acute Third Line Wk 2	0.302	0.372	-0.070	0.070	0.24%
Acute Third Line Wk 3	0.198	0.193	0.005	0.005	0.02%
Acute Third Line Wk 4	0.000	0.000	0.000	0.000	0.00%
Therapy Resistant - Hospitalized	2.837	3.123	-0.286	0.286	0.99%
Therapy Resistant - Outpatient	23.259	25.713	-2.453	2.453	8.47%
Therapy Resistant - Euthymic Treated	1.721	1.904	-0.183	0.183	0.63%
Therapy Resistant - Euthymic Not Treated	19.628	21.866	-2.238	2.238	7.73%
First Line Responder Observation	3.864	3.864	0.000	0.000	0.00%
Second Line Responder Observation	2.426	1.725	0.701	0.701	2.42%
Third Line Responder Observation	1.116	1.506	-0.390	0.390	1.35%
First Line Euthymic	4.909	4.909	0.000	0.000	0.00%
Second Line Euthymic	3.150	2.188	0.963	0.963	3.33%
Third Line Euthymic	1.405	1.895	-0.490	0.490	1.69%
First Line Euthymic Not-treated	85.895	85.895	0.000	0.000	0.00%
Second Line Euthymic Not-treated	49.513	36.452	13.062	13.062	45.12%
Third Line Euthymic Not-treated	21.338	29.245	-7.908	7.908	27.31%
Dead	0.000	0.000	0.000	0.000	0.00%
Total QALYs	225.642	224.971	0.671	28.952	100.00%

QALY, quality-adjusted life year .Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table B72 Summary of undiscounted QALY gain by health state – Usual care versus Strategy 3

Health state	QALY intervention (Strategy 3)	QALY comparator (Usual Care)	Increment	Absolute increment	% absolute increment
Acute First Line Wk1	1.031	1.070	-0.039	0.039	0.12%

Acute First Line Wk 2	0.719	0.787	-0.068	0.068	0.20%
Acute First Line Wk 3	0.398	0.394	0.005	0.005	0.01%
Acute First Line Wk 4	0.000	0.000	0.000	0.000	0.00%
Acute Second Line Wk1	0.721	0.616	0.105	0.105	0.31%
Acute Second Line Wk 2	0.530	0.466	0.063	0.063	0.19%
Acute Second Line Wk 3	0.265	0.306	-0.041	0.041	0.12%
Acute Second Line Wk 4	0.000	0.000	0.000	0.000	0.00%
Acute Third Line Wk1	0.400	0.481	-0.081	0.081	0.24%
Acute Third Line Wk 2	0.302	0.372	-0.070	0.070	0.21%
Acute Third Line Wk 3	0.198	0.193	0.005	0.005	0.01%
Acute Third Line Wk 4	0.000	0.000	0.000	0.000	0.00%
Therapy Resistant - Hospitalized	2.837	3.123	-0.286	0.286	0.85%
Therapy Resistant - Outpatient	23.259	25.713	-2.453	2.453	7.31%
Therapy Resistant - Euthymic Treated	1.721	1.904	-0.183	0.183	0.54%
Therapy Resistant - Euthymic Not Treated	19.628	21.866	-2.238	2.238	6.67%
First Line Responder Observation	3.661	3.864	-0.202	0.202	0.60%
Second Line Responder Observation	2.593	1.725	0.868	0.868	2.58%
Third Line Responder Observation	1.116	1.506	-0.390	0.390	1.16%
First Line Euthymic	4.790	4.909	-0.119	0.119	0.35%
Second Line Euthymic	3.270	2.188	1.083	1.083	3.23%
Third Line Euthymic	1.405	1.895	-0.490	0.490	1.46%
First Line Euthymic Not-treated	83.986	85.895	-1.909	1.909	5.69%
Second Line Euthymic Not-treated	51.415	36.452	14.964	14.964	44.58%
Third Line Euthymic Not-treated	21.338	29.245	-7.908	7.908	23.56%
Dead	0.000	0.000	0.000	0.000	0.00%

Total QALYs	225.585	224.971	0.613	33.569	100.00%

QALY, quality-adjusted life year .Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table B73 Summary of undiscounted QALY gain by health state – Usual care versus Strategy 4

Health state	QALY intervention (Strategy 4)	QALY comparator (Usual Care)	Increment	Absolute increment	% absolute increment
Acute First Line Wk1	1.070	1.070	0.000	0.000	0.00%
Acute First Line Wk 2	0.787	0.787	0.000	0.000	0.00%
Acute First Line Wk 3	0.394	0.394	0.000	0.000	0.00%
Acute First Line Wk 4	0.000	0.000	0.000	0.000	0.00%
Acute Second Line Wk1	0.616	0.616	0.000	0.000	0.00%
Acute Second Line Wk 2	0.466	0.466	0.000	0.000	0.00%
Acute Second Line Wk 3	0.306	0.306	0.000	0.000	0.00%
Acute Second Line Wk 4	0.000	0.000	0.000	0.000	0.00%
Acute Third Line Wk1	0.512	0.481	0.030	0.030	0.28%
Acute Third Line Wk 2	0.356	0.372	-0.016	0.016	0.15%
Acute Third Line Wk 3	0.197	0.193	0.004	0.004	0.03%
Acute Third Line Wk 4	0.000	0.000	0.000	0.000	0.00%
Therapy Resistant - Hospitalized	2.837	3.123	-0.286	0.286	2.62%
Therapy Resistant - Outpatient	23.259	25.713	-2.453	2.453	22.45%
Therapy Resistant - Euthymic Treated	1.721	1.904	-0.183	0.183	1.67%
Therapy Resistant - Euthymic Not Treated	19.628	21.866	-2.238	2.238	20.48%
First Line Responder Observation	3.864	3.864	0.000	0.000	0.00%
Second Line Responder Observation	1.725	1.725	0.000	0.000	0.00%
Third Line Responder Observation	1.806	1.506	0.300	0.300	2.75%
First Line	4.909	4.909	0.000	0.000	0.00%

Euthymic					
Second Line Euthymic	2.188	2.188	0.000	0.000	0.00%
Third Line Euthymic	2.333	1.895	0.438	0.438	4.01%
First Line Euthymic Not-treated	85.895	85.895	0.000	0.000	0.00%
Second Line Euthymic Not-treated	36.452	36.452	0.000	0.000	0.00%
Third Line Euthymic Not-treated	34.226	29.245	4.980	4.980	45.57%
Dead	0.000	0.000	0.000	0.000	0.00%
Total QALYs	225.548	224.971	0.577	10.928	100.00%

QALY, quality-adjusted life year .Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table B74 Summary of undiscounted costs by health state – Usual care versus Strategy 2

Health state	Cost intervention (Strategy 2)	Cost comparator (Usual Care)	Increment	Absolute increment	% absolute increment
Acute First Line Wk1	£6,998.97	£6,998.97	£0.00	£0.00	0.00%
Acute First Line Wk 2	£5,143.56	£5,143.56	£0.00	£0.00	0.00%
Acute First Line Wk 3	£2,571.20	£2,571.20	£0.00	£0.00	0.00%
Acute First Line Wk 4	£0.00	£0.00	£0.00	£0.00	0.00%
Acute Second Line Wk1	£4,724.56	£4,210.14	£514.43	£514.43	4.53%
Acute Second Line Wk 2	£3,242.44	£3,186.64	£55.80	£55.80	0.49%
Acute Second Line Wk 3	£1,792.88	£2,088.80	-£295.91	£295.91	2.61%
Acute Second Line Wk 4	£0.00	£0.00	£0.00	£0.00	0.00%
Acute Third Line Wk1	£2,733.51	£3,284.62	-£551.11	£551.11	4.86%
Acute Third Line Wk 2	£2,067.17	£2,540.65	-£473.48	£473.48	4.17%
Acute Third Line Wk 3	£1,353.81	£1,318.51	£35.31	£35.31	0.31%
Acute Third Line Wk 4	£0.00	£0.00	£0.00	£0.00	0.00%
Therapy Resistant - Hospitalized	£16,920.35	£18,626.42	-£1,706.06	£1,706.06	15.03%
Therapy Resistant - Outpatient	£4,923.71	£5,442.84	-£519.13	£519.13	4.57%
Therapy Resistant - Euthymic Treated	£155.59	£172.11	-£16.51	£16.51	0.15%
Therapy Resistant - Euthymic Not Treated	£919.87	£1,024.73	-£104.86	£104.86	0.92%
First Line Responder Observation	£20,493.93	£20,493.93	£0.00	£0.00	0.00%
Second Line Responder Observation	£13,362.92	£9,568.71	£3,794.21	£3,794.21	33.43%
Third Line Responder Observation	£6,192.80	£8,345.40	-£2,152.61	£2,152.61	18.96%
First Line Euthymic	£439.29	£439.29	£0.00	£0.00	0.00%
Second Line Euthymic	£405.82	£279.34	£126.48	£126.48	1.11%
Third Line Euthymic	£179.53	£203.04	-£23.52	£23.52	0.21%

First Line Euthymic Not-treated	£4,019.30	£4,019.30	£0.00	£0.00	0.00%
Second Line Euthymic Not-treated	£2,317.82	£1,706.23	£611.59	£611.59	5.39%
Third Line Euthymic Not-treated	£999.12	£1,369.34	-£370.22	£370.22	3.26%
Dead	£0.00	£0.00	£0.00	£0.00	0.00%
Total Cost	£101,958.17	£103,033.75	-£1,075.59	£11,351.22	100.00%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table B75 Summary of undiscounted costs by health state – Usual care versus Strategy 3

Health state	Cost intervention (Strategy 3)	Cost comparator (Usual Care)	Increment	Absolute increment	% absolute increment
Acute First Line Wk1	£7,098.92	£6,998.97	£99.96	£99.96	0.76%
Acute First Line Wk 2	£4,876.57	£5,143.56	-£267.00	£267.00	2.04%
Acute First Line Wk 3	£2,699.02	£2,571.20	£127.83	£127.83	0.97%
Acute First Line Wk 4	£0.00	£0.00	£0.00	£0.00	0.00%
Acute Second Line Wk1	£4,717.02	£4,210.14	£506.88	£506.88	3.87%
Acute Second Line Wk 2	£3,463.35	£3,186.64	£276.72	£276.72	2.11%
Acute Second Line Wk 3	£1,729.68	£2,088.80	-£359.12	£359.12	2.74%
Acute Second Line Wk 4	£0.00	£0.00	£0.00	£0.00	0.00%
Acute Third Line Wk1	£2,733.51	£3,284.62	-£551.11	£551.11	4.20%
Acute Third Line Wk 2	£2,067.17	£2,540.65	-£473.48	£473.48	3.61%
Acute Third Line Wk 3	£1,353.81	£1,318.51	£35.31	£35.31	0.27%
Acute Third Line Wk 4	£0.00	£0.00	£0.00	£0.00	0.00%
Therapy Resistant - Hospitalized	£16,920.35	£18,626.42	-£1,706.06	£1,706.06	13.01%
Therapy Resistant - Outpatient	£4,923.71	£5,442.84	-£519.13	£519.13	3.96%
Therapy Resistant - Euthymic Treated	£155.59	£172.11	-£16.51	£16.51	0.13%

Therapy Resistant - Euthymic Not Treated	£919.87	£1,024.73	-£104.86	£104.86	0.80%
First Line Responder Observation	£20,148.34	£20,493.93	-£345.59	£345.59	2.64%
Second Line Responder Observation	£13,764.17	£9,568.71	£4,195.47	£4,195.47	32.00%
Third Line Responder Observation	£6,192.80	£8,345.40	-£2,152.61	£2,152.61	16.42%
First Line Euthymic	£616.56	£439.29	£177.27	£177.27	1.35%
Second Line Euthymic	£292.86	£279.34	£13.52	£13.52	0.10%
Third Line Euthymic	£179.53	£203.04	-£23.52	£23.52	0.18%
First Line Euthymic Not-treated	£3,929.93	£4,019.30	-£89.36	£89.36	0.68%
Second Line Euthymic Not-treated	£2,406.85	£1,706.23	£700.62	£700.62	5.34%
Third Line Euthymic Not-treated	£999.12	£1,369.34	-£370.22	£370.22	2.82%
Dead	£0.00	£0.00	£0.00	£0.00	0.00%
Total Cost	£102,188.76	£103,033.75	-£845.00	£13,112.12	100.00%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table B76 Summary of undiscounted costs by health state – Usual care versus Strategy 4

Health state	Cost intervention (Strategy 4)	Cost comparator (Usual Care)	Increment	Absolute increment	% absolute increment
Acute First Line Wk1	£6,998.97	£6,998.97	£0.00	£0.00	0.00%
Acute First Line Wk 2	£5,143.56	£5,143.56	£0.00	£0.00	0.00%
Acute First Line Wk 3	£2,571.20	£2,571.20	£0.00	£0.00	0.00%
Acute First Line Wk 4	£0.00	£0.00	£0.00	£0.00	0.00%
Acute Second Line Wk1	£4,210.14	£4,210.14	£0.00	£0.00	0.00%
Acute Second Line Wk 2	£3,186.64	£3,186.64	£0.00	£0.00	0.00%
Acute Second Line Wk 3	£2,088.80	£2,088.80	£0.00	£0.00	0.00%
Acute Second Line Wk 4	£0.00	£0.00	£0.00	£0.00	0.00%

Acute Third Line Wk1	£3,526.65	£3,284.62	£242.03	£242.03	5.19%
Acute Third Line Wk 2	£2,418.78	£2,540.65	-£121.87	£121.87	2.61%
Acute Third Line Wk 3	£1,336.60	£1,318.51	£18.09	£18.09	0.39%
Acute Third Line Wk 4	£0.00	£0.00	£0.00	£0.00	0.00%
Therapy Resistant - Hospitalized	£16,920.35	£18,626.42	-£1,706.06	£1,706.06	36.57%
Therapy Resistant - Outpatient	£4,923.71	£5,442.84	-£519.13	£519.13	11.13%
Therapy Resistant - Euthymic Treated	£155.59	£172.11	-£16.51	£16.51	0.35%
Therapy Resistant - Euthymic Not Treated	£919.87	£1,024.73	-£104.86	£104.86	2.25%
First Line Responder Observation	£20,493.93	£20,493.93	£0.00	£0.00	0.00%
Second Line Responder Observation	£9,568.71	£9,568.71	£0.00	£0.00	0.00%
Third Line Responder Observation	£9,951.61	£8,345.40	£1,606.20	£1,606.20	34.43%
First Line Euthymic	£439.29	£439.29	£0.00	£0.00	0.00%
Second Line Euthymic	£279.34	£279.34	£0.00	£0.00	0.00%
Third Line Euthymic	£300.69	£203.04	£97.65	£97.65	2.09%
First Line Euthymic Not-treated	£4,019.30	£4,019.30	£0.00	£0.00	0.00%
Second Line Euthymic Not-treated	£1,706.23	£1,706.23	£0.00	£0.00	0.00%
Third Line Euthymic Not-treated	£1,602.60	£1,369.34	£233.26	£233.26	5.00%
Dead	£0.00	£0.00	£0.00	£0.00	0.00%
Total Cost	£102,762.56	£103,033.75	-£271.20	£4,665.67	100.00%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Base-case analysis

6.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs

in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table B77 presents the base-case results versus usual care (strategy 1), while Table B78 presents the incremental analysis by cost (both with discounted costs and QALYs). It can be seen in the base-case that aripiprazole used at any stage of the treatment pathway is dominant to usual care, and is therefore a cost-effective option for the NHS. Aripiprazole used as second line therapy after risperidone has the lowest ICER and dominates all other strategies.

Table B77 Base-case results – All Strategies vs. Usual Care

Technologies	Total costs (£)	Total QALYs	Incremental costs (£) vs. Usual Care	Incremental QALYs vs. Usual Care	ICER (£) (cost per QALY) vs. Usual Care
Usual Care (Strategy 1)	£75,066	2.51637			
Second Line (Strategy 2)	£74,133	2.52466	-£932	0.00830	Dominant
First Line (Strategy 3)	£74,379	2.52348	-£686	0.00712	Dominant
Third Line (Strategy 4)	£74,888	2.52297	-£178	0.00660	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Table B78 Base-case results – Incremental Analysis

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Second Line (Strategy 2)	£74,133	2.52466			
First Line (Strategy 3)	£74,379	2.52348	£246	-0.00118	Dominated
Third Line (Strategy 4)	£74,888	2.52297	£508	-0.00052	Dominated
Usual Care (Strategy 1)	£75,066	2.51637	£178	-0.00660	Dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

All inputs described in Section 6.6.2 were varied in a one way deterministic sensitivity analysis. Where appropriate, a tornado diagram was generated to demonstrate the effect on the ICER of varying these parameters; the top 25 parameters that influenced the ICER are presented.

The results of the deterministic sensitivity analysis are further discussed below and in Section 6.7.10.

Usual Care versus Strategy 2

When comparing strategy 2 (aripiprazole second line) to usual care, the majority of ICERs remained dominant when the parameters were varied in isolation, except:

- Prob. response Wk 3: ARP
  Strategy 2 was inferior to usual care at the lower limit of aripiprazole effectiveness (incremental cost = £227, incremental QALYs = -0.00554).
- Prob. response Wk 3: OLA
  Strategy 2 had an ICER of £86,790 per QALY versus usual care for the upper limit of effectiveness of olanzapine (incremental cost = £630, incremental QALYs = -0.00303).

Usual Care versus Strategy 3

When comparing strategy 3 (aripiprazole first line) to usual care, the majority of ICERs remained dominant when the parameters were varied in isolation, except for those listed in Table B79.

Table B79: Deterministic sensitivity analysis results for strategy 3 versus usual care (parameters that changed the ICER from dominant)

Variable	Change	Incremental costs (£) vs. Usual Care	Incremental QALYs vs. Usual Care	ICER (£) (cost per QALY) vs. Usual Care
Response at week 3 - ARP	-30%	£1,694	-0.00796	Inferior
Response at week 3 – RIS	+30%	£1,381	0.00166	£833,270
Response at week 3 - OLA	+30%	-£384	-0.00421	Inferior
Probability of response at week 2 - ARP	-30%	£167	0.00604	£27,694

Proportion of wk 3 responders responding by wk 2 - ARP	-30%	£399	0.00576	£69,258
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years				

Usual Care versus Strategy 4

When comparing strategy 4 (aripiprazole third line) to usual care, the majority of ICERs remained dominant when the parameters were varied in isolation, except for those listed in Table B80.

Table B80: Deterministic sensitivity analysis results for strategy 4 versus usual care (parameters that changed the ICER from dominant)

Variable	Change	Incremental costs (£) vs. Usual Care	Incremental QALYs vs. Usual Care	ICER (£) (cost per QALY) vs. Usual Care
Response at week 3 - ARP	-30%	£121	-0.0059	Inferior
Response at week 3 - OLA	+30%	£124	-0.0047	Inferior
Probability of response at week 2 - ARP	-30%	£161	0.0062	£26,086
Probability of response at week 1 - ARP	-30%	£11	0.0064	£1,701
Proportion of wk 3 responders responding by wk 2 - ARP	-30%	£350	0.0060	£58,756
Proportion of wk 2 responders responding by wk 1 - ARP	-30%	£11	0.0064	£1,706
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years				

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

A PSA was performed as described in Section 6.6.3. The scatter plots of aripiprazole second line, first line, and third line versus no aripiprazole are presented in Figure B19, Figure B20 and Figure B21, respectively.

Figure B19 Scatter plot of strategy 2 (aripiprazole second line) vs Strategy 1 (usual care)

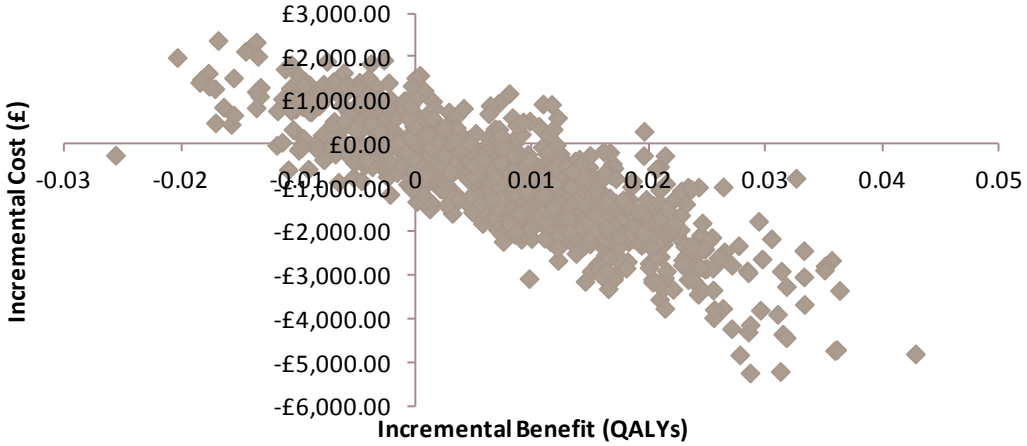


Figure B20 Scatter plot of strategy 3 (aripiprazole first line) vs Strategy 1 (usual care)

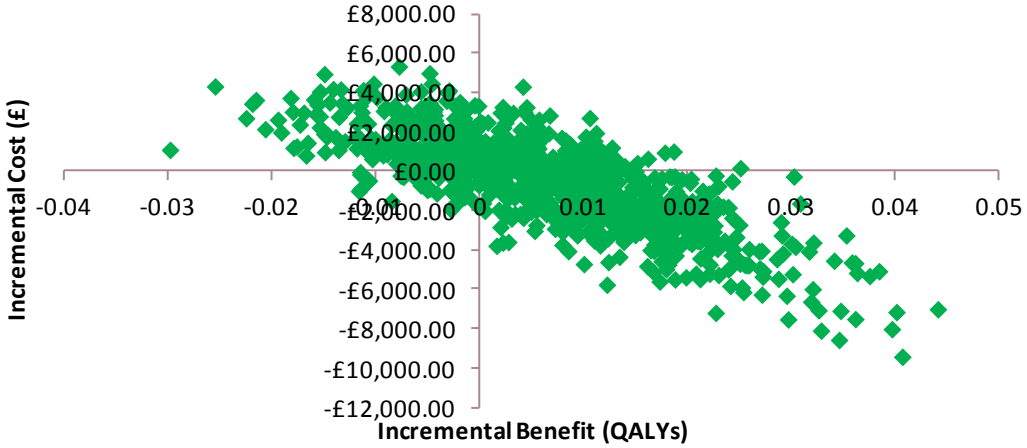
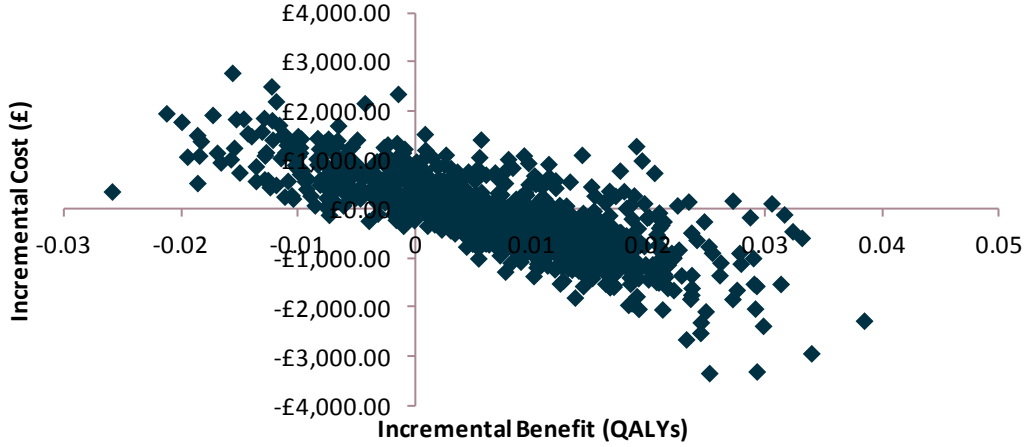


Figure B21 Scatter plot of strategy 4 (aripiprazole third line) vs Strategy 1 (usual care)



The scatter plots indicate that there is some uncertainty surrounding the expected ICERs, which is unsurprising given the lack of statistically significant differences in response rates between the four atypical antipsychotics. For all three aripiprazole strategies the majority of the PSA iterations lie in the lower half of the north-east quadrant (indicating cost-effectiveness) and the south-east quadrant (indicating dominance).

6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

10 mg dose aripiprazole

Efficacy and safety from the NMA run only on the 10 mg arm of the trial was incorporated into a scenario analysis (Section 5.7.6), as well as the costs of the 10 mg dose.

As can be seen from Table B81, the second and third line aripiprazole strategies are no longer dominant.

Table B81 Scenario analysis of 10 mg dose

Technologies	Total costs (£)	Total QALYs	Incremental costs (£) vs. Usual Care	Incremental QALYs vs. Usual Care	ICER (£) (QALYs) vs. Usual Care
Usual Care (Strategy 1)	£75,015	2.51658			
Second Line (Strategy 2)	£74,815	2.51991	-£200	0.00334	Dominant
First Line (Strategy 3)	£75,741	2.51858	£726	0.00200	£363,571
Third Line (Strategy 4)	£75,125	2.51865	£110	0.00208	£52,952
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Efficacy and safety results from the NMA including all studies

A sensitivity analysis of the NMA was run to include all studies, including the small co-morbid ADHD aripiprazole trial NCT00116259 (Tramontina 2009[57]). The result of including studies outside of the pivotal four RCTs was to increase the uncertainty in the NMA and to alter the efficacy results for aripiprazole (Section 9.15, Appendix 15). For completeness, the effect of using these results instead of the results derived only from the four pivotal RCTs has been investigated and is presented in Table B82. Second line aripiprazole remains dominant compared to usual care. First line aripiprazole is inferior to usual care and the ICER for third line aripiprazole versus usual care is high; however, these results must be treated with caution due to the uncertainty created in the NMA results by the inclusion of small trials.

Table B82 Scenario analysis with NMA sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£) vs. Usual Care	Incremental QALYs vs. Usual Care	ICER (£) (QALYs) vs. Usual Care
Usual Care (Strategy 1)	£72,352	2.53187			
Second Line (Strategy 2)	£72,178	2.53391	-£173	0.00204	Dominant
First Line (Strategy 3)	£73,164	2.53173	£812	-0.00014	Inferior
Third Line (Strategy 4)	£72,441	2.53284	£89	0.00097	£91,773
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Manic Symptom utilities from Revicki 2005[87]

As an alternative to Hayhurst 2006[94], the utilities from Revicki 2005[87] were investigated for the states defined by the level of manic symptoms. The utility multipliers derived from Revicki 2005 for each of these states are presented below in Table B83. The model results when these utilities are used are presented in Table B84. The use of the Revicki utilities for manic symptoms does not alter the ICERs considerably from the base case.

Table B83 Summary of Revicki 2005 quality-of-life values for scenario analysis

State	Age of population	Proportion male in population	General population utility	Reported utility for health state, mean (SE)	Utility multiplier (φ)	Reference in submission	Justification
Acute mania	42.4	0.445	0.890	0.230	0.259	Revicki 2005[87]	Utility for inpatient mania with moderate symptoms
Responder observation	42.4	0.445	0.890	0.756	0.849	Revicki 2005[87]	Stable state utility - weighted mean of risperidone and olanzapine treatment, plus a decrement of 0.07 (Glennie 1999) for hospitalisation
Euthymic treated	42.4	0.445	0.890	0.830	0.933	Revicki 2005[87]	Utility for stable state with risperidone treatment
Euthymic not treated	42.4	0.445	0.890	0.740	0.832	Revicki 2005[87]	Utility for stable state with no treatment. Can change to equal euthymic treated if necessary
Therapy resistance - inpatient	42.4	0.445	0.890	0.260	0.292	Revicki 2005[87]	Inpatient mania - mild symptoms
Therapy resistance - outpatient	42.4	0.445	0.890	0.600	0.674	Revicki 2005[87]	Outpatient mania - weighted mean of risperidone and olanzapine treatment.
Hospitalisation					0		No hospitalisation multiplier was used, as the utilities from Revicki 2005 were derived from inpatient and outpatient populations, thus meaning that the impact of hospitalisations has already been taken into account (apart from for the responder observation state)

Table B84 Scenario analysis with manic symptom utilities from Revicki 2005

Technologies	Total costs (£)	Total QALYs	Incremental costs (£) vs. Usual Care	Incremental QALYs vs. Usual Care	ICER (£) (QALYs) vs. Usual Care
Usual Care (Strategy 1)	£75,066	2.01152			
Second Line (Strategy 2)	£74,133	2.02172	-£932	0.01020	Dominant
First Line (Strategy 3)	£74,379	2.02160	-£686	0.01009	Dominant
Third Line (Strategy 4)	£74,888	2.01838	-£178	0.00686	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Weight gain utility from Revicki 2005[87]

As an alternative to Boyle 2010[97], the decrement for weight gain from Revicki 2005[87] was investigated. The utility decrement reported by Revicki 2005 for weight gain in an adult bipolar population was 0.066.[87] This was taken from the general population utility calculated for the Revicki 2005 population (0.890), and the φ of 0.926 was then calculated by comparing this value back to the general population value.

The model results when this utility multiplier is used are presented in Table B85. The use of the Revicki utility for weight gain does not alter the ICERs considerably from the base case.

Table B85 Scenario analysis with weight gain utility from Revicki 2005

Technologies	Total costs (£)	Total QALYs	Incremental costs (£) vs. Usual Care	Incremental QALYs vs. Usual Care	ICER (£) (QALYs) vs. Usual Care
Usual Care (Strategy 1)	£75,066	2.51765			
Second Line (Strategy 2)	£74,133	2.52522	-£932	0.00757	Dominant
First Line (Strategy 3)	£74,379	2.52403	-£686	0.00638	Dominant
Third Line (Strategy 4)	£74,888	2.52377	-£178	0.00612	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Changing the Order of the Reference Treatment Strategy

A scenario analysis was conducted to assess the influence of changing the order of the base case treatment strategy to swap the position of quetiapine and olanzapine in second and third line treatment.

Table B86 shows the treatment strategies used in the scenario analyses; in usual care risperidone is still used a first line, olanzapine is used as second line and quetiapine is used as third line.

Table B86: Scenario Analysis – Changing treatment strategy

	Strategy 1 (Usual care)	Strategy 2	Strategy 3	Strategy 4
First line	RIS	RIS	ARI	RIS
Second line	OLA	ARI	RIS	OLA
Third line	QTP	OLA	OLA	ARI

Table B87 provides the cost and QALY results for the treatment strategy scenario analysis. All strategies incorporating aripiprazole were dominant versus usual care.

Table B87 Scenario analysis results vs. Usual Care

Technologies	Total costs (£)	Total QALYs	Incremental costs (£) vs. Usual Care	Incremental QALYs vs. Usual Care	ICER (£) (QALYs) vs. Usual Care
Usual Care (Strategy 1)	£74,687	2.51672			
Second Line (Strategy 2)	£73,856	2.52778	-£831	0.01106	Dominant
First Line (Strategy 3)	£74,102	2.52660	-£585	0.00988	Dominant
Third Line (Strategy 4)	£74,214	2.52630	-£473	0.00958	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

6.7.10 What were the main findings of each of the sensitivity analyses?

Deterministic Sensitivity Analysis

When the parameters in the model were varied in a one-way analysis, the main parameters that influenced the ICER in such a way that the intervention became not cost effective were the rates of response applied during the acute treatment phase. For strategy 2, only the lower limit of the week 3 response rates for aripiprazole and the upper limit of the week 3 response rate for olanzapine affected the dominance of the strategy versus usual care. Similarly for strategies 3 and 4, the probabilities of response at weeks 3, 2 and 1 were identified as a key influence on the ICER. This was expected, as the response rate during the acute inpatient phase is the key driver of the transition probabilities between states, and therefore variations in these rates will have a significant effect on the ICER.

Probabilistic Sensitivity Analysis

The PSA indicates that there is some uncertainty surrounding the expected ICERs, which is unsurprising given the lack of statistically significant differences in response rates between the four atypical antipsychotics. For all three aripiprazole strategies the majority of the PSA iterations indicate cost-effectiveness or dominance.

Scenario Analysis

The ICERs for all three aripiprazole strategies were stable to changes in the source of utilities and the order of treatment in usual care. Second line aripiprazole remained dominant or cost-effective (ICER <£20,000 per QALY) versus usual care in all scenarios investigated.

The use of the 10 mg aripiprazole dose (with or without short treatment duration) and the NMA results including all possible trials were unfavourable for first and third line aripiprazole. However, the cost and QALY differences between the strategies remained small in all cases.

6.7.11 What are the key drivers of the cost-effectiveness results?

The main drivers of the cost-effectiveness analysis are the response rates associated with all treatments over the first 3 weeks of treatment. A favourable response rate drives patients to leave hospital earlier, which has both cost and HRQoL benefits. The results are sensitive to changes in response rate due to the fact that there was no significant difference in rate between any of the four atypical antipsychotics (aripiprazole, risperidone, quetiapine and olanzapine). Given the evidence available, aripiprazole has a favourable efficacy at some time points in the first 3 weeks of treatment compared to the comparators, which drives the model in favour of strategies that include aripiprazole.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The model was validated and quality assured in the following ways:

- All data extracted in the systematic review was double extracted and double checked by at least two analysts.
- The results were found to be aligned with the currently available literature in adults.[89, 115] The QALY differences between the treatment strategies were minimal, reflecting the similar efficacy of all interventions.
- Key variables were changed systematically in the model to ensure that the results responded appropriately in order to internally validate the model.
- The distribution of patients across health states over time was also assessed. It was identified that a large proportion of patients end up in the therapy resistance state and therefore it would unfairly disadvantage the treatment placed as third line if patient were continue on this. If a patients has not responded to 3 lines of atypical antipsychotics it was considered appropriate to move them on to lithium as maintenance therapy in therapy resistance, as clinical experts stated that these patients would not go untreated (Appendix 14).
- The model assumptions and inputs were validated by three clinical experts as described in Section 6.3.5 and Appendix 14.

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7

No subgroup analyses are presented in this submission.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

N/A

6.9.3 Please describe how the statistical analysis was undertaken.

N/A

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

N/A

6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

No

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No previous cost-effectiveness analysis has been performed that compares atypical antipsychotic treatment regimens for paediatric bipolar I disorder. Therefore there is no directly comparable literature to compare this de novo economic evaluation to.

A recent meta-analysis has been published that looked at the RCTs used in the network meta-analysis in this submission (Liu 2011). This analysis combined all the trial data for the antipsychotics, rather than assessing the differences between them. The forest plots presented in this meta-analysis do, however, corroborate the lack of statistically significant differences between the four atypical antipsychotics in terms of YMRS response by study endpoint.

Several economic evaluations were identified that compared two or more atypical antipsychotics for adult bipolar disorder:

- One evaluation was performed in the Spanish healthcare setting and found that aripiprazole was associated with lower rates of hospitalisation and cost savings compared to risperidone, olanzapine and quetiapine, as well as ziprasidone.[115] This analysis, although it was not specific to the treatment of manic episodes of bipolar, does support the conclusion that aripiprazole may have economic benefits over the other atypical antipsychotics.

- Bridle 2005 assessed the cost-effectiveness of quetiapine and olanzapine (as well as lithium, valproate and haloperidol) in the UK setting for the treatment of mania associated with bipolar disorder in adults.[89] They found that olanzapine dominated quetiapine, but the cost and QALY differences were small.[89] These small incremental costs and QALYs are reflective of the current model in children and adolescents.

- Woodward 2010 performed a cost-effectiveness analysis comparing quetiapine extended release tablets in combination with lithium to aripiprazole and olanzapine in the US setting.[116] Quetiapine in this formulation and setting was found to dominate both aripiprazole and olanzapine, but the many

differences of this evaluation to the current model presented in this submission mean that they are not comparable.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

Yes, the base case analysis includes all bipolar I disorder patients with manic episodes who would be eligible for aripiprazole under its expected paediatric licence for this condition.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The following strengths of the model have been identified:

- The model captures the complexity of the treatment and clinical pathway, and has been validated by clinical experts.
- A reliable indirect comparison of the four atypical antipsychotics was able to be made for the first 3 weeks of treatment. Each agent had been assessed in a large, well-designed RCT and all these RCTs were deemed to be comparable for indirect comparison purposes.

The following weaknesses of the model have been identified:

- The lack of head-to-head data means that uncertainty remains over the relative effectiveness of the atypical antipsychotics for the treatment of acute manic episodes of bipolar I disorder in children and adolescents.
- The use of the safety data from the whole population of the pivotal aripiprazole trial (aged 10-17) in the NMA and therefore in the model is a limitation, as the safety profile of aripiprazole is more favourable in the older age group of 13-17 years old than in the younger age group (10-12). The current approach in the model is therefore a conservative approach for aripiprazole. If the safety data from the 13-17 year old subgroup data could be used in the model, this would make the model more reflective of clinical practice and it would be expected to be more favourable for aripiprazole. This was not possible in the current model due to the fact that the subgroup data

came available too late in the submission process to be incorporated into the NMA and model.

- The lack of long term data for the comparator atypical antipsychotics (particularly for adverse events) in children and adolescents meant that the model is driven by the acute phase. This is not a major weakness, however, as aripiprazole is being appraised for the acute treatment of manic episodes rather than the maintenance phase. Although the maintenance phase was modelled in order to reflect true clinical practice, it should not drive the model to inform a decision about acute phase treatment.
- The lack of data on the relapse rate after discontinuing treatment after 12 weeks is a limitation of the model. This has been investigated in deterministic sensitivity analysis and found not to affect the final conclusions.
- The lack of utility and resource use data specifically for children and adolescents is another weakness of the model. The adult utility data has been adjusted to a child population and the resource use data has been taken from the opinion of UK experts in child and adolescent psychiatry (Appendix 14). However, more robust data collected in a clinical study would be desirable.
- The YMRS response was the only tool from the clinical trial data that was appropriate to use to model treatment decisions regarding switching treatments. However, in clinical practice switching of treatment is not decided on YMRS response. It could be that clinicians actually keep patients on treatment if they have a partial response. This would explain why the model accrues more patients in the therapy resistant state than would be expected to have failed three lines of treatment in clinical practice. However, without real-life data on switching treatment practice, the model cannot be adapted.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Due to the fact the age subgroup data became available too late in the submission process, it was not possible to include the safety data for the 13-17 year old subgroup in the NMA and model. The model would be made more robust if this additional analysis could be performed.

A simpler model structure that does not assess 3 lines of treatment, but simply compares the four atypical antipsychotics against each other may also be useful to

inform on the small differences between each individual treatment. If utility could accurately be mapped to YMRS score, a model that assesses change in YMRS score, than relying on the dichotomous response or non-response switch, could also be informative to better differentiate between the effectiveness of the atypical antipsychotics.

Several analyses were not possible due to the lack of data. Therefore the following data generation may be required in order to enhance the robustness of the model:

- Head-to-head effectiveness data for the aripiprazole versus the other antipsychotics.
- Data on relapse rates after discontinuation of treatment for all comparators.
- UK-specific data to inform the usual treatment pathway of paediatric bipolar disorder.
- Utility data for UK children experiencing manic episodes of bipolar I disorder.
- Further long term data on prevention of recurrent episodes in children and adolescents, both for aripiprazole and for other agents.

Although the analyses mentioned above could make the model more robust, consideration should be given to the expected impact of this information, which given the small QALY differences between the comparators and the small patient population is likely to be low.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

Summary of Budget Impact

- From 2012-2016, the estimated number of children and adolescents with bipolar disorder in England and Wales eligible for treatment ranged from 150 to 154 per year.
- The estimated annual impact of aripiprazole, following its recommendation, is 10% for the first year, which tapered off to 0% in the fifth year.
- Considering the different treatment, monitoring and adverse event costs across the atypical antipsychotics, the recommendation of aripiprazole would be expected to have a budget impact of £34,475 over the next 5 years.
- Considering the overall NHS budget, this budget impact can be considered as minimal.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The Office of National Statistics (ONS) reports that there were 3,409,849 13-17 year olds in England and Wales in 2011.[117] Based on the projected population percentage change for this age group in England for each year from 2011 to 2017 (Table C1)[118], the total expected number of people aged 13-17 in England and Wales were calculated for the next 5 years (Table C2). Using these values, the number of

patients eligible for treatment was calculating using incidence and prevalence data of bipolar disorder in this population.

Table C1: Projected percentage population changes from 2011 to 2017 for children aged 13-17 in England[118]

	2011-2012	2012-2013	2013-2014	2014-2015	2015-2016	2016-2017
Percentage population change	-1.21%	-1.22%	-1.82%	-2.34%	-1.45%	-0.61%

Incidence

Under the new licence, 100% of the new patient cohort each year are considered eligible for treatment. An incidence rate of 0.00091% per year was employed in the budget impact model. This incidence was calculated using data from a surveillance study of paediatric bipolar disorder in the UK and Republic of Ireland.[119] The study showed that there were an estimated 42 cases of paediatric bipolar disorder (defined as onset <16 years) in the year leading up to July 2010.[119] Following the application of this incidence to the 2010 population of 10-15 year olds in these two countries (UK:4,303,300; ROI:342,974[120]), an incidence rate of 0.00091% was established, which could then be applied to the populations of England and Wales alone. As this incidence excludes 16 and 17 year olds, it is recognised that this may represent an underestimation of the true incidence.

Prevalence

A retrospective review of patients evaluated at Maudsley Hospital in South London identified 38 cases of paediatric bipolar disorder over 22 years, which was approximately 1.7 cases per year for a specialist psychiatric centre.[121] Given that there are approximately 80 child and adolescent mental health inpatient units in England and Wales,[41] this gave an estimate of 136 hospitalised cases seen per year. However, the results of this study are from 1996 and may not accurately reflect the current prevalence of paediatric bipolar disorder in England and Wales. Therefore, the incidence rate of 0.00091% was applied to the population of 13-17 year olds each year from 1996 to 2017,[122] which was then added to the prevalence of the each prior year (starting at 136 in 1996). Additionally, it was assumed that the prevalence rate did not include any children below the age of 13, as this would be rare in the UK and therefore that the rate could be applied to the population aged 13-17. It was also

assumed that the prevalence would decrease by 1/5 each year, as this proportion of patients would turn 18 and would not be eligible for treatment as children.

It was assumed that 30% of patients would relapse within the first year and therefore receive two courses of treatment in that year. It was further assumed that 30% of prevalent patients would relapse each year and require a course of treatment. The relapse rate was derived from expert opinion (Appendix 14) and matched the relapse used in the economic model for the "euthymic, not treated" state (see Section 6.3.5).

Therefore, following the addition of the yearly prevalence and incidence values, and accounting for the relapse rate and proportion of patients eligible for treatment, respectively, the estimated numbers of patients starting treatment each year are summarised in Table C2 below.

Table C2: The proportion of children and adolescents eligible for treatment

	Year 1	Year 2	Year 3	Year 4	Year 5	Reference
England and Wales population 13-17 years	3,327,493	3,266,933	3,190,486	3,144,224	3,125,045	ONS[117, 118]
Incidence rate	0.00091%	0.00091%	0.00091%	0.00091%	0.00091%	Sharma 2010[119]
Incidence	30	30	29	29	29	
Prevalence	154	154	153	151	150	Sigurdsson 1999[121]
Eligible patient population						
Proportion of incidence patient cohort eligible for treatment	100%	100%	100%	100%	100%	Assumption that all newly diagnosed patients treated with one course of therapy
Proportion of incidence patient cohort who would not relapse within the 1st year	70%	70%	70%	70%	70%	Expert opinion (Appendix 14)
Proportion of new patient cohort who will relapse and therefore receive 2 courses of treatment in first year	30%	30%	30%	30%	30%	Expert opinion (Appendix 14)

Proportion of prevalent patients eligible for treatment (due to relapse)	30%	30%	30%	30%	30%	Expert opinion (Appendix 14)
Results						
Patients starting treatment	77	76	75	74	73	

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

An estimate of the current proportion of antipsychotics prescribed for bipolar disorder UK children was adapted from data presented by the Royal College of Psychiatrists, which analysed the prescribing prevalence of antipsychotics for any disorder in this age group.[123] This information was used to calculate the current market share of aripiprazole, risperidone, quetiapine and olanzapine. Haloperidol was also included in the Royal College of Psychiatrists study; however, as this was not a comparator in the initial scope for bipolar I disorder manic episodes, the prescribing prevalence of aripiprazole, risperidone, quetiapine and olanzapine were adjusted to exclude this antipsychotic. The prescribing prevalence of the current treatment options are described in Table C3.

Table C3: The current treatment options for paediatric bipolar disorder

	Aripiprazole	Risperidone	Quetiapine	Olanzapine	Reference Source
Year 1	13%	65%	8%	14%	Royal College of Psychiatrists prescribing estimates for under 18s 2010.[123]
Year 2	13%	65%	8%	14%	
Year 3	13%	65%	8%	14%	
Year 4	13%	65%	8%	14%	
Year 5	13%	65%	8%	14%	

It is important to note that the prescribing prevalence of the current treatment options included a range of disorders. Therefore, there are limitations to the market share as risperidone is used frequently for autism spectrum disorders in children and adolescents, due to its reported high efficacy in adults.[124] Decreasing the market share for risperidone compared to the other comparators decreases the budget impact of aripiprazole recommendation as aripiprazole is the cheapest alternative. Therefore, the current market shares are a conservative estimate for aripiprazole's budget impact.

Following the recommendation of aripiprazole, the anticipated yearly uptake rate from the manufacturers forecast is summarised in Table C4. This uptake rate was applied to the market share each year to estimate the market share of aripiprazole in subsequent years (see Section 7.3).

Table C4: The anticipated yearly uptake rate of aripiprazole compared to previous year

	Aripiprazole	Reference source
Year 1	10%	Manufacturer forecast
Year 2	5%	Manufacturer forecast
Year 3	2%	Manufacturer forecast
Year 4	2%	Manufacturer forecast
Year 5	0%	Manufacturer forecast

7.3 What assumption(s) were made about market share (when relevant)?

In order to calculate the decrease in the market share of the comparators, which occurs in conjunction with the annual aripiprazole uptake, the weightings of each comparator were established. This was based on the Royal College of Psychiatrists estimation of prescribing prevalence with the exclusion of aripiprazole.[123] The weightings given to each treatment option are outlined in Table C5.

Table C5: The prescribing prevalence weightings given to the comparator antipsychotics

Risperidone	Quetiapine	Olanzapine
0.747	0.096	0.157

These weightings were then used to provide an estimate of the change in market share for each treatment option each year, taking into account the anticipated aripiprazole uptake rate. The projected market share for the antipsychotics following the recommendation of aripiprazole is summarised in Table C6.

Table C6: The annual projected market share of antipsychotics following the recommendation of aripiprazole

	Aripiprazole	Risperidone	Quetiapine	Olanzapine
Year 1	22.63%	57.79%	7.46%	12.12%
Year 2	27.63%	54.06%	6.98%	11.33%
Year 3	32.63%	50.32%	6.49%	10.55%
Year 4	34.63%	48.83%	6.30%	10.24%
Year 5	34.63%	48.83%	6.30%	10.24%

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

An additional blood glucose measurement is required for patients starting treatment with olanzapine, amounting to a single monitoring cost of £0.81 per patient (accounting for inflation from the 2007 value of £0.68[100,99]) The cost of blood glucose monitoring was considered to be equivalent for the rest of the antipsychotics, as there was no difference in the NICE recommendations. Additionally, NICE recommendations recognise that treating children and adolescents with risperidone is associated with an increase in prolactin related adverse events.[1] Therefore, the monitoring of prolactin was included as an additional cost at a rate of £3.36 per treatment course.[108]

Due to the fact that no significant difference in effectiveness was found between the atypical antipsychotics, the costs associated with hospital stay have not been included in the budget impact.

In line with the economic model, additional costs for somnolence and EPS were not included, as costs for these adverse events are likely to be included in the hospital costs for each treatment (which are not modelled in the budget impact model due to uncertainty). Therefore, only annual costs associated with weight gain were included in the budget impact model. The cost of visitations to health care professionals per 12 week treatment course for weight gain was £250 according the unit costs used in the economic model (Table B69) and this was multiplied by the probability of experiencing weight gain for each antipsychotic. The costs of weight gain for all antipsychotics per 12 week course are shown in Table C7.

Table C7: The cost of weight gain in patients treated with antipsychotics

	Aripiprazole	Risperidone	Quetiapine	Olanzapine
Probability of weight gain	0.03403	0.04083	0.4032	0.4501
Cost per 12 week course	£250	£250	£250	£250
Adjusted cost per treatment course	£8.51	£10.21	£100.80	£112.53

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The average treatment unit costs per day as used in the cost-effectiveness model (Table B67, Section 6.5.5) were used to calculate the costs per 12 week treatment course per patient, which are outlined in Table C8. Generic forms of aripiprazole are due to be launched in 2014 and therefore a scenario analysis was performed in which the acquisition cost of aripiprazole is reduced by 50% in years 3-5 of the model.

The monitoring costs and the unit costs for weight gain are described above in Section 7.5. As described previously, it was assumed 30% of patients would have two courses of treatment per year, and therefore the cost per treatment course was doubled for 30% of patients.

Table C8: Acquisition, AE, and monitoring costs associated with a 12 week (84 day) course of the atypical antipsychotics

Drug name	Acquisition	AEs (weight gain)	Monitoring
Aripiprazole	**Base case:** £430.92 **Scenario analysis:** Years 1-2: £430.92 Years 3-5: £215.46	£8.51	
Risperidone	£5.04	£10.21	£3.36
Quetiapine	£339.36	£100.80	
Olanzapine	£110.88	£112.53	£0.81

7.6 Were there any estimates of resource savings? If so, what were they?

The increased uptake of aripiprazole leads to a decrease in the number of patients treated with risperidone and olanzapine, and therefore reduces monitoring costs, as discussed in Section 7.4. Over five years, the total monitoring costs that are saved following the recommendation of aripiprazole amounted to £228. Additionally, the total savings due to a reduction in the number of adverse events following the recommendation of aripiprazole was estimated to be £2,286.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The annual costs associated with the antipsychotics, as outlined in Table C8, were applied to the number of patients starting treatment, which was calculated using the market share of each antipsychotic and the number of patients starting treatment each year. The estimated annual budget impact following the recommendation of aripiprazole is shown in Table C9 and the scenario analysis where the generic price of aripiprazole is taken into account is shown in Table C10.

Given the size of the overall NHS budget, a budget impact of £16,785- £30,070 over 5 years can be considered to be minimal.

Table C9: The estimated annual budget impact following the recommendation of aripiprazole (not incorporating generic aripiprazole price)

Year	Before recommendation	After recommendation	Incremental
1	£13,477.60	£16,941.38	£3,463.78
2	£13,357.28	£18,506.57	£5,149.28
3	£13,186.87	£19,964.99	£6,778.12
4	£13,037.63	£20,409.18	£7,371.55
5	£12,924.58	£20,232.21	£7,307.63
Total	£65,983.97	£96,054.33	**£30,070.36**

Table C10: The estimated annual budget impact following the recommendation of aripiprazole incorporating a generic aripiprazole price in years 3-5

Year	Before recommendation	After recommendation	Incremental
1	£13,477.60	£16,941.38	£3,463.78
2	£13,357.28	£18,506.57	£5,149.28
3	£10,536.28	£13,117.62	£2,581.34
4	£10,417.03	£13,224.37	£2,807.34
5	£10,326.71	£13,109.71	£2,783.00
Total	£58,114.90	£74,899.65	**£16,784.75**

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

As this budget impact model is being considered from a healthcare perspective, rather than a societal perspective, the costs associated with the productivity of caregivers was not included. However, the treatment of bipolar symptoms in children could allow their parents, carers and teachers to be more productive at work, which has implications for the country as a whole.

8 References

1. NICE. Bipolar Disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. National Institute for Health and Clinical Excellence. 2006;Clinical Guideline 38.
2. Expert opinion of Dr Anne Shortall, Consultant Child and Adolescent Psychiatrist, Carol Kendrick Centre.
3. Expert opinion of Dr Marinos Kyriakopoulos, Consultant Child & Adolescent Psychiatrist, Acorn Lodge Inpatient Children's Unit, Bethlem Royal Hospital.
4. Expert opinion of Dr Richard Corrigall, Consultant Adolescent Psychiatrist, Snowsfields Adolescent Unit, Mapother House, Maudsely Hospital.
5. Findling RL, Nyilas M, Forbes RA, McQuade RD, Jin N, Iwamoto T, et al. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: A randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry. [Journal Article]. 2009;70(10):1441-51.
6. Findling RL, Nyilas M, Aurang C, van Beek A, Jin N, Marcus R, et al. Long term efficacy of aripiprazole in children (ages 10-17 years) with bipolar I disorder. American College of Neuropsychopharmacology 46th Annual Meeting2007.
7. Correll C, Nyilas M, Forbes R, Jin N, Aurang C, Owen R, et al. Long-term Tolerability and Safety of Aripiprazole in the Treatment of Pediatric Patients with Schizophrenia or Bipolar I Disorder. XXVI CINP Congress Collegium Internationale Neuro-Psychopharmacologicum Conference July 13–17, 2008, Munich, Germany.
8. Aripiprazole Summary of Product Characteristics.
9. Risperidone Summary of Product Characteristics. [http://www.medicines.org.uk/emc/medicine/12818#PHARMACOLOGICAL_PROPS accessed 13.04.12].
10. Quetiapine Summary of Product Characteristics [http://www.medicines.org.uk/EMC/medicine/2295/SPC/SEROQUEL+25+mg%2c+100+mg%2c+150+mg%2c+200+mg%2c+300+mg+film-coated+tablets/#PHARMACOLOGICAL_PROPS accessed 13.04.12].
11. Olanzapine Summary Product of Characteristics.
12. Forbes A. Long-term efficacy and safety of aripiprazole in children and adolescents with mania. European Neuropsychopharmacology Conference: 21st ECNP Congress Barcelona Spain. 2008;18(S4):S556-S7.
13. Federal University of Rio Grande do Sul. Aripiprazole Associated With Methylphenidate in Children and Adolescents With Bipolar Disorder and ADHD. NCT00305370 [http://clinicaltrials.gov/ct2/show/NCT00305370?term=aripiprazole&rank=88 accessed 13.04.12]. Clinicaltrialsgov.
14. Washington University School of Medicine. Metabolic Effects of Antipsychotics in Children (MEAC). NCT00205699. [http://clinicaltrials.gov/ct2/show/NCT00205699?term=aripiprazole&rank=198 accessed 13.04.12].
15. University of Maryland. Side Effect Study of Antipsychotic Medicines to Treat Childhood Bipolar Disorder (PAMS). NCT00746252. [http://clinicaltrials.gov/ct2/show/NCT00746252?term=aripiprazole&rank=216 accessed 13.04.12].
16. National Institute of Mental Health. Bipolar Disorder in Children and Teens: A Parent's Guide. 2009.
17. Youngstrom E, Freeman A. The Assessment of Children and Adolescents with Bipolar Disorder. Child Adolesc Psychiatric Clin N Am. 2009;18:353-90.
18. Goodwin GM, Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2009;23(4):346-88.
19. Haas M, DelBello MP, Pandina G, Kushner S, Van Hove I, Augustyns I, et al. Risperidone for the treatment of acute mania in children and adolescents with bipolar

disorder: A randomized, double-blind, placebo-controlled study. Bipolar Disorders. [Journal Article]. 2009;11(7):687-700.
20. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry. 2005 Sep;44(9):846-71.
21. Dubicka B, Carlson G, Vail A, Harrington R. Prepubertal mania: diagnostic differences between US and UK clinicians. Eur Child Adolesc Psychiatry. 2008;17(3):153-61.
22. Faedda GL, Baldessarini RJ, Glovinsky IP, Austin NB. Pediatric bipolar disorder: phenomenology and course of illness. Bipolar Disord. 2004 Aug;6(4):305-13.
23. Braun-Scharm H, Bilke O. Differential diagnosis and pharmacotherapy of juvenile mania -- a review. Psychiatr Prax. 2006 Mar;33 Suppl 1:S40-6.
24. DelBello MP, Kowatch RA, Adler CM, Stanford KE, Welge JA, Barzman DH, et al. A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. J Am Acad Child Adolesc Psychiatry. [Journal Article]. 2006;45(3):305-13.
25. Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: A review of the existing literature. Development and Psychopathology. [Journal Review]. 2006;18:1023-35.
26. Rajeev J, Srinath S, Reddy YC, Shashikiran MG, Girimaji SC, Seshadri SP, et al. The index manic episode in juvenile-onset bipolar disorder: the pattern of recovery. Can J Psychiatry. 2003 Feb;48(1):52-5.
27. Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M. Treatment guidelines for children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2005 Mar;44(3):213-35.
28. Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, et al. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry. 2004 May 1;55(9):875-81.
29. Tohen M, Kryzhanovskaya L, Carlson G, DelBello M, Wozniak J, Kowatch R, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. American Journal of Psychiatry. [Journal Article]. 2007;164(10):1547-56.
30. Roke Y, van Harten PN, Boot AM, Buitelaar JK. Antipsychotic medication in children and adolescents: a descriptive review of the effects on prolactin level and associated side effects. Journal of Child and Adolescent Psychopharmacology. 2009;19(4):403-14.
31. Correll CU. Assessing and maximizing the safety and tolerability of antipsychotics used in the treatment of children and adolescents. The Journal of clinical psychiatry. 2008;69:26.
32. McDougall T. Nursing Children and Adolescents With Bipolar Disorder: Assessment, Diagnosis, Treatment, and Management. J Child Adolesc Psychiatr Nurs. 2009;22:33-9.
33. Daniels SR, Arnett DK, Eckel RH, Gidding SS, Hayman LL, Kumanyika S, et al. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. Circulation. 2005 Apr 19;111(15):1999-2012.
34. Freeman AJ, Youngstrom EA, Michalak E, Siegel R, Meyers OI, Findling RL. Quality of life in pediatric bipolar disorder. Pediatrics. [Journal; Peer Reviewed Journal]. 2009;123(3):446-52.
35. Perlis R, Dennehy E, Miklowitz D, DelBello M, Ostacher M, Calabrese J, et al. Retrospective age at onset of bipolar disorder and outcome during two-year follow-up: results from the STEP-BD study. Bipolar Disord. 2009;11:391-400.
36. Rademacher J, DelBello MP, Adler C, Stanford K, Strakowski SM. Health-related quality of life in adolescents with bipolar I disorder. J Child Adolesc Psychopharmacol. [Journal Article]. 2007;17(1):97-103.
37. Whitehead RE, Chen CF, Kim E, Carson WH, Iwamoto T, Mathew S, et al. Patient assessed quality of life vs. clinician assessment in a trial of aripiprazole in pediatric patients with bipolar disorder. Bipolar Disorders 8th International Conference on Bipolar Disorder 2009;11(S1):89. [Journal Conference Abstract]. 2009.
38. Ostacher MJ, Nierenberg AA, Iosifescu DV, Eidelman P, Lund HG, Ametrano RM, et al. Correlates of subjective and objective burden among caregivers of patients with bipolar disorder. Acta Psychiatr Scand. 2008 Jul;118(1):49-56.
39. Soutullo CA, Chang KD, Diez-Suarez A, Figueroa-Quintana A, Escamilla-Canales I, Rapado-Castro M, et al. Bipolar disorder in children and adolescents: international perspective on epidemiology and phenomenology. Bipolar Disord. 2005 Dec;7(6):497-506.

40. Rani F, Murray ML, Byrne PJ, Wong IC. Epidemiologic features of antipsychotic prescribing to children and adolescents in primary care in the United Kingdom. Pediatrics. 2008 May;121(5):1002-9.
41. National in-patient child and adolescent psychiatric study investigators. National in-patient child and adolescent psychiatric study (NICAPS) report [http://www.rcpsych.ac.uk/PDF/NICAPS%20report%20full.pdf accessed 25.04.12]. 2001.
42. Brunelle J, Consoli A, Tanguy M, Huynh C, Perisse D, Denisu E, et al. Phenomenology, socio-demographic factors and outcome upon discharge of manic and mixed episodes in hospitalized adolescents. European Child & Adolescent Psychiatry. 2009;18(3):185-93.
43. Ben Amor L. Antipsychotics in pediatric and adolescent patients: A review of comparative safety data. J Affect Disord. 2012;138 Suppl:S22-30.
44. Doey T. Aripiprazole in pediatric psychosis and bipolar disorder: A clinical review. J Affect Disord. 2012;138 Suppl:S15-21.
45. Correll C, Manu P, Olshansky V. Cardiometabolic Risk of Second-Generation Antipsychotic Medications During First-Time Use in Children and Adolescents. JAMA. 2009;302(16):1765-73.
46. De Hert M, Dobbelaere M, Sheridan EM, Cohen D, Correll CU. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: A systematic review of randomized, placebo controlled trials and guidelines for clinical practice. Eur Psychiatry. 2011 Apr;26(3):144-58.
47. National Collaborating Centre for Mental Health. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care: The British Psychological Society and Gaskell; 2006.
48. Jensen PS, Buitelaar J, Pandina GJ, Binder C, Haas M. Management of psychiatric disorders in children and adolescents with atypical antipsychotics: a systematic review of published clinical trials. Eur Child Adolesc Psychiatry. 2007 Mar;16(2):104-20.
49. Zuddas A, Zanni R, Usala T. Second generation antipsychotics (SGAs) for non-psychotic disorders in children and adolescents: a review of the randomized controlled studies. Eur Neuropsychopharmacol. 2011 Aug;21(8):600-20.
50. Fraguas D, Correll CU, Merchan-Naranjo J, Rapado-Castro M, Parellada M, Moreno C, et al. Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. Eur Neuropsychopharmacol. 2011 Aug;21(8):621-45.
51. Liu H, Potter M, Woodworth Y, Yorks D, Petty C, Wozniak J, et al. Pharmacologic Treatments for Pediatric Bipolar Disorder: A Review and Meta-Analysis. J Am Acad Child Adolesc Psychiatry. 2011;50(8):749-62.
52. Loze JY, Forbes RA, Zhao J, Chen CF, Carson W, Iwamoto T, et al. Line item analysis in child and adolescent patients with bipolar I disorder treated with Aripiprazole in an acute study (31-03-240). European Child and Adolescent Psychiatry Conference: 14th International Congress of ESCAP European Society for Child and Adolescent Psychiatry Helsinki Finland 2011;20:S185). [Journal Conference Abstract]. 2011.
53. Loze JY, Mankoski R, Zhao J, Carson W, Youngstrom E, Findling R, et al. Line item analysis in paediatric patients with bipolar I disorder treated with aripiprazole. European Psychiatry Conference: 19th European Congress of Psychiatry, EPA 2011 Vienna Austria 2011;26. [Journal Conference Abstract]. 2011.
54. Mankoski R, Zhao J, Carson WH, Mathew SJ, Forbes RA. Young mania rating scale line item analysis in pediatric subjects with bipolar i disorder treated with aripiprazole in a short-term, double-blind, randomized study. Journal of Child and Adolescent Psychopharmacology. [Journal Article]. 2011;21(4):359-64.
55. National Horizon Scanning Centre. Aripiprazole (Abilify) for children and adolescents with bipolar disorder (Structured abstract). Birmingham: National Horizon Scanning Centre (NHSC) [serial on the Internet]. 2008 [cited i1: Available from: http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32010000565/frame.html.
56. Pikalov A, McQuade RD, Carson WH, Nyilas M, Forbes RA, Iwamoto T, et al. Somnolence and sedation in child and adolescent patients with bipolar I disorder treated with aripiprazole in an acute study with long term follow-up. Bipolar Disorders Conference: 8th International Conference on Bipolar Disorder 2009;11(S1);69. [Journal Conference Abstract]. 2009.

57. Tramontina S. Aripiprazole in children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder: a pilot randomized clinical trial. J Clin Psychiatry. 2009;70:756-64.
58. Tramontina S, Zeni C, Pheula G, Ketzer de Souza C, Augusto Rohde L. Aripiprazole in juvenile bipolar disorder comorbid with attention-deficit/hyperactivity disorder: an open clinical trial. CNS Spectr. 2007;12(10):758-62.
59. Findling RL, Youngstrom EA, McNamara NK, Stansbrey RJ, Wynbrandt JL, Adegbite C, et al. Double-blind, randomized, placebo-controlled long-term maintenance study of aripiprazole in children with bipolar disorder. The Journal of clinical psychiatry. 2012;73:57-63.
60. Findling RL, Youngstrom EA, McNamara NK, Stansbrey RJ, Demeter CA, Rowles BM, et al. A double-blind, randomized, placebo-controlled long-term study of aripiprazole in children with bipolar disorder. Neuropsychopharmacology 50th Annual Meeting of the American College of Neuropsychopharmacology, ACNP 2011;36:S349-S350), 2011. [Journal Conference Abstract]. 2011.
61. Otsuka Pharmaceutical Development & Commercialization Inc. Aripiprazole (Abilify, OPC-14597, BMS-337039) Clinical Study Report. Protocol No. 31-03-240. 2007.
62. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, et al. A children's global assessment scale (CGAS). Archives of General Psychiatry. 1983;40(11):1228.
63. Busner J, Targum SD. The Clinical Global Impressions Scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007;4(7):28.
64. Poznanski EO, Cook SC, Carroll BJ. A depression rating scale for children. Pediatrics. 1979;64(4):442-50.
65. Poznanski EO, Grossman JA, Buchbaum Y, Banegas M, Freeman L, Gibbons R. Preliminary studies of the reliability and validity of the Children's Depression Rating Scale. Journal of the American Academy of Child Psychiatry. 1984;23(2):191-7.
66. Depue RA, Krauss S, Spoont MR, Arbisi P. General Behavior Inventory identification of unipolar and bipolar affective conditions in a nonclinical university population. Journal of Abnormal Psychology. 1989;98(2):117.
67. Faries DE, Yalcin I, Harder D, Heiligenstein JH. Validation of the ADHD Rating Scale as a clirlician administered and scored instrument. Journal of Attention Disorders. 2001;5(2):107-15.
68. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD Rating Scale—IV: Checklists, norms, and clinical interpretation: Guilford Press; 1998.
69. Barbosa GA, Dias MR, Gaião A, Di Lorenzo WF. Escala para avaliação de depressão em crianças-Revisada (CDRS-R): uma análise exploratória. Infanto. 1997;5(1):15-8.
70. Personal communication with study authors. 13th April 2012.
71. Delbello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. J Am Acad Child Adolesc Psychiatry. 2002 Oct;41(10):1216-23.
72. Pavuluri MN, Henry DB, Carbray JA, Sampson G, Naylor MW, Janicak PG. Open-label prospective trial of risperidone in combination with lithium or divalproex sodium in pediatric mania. J Affect Disord. 2004 Oct;82 Suppl 1:S103-11.
73. Biederman J, Mick E, Hammerness P, Harpold T, Aleardi M, Dougherty M, et al. Open-label, 8-week trial of olanzapine and risperidone for the treatment of bipolar disorder in preschool-age children. Biol Psychiatry. 2005 Oct 1;58(7):589-94.
74. Findling RL, McNamara NK, Youngstrom EA, Stansbrey R, Gracious BL, Reed MD, et al. Double-blind 18-month trial of lithium versus divalproex maintenance treatment in pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2005 May;44(5):409-17.
75. Pavuluri MN, Passarotti AM, Lu LH, Carbray JA, Sweeney JA. Double-blind randomized trial of risperidone versus divalproex in pediatric bipolar disorder: fMRI outcomes. Psychiatry Research - Neuroimaging. [Journal Article]. 2011;193(1):28-37.
76. AstraZeneca. Seroquel® (quetiapine fumarate) Tablets for the treatment of pediatric patients with schizophrenia (13-17 years old) or bipolar mania (10-17 years old). Briefing Document for Psychopharmacologic Drugs Advisory Committee Meeting of June 9 and 10, 2009 [cited I1.
77. Pavuluri MN, Henry DB, Findling RL, Parnes S, Carbray JA, Mohammed T, et al. Double-blind randomized trial of risperidone versus divalproex in pediatric bipolar disorder. Bipolar Disorders. [Journal Article]. 2010;12(6):593-605.
78. Geller B, Luby J, Joshi P, Dineen Wagner K, Emslie G, Walkup J, et al. A Randomized Controlled Trial of Risperidone, Lithium, or Divalproex Sodium for Initial

Treatment of Bipolar I Disorder, Manic or Mixed Phase, in Children and Adolescents. Arch Gen Psychiatry. 2012;69(5):515-28.
79. Mick E, Biederman J. Risperidone for the treatment of ADHD in children with bipolar disorder. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta, GA [serial on the Internet]. 2005 [cited i2: Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/774/CN-00592774/frame.html.
80. Biederman J, Hammerness P, Doyle R, Joshi G, Aleardi M, Mick E. Risperidone treatment for ADHD in children and adolescents with bipolar disorder. Neuropsychiatric Disease and Treatment 4 (1 B) (pp 203-207), 2008 Date of Publication: 2008. [Journal Article]. 2008;4(1B):203-7.
81. Moore CM, Biederman J, Wozniak J, Mick E, Aleardi M, Wardrop M, et al. Mania, glutamate/glutamine and risperidone in pediatric bipolar disorder: a proton magnetic resonance spectroscopy study of the anterior cingulate cortex. Journal of Affective Disorders 99(1-3):19-25, 2007 Apr. [Journal Article Research Support N I H Extramural Research Support Non-U S Gov't]. 2007;99(1-3):19-25.
82. Pavuluri MN, Henry DB, Carbray JA, Sampson GA, Naylor MW, Janicak PG. A one-year open-label trial of risperidone augmentation in lithium nonresponder youth with preschool-onset bipolar disorder. Journal of Child and Adolescent Psychopharmacology. [Journal Article]. 2006;16(3):336-50.
83. DelBello MP, Cecil KM, Adler CM, Daniels JP, Strakowski SM. Neurochemical effects of olanzapine in first-hospitalization manic adolescents: a proton magnetic resonance spectroscopy study. Neuropsychopharmacology. [Clinical Trial Comparative Study Journal Article Research Support N I H Extramural Research Support Non-U S Gov't]. 2006;31(6):1264-73.
84. Tohen M, Sanger TM, McElroy SL, Tollefson GD, Chengappa KN, Daniel DG, et al. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. Am J Psychiatry. 1999 May;156(5):702-9.
85. Zajecka JM, Weisler R, Sachs G, Swann AC, Wozniak P, Sommerville KW. A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. J Clin Psychiatry. 2002 Dec;63(12):1148-55.
86. Tohen M, Baker RW, Altshuler LL, Zarate CA, Suppes T, Ketter TA, et al. Olanzapine versus divalproex in the treatment of acute mania. Am J Psychiatry. 2002 Jun;159(6):1011-7.
87. Revicki D, Hanlon J, Martin S, Gyulai L, Nassir Ghaemi S, Lynch F, et al. Patient-based utilities for bipolar disorder-related health states. Journal of Affective Disorders. 2005;87:203-10.
88. Keck PE, Jr., Nabulsi AA, Taylor JL, Henke CJ, Chmiel JJ, Stanton SP, et al. A pharmacoeconomic model of divalproex vs. lithium in the acute and prophylactic treatment of bipolar I disorder. J Clin Psychiatry. 1996 May;57(5):213-22.
89. Bridle C, Palmer S, Bagnall AM, Darba J, Duffy S, Sculpher M, et al. A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder. Health Technol Assess. 2004 May;8(19):iii-iv, 1-187.
90. Joint Royal College of Paediatrics and Child Health/Neonatal and Paediatric Pharmacists Group Standing Committee on Medicines. The Use of Unlicensed Medicines or Licensed Medicines for Unlicensed Applications in Paediatric Practice - Policy Statement. London: Royal College of Paediatrics and Child Health. 2000.
91. Beynon S, Soares-Weiser K, Woolacott N, Duffy S, Geddes J. Pharmacological interventions for the prevention of relapse in bipolar disorder: a systematic review of controlled trials. J Psychopharmacol. 2009;23(5):574-91.
92. Office for National Statistics. Historic and projected mortality rates (qx) from the 2010-based UK life tables - Principal projection [http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-257453 accessed May 2012].
93. Laursen T, Munk-Olsen T, Nordentoft M, Mortensen P. Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. J Clin Psychiatry. 2007;68(6):899-907.
94. Hayhurst H, Palmer S, Abbott R, Johnson T, Scott J. Measuring health-related quality of life in bipolar disorder: Relationship of the EuroQol (EQ-5D) to condition-specific measures. Quality of Life Research. 2006;15:1271-80.

95. Mangalore R. Mental Health Research review 7, May 2000: The utility approach to valuing health states in schizophrenia.
96. Briggs A, Wild D, Lees M, Reaney M, Dursun S, Parry D, et al. Impact of schizophrenia and schizophrenia treatment-related adverse events on quality of life: direct utility elicitation. Health and Quality of Life Outcomes. 2008;6:105.
97. Boyle S, Jones G, Walters S. Physical activity, quality of life, weight status and diet in adolescents. Quality Life Res. 2010;19:943-54.
98. Heeg B, Buskens E, Botteman M, Caleo S, Ingham M, Damen J, et al. The Cost-Effectiveness of Atypicals in the UK. Value in Health 2008;11(7):1007-21.
99. Curtis L. Unit Costs of Health and Social Care 20112011.
100. Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, et al. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. Health Technology Assessment. 2007;11(39).
101. Robb J, Cooke R, Devins G, Young L, Joffe R. Quality of life and lifestyle disruption in euthymic bipolar disorder. J Psychiatr Res. 1997;31(5):509-17.
102. Domino M, Foster M, Vitiello B, Kratochvil C, Burns B, Silva S, et al. Relative Cost-Effectiveness of Treatments for Adolescent Depression: 36-Week Results From the TADS Randomized Trial. J Am Acad Child Adolesc Psychiatry. 2009;48(7):711-20.
103. Endicott J, Chen CF, Whitehead R, Kim E, Nyilas M, Carson WH, et al. Quality of life improvement in adolescent schizophrenia and pediatric bipolar disorder following treatment with aripiprazole. Bipolar Disorders Conference: 8th International Conference on Bipolar Disorder Pittsburgh, PA United States Conference Start: 20090625 Conference End: 20090627 Conference Publication: (varpagings) 11 (S1) (pp 36-37), 2009 Date of Publication: June 2009. [Journal Conference Abstract]. 2009;11(S1):36-7.
104. Clayton EH, Hirneth S, Hazell P, Kable C, Hanstock T. Validity of a paediatric quality of life questionnaire for participants with juvenile bipolar disorder. Bipolar Disorders Conference: Australasian Society for Bipolar Disorders Conference 2009 Brisbane, QLD Australia 2009;11(7):784. [Journal Conference Abstract]. 2009;11(7):784.
105. Freeman AJ, Youngstrom EA, Michalak E, Siegel R, Meyers OI, Findling RL. Quality of life in pediatric bipolar disorder. Pediatrics. [Journal; Peer Reviewed Journal]. 2009;123(3):446-52.
106. Ara R, Brazier J, ScHARR. Populating an economic model with health state utility values: moving towards better practice. Health Economics and Decision Science Discussion Paper Series No 09/11.
107. Chabroux S, Haffen E, Penfornis A. [Diabetes and second-generation (atypical) antipsychotics]. Ann Endocrinol (Paris). 2009;70(4):202-10.
108. Department of Health: NHS Reference Costs 2010-20112011.
109. NICE. TA213 Aripiprazole for Schizophrenia in People Aged 15 to 17 Years. 2011.
110. Hong J, Reed C, Novick D, Haro JM, Aguado J. Clinical and economic consequences of medication nonadherence in the treatment of patients with a manic/ mixed episode of bipolar disorder: Results from the european mania in bipolar longitudinal evaluation of medication (EMBLEM) study. Psychiatry Research. [Journal Conference Abstract]. 2009;190:110-4.
111. Hong J, Reed C, Novick D, Haro JM, Windmeijer F, Knapp M. The cost of relapse for patients with a manic/mixed episode of bipolar disorder in the EMBLEM study. Pharmacoeconomics 28(7):555-66, 2010. [Journal Article Research Support Non-U S Gov't]. 2010;28(7):555-66.
112. Lam DH, McCrone P, Wright K, Kerr N. Cost-effectiveness of relapse-prevention cognitive therapy for bipolar disorder: 30-Month study. British Journal of Psychiatry. [Journal Article]. 2005;186:500-6.
113. Young AH, Rigney U, Shaw S, Emmas C, Thompson JM. Annual cost of managing bipolar disorder to the UK healthcare system. Journal of Affective Disorders. [Journal Article]. 2011;133(3):450-6.
114. National Health Services England and Wales. Electronic Drug Tariff May 2012 [http://www.ppa.org.uk/edt/May_2012/mindex.htm accessed May 2012].
115. Ramirez De Arellano A, Rubio-Terres C, Baca E, Riesgo Y, Luque J, Mena E. Economic evaluation analysis in the treatment of bipolar disorder with aripiprazole and other atypical antipsychotic drugs in Spain. Value in Health Conference: ISPOR 13th Annual

European Congress Prague Czech Republic 2010;13(7):A452. [Journal Conference Abstract]. 2010.
116. Woodward TC, Tafesse E, Quon P, A. L. Cost effectiveness of adjunctive quetiapine fumarate extended-release tablets with mood stabilizers in the maintenance treatment of bipolar I disorder. References. PharmacoEconomics Vol28(9), Sep 2010, pp 751-764. [Journal; Peer Reviewed Journal]. 2010;28(9):751-64.
117. Office for National Statistics. Annual Mid-year Population Estimates for England and Wales, Mid 2011, Figure 2 [accessed 24.12.12]. 2012.
118. Office for National Statistics. Subnational population projections for England, 2011-based [accessed 24.12.12]. 2012.
119. Sharma A, Neely J, Camillen N, Grunze H, James T, Le Couteur A. A Surveillance Study of Paediatric Bipolar I Disorder in the United Kingdom and the Republic of Ireland - Preliminary Results. [http://wwwrcpsychacuk/pdf/12%20months%20posterpdf] Accessed May 2012. 2010.
120. Office of the Minister for Children and Youth Affairs. State of the Nation's Children, Ireland 2010.
121. Sigurdsson E, Fombonne E, Sayal K, Checkley S. Neurodevelopmental antecedents of early-onset bipolar affective disorder. Br J Psychiatry. 1999 Feb;174:121-7.
122. Office for National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland. [http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/population-estimates-timeseries-1971-to-current-year/index.html accessed 13.04.12].
123. Prescribing Observatory for Mental Health. Topic 10a baseline report: Prescribing Antipsychotics for Children and Adolescents. 2010;CRTU095.
124. IMS Anonymized patient-level data, US.
125. Holtmann M, Duketis E, Poustka L, Zepf F, Poustka F, Bölte S. Bipolar disorder in children and adolescents in Germany: national trends in the rates of inpatients, 2000-2007. Bipolar Disord. 2010 12(2):155-63.
126. Jaju S, Al-Adawi S, Al-Kharusi H, Morsi M, Al-Riyami A. Prevalence and age-of-onset distributions of DSM IV mental disorders and their severity among school going Omani adolescents and youths: WMH-CIDI findings. Child Adolesc Psychiatry Ment Health. 2009;3(1):29.
127. Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996-2004. Biol Psychiatry. 2007 Jul 15;62(2):107-14.
128. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. J Am Acad Child Adolesc Psychiatry. 1995 Apr;34(4):454-63.
129. Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. Arch Gen Psychiatry. 2007 Sep;64(9):1032-9.
130. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the National Cancer Institute 1959;22:719-48.
131. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986;7:177-88.

9 Appendices

9.1 Appendix 1

9.1.1 Appendix 1a: Studies that estimate the prevalence of paediatric bipolar disorder

A systematic review of paediatric bipolar disorder, conducted in 2005 provided the prevalence rates from various countries.[39] A summary of these studies is provided in Table A4.

Table A4 A summary of the studies estimating the prevalence of paediatric bipolar disorder (adapted from Soutullo et al. 2005[39])

Country	Year of publication	Study population, n (age, years)	Prevalence/ Incidence	Sample
The Netherlands	1997	780 (13-18)	1.9% mania	Epidemiological
Denmark	1992	3250 (<15)	1.2% (39 cases) BD	Clinical
UK	2003	10438 (5-15)	9.5% any DSM-IV psychiatric disorder 0% BD	Epidemiological
	1999	38 (11-18)	38 cases in 22 years, 1.7 cases per year	Clinical, inpatients and outpatients
Ireland	2002	102,810 (≥15)	2.2 cases/100,000 per year of BD with psychosis (8 cases)	Epidemiological, 1st lifetime episode of BD
Finland	1998	(10-19)	1.7 cases/100,000 per year	Clinical, inpatients
	2004	475 (2-18)	1.7% BD (8 cases)	Clinical, inpatients
Spain	2003	714 (<18)	4% BD	Clinical, outpatients
India	1997	840 (children and adolescents)	2.5% BD, 21 cases	Clinical, inpatients
	1997	119 (10-13)	4.2% BD	Clinical, inpatients
Brazil	2003	35 (<15)	7.2% BD	Clinical, outpatients
Turkey	2004	(7-15)	7 cases BD	Clinical

Other studies have been identified that report prevalence rates of bipolar disorder in children and adolescents. A summary of additional studies is provided in Table A5.

Table A5 A summary of additional studies presenting prevalence data of bipolar disorder in children and adolescents

Country	Year of publication	Study population, n (age, years)	Prevalence/ Incidence	Sample
France[42]	2009	4165 (12-20)	80/4165. This hospital has 30-50% of all hospital inpatient stays for paediatric BD in France	Clinical, inpatients
Germany[125]	2010	NR	1.91 per 100,000 in 2007	Clinical, inpatients
Oman[126]	2009	5409 (14-18)	0.9% BD 12 month prevalence	Epidemiological
US[127]	2007	(5-64)	1.3/100,00 in 1996 7.3/10,000 in 2004 (Diagnosis rates, BD in children)	Clinical, inpatients
US[128]	1995	1709 (14-18)	1% (primarily bipolar II/ cyclothymia) 5.7% had subsyndromal symptoms of bipolar	Epidemiological
US[129]	2007	962 (0-19 and ≥20)	25/100,000 (1994-95) 1003/100,000 (2002-03)	Clinical, outpatients

9.1.2 Appendix 1b

9.1.2.1 SPC/IFU, scientific discussion or drafts.

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Databases

The following databases were searched:

- MEDLINE – OVID interface
- MEDLINE In Process – OVID interface
- EMBASE - OVID interface
- EconLit – OVID interface
- CINAHL – OVID interface
- PsycINFO – OVID interface
- The Cochrane Library (including: Cochrane database of systematic reviews (Systematic Reviews), Database of Abstracts of Reviews of Effects (Other Reviews), Cochrane Central Register of Controlled Trials (Clinical Trials), Cochrane Methodology Register (Methods Studies), Health Technology Assessment Database (Technology Assessments), NHS Economic Evaluation Database (Economic Evaluations))

Search of Congress Abstracts

It was checked that abstracts from the following congresses were identified by the database search:

- American Academy of Pediatrics National Conference and Exhibition
- Congress of the European Academy of Paediatric Societies
- The Annual Meeting of the European Bipolar Forum
- Biennial Conference of the International Society for Bipolar Diso\rders
- International Conference on Bipolar Disorders (ICBD)
- European College of Neuropsychopharmacology (ECNP)
- American Psychiatric Association (APA)
- European Congress of Psychiatry
- Congress Collegium Internationale Neuro-psychopharmacologicum Conference (CINP)
- American Academy of Child and Adolescent Psychiatry (AACAP)
- European Psychiatric Association (EPA)
- European Society for Child and Adolescent Psychiatry (ESCAP)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

9.2.2 The date on which the search was conducted.

19th January 2012

9.2.3 The date span of the search.

1st September 2005- 19th January 2012

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search terms were taken from the previous systematic review commissioned by NICE in 2005. The differences to the previous review are as follows:

- The search terms on bipolar disorder from this review have been adapted for use in the Cochrane library

- The term “Epidemiologic study characteristics/” has been added to the RCT filter in order to also capture non-RCTs

- Filters for studies on children and adolescents have been added to the RCT and non-RCT filter (terms based on those from Jensen 2007[48], Zuddas 2011[49] and Fraguas 2011[50])

BIPOLAR DISORDER

OVID interface

1. exp bipolar disorder/
2. ((bipolar or bi polar) adj5 (disorder$ or depress$)).tw.
3. (hypomania$ or mania$ or manic$).tw.
4. (((cyclothymi$ or rapid or ultradian) adj5 cycl$) or RCBD).tw.
5. or/1-4

Cochrane library interface

1. MeSH descriptor Bipolar Disorder explode all trees

2. bipolar disorder* OR bi polar disorder* OR bipolar depression* OR bi polar depression*

3. hypomania* OR mania* OR manic*

4. cyclothymi* cycl* OR rapid cycl* OR ultradian cycl* OR RCBD

5. (#1 OR #2 OR #3 OR #4)

6. (#5), from 2005 to 2012

RCT and non-RCT SEARCH FILTERS (for OVID databases only)

OVID interface

1. exp clinical trials/ or exp clinical trial/ or exp controlled clinical trials/

2. exp crossover procedure/ or exp cross over studies/ or exp crossover design/

3. exp double blind procedure/ or exp double blind method/ or exp double blind studies/

or exp single blind procedure/ or exp single blind method/ or exp single blind studies/

4. exp random allocation/ or exp randomization/ or exp random assignment/ or exp

random sample/ or exp random sampling/

5. exp randomized controlled trials/ or exp randomized controlled trial/

6. (clinical adj2 trial$).tw.

7. (crossover or cross over).tw.

8. (((single$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$ or dummy)) or (singleblind$ or doubleblind$ or trebleblind$)).tw.

9. (placebo$ or random$).mp.

10. (clinical trial$ or clinical control trial or random$).pt,dt.

11. exp epidemiologic study characteristics/

12. animals/ not (animals/ and human$.mp.)

13. animal$/ not (animal$/ and human$/)

14. (animal not (animal and human)).po.

15. (or/1-11) not (or/12-14)

16. exp child/ or exp adult children/ or exp adolescent/

17. (child$ or adolescen$ or youth$ or preschool or juvenile or pediatric or paediatric).tw.

18. (young adj3 (person$ or people)).tw.

19. (under 18).tw.

20. (under eighteen).tw.

21. 15 and (or/16-20)

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Horizon Scanning

Horizon scanning through the use of the Google search engine and media reports was performed.

Reference List Searching

The reference lists of all included studies and additional systematic reviews (Jensen 2007,[48] Zuddas 2011,[49] Fraguas 2011,[50] and Liu et al. 2011[51]) were hand-searched.

9.2.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria were detailed in the main text.

9.2.7 The data abstraction strategy.

For each study that met the inclusion criteria, a data extraction grid was completed independently by two reviewers to ensure systematic retrieval of data across studies. The extraction grid was based on that prepared for the clinical guideline development, with all studies published since this time extracted in full.

With respect to outcomes data, the authors' definitions of outcomes were noted and used. Such definitions may vary between included studies but would be consistent within studies and hence would be useful when estimating relative size effects.

9.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

9.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym: NCT00110461		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Trial was randomised, but no details provided on how this was achieved in paper – but in CSR, says computer generated randomisation codes were used	Y
Was the concealment of treatment allocation adequate?	Trial was double-blind, but no details provided in the paper – but the CSR says that interactive voice response system was used	Y

Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	'Demographic and clinical characteristics...were similar for all 3 groups'. Large table of patient characteristics presented. However, "it should be noted that data on some clnical characteristics were missing for nearly a quarter of subjects"	Yes
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)?	Trial was double-blind, but no details provided in paper – CSR says yes	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	23.2% of patients discontinued in the placebo group, compared to 14.3% and 22.2% of patients in the aripiprazole 10 mg/day and 30 mg/day groups. Authors state that "study completion rates were high, and rates of discontinuation due to adverse events were low". Although a similar proportion of patients discontinued treatment in the placebo and aripiprazole 30 mg/day groups, in the PBO group the most common reason was lack of efficacy (8/23 patients) while in the aripiprazole 30 mg/day group, the second most common reason was adverse events (7/22).	No: Less dropouts in the aripiprazole 10 mg/day group – no explanation or discussion provided in text
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Medication adherence and well-being	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	No
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

9.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Please refer to Section 9.2.1

9.4.2 The date on which the search was conducted.

Please refer to Section 9.2.2

9.4.3 The date span of the search.

Please refer to Section 9.2.3

9.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Please refer to Section 9.2.4

9.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Please refer to Section 9.2.5

9.4.6 The inclusion and exclusion criteria.

Please refer to Section 9.2.6

9.4.7 The data abstraction strategy.

Please refer to Section 9.2.7

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

9.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym: Haas 2009[19]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Randomisation was performed but no details are provided to enable an evaluation of whether the method was appropriate	Not clear
Was the concealment of treatment allocation adequate?	Study is described as double-blind but no details are provided on allocation method	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline demographic and clinical characteristics were generally comparable across treatment groups	Yes
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)?	Study is described as double-blind but no details are provided	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	A greater proportion of patients in the higher dose group discontinued due to adverse events (16.4%) compared to the low dose (6.0%)	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No, but no clinical study report is available	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy and safety were analysed using the ITT sample. Change at endpoint was analysed using LOCF.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study ID or acronym: Study 149[76]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Randomisation was performed but no details are provided to enable an evaluation of whether the method was appropriate	Not clear
Was the concealment of treatment allocation adequate?	Study is described as double-blind but no details are provided on allocation method	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The 3 treatment groups were well matched in number and demographic and baseline disease characteristics	Yes
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)?	Study is described as double-blind but no details are provided	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	A greater proportion of patients on quetiapine discontinued due to adverse events than those on placebo (400 mg: 15.8%; 600 mg: 7.1%; placebo: 4.4%)	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Clinically significant prolactin increase was recorded but not reported separately for Study 149, it was only reported in combination with the schizophrenia trial.	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Outcomes were reported for both the ITT and per protocol populations. Observed cases only were reported. Therefore appropriate methods were not used to account for missing data	Yes.
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study ID or acronym: Tohen 2007[29]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Randomisation was performed but no details are provided to enable an evaluation of whether the method was appropriate	Not clear
Was the concealment of treatment allocation adequate?	Study is described as double-blind but no details are provided on allocation method	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were no statistically significant group differences in baseline demographic characteristics	Yes
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)?	Study is described as double-blind but no details are provided	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	A significantly greater number of patients receiving placebo discontinued due to lack of efficacy (29.6% in the placebo group, vs. 11.2% in the olanzapine group, p=0.007)	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No, but no clinical study report is available	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	All analyses were conducted on an intention-to-treat basis. The primary analysis used LOCF to account for missing data, but it is unclear what method was used for other outcomes	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.6 Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

The following information should be provided.

9.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Please refer to Section 9.2.1

9.6.2 The date on which the search was conducted.

Please refer to Section 9.2.2

9.6.3 The date span of the search.

Please refer to Section 9.2.3

9.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Please refer to Section 9.2.4

9.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Please refer to Section 9.2.5

9.6.6 The inclusion and exclusion criteria.

Please refer to Section 9.2.6

9.6.7 The data abstraction strategy.

Please refer to Section 9.2.7

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

9.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

No relevant non-RCTs identified.

9.8 Appendix 8: Search strategy for section 5.9 (Adverse events)

The following information should be provided.

9.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Please refer to Section 9.2.1

9.8.2 The date on which the search was conducted.

Please refer to Section 9.2.2

9.8.3 The date span of the search.

Please refer to Section 9.2.3

9.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example,

MeSH) and the relationship between the search terms (for example, Boolean).

Please refer to Section 9.2.4

9.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Please refer to Section 9.2.5

9.8.6 The inclusion and exclusion criteria.

Please refer to Section 9.2.6

9.8.7 The data abstraction strategy.

Please refer to Section 9.2.7

9.9 Appendix 9: Quality assessment of adverse event data in section 5.9 (Adverse events)

9.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

No relevant non-RCTs identified.

9.10 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

9.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT

- NHS EED.

Databases
The following databases were searched:

- MEDLINE – OVID interface
- MEDLINE In Process – OVID interface
- EMBASE - OVID interface
- EconLit – OVID interface
- CINAHL – OVID interface
- PsycINFO – OVID interface
- The Cochrane Library (including: Cochrane database of systematic reviews (Systematic Reviews), Database of Abstracts of Reviews of Effects (Other Reviews), Cochrane Central Register of Controlled Trials (Clinical Trials), Cochrane Methodology Register (Methods Studies), Health Technology Assessment Database (Technology Assessments), NHS Economic Evaluation Database (Economic Evaluations))

Search of Congress Abstracts
It was checked that abstracts from the following congresses were identified by the database search:

- American Academy of Pediatrics National Conference and Exhibition
- Congress of the European Academy of Paediatric Societies
- The Annual Meeting of the European Bipolar Forum
- Biennial Conference of the International Society for Bipolar Diso\rders
- International Conference on Bipolar Disorders (ICBD)
- European College of Neuropsychopharmacology (ECNP)
- American Psychiatric Association (APA)
- European Congress of Psychiatry
- Congress Collegium Internationale Neuro-psychopharmacologicum Conference (CINP)
- American Academy of Child and Adolescent Psychiatry (AACAP)
- European Psychiatric Association (EPA)
- European Society for Child and Adolescent Psychiatry (ESCAP)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

9.10.2 The date on which the search was conducted.

19th January 2012

9.10.3 The date span of the search.

1st September 2005- 19th January 2012

9.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search terms were taken from the previous systematic review commissioned by NICE in 2005. The differences to the previous review are as follows:

- The search terms on bipolar disorder from this review have been adapted for use in the Cochrane library

BIPOLAR DISORDER

OVID interface

1. exp bipolar disorder/
2. ((bipolar or bi polar) adj5 (disorder$ or depress$)).tw.
3. (hypomania$ or mania$ or manic$).tw.
4. (((cyclothymi$ or rapid or ultradian) adj5 cycl$) or RCBD).tw.
5. or/1-4

Cochrane library interface

1. MeSH descriptor Bipolar Disorder explode all trees
2. bipolar disorder* OR bi polar disorder* OR bipolar depression* OR bi polar depression*
3. hypomania* OR mania* OR manic*
4. cyclothymi* cycl* OR rapid cycl* OR ultradian cycl* OR RCBD
5. (#1 OR #2 OR #3 OR #4)
6. (#5), from 2005 to 2012

HEALTH ECONOMICS AND QUALITY OF LIFE SEARCH FILTERS (for OVID databases only)

1. exp “costs and cost analysis”/ or “health care costs”/

2. exp health resource allocation/ or exp health resource utilization/

3. exp economics/ or exp economic aspect/ or exp health economics/

4. exp value of life/

5. (burden adj5 (disease or illness)).tw.

6. (cost$ or economic$ or expenditure$ or price$1 or pricing or pharmacoeconomic$).

tw.

7. (budget$ or fiscal or funding or financial or finance$).tw.

8. (resource adj5 (allocation$ or utilit$)).tw.

9. or/1-8

10. (value adj5 money).tw.

11. exp quality of life/

12. (quality$ adj5 (life or survival)).tw.

13. (health status or QOL or well being or wellbeing).tw.

14. or/9-13

9.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Horizon Scanning

Horizon scanning through the use of the Google search engine and media reports was performed.

Reference List Searching

The reference lists of all included studies and additional systematic reviews (Jensen 2007,[48] Zuddas 2011,[49] Fraguas 2011,[50] and Liu et al. 2011[51]) were hand-searched.

9.10.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria were detailed in the main text.

9.10.7 The data abstraction strategy.

9.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

Not applicable, no relevant cost-effectiveness studies were identified.

9.12 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

9.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

Please refer to Section 9.10.1

9.12.2 The date on which the search was conducted.

Please refer to Section 9.10.2

9.12.3 The date span of the search.

Please refer to 9.10.3

9.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Please refer to Section 9.10.4

9.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Please refer to Section 9.10.5

9.12.6 The inclusion and exclusion criteria.

Please refer to Section 9.10.6

9.12.7 The data abstraction strategy.

Please refer to Section 9.10.7

9.13 Appendix 13: Resource identification, measurement and valuation (section 6.5)

The following information should be provided.

9.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

Please refer to Section 9.10.1

9.13.2 The date on which the search was conducted.

Please refer to Section 9.10.2

9.13.3 The date span of the search.

Please refer to Section 9.10.3

9.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example,

MeSH) and the relationship between the search terms (for example, Boolean).

Please refer to Section 9.10.4

9.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Please refer to Section 9.10.5

9.13.6 The inclusion and exclusion criteria.

Please refer to Section 9.10.6

9.13.7 The data abstraction strategy.

Please refer to Section 9.10.7

9.14 Appendix 14: Clinical Expert Input Validation

Expert Consultation Briefing Document

Aripiprazole Bipolar I Disorder in Children and Adolescents

NICE Submission

(prior to model development)

Red text indicates responses from Expert 1, [redacted]

Green text indicates responses from Expert 2, [redacted]

Purple text indicates responses from Expert 3, [redacted]

Overview

Bristol-Myers Squibb (BMS) is preparing a NICE submission for aripiprazole for the treatment and prevention of acute manic and mixed episodes in bipolar I disorder (BD-I) in children and adolescents. As part of the NICE submission process, BMS must present an economic model that examines the costs and benefits associated with aripiprazole versus relevant comparator therapies for the treatment of children and adolescents with BD-I.

BMS has previously developed a model for aripiprazole in adults for BD-I and would like to adapt this model so that it is appropriate for the current submission in children and adolescents. In order to adapt the model for the new patient population, BMS would like to ask for your expert clinical opinion on whether the structure accurately reflects the treatment pathway for children and adolescents with BD-I. If this is not the case, the model will be re-designed based on this expert consultation so that it closely mirrors this treatment pathway for children and adolescents.

This briefing document is split into two main sections: the overview of the model structure and the treatment strategies considered in the model. Each section presents details of how the current model has been designed and then asks questions as to whether the current model is appropriate for the clinical pathway in children/adolescents and, if not, asks you to provide details to help revise the model.

Overview of the model structure

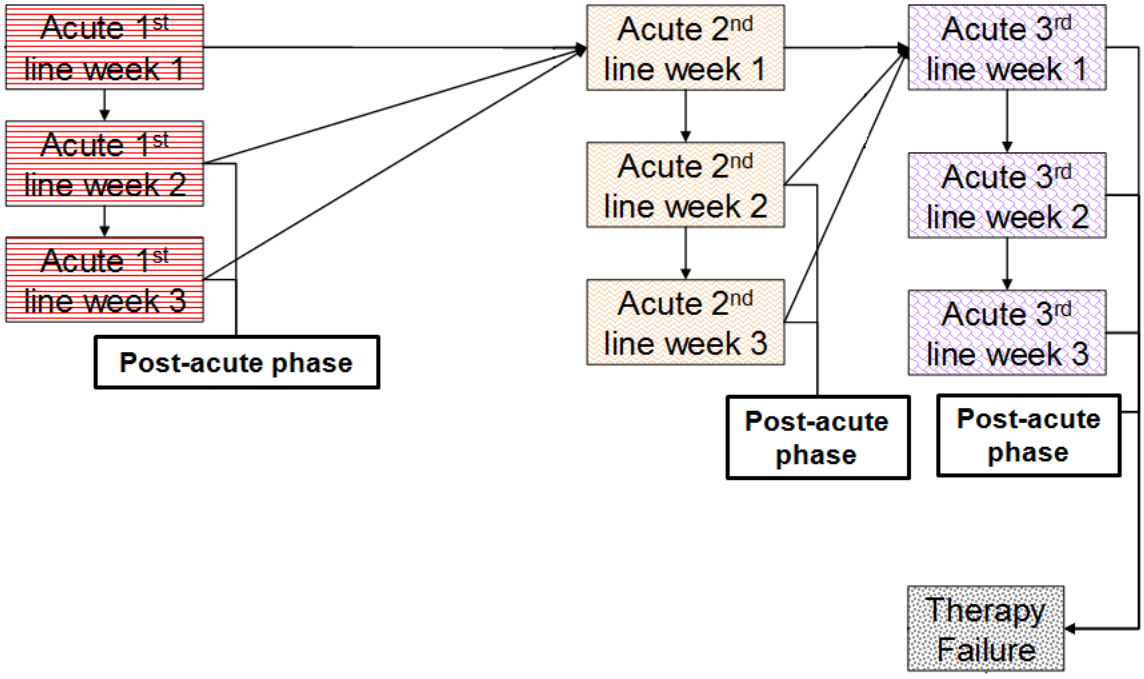
The model developed to reflect the treatment pathway for adults with BD-I comprises of four distinct phases:

1. The **acute phase** where the patient is treated as an inpatient in hospital to manage their acute manic event.
2. The **post-acute (relapse prevention) phase** where the patient is considered sufficiently improved to be discharged from hospital.
3. The **relapse phase**, where patients in the post-acute phase have a relapse and re-enter the acute phase.
4. The **therapy failure phase**, where patients have failed all therapies available.

This section of the briefing document will discuss the structure of the model for the above phases and put these into the context of the treatment pathway. It is worth noting that patients in any of the phases may also die; however the probability of death is assumed to be the same for all of the states.

Acute phase

Figure 1: Model structure for the acute treatment phase



The **acute phase** where the patient is treated as an inpatient in hospital to manage their acute manic event.

5. The **post-acute (relapse prevention) phase** where the patient is considered sufficiently improved to be discharged from hospital.

6. The **relapse phase**, where patients in the post-acute phase have a relapse and re-enter the acute phase.

7. The **therapy failure phase**, where patients have failed all therapies available.

This section of the briefing document will discuss the structure of the model for the above phases and put these into the context of the treatment pathway. It is worth noting that patients in any of the phases may also die; however the probability of death is assumed to be the same for all of the states.

Acute phase

Figure 1 illustrates the model structure for the acute phase. Patients enter the model while they are experiencing acute mania and are in hospital for treatment. Patients initially receive first line therapy for two weeks; if they respond to treatment (defined as a 50% change in the YMRS score) at the end of week 2 they are discharged and move to the post-acute phase. If the patient fails first line therapy (i.e. dropped out of first-line treatment), at week 1, 2 or 3, they are switched to a second line of therapy, beginning again at week 1.

If the patient has neither responded nor failed by the end of the first two weeks, they continue to receive the first line therapy for the third week. Patients who continue to receive therapy in the third week may move to the post-acute phase if they have improved sufficiently to be discharged. Patients who have not responded by the third week move to second line therapy.

Second line therapy and third line therapy follow the same pattern described above. Patients who do not respond to third line therapy move to the “therapy failure” phase.

Questions for discussion:

a. **Does the structure outlined above reflect the treatment pathway for children and adolescents with BD-I? If it does not, please give details as to how the structure should be amended to more accurately reflect the treatment pathway.**

Yes. However, patients would stay in hospital much longer in the acute phase. Furthermore, if the patient does not respond to the 1st medication, there is a transition period (of 7-10 days) between 1st and 2nd line. This involves dose reduction of the first antipsychotic and dose escalation of the second antipsychotic. Also based on medication half life.

Yes, 3 weeks of treatment is sufficient to assess response. In patients presenting with first episode, 4 weeks may be given for response due to overlap with diagnosis.

Yes. 3 weeks is the minimum amount of time a patient would spend in hospital. This is likely to be longer depending on the severity of the episode.

b. **Is a 50% change in YMRS score a suitable measure of response in this patient population?**

Yes, this is a suitable and relevant measure of response. However, clinicians don't tend to use YMRS in clinical practice. In clinical practice, function is the important measure, specifically the CGAF is used to assess function.

Yes, although it is not always used by clinicians, but it is an appropriate measure for children/adolescents. In reality, clinical judgement is often used.

Yes, although this is not used in clinical practise - assessment of response is based on clinical impression and functioning.

c. **How long would children/adolescents typically remain in hospital in the acute state before being discharged into the post-acute state, assuming that they respond to therapy?**

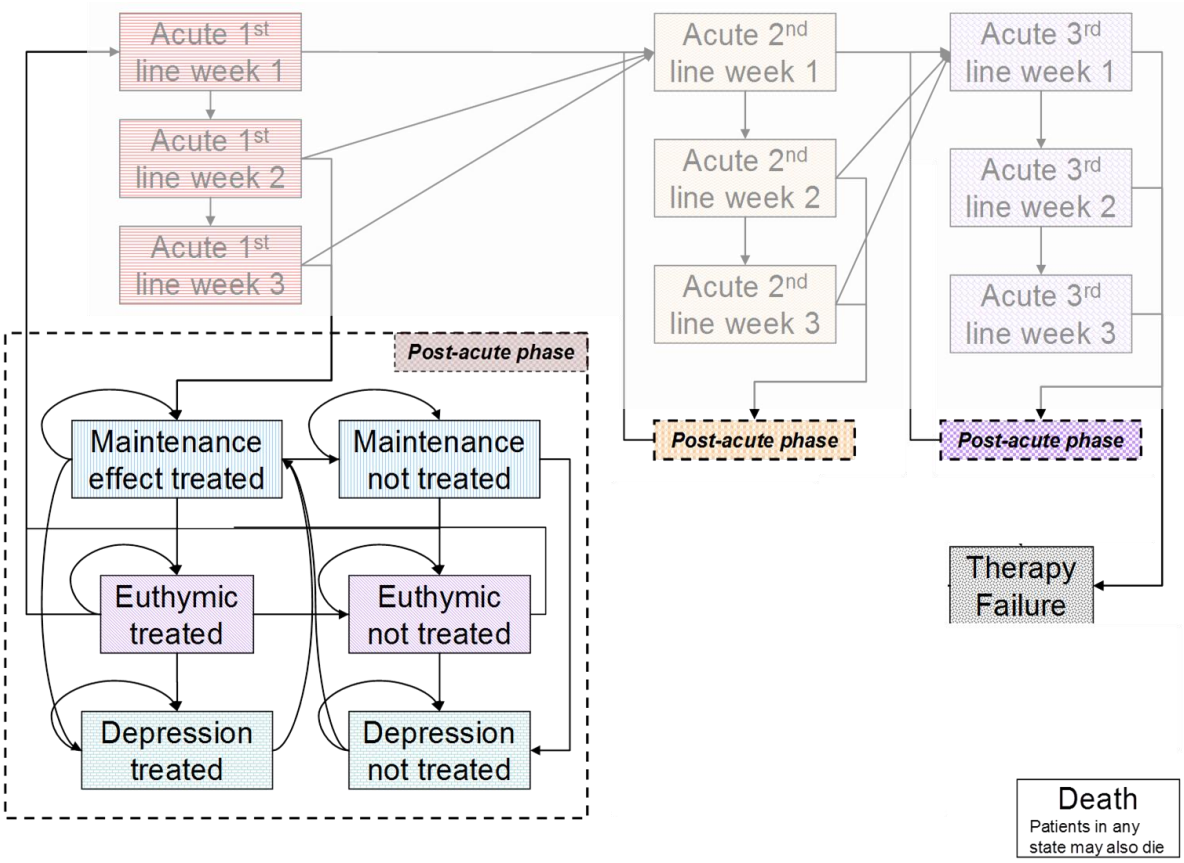
If they respond to 1st line therapy, they would stay 1.5 to 2 months. Contrary to adults, children must be reintegrated into the community, which takes time. When they are stable, they will have meetings with the school, social workers etc. and gradually reintegrate into the community.

Likely at least a month after symptoms have resolved (therefore at least 7 weeks if responding to first-line therapy). Children/adolescents may be more likely to stay in hospital than adults, particularly with a first manic episode. As child mental health services are lacking in community outreach programmes, clinicians are often reluctant to discharge from hospital until they are certain that the patient is fully in the euthymic state. Discharge may also be dependent on family/school support for patient.

3 weeks is minimum, but likely to stay for longer. Length of stay depends on circumstances - there is much more consideration of a child's home environment, school function etc. The clinician is more likely to take a conservative view and keep the patient in.

Post-acute phase

Figure 2: Model structure focusing on the post-acute (relapse prevention) phase



Post-acute phase

Figure 2 outlines the structure of the post-acute (relapse prevention) phase. This phase is firstly split into two pathways: patients who continue to receive treatment and patients who are not receiving treatment (predominantly due to individual decisions to stop complying with the treatment regimen). For each of these pathways, there are three possible states: maintenance effect treated, euthymic treated and depression treated; the three states are discussed further below. For each of the states, patients may either remain in that state (the arrow that curves back to the same state) or move to another state.

Maintenance of effect state

Patients who experience sufficient improvement to be discharged from hospital move into the maintenance of effect state. Although many studies of bipolar acute mania have focused on the initial three weeks of therapy, Bristol-Myers Squibb and Otsuka Pharmaceuticals were advised by clinical experts that patients do not achieve full euthymia (where they are in neither elated nor depressed psychological state) until some weeks after hospital discharge.

The maintenance of effect state was included to reflect this period of sub-acute mood disturbance.

Patients can move from the maintenance of effect state to the euthymic state, relapse to acute mania again or move to the depression state. Patients can also move into the maintenance not treated state, if they stop taking their treatment.

Euthymic state
In the euthymic state, patients are in a state where they are neither elated nor depressed but still receive maintenance treatment. From this state, patients can relapse to acute mania or move to the depression state. As in the maintenance of effect phase, there is a risk that euthymic patients will stop taking their medication and move to a “euthymic not treated” state. Patients can also relapse from the “euthymic not treated” state to the acute phase or move to the “depressed not treated” state.

Depression state
Patients who enter the depression state may either remain in that state, or move back to the maintenance treated state. The probability of leaving the depression state is assumed to be equal for all treatments and was based on a recent UK publication by McKendrick et al., due to the absence of long term data for atypicals. The probability of leaving the depression state was derived so that the mean time spent in the depression state was 5 weeks, consistent with McKendrick et al.

Questions for discussion:

1. **Do the states in the post-acute phase accurately reflect clinical practice for children and adolescents? If not, please give details as to how this should be revised.**

In general, this is correct. However, the post-acute phase should only be used to describe patients who are euthymic and have no residual effects (e.g. not the "maintenance of effect" state).

Yes. Patients are likely to remain on treatment, even in the euthymic stage.

Yes, but it does vary depending on the severity of the patient - sometimes they can recover in days but for may it can take weeks.

2. **Is the “maintenance effect treated” phase relevant to children and adolescents in terms of representing patients who are sufficiently improved to be discharged from hospital but who are not necessarily in the euthymic state?**

No. Children would still be in hospital until they are fully euthymic, when they could be discharged.

No. Children/adolescents are likely to remain as inpatients for longer until they are fully in the euthymic state and then will be discharged.

No. Patients are likely to remain in hospital past the initial response.

3. **When children/adolescents are discharged from hospital after receiving therapy, what further healthcare support is provided to them in the post-acute phase (e.g. regular meetings with healthcare professionals)?**

Community services. Regular medication reviews, psychosocial interventions. If they have responded well to treatment, they will have a psychiatrist visit 7 days after discharge and then a psychiatrist visit once a month at least.

May also have sessions with psychologists (individual and family sessions). This is only a minority (25%) patients with manic episodes (approximately).

Sometimes services from the voluntary sector are also used, youth clubs etc. However, many of the patients have OTHER problems as well as bipolar disorder and need support for these problems.

Psychiatrist appointments for monitoring (weekly/fortnightly initially, then dependent on progress). Family psychoeducation or even family therapy to help the whole family support the patient. In places with an early intervention/outreach programme, a CPN or mental health practitioner may visit twice a week after discharge. However, this is highly dependent on services available and is not the standard of care. Might have psychologist appointments for relapse prevention. Again, not standard care.

Patients will go back into Tier 3 outpatient CAMHS system and be assigned to a care co-ordinator. There is an obligation to provide a 7 day follow-up after discharge, and weekly follow-ups after. Visits to a psychologist will depend on whether the patient received CBT as an inpatient; if this was effective there will be a recommendation to continue.

4. **How long would you expect a child/adolescent to remain on antipsychotic therapy?**

1-2 years, if all symptoms have resolved, with no residual symptoms. If residual symptoms still persist, then longer. Some will stay on therapy for the rest of their lives.

12 months minimum before considering treatment withdrawal, if the patient has maintained response. However, if patients have a pattern of relapse, then maintenance therapy may be 2 to 5 years.

Recommendation is 6 months, but Expert 3 mainly deals with the inpatient phase and therefore has limited experience with maintenance treatment. Children/adolescents are often reluctant to be dependent on therapy for extended periods of time.

5. **Are there any other states which should be captured in the post-acute phase?**

Patients can also relapse from "euthymic treated" phase. Could also consider patients who have "mixed" states (e.g. manic and depressed)

No

No

Relapse phase

Figure 3: Model structure focusing on patients who relapse and re-enter the acute phase

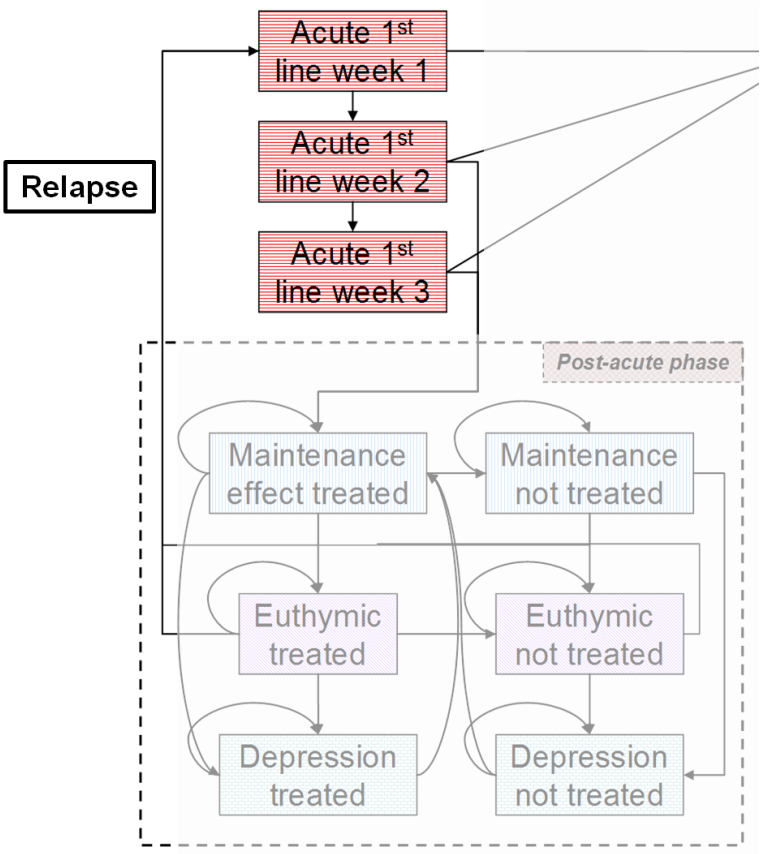


Figure 3 illustrates the treatment pathway for patients who had been discharged from hospital and entered the post-acute stage, but who subsequently had a relapse episode. In such cases, patients were assumed to re-enter the acute phase of the model and receive the same acute therapy strategies as previously described.

Questions for discussion:

1. **Does the structure outlined above reflect the clinical practice for children or adolescents who suffer a relapse episode of BD-I? If not, please provide details for how this should be revised.**

Yes. Sometimes relapsed patients may be treated in the community, however this will depend on the severity of relapse. Furthermore, the decision to admit them is also based on the risk of harming themselves, others or other issues. Rather than changing medication, some patients would increase their dose.

Yes

Yes. If patients are suffering from acute mania they are very likely to be hospitalised again. However, outpatient teams are becoming better at managing patients.

Treatment failure phase

Figure 4: Model structure focusing on the treatment failure phase

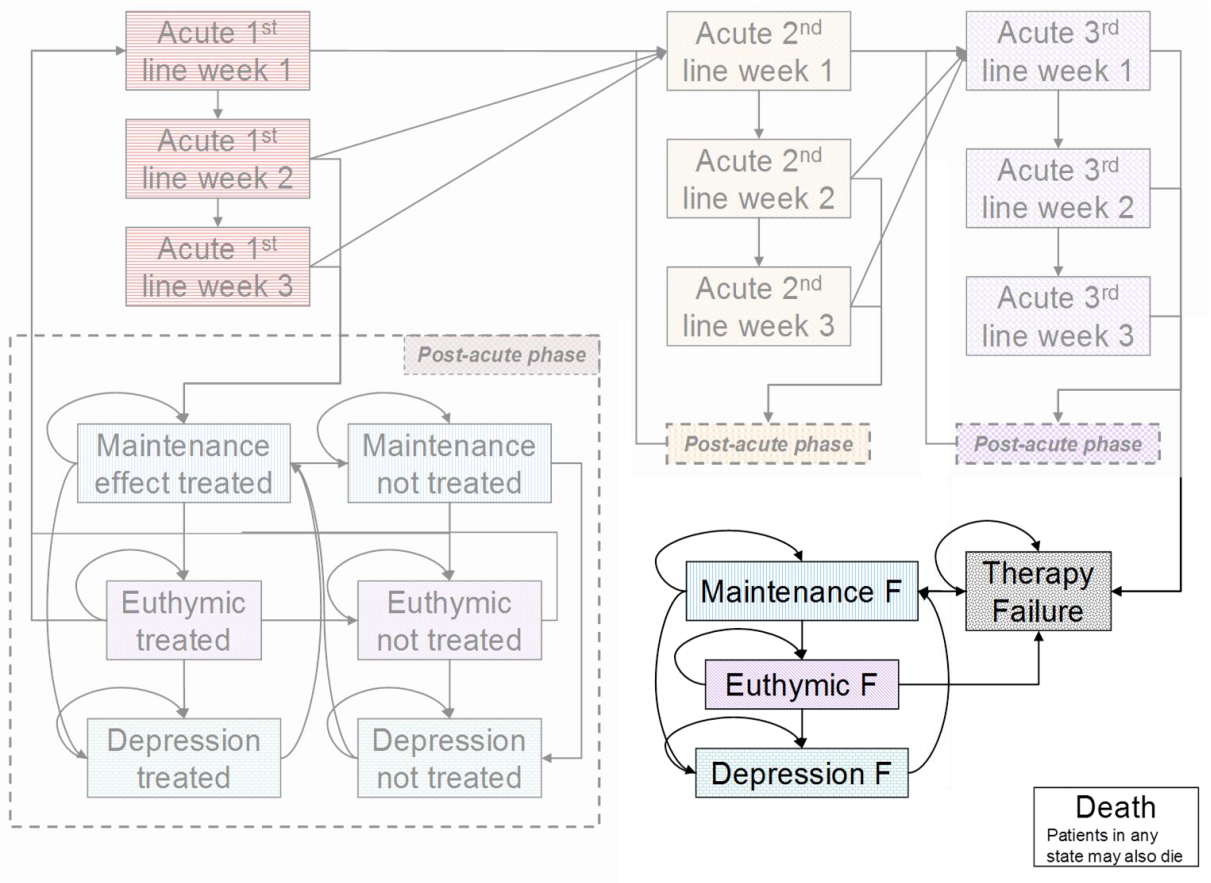


Figure 4 focuses specifically on the structure of the therapy failure state and how this integrates with the rest of the model. Patients in the therapy failure state will not be treated with any medications as they would already have failed on all three drugs in the acute phase. Patients in this phase could have their disease resolved over time and move to maintenance of effect failure (maintenance F), euthymic failure (euthymic F) or the depression failure (depression F) states. As patients have failed all the therapies in the model, they cannot return to any of the other treatment phases once they have entered the therapy failure phase.

Questions for discussion:

1. **Do the states in the therapy failure phase accurately reflect the clinical practice for children/adolescents who have failed three lines of therapy? If not, please give details as to how this should be revised.**

Generally the term used is "treatment resistance" not "treatment failure". Expert 1 uses antipsychotic monotherapy to begin with, then switches to another, then may try a third one and finally may switch to combination. All patients he's treated with combination have responded.

Even if patients haven't fully responded, they are usually better on medication than when they arrived. So they continue on treatment, even without a YMRS response.

Only a very small minority of patients would not respond to three lines of therapy, therefore the treatment pathway after that is unclear.

Three lines of therapy is generally enough to gauge treatment resistance, but they will probably stay on some form of medication. Adherence could be the problem for non-response, so an assessment must be made as to whether this is the case.

2. **What are the treatment options for children/adolescents who have failed three lines of therapy?**

In the depressed state, doctors may add an antidepressant. Or may use a mood stabiliser with better depression efficacy. However, depression is not common.

Reassessment of diagnosis, psychoeducation, lifestyle modification etc.

CBT, psychosocial interventions, family work etc. But these would probably have run in parallel.

3. **Are there any further points you would like to raise regarding the model structure, not reflected in any of the previous questions in this section?**

There may be a diagnostic overlap (with ADHD, autism spectrum, other co-morbidities) which makes things difficult to assess.

Treatment Strategies in the Model

The model is designed to compare different treatment strategies, each consisting of three BD-I therapies; 'usual care' reflects the treatment strategy currently used in clinical practice, without aripiprazole.

Currently, the only drug with UK marketing authorisation in this population is lithium. However, other therapies, including atypical antipsychotics, are also used to treat BD-I in children and adolescents, even though they are not specifically licensed for these patients.

Questions for discussion:

1. **Please complete the table below to indicate which therapies are used as first, second and third line in the 'usual care' treatment pathway for children and adolescents, and where you would incorporate aripiprazole into the treatment strategy, if it is not currently included in 'usual care'.**

	First line	Second line	Third line
Usual care strategy	aripiprazole	quetiapine	olanzapine
	risperidone	quetiapine	Combination (add mood stabiliser)
	Olanzapine/ aripiprazole/ risperidone		
Strategy 2 (incorporating aripiprazole)	Aripiprazole is already in use in usual care		
	risperidone	aripiprazole	Combination (add mood stabiliser)
	Aripiprazole is already in use in usual care		

Sometimes patients come in already on medication and will be kept on the same medication.

Expert 2 currently doesn't use aripiprazole, but is considering using it.

Expert 3 does not have a "standard" usual care pathway. Treatment choice is based on severity of the manic episode, co-morbidities, side effects of treatment, and likelihood of adherence.

For more severe and difficult patients he would chose olanzapine IM as this is easier to administer against the patients will.

Would be most likely to use a monotherapy treatment as first line, and switch to another if no response, but if there is a partial response a mood stabilizer may be added.

In theory, an anti-manic could be used as a monotherapy, but he can't remember the last time he used lithium. The evidence base is now much better for antipsychotics, therefore these are the treatments of choice.

2. **Are there any further points you would like to raise regarding the treatment pathway, not reflected in the table above?**

When prescribing therapies, Expert 1 makes his decision based on the safety profile and therefore chooses aripiprazole first line. Whilst he believes that olanzapine has slightly better efficacy, the safety profile is much worse and so he will use it third line.

Expert Input Validation

Aripiprazole Bipolar I Disorder in Children and Adolescents

NICE Submission

(post model development)

Overview

Bristol-Myers Squibb (BMS) is preparing a NICE submission for aripiprazole for the treatment and prevention of acute manic and mixed episodes in bipolar I disorder (BD-I) in children and adolescents. As part of the NICE submission process, BMS must present an economic model that examines the costs and benefits associated with aripiprazole versus relevant comparator therapies for the treatment of children and adolescents with BD-I.

BMS have developed a model which represents the treatment pathway for children and adolescents with BD-I and have selected what they believe to be appropriate and relevant inputs for costs, resource utilisation and health state utilities.

The aim of this review is to validate these inputs in line with clinical practice.

Red text indicates responses from Expert 1, [redacted]

Green text indicates responses from Expert 2, [redacted]

Purple text indicates responses from Expert 3, [redacted]

Questions

Model Structure

Acute Inpatient Phase

1. In the model, patients stay in hospital for a minimum of 6-8 weeks if they respond to first line treatment; does this reflect clinical practice?
    - 4-8 weeks is the average as there is some variability, some patients respond very quickly. Children's units tend to keep patients for longer, adolescents may be discharged more quickly.
    - Yes
    - Yes, this is the minimum

2. Based on your clinical experience, after initial response to therapy in the acute inpatient stage, what percentage of patients would relapse before being discharged?
    - After manic symptoms have resolved, most patients won't relapse.
    - 5%
    - It is difficult to assess whether patients relapse after response or whether they are still experiencing the original manic episode. Around 20% will experience symptoms but this will include some who may not have actually

responded in the first place and therefore is not the true rate of relapse of responders.

Euthymic Outpatient Phase

3. Based on your clinical experience, after discharge from hospital what percentage of patients would relapse within the first 6 months?
   - Small percentage, less than a quarter even up to a year. Keeping them for a long time as inpatients ensures that patients are very stable before discharge.
   - 20%
   - 10%

Adverse Events

4. The three main adverse events considered in the economic model are extrapyramidal symptoms (EPS), weight gain and somnolence. For patients who experience mild to moderate adverse events (and who do not discontinue or switch antipsychotic therapy), please complete the following table based on your clinical experience.

	Adverse events		
	Extrapyramidal symptoms	**Weight gain**	**Somnolence**
Duration of symptoms (Short-term, medium-term, long-term)	Rare, Expert 1 has hardly experienced this.	Potential for weight gain not to stop (like in adults) as they are maturing as well. Once medication is stopped, weight gain can stop or even decrease (but depends on patient)	Can be associated just with initiation of treatment. Relatively common (~50%). As bipolar patients often have problems sleeping, somnolence may not be such a problem!
	Short-term if managed (as below), otherwise could be long-term	Long-term (continues until treatment is discontinued or switched)	Short-term
	Rare. Short-term, would expect to be resolved. Only really seen at treatment initiation.	Medium to long.	Short

Management strategy	Reduce medication, going back to an earlier dose and increase more gradually. Switch medication if a balanced cannot be found between bipolar symptoms and EPS. Don't use medication for EPS particularly. Generally not happy with adolescents and children being on EPS medication.	Try to start treatment with an antipsychotic not associated with substantial weight gain. If weight gain is excessive and ongoing, consider switch to another antipsychotic (but may not if already on the "best" in terms of weight gain) Dietary advice (dieticians), exercise advice Consider medication strategies as last line: 1. Metformin 2. Low dose aripiprazole (stops weight gain – limited evidence)	Dose reduction is the main strategy. Expert 1 has never had experience of any patient being so sedated on low dose that they were severely affected. Somnolence may signify overmedication. Issue with dose reduction may be that symptoms re-emerge. Switch could be possible if dose reduction doesn't help. Expert 1 has not had to do this for somnolence.
	Dose reduction or switch; possible use of other medications to counteract symptoms. Expert 2 would probably switch treatment; if events were mild they would reduce dose unless it would affect treatment compliance.	Weight loss advice; referral to dietician. If that doesn't work, either reduce the dose (not likely to be responsive) or more likely, switch to another antipsychotic if the event is serious enough.	Reduce dose – it is usually a symptom that the patient is on too much medication
	Switching or lower dose	Dietary regulation, switch treatment if symptoms persist and become severe. But if the patient has responded well to treatment and the weight gain is not too severe then switching would not be advisable.	Dose reduction or switch
Does the management strategy resolve the adverse event?	Yes	Rarely resolved – sometimes can stop the weight increasing, but difficult to actually reduce weight again. Long-term problem.	Yes
	Yes	Management does not generally resolve weight gain completely until the patient switches treatment. Expert 2 wouldn't consider other medications in children.	Yes - hopefully
	Yes	Not usual, depends on severity of AE.	Yes

Resource Use

In the model, we assume that patients in different states are associated with different costs to the healthcare system. These costs include the treatment costs of the antipsychotics, but also the costs of hospitalisation, psychiatrist consultations, GP consultations, specialist consultation for adverse events, therapies to manage adverse events etc.

For each of the out-patient health states we need to understand the different NHS healthcare services that patients may use.

1. Please complete the table below to indicate how often in **one month** a patient in each of the three states (euthymic treated outpatient, euthymic not treated outpatient and therapy resistant outpatient) would utilise/receive the listed services.
    a. If you think that the patient would use the service less than once a month then please indicate how often (i.e. once every 6 weeks, 2 months, 6 months etc.) they would use the service.
    b. If you think that the patient would use a service not mentioned below, then please add this to the table.

- The difference in adolescent services is that there are no home treatment teams, crisis resolution teams etc.
- Outpatient appointments are the mainstay of contacts
- Consultants do not do a lot of home visits; they generally see pts on the basis that they are well enough to attend appointments. However, home visits can be arranged at short notice and are more expensive – these should be accounted for in the model if possible.
- Expert 3 does not generally see outpatients – they are passed on to the Tier 3 support team. For treatment resistant patients there may be the option of admittance as a day patient.

Resource	Visits per month		
	Euthymic treated outpatients	Euthymic not treated outpatients	Therapy resistant outpatients
Community psychiatric nurse visit	No	No	No
	None	None	Expert 2 would involve nurse practitioner; the patient may see them twice a month on alternate weeks with consultant
	None	None	None
Consultant psychiatrist visit	Weekly for the first month, then fortnightly to monthly	Monthly – may close the case if no relapse, although it is a very rare occurrence that the case is closed. Probably won't have close monitoring from CAMHS teams – patient/carer encouraged to come to CAMHS if they suspect symptoms	Monthly (if psychologist Involved) Fortnightly if no psychologist involved.

		are re-emerging	
	Once a month while patient is on treatment	Once every 6 to 8 weeks	Twice a month. Half of these could be home visits if patient is very unwell
	Generally advise once a month	No comment	More frequent treatment review
GP visit	No – usually CAMHS teams	No	No
	None	None	None
	None	None	None
Psychologist visit	Varies… 2 first month Fortnightly for 3 months	No	More regular Weekly to fortnightly
	None	None	Once or twice a month
	May see a psychologist if they saw one as an inpatient	No comment	No comment
Family therapist/ psychotherapist			Weekly to fortnightly
Care coordinator	Outpatient care is co-ordinate by a member of the Tier 3 team. This depends on availability		

When patients experience adverse events related to their therapy their use of health services may change as they seek treatment for these adverse events. The three main adverse events considered in the economic model are extrapyramidal symptoms (EPS), weight gain and somnolence. We need to understand the additional services that patients may use if they experience any of the above adverse events.

2. Please complete the table below to indicate the additional services required by a patient when they experience one of the three listed adverse events.
    - If you think that the patient would use a service not mentioned below, then please add this to the table.

Resource	Extrapyramidal symptoms	Weight gain	Somnolence
Community psychiatric nurse visit	None	None	None
	No	Once a month	No
	None	Would monitor after dietician visit	None
Consultant psychiatrist visit	Managed mainly by the consultant Increased input from CAMHS (e.g. weekly appointment and regular TC with family/patient)	Appointments with consultants would increase only if weight change was extreme. Do the best not to change medication.	No extra visits.
	Yes – increase frequency from once a month to twice a month for duration of EPS episode until	Patient would need to be seen more often but not necessarily by the consultant –probably more by the GP	Yes – 1 or 2 extra visits to understand underlying reasons for the adverse event; investigate sleeping

	EPS resolves or pt switches tx		patterns, other medications etc. Doesn't occur with discharged pts that often – more in pts who have just started treatment.
	Limited experience in outpatient management, but generally if the adverse event is deemed to be due to treatment then visits to the consultant mat be increased or an extra visit may occur		
GP visit	None	None	None
	No	Once a month	No
	None	None	None
Psychologist visit	None	None	None
	No	None	No
	None	None	None
Other specialist (please state which specialist, e.g. dietician)	None	Yes dietician – 2-3 visits maximum	None
	None	Dietician for more support around weight loss once a month. Only once or twice if pt was not that overweight just for advice, but potentially more than that if pt reaches some kind of critical level. Beyond a critical level they might be referred to an eating specialist	None
	None	Would see a dietician 1-2 times then community nurse may take over monitoring	None
Pharmaceutical therapy (please state which therapy)	Not used often in children/adolescents	Metformin and low dose ARP last line. Not routinely used. If they respond, they are advised to remain on this therapy as long as they are on antipsychotics.	None
	Not used very often	None	None
	None	None	None
Diagnostic test (please state which tests) …	None	Yearly blood, ECG tests (baseline, before discharge and 12 monthly) Maudsley guidelines – details medication strategies (inc. blood tests).	None
	None	Nothing additional to routine testing	
	None	None	None
Care co-ordinator	Patient would be advised to go to care co-ordinator first, then would be referred on		

Utilities and Quality of Life

In the model, utilities were applied to each state to adjust for different quality of life. A utility of 0 represents death and a utility of 1 represents perfect health.

1. Would you expect the quality of life experienced by children and adolescents with bipolar I disorder to be greater or less than adults with bipolar I disorder?
    - Generally BD presenting earlier in life has a worst prognosis. However, to compare QoL of adolescent with BD and adult with BD, it may be that adolescent has better QoL. May have more support (family etc.). Adults with bipolar may have many other issues (work, starting a family etc.)
    - Less, because bipolar impacts on social functioning. Social functioning is particularly important in adolescence – adolescents need to establish friendships and gain a support network to help them into adult life. Adolescents see themselves as being a success depending on their friendships. Older patients may already have established a steady network of friends.
    - Less, due to developmental pressure, disruption of daily and social life eg school; particularly if it is a severe episode which requires weeks of hospitalisation.

2. When a patient experiences an adverse event, their quality of life declines and their utility decreases. Please rank the following adverse events in order of their negative impact on a patient's quality of life.

Extrapyramidal symptoms	3rd	3 – largely because it is not that common	3
Somnolence	2nd	2	2
Weight gain	Worst (1)	1	1

3. Would you expect any change in quality of life when children/adolescents are taken off long-term treatment when they have been euthymic for at least 6 months?
    - Yes, mild symptoms may occur, (mild elation, mild depression) so may affect their quality of life.
    - Improvements in side effects like weight gain would lead to an improvement in QoL when patient stops treatment. Weight loss can happen very quickly – if patients are going to see improvements they will probably see improvements relatively soon.
    - Balance between pros and cons. There will be a higher chance of relapse and emergence of manic symptoms so the patient may have worse quality of life, but there will be a positive psychological impact, greater practicality in not having to take medication etc.

9.15 Appendix 15: Network Meta-Analysis Sensitivity Analyses

YMRS response week 1

	PIVOTAL STUDIES ONLY						ALL STUDIES	
	ARIPIPRAZOLE 10MG		ARIPIPRAZOLE 30MG		ARIPIPRAZOLE POOLED DOSE		ARIPIPRAZOLE POOLED DOSE	
	median	95% CrI	median	95% CrI	median	95% CrI	median	95% CrI
Probability of experiencing the event								
PBO	0.080	0.048, 0.124	0.080	0.048, 0.123	0.080	0.048, 0.123	0.117	0.077, 0.167
ARP	0.283	0.145, 0.487	0.275	0.14, 0.477	0.281	0.154, 0.469	0.333	0.214, 0.481
OLZ	0.209	0.104, 0.385	0.209	0.103, 0.386	0.209	0.103, 0.385	0.286	0.147, 0.498
RISP	0.239	0.119, 0.437	0.239	0.119, 0.438	0.239	0.118, 0.437	0.323	0.167, 0.557
RR comparators vs aripiprazole								
PBO	0.29	0.13, 0.59	0.29	0.14, 0.61	0.29	0.14, 0.57	0.35	0.20, 0.59
ARP	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1
OLZ	0.74	0.27, 2.08	0.76	0.27, 2.16	0.74	0.27, 2.01	0.86	0.37, 1.95
RISP	0.84	0.30, 2.43	0.87	0.31, 2.51	0.85	0.31, 2.34	0.97	0.41, 2.22
RR comparators vs placebo								
PBO	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1
ARP	3.50	1.69, 7.54	3.40	1.63, 7.37	3.47	1.77, 7.31	2.84	1.69, 4.92
OLZ	2.59	1.19, 5.94	2.59	1.20, 5.94	2.59	1.20, 5.93	2.43	1.18, 5.03
RISP	2.95	1.33, 7.08	2.94	1.32, 7.11	2.95	1.32, 7.07	2.74	1.31, 5.82
Probability treatment is best								
PBO	0.0%		0.0%		0.0%		0.0%	
ARP	51.3%		48.8%		50.5%		39.0%	
OLZ	18.5%		19.5%		18.8%		23.3%	
RISP	30.3%		31.7%		30.7%		37.7%	

YMRS response week 2

	PIVOTAL STUDIES ONLY						ALL STUDIES	
	ARIPIPRAZOLE 10MG		ARIPIPRAZOLE 30MG		ARIPIPRAZOLE POOLED DOSE		ARIPIPRAZOLE POOLED DOSE	
	median	95% CrI	median	95% CrI	median	95% CrI	median	95% CrI
Probability of experiencing the event								
PBO	0.192	0.14, 0.252	0.192	0.14, 0.252	0.192	0.14, 0.252	0.236	0.18, 0.299
ARP	0.435	0.291, 0.591	0.576	0.423, 0.718	0.507	0.371, 0.644	0.538	0.419, 0.655
OLZ	0.516	0.356, 0.682	0.517	0.355, 0.681	0.517	0.357, 0.681	0.582	0.408, 0.746
RISP	0.503	0.352, 0.656	0.503	0.352, 0.657	0.504	0.352, 0.656	0.569	0.409, 0.72
RR comparators vs aripiprazole								
PBO	0.44	0.29, 0.69	0.34	0.23, 0.48	0.38	0.26, 0.55	0.44	0.32, 0.60
ARP	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1
OLZ	1.19	0.68, 2.09	0.90	0.55, 1.46	1.02	0.61, 1.67	1.08	0.69, 1.63
RISP	1.16	0.69, 1.96	0.87	0.55, 1.37	0.99	0.62, 1.57	1.06	0.70, 1.54
RR comparators vs placebo								
PBO	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1
ARP	2.26	1.45, 3.43	2.98	2.07, 4.3	2.63	1.83, 3.83	2.27	1.67, 3.13
OLZ	2.68	1.66, 4.3	2.68	1.65, 4.3	2.68	1.66, 4.32	2.45	1.60, 3.66
RISP	2.61	1.71, 3.94	2.61	1.71, 3.93	2.62	1.72, 3.93	2.40	1.65, 3.42
Probability treatment is best								
PBO	0.0%		0.0%		0.0%		0.0%	
ARP	13.6%		54.0%		30.5%		19.1%	
OLZ	47.0%		26.5%		38.7%		44.3%	
RISP	39.4%		19.5%		30.9%		36.5%	

YMRS response week 3

	PIVOTAL STUDIES ONLY						ALL STUDIES	
	ARIPIPRAZOLE 10MG		ARIPIPRAZOLE 30MG		ARIPIPRAZOLE POOLED DOSE		ARIPIPRAZOLE POOLED DOSE	
	median	95% CrI	median	95% CrI	median	95% CrI	median	95% CrI
Probability of experiencing the event								
PBO	0.246	0.197, 0.3	0.246	0.196, 0.3	0.246	0.196, 0.3	0.294	0.241, 0.352
ARP	0.524	0.372, 0.675	0.651	0.503, 0.778	0.591	0.457, 0.717	0.577	0.461, 0.689
OLZ	0.524	0.365, 0.684	0.524	0.366, 0.685	0.523	0.366, 0.683	0.584	0.418, 0.741
RISP	0.601	0.447, 0.741	0.601	0.446, 0.741	0.601	0.445, 0.741	0.658	0.504, 0.789
QUET	0.467	0.345, 0.594	0.467	0.345, 0.593	0.467	0.345, 0.594	0.528	0.400, 0.654
RR comparators vs aripiprazole								
PBO	0.47	0.33, 0.69	0.38	0.28, 0.52	0.42	0.31, 0.57	0.51	0.39, 0.67
ARP	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1
OLZ	1.00	0.61, 1.62	0.81	0.52, 1.22	0.89	0.56, 1.35	1.01	0.67, 1.46
RISP	1.15	0.75, 1.77	0.93	0.63, 1.33	1.02	0.69, 1.47	1.14	0.8, 1.57
QUET	0.89	0.59, 1.38	0.72	0.5, 1.04	0.79	0.54, 1.15	0.92	0.65, 1.27
RR comparators vs placebo								
PBO	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1
ARP	2.13	1.45, 2.99	2.63	1.94, 3.53	2.39	1.76, 3.24	1.96	1.49, 2.55
OLZ	2.12	1.39, 3.12	2.12	1.39, 3.12	2.12	1.39, 3.11	1.98	1.36, 2.76
RISP	2.43	1.71, 3.37	2.44	1.71, 3.37	2.44	1.70, 3.37	2.23	1.63, 2.94
QUET	1.90	1.38, 2.55	1.90	1.39, 2.54	1.90	1.38, 2.54	1.79	1.35, 2.32
Probability treatment is best								
PBO	0.0%		0.0%		0.0%		0.0%	
ARP	18.7%		59.9%		37.6%		13.6%	
OLZ	20.4%		9.4%		15.3%		21.9%	
RISP	57.1%		29.8%		44.9%		60.4%	
QUET	3.8%		1.0%		2.2%		4.1%	

Discontinuation week 3

	PIVOTAL STUDIES ONLY						ALL STUDIES EXCEPT TRAMONTINA						ALL STUDIES	
	ARIPIPRAZOLE 10MG		ARIPIPRAZOLE 30MG		ARIPIPRAZOLE POOLED DOSE		ARIPIPRAZOLE 10MG		ARIPIPRAZOLE 30MG		ARIPIPRAZOLE POOLED DOSE		ARIPIPRAZOLE POOLED DOSE	
	med	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**
Probability of experiencing the event														
PBO	0.241	0.193, 0.294	0.241	0.193, 0.294	0.241	0.193, 0.294	0.241	0.193, 0.294	0.241	0.193, 0.294	0.241	0.193, 0.294	0.174	0.119, 0.231
ARP	0.132	0.059, 0.254	0.214	0.116, 0.358	0.176	0.101, 0.286	0.132	0.059, 0.253	0.215	0.115, 0.357	0.176	0.101, 0.286	0.134	0.073, 0.226
OLZ	0.131	0.071, 0.228	0.131	0.071, 0.228	0.131	0.071, 0.228	0.131	0.071, 0.228	0.131	0.071, 0.228	0.131	0.071, 0.229	0.090	0.044, 0.173
RISP	0.212	0.116, 0.358	0.213	0.116, 0.357	0.212	0.116, 0.358	0.212	0.116, 0.356	0.212	0.116, 0.357	0.212	0.116, 0.358	0.151	0.073, 0.282
QUET	0.168	0.104, 0.261	0.168	0.103, 0.261	0.168	0.104, 0.261	0.168	0.103, 0.261	0.168	0.103, 0.261	0.168	0.104, 0.261	0.118	0.064, 0.2
DVP							0.507	0.198, 0.833	0.509	0.198, 0.833	0.509	0.196, 0.833	0.405	0.134, 0.774
RR comparators vs aripiprazole														
PBO	1.82	0.91, 4.12	1.13	0.64, 2.13	1.37	0.8, 2.43	1.82	0.92, 4.14	1.13	0.65, 2.14	1.37	0.8, 2.43	1.30	0.74, 2.31
ARP	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1
OLZ	1.00	0.38, 2.76	0.61	0.26, 1.49	0.75	0.32, 1.72	1.00	0.38, 2.77	0.61	0.26, 1.49	0.74	0.32, 1.74	0.68	0.28, 1.62
RISP	1.61	0.61, 4.48	0.99	0.42, 2.39	1.21	0.52, 2.78	1.61	0.61, 4.44	0.99	0.42, 2.4	1.20	0.52, 2.79	1.13	0.46, 2.72
QUET	1.28	0.54, 3.27	0.79	0.37, 1.74	0.96	0.46, 2.01	1.28	0.54, 3.29	0.79	0.37, 1.74	0.96	0.46, 2.02	0.88	0.4, 1.9
DVP							3.77	1.18, 10.32	2.35	0.78, 5.51	2.85	0.95, 6.41	3.00	0.9, 7.49
RR comparators vs placebo														
PBO	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1
ARP	0.55	0.24, 1.1	0.89	0.47, 1.55	0.73	0.41, 1.24	0.55	0.24, 1.09	0.89	0.47, 1.55	0.73	0.41, 1.25	0.77	0.43, 1.36
OLZ	0.54	0.28, 0.99	0.54	0.28, 0.99	0.54	0.28, 0.99	0.54	0.28, 0.99	0.54	0.28, 1.00	0.54	0.28, 1	0.52	0.27, 0.99
RISP	0.88	0.46, 1.62	0.88	0.46, 1.6	0.88	0.46, 1.61	0.88	0.46, 1.6	0.88	0.46, 1.61	0.88	0.46, 1.6	0.87	0.43, 1.68
QUET	0.70	0.43, 1.11	0.70	0.43, 1.11	0.70	0.43, 1.11	0.70	0.43, 1.11	0.70	0.43, 1.11	0.70	0.43, 1.11	0.68	0.4, 1.12
DVP							2.10	0.8, 3.69	2.10	0.8, 3.71	2.10	0.79, 3.7	2.34	0.78, 4.77
Probability treatment is best														
PBO	0.0%		0.0%		0.0%		0.0%		0.0%		0.0%		0.0%	
ARP	42.5%		7.8%		16.2%		42.4%		7.9%		16.3%		11.3%	
OLZ	41.5%		62.7%		58.1%		41.5%		62.6%		57.9%		60.9%	

RISP	4.9%	8.8%	7.7%	4.9%	8.7%	7.6%	8.2%
QUET	11.1%	20.7%	18.0%	11.1%	20.5%	17.9%	19.4%
DVP				0.2%	0.3%	0.3%	0.3%

Extra-pyramidal symptoms

	PIVOTAL STUDIES ONLY						ALL STUDIES EXCEPT TRAMONTINA						ALL STUDIES	
	ARIPIPRAZOLE 10MG		ARIPIPRAZOLE 30MG		ARIPIPRAZOLE POOLED DOSE		ARIPIPRAZOLE 10MG		ARIPIPRAZOLE 30MG		ARIPIPRAZOLE POOLED DOSE		ARIPIPRAZOLE POOLED DOSE	
	med	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**
Probability of experiencing the event														
PBO	0.030	0.01, 0.06	0.030	0.01, 0.06	0.030	0.01, 0.06	0.030	0.01, 0.06	0.030	0.01, 0.06	0.030	0.01, 0.06	0.026	0.011, 0.051
ARP	0.110	0.034, 0.256	0.210	0.072, 0.417	0.158	0.053, 0.328	0.109	0.034, 0.255	0.209	0.073, 0.416	0.158	0.055, 0.327	0.144	0.062, 0.268
RISP	0.111	0.033, 0.304	0.112	0.033, 0.302	0.112	0.033, 0.305	0.112	0.033, 0.305	0.112	0.033, 0.308	0.113	0.034, 0.309	0.101	0.031, 0.296
QUET	0.117	0.028, 0.524	0.116	0.028, 0.521	0.116	0.028, 0.528	0.117	0.028, 0.523	0.116	0.028, 0.517	0.115	0.028, 0.516	0.103	0.022, 0.542
DVP							0.012	0, 0.234	0.012	0, 0.235	0.012	0, 0.237	0.011	0, 0.219
RR comparators vs aripiprazole														
PBO	0.27	0.11, 0.6	0.14	0.06, 0.29	0.19	0.09, 0.38	0.27	0.11, 0.6	0.14	0.06, 0.29	0.19	0.09, 0.38	0.19	0.08, 0.37
ARP	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1
RISP	1.01	0.26, 4.47	0.53	0.15, 2.18	0.71	0.2, 2.93	1.02	0.26, 4.52	0.54	0.15, 2.2	0.71	0.2, 2.95	0.70	0.19, 2.86
QUET	1.04	0.15, 12.47	0.54	0.09, 6	0.72	0.12, 8.38	1.05	0.16, 12.51	0.55	0.09, 5.9	0.72	0.12, 7.94	0.70	0.11, 7.36
DVP							0.11	0, 2.6	0.06	0, 1.32	0.08	0, 1.77	0.08	0, 1.75
RR comparators vs placebo														
PBO	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1
ARP	3.71	1.66, 8.87	6.99	3.43, 15.51	5.28	2.65, 11.74	3.70	1.66, 8.84	6.98	3.43, 15.49	5.25	2.63, 11.69	5.39	2.73, 11.95
RISP	3.73	1.27, 13.84	3.72	1.28, 13.78	3.73	1.28, 13.84	3.73	1.28, 13.92	3.75	1.28, 14.11	3.74	1.27, 14.14	3.78	1.27, 14.09
QUET	3.80	0.66, 44.12	3.80	0.67, 43.82	3.79	0.67, 44.77	3.84	0.67, 44.06	3.80	0.66, 42.55	3.77	0.66, 42.08	3.79	0.66, 39.31
DVP							0.42	0, 8.83	0.42	0, 8.77	0.42	0, 8.79	0.42	0, 8.93
Probability treatment is best														
PBO	92.0%		92.1%		92.0%		29.4%		29.5%		29.5%		29.5%	
ARP	0.0%		0.0%		0.0%		0.0%		0.0%		0.0%		0.0%	
RISP	0.7%		0.7%		0.7%		0.0%		0.1%		0.1%		0.1%	
QUET	7.3%		7.2%		7.3%		2.9%		3.0%		2.9%		2.9%	
DVP							67.7%		67.5%		67.6%		67.6%	

Clinically significant weight gain

	PIVOTAL STUDIES ONLY					
	ARIPIPRAZOLE 10MG		ARIPIPRAZOLE 30MG		ARIPIPRAZOLE POOLED DOSE	
	median	95% CrI	median	95% CrI	median	95% CrI
Probability of experiencing the event						
PBO	0.016	0.004, 0.038	0.016	0.004, 0.038	0.016	0.004, 0.038
ARP	0.016	0.003, 0.071	0.053	0.011, 0.18	0.034	0.007, 0.119
OLZ	0.453	0.13, 0.894	0.455	0.127, 0.899	0.450	0.123, 0.896
RISP	0.041	0.009, 0.158	0.042	0.009, 0.158	0.041	0.008, 0.159
QUET	0.394	0.09, 0.956	0.390	0.089, 0.959	0.403	0.092, 0.964
RR comparators vs aripiprazole						
PBO	1.02	0.24, 4.55	0.31	0.09, 0.91	0.47	0.14, 1.32
ARP	1.00	1, 1	1.00	1, 1	1.00	1, 1
OLZ	27.57	4.12, 216.2	8.24	1.53, 50.23	12.52	2.31, 76.22
RISP	2.65	0.39, 20.21	0.79	0.15, 4.61	1.19	0.22, 6.94
QUET	23.99	2.34, 297	6.98	0.84, 72.47	11.1	1.3, 116.1
RR comparators vs placebo						
PBO	1.00	1, 1	1.00	1, 1	1.00	1, 1
ARP	0.98	0.22, 4.24	3.22	1.1, 10.91	2.13	0.76, 7.2
OLZ	26.30	7.49, 127.6	26.35	7.49, 128.4	26.44	7.46, 130.3
RISP	2.53	0.78, 10.74	2.55	0.78, 10.62	2.54	0.78, 10.78
QUET	22.67	3.8, 195.6	22.32	3.79, 196.8	23.54	3.92, 217.9
Probability treatment is best						
PBO	45.9%		92.1%		86.2%	
ARP	50.2%		1.5%		7.8%	
OLZ	0.0%		0.0%		0.0%	
RISP	3.9%		6.4%		6.1%	
QUET	0.0%		0.0%		0.0%	

Clinically significant increase in prolactin

	PIVOTAL STUDIES ONLY					
	ARIPIPRAZOLE 10MG		ARIPIPRAZOLE 30MG		ARIPIPRAZOLE POOLED DOSE	
	median	95% CrI	median	95% CrI	median	95% CrI
Probability of experiencing the event						
PBO	0.012	0.003, 0.031	0.012	0.003, 0.029	0.012	0.003, 0.029
ARP	0.001	0, 0.024	0.004	0, 0.048	0.002	0, 0.025
OLZ	0.433	0.116, 0.887	0.413	0.101, 0.882	0.416	0.106, 0.883
RISP	0.330	0.066, 0.947	0.323	0.062, 0.956	0.321	0.062, 0.95
QUET	0.076	0.015, 0.308	0.070	0.013, 0.294	0.070	0.014, 0.29
RR comparators vs aripiprazole						
PBO	8.74	0.52, 2179	2.47	0.21, 72.42	4.89	0.41, 140.3
ARP	1.00	1, 1	1.00	1, 1	1.00	1, 1
OLZ	310.70	12.84, 85630	88.75	5.48, 3267	175.70	10.86, 6414
RISP	251.20	6.82, 82530	71.13	2.84, 3736	139.80	5.52, 7202
QUET	57.86	2.33, 16060	15.85	0.93, 618.5	31.22	1.81, 1191
RR comparators vs placebo						
PBO	1.00	1, 1	1.00	1, 1	1.00	1, 1
ARP	0.11	0, 1.93	0.40	0.01, 4.81	0.20	0.01, 2.43
OLZ	32.82	9.06, 169.8	33.47	9.09, 185.2	33.83	9.15, 186.1
RISP	24.84	3.78, 261	25.81	3.8, 308.1	25.88	3.82, 291.8
QUET	5.97	1.72, 31.87	5.97	1.72, 32.36	5.97	1.72, 32.14
Probability treatment is best						
PBO	7.5%		23.8%		10.3%	
ARP	92.5%		76.2%		89.7%	
OLZ	0.0%		0.0%		0.0%	
RISP	0.0%		0.0%		0.0%	
QUET	0.0%		0.0%		0.0%	

Somnolence

	PIVOTAL STUDIES ONLY						ALL STUDIES EXCEPT TRAMONTINA						ALL STUDIES	
	ARIPIPRAZOLE 10MG		ARIPIPRAZOLE 30MG		ARIPIPRAZOLE POOLED DOSE		ARIPIPRAZOLE 10MG		ARIPIPRAZOLE 30MG		ARIPIPRAZOLE POOLED DOSE		ARIPIPRAZOLE POOLED DOSE	
	med	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**	**med**	**95% CrI**
Probability of experiencing the event														
PBO	0.078	0.045, 0.12	0.078	0.045, 0.12	0.078	0.045, 0.12	0.078	0.046, 0.12	0.078	0.045, 0.12	0.078	0.045, 0.12	0.165	0.114, 0.227
ARP	0.411	0.214, 0.677	0.509	0.296, 0.752	0.463	0.271, 0.711	0.410	0.215, 0.676	0.508	0.296, 0.755	0.462	0.271, 0.709	0.589	0.423, 0.758
RISP	0.265	0.143, 0.431	0.266	0.144, 0.431	0.266	0.145, 0.432	0.265	0.144, 0.432	0.266	0.144, 0.433	0.266	0.145, 0.433	0.459	0.294, 0.641
QUET	0.273	0.151, 0.442	0.273	0.15, 0.441	0.273	0.15, 0.441	0.273	0.151, 0.442	0.274	0.15, 0.443	0.274	0.151, 0.443	0.468	0.302, 0.653
DVP							0.159	0.067, 0.329	0.159	0.067, 0.327	0.159	0.067, 0.329	0.308	0.15, 0.536
RR comparators vs aripiprazole														
PBO	0.19	0.08, 0.45	0.16	0.07, 0.33	0.17	0.07, 0.36	0.19	0.08, 0.45	0.16	0.07, 0.33	0.17	0.07, 0.36	0.28	0.17, 0.46
ARP	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1
RISP	0.65	0.24, 1.68	0.53	0.21, 1.24	0.58	0.23, 1.38	0.65	0.24, 1.69	0.53	0.21, 1.25	0.58	0.23, 1.38	0.78	0.43, 1.34
QUET	0.67	0.25, 1.76	0.54	0.22, 1.29	0.59	0.23, 1.43	0.67	0.25, 1.76	0.54	0.22, 1.3	0.60	0.23, 1.44	0.80	0.44, 1.38
DVP							0.39	0.12, 1.19	0.32	0.1, 0.89	0.35	0.11, 0.98	0.53	0.23, 1.07
RR comparators vs placebo														
PBO	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1	1.00	1, 1
ARP	5.21	2.21, 13.27	6.41	3.02, 14.87	5.85	2.75, 14.1	5.18	2.22, 13.1	6.43	3, 15.16	5.84	2.75, 13.98	3.54	2.18, 5.92
RISP	3.40	1.88, 6.25	3.40	1.88, 6.24	3.39	1.87, 6.27	3.39	1.87, 6.24	3.40	1.87, 6.24	3.39	1.87, 6.26	2.76	1.72, 4.39
QUET	3.49	1.91, 6.76	3.48	1.89, 6.73	3.47	1.9, 6.69	3.47	1.89, 6.71	3.48	1.9, 6.76	3.49	1.9, 6.73	2.81	1.73, 4.62
DVP									2.05	0.88, 4.54	2.05	0.88, 4.55	1.86	0.9, 3.49
Probability treatment is best														
PBO	100%		100%		100%		95.2%		95.3%		95.3%		95.5%	
ARP	0%		0%		0%		0.0%		0.0%		0.0%		0.0%	
RISP	0%		0%		0%		0.0%		0.0%		0.0%		0.0%	
QUET	0%		0%		0%		0.0%		0.0%		0.0%		0.0%	
DVP							4.8%		4.7%		4.7%		4.5%	

9.16 Appendix 16: Winbugs code for Network Meta-Analysis Fixed Effects Model

```
model {


for (i in 1:N.d)
{
        n[i]~dbin(p[i],total[i] )
logit(p[i])<-lambda[s[i]] + theta[s[i],b[i],t[i]]
}



for (j in 1:N.s)
{
lambda[j]~dnorm(0,0.01)

for (c in 1:(N.t -1))
{
theta[j,c,c]<-0

for (k in (c+1):N.t)
{
theta[j,c,k] <- dshift[c,k]
 }
}
}


for (c in 1:(N.t -1))
{
for (k in (c+1):N.t)
{
dshift[c,k]<-mu[k]-mu[c]
}
}

mu[1]<-0
for (i in 2:N.t) { mu[i]~dnorm(0,0.01) }


for (i in 1:N.d) {lambda1[i] <- lambda[s[i]] * equals(t[i],1) }
ref <- sum(lambda1[])/N1

for (k in 1:N.t)
{
logit(T[k])<- ref +mu[k]
rr_pbo[k] <- T[k]/T[1]
 rr_ari[k] <- T[k]/T[2]
}
```

```
for (k in 1:N.t)
{
rk_neg[k] <- rank(T[],k)
best_neg[k] <- equals(rk_neg[k],1)

rk_pos[k] <- (N.t+1)-rank(T[],k)
best_pos[k] <- equals(rk_pos[k],1)
}


}
```

Example of input data: YMRS1, Aripiprazole pooled dose, pivotal studies only

```
list(

N.d=6,
N.s=3,
N.t=4,

N1=3,

s=c(1,1,2,2,3,3),

#study,Findling 2009,Findling 2009,Findling 2009,Findling 2009,Tohen 2007,Tohen
2007,Haas 2009,Haas 2009,,,,,,
#trt,pbo,aripi_10,aripi_30,aripi_pooled,pbo,olz,pbo,risp,,,,,,

t=c(1,2,1,3,1,4),

b=c(1,1,1,1,1,1),

total=c(94,195,54,105,58,111),

n=c(6,44,6,28,5,27)

)
```

Initial values

```
list(mu=c(NA,0,0,0), lambda=c(0,0,0))
list(mu=c(NA,-1,-1,-1), lambda=c(-3,-3,-3))
list(mu=c(NA,2,2,2), lambda=c(-3,5,-1))
```

9.17 Appendix 17: Meta-analysis of NCT00110461 (pooled 10-30 mg dose) and NCT00116259

Meta-analyses were run for the following efficacy outcomes:

- YMRS response (defined as ≥50% reduction in YMRS total score from baseline) at week 1
- YMRS response at week 2
- YMRS response at week 3
- YMRS response at week 4 *[results still pending]*
- Discontinuation at week 3

Meta-analyses were run for the following safety outcomes:

- Extrapyramidal symptoms
- Somnolence

The other clinically important adverse events of clinically significant weight gain and clinically significant increase in prolactin were not measured in NCT00116259 (according to correspondence with the authors), so no meta-analysis could be performed on these outcomes. The safety outcomes pooled the 4-week event rate from the NCT00110461 trial and the 6-week event rate from the NCT00116259 trial. No adjustment was made for drug exposure time, as the difference between the studies was small at only two weeks.

Meta-analyses methodology

The results (Relative Risk [RR] and Risk Difference [RD]) of the NCT00110461 and NCT00116259 studies were meta-analysed to produce a pooled estimate of the effect of aripiprazole versus placebo for each of the above-mentioned outcomes. Pooling was done using both fixed-effect and random-effect models. The fixed-effect model was run using the Mantel-Haenszel method.[130] The random-effect model was run using the DerSimonian and Laird method,[131] with the estimate of heterogeneity being taken from the Mantel-Haenszel model.

Heterogeneity was assessed by the Cochran's Q test and the I^2 statistics:

- Cochran's Q is the standard test for heterogeneity and examines the null hypothesis that all studies are evaluating the same effect. However, the power of this test is low when the meta-analysis includes a small number of studies, which is the case in this analysis.

- The I^2 statistics is a measure that lies between 0% and 100% and gives an indication of the magnitude of heterogeneity in the meta-analysis, a value of 0% representing no observed heterogeneity and larger values indicating increasing heterogeneity. This measure can be interpreted as the percentage of the total variability in a set of effect sizes due to true heterogeneity. The I^2 results are interpreted according to the classification proposed by Higgins and Thompson in 2002.*[reference to be added]* Values of around 25% represent a low level of heterogeneity, values around 50% a medium level and values around 75% indicates a high amount of heterogeneity.

Both heterogeneity measures are reported for each model and a recommendation on which model is the most appropriate is made. For analyses where high heterogeneity is found, a random effects approach is usually preferred.

Meta-analyses results

YMRS response at week 1

There is a moderate amount of heterogeneity in the meta-analysis on relative risks for YMRS response at week 1, but it does not come out as significant. There is no heterogeneity in the meta-analysis on risk differences. The fixed-effect model is therefore the most appropriate in both cases.

The analyses on both RR and RD measures show that there is a significantly greater chance of achieving YMRS response at week 1 with aripiprazole than with placebo (Table B88).

Table B88 RR and RD for YMRS response at week 1

Study	RR	95% CI	Weights (%) fixed-effect meta-analysis	Weights (%) random-effect meta-analysis
NCT00110461	3.54	1.56, 8.00	54.7	46.3
NCT00116259	1.74	0.86, 3.51	45.3	53.7
Pooled RR			**2.72 (1.54, 4.81)**	**2.41 (1.14, 5.12)**
p-value			**0.001**	**0.022**
Heterogeneity			**I^2=48.8%, chi-square p-value=0.162**	

Study	RD	95% CI	Weights (%) fixed-effect meta-analysis	Weights (%) random-effect meta-analysis
NCT00110461	16.2	8.5, 23.9	85.8	93.6
NCT00116259	23.6	-5.8, 52.9	14.2	6.4
Pooled RD			**17.2 (9.4, 25.0)**	**16.7 (9.2, 24.1)**
p-value			**<0.001**	**<0.001**
Heterogeneity			**I^2=0%, chi-square p-value=0.617**	

YMRS response at week 2

There is a high amount of heterogeneity in the meta-analysis on relative risks for YMRS response at week 2 that just fails to reach significance. There is no heterogeneity in the meta-analysis on risk differences. The fixed-effect model is therefore the most appropriate in both cases.

The analyses on both RR and RD measures show that there is a significantly greater chance of achieving YMRS response at week 2 with aripiprazole than with placebo (Table B89).

Table B89 RR and RD for YMRS response at week 2

Study	RR	95% CI	Weights (%) fixed-effect meta-analysis	Weights (%) random-effect meta-analysis
NCT00110461	2.74	1.71, 4.39	70.1	52.8
NCT00116259	1.39	0.78, 2.47	29.9	47.2
Pooled RR			**2.34 (1.60, 3.42)**	**1.99 (0.99, 4.02)**
p-value			**<0.001**	**0.055**
Heterogeneity			**I^2=72.1%, chi-square p-value=0.058**	

Study	RD	95% CI	Weights (%) fixed-effect meta-analysis	Weights (%) random-effect meta-analysis
NCT00110461	29.6	19.3, 40.0	85.8	89.2
NCT00116259	17.1	-12.7, 46.9	14.2	10.8
Pooled RD			**27.9 (18.1, 37.7)**	**28.3 (18.5, 38.1)**
p-value			**<0.001**	**<0.001**
Heterogeneity			**I^2=0%, chi-square p-value=0.433**	

YMRS response at week 3

There is a significant high amount of heterogeneity in both meta-analyses. The random-effect model is therefore the most appropriate in both cases. The analyses on both RR and RD measures show that there is a greater chance of achieving YMRS response at week 3 with aripiprazole than with placebo, but that the difference between treatments is not significant (Table B90).

The poor results for aripiprazole from study NCT00116259 are likely a product of the small patient sample size in this trial. The week 4 YMRS results indicate that this week 3 result is an anomaly.

Table B90 RR and RD for YMRS response at week 3

Study	RR	95% CI	Weights (%) fixed-effect meta-analysis	Weights (%) random-effect meta-analysis
NCT00110461	2.77	1.73, 4.44	63.2	50.5
NCT00116259	0.93	0.55, 1.56	36.8	49.5
Pooled RR			**2.09 (1.45, 3.02)**	**1.61 (0.51, 5.09)**
p-value			**<0.001**	**0.417**
Heterogeneity			**I^2=90.7%, chi-square p-value=0.001**	

Study	RD	95% CI	Weights (%) fixed-effect meta-analysis	Weights (%) random-effect meta-analysis
NCT00110461	30.2	19.8, 40.5	85.8	58.5
NCT00116259	-4.4	-34.4, 25.5	14.2	41.8
Pooled RD			**25.3 (15.4, 35.1)**	**15.8 (-17.8, 49.4)**
p-value			**<0.001**	**0.358**
Heterogeneity			**I^2=78.5%, chi-square p-value=0.031**	

YMRS response at week 4

There is a small to moderate amount of heterogeneity in the meta-analysis on relative risks for YMRS at week 4, but it does not come out as significant. There is no heterogeneity in the meta-analysis on risk differences. The fixed-effect model is therefore the most appropriate in both cases.

The analyses on both RR and RD measures show that there is a significantly greater chance of achieving YMRS response at week 4 with aripiprazole than with placebo. This indicates that the week 3 YMRS results for NCT00116259 are anomolous.

Table B91 RR and RD for YMRS response at week 4

Study	RR	95% CI	Weights (%) fixed-effect meta-analysis	Weights (%) random-effect meta-analysis
Findling 2009	2.04	1.43, 2.93	74.2	53.7
Tramontina 2009	1.49	0.99, 2.23	25.8	46.3
Pooled RR			**1.90 (1.42, 2.54)**	**1.77 (1.26, 2.47)**
p-value			**<0.001**	**0.001**
Heterogeneity			**I^2=36.1%, chi-square p-value=0.211**	

Study	RD	95% CI	Weights (%) fixed-effect meta-analysis	Weights (%) random-effect meta-analysis
Findling 2009	27.8	16.4, 39.1	85.8	84.0
Tramontina 2009	27.3	1.4, 53.3	14.2	16.0
Pooled RD			**27.7 (17.3, 38.1)**	**27.7 (17.3, 38.1)**
p-value			**<0.001**	**<0.001**
Heterogeneity			**I^2=0%, chi-square p-value=0.976**	

Discontinuation at week 3

There is a small amount of heterogeneity in the meta-analysis on relative risks for discontinuation at week 3, and a moderate amount in the one on risk differences. Neither comes out as significant. The fixed-effect model is therefore the most appropriate in both cases.

The analyses on both RR and RD measures show there are less patients discontinuing treatment at week 3 with aripiprazole than with placebo, but not significantly so (Table B92).

Table B92 RR and RD for discontinuation rate at week 3

Study	RR	95% CI	Weights (%) fixed-effect meta-analysis	Weights (%) random-effect meta-analysis
NCT00110461	0.71	0.40, 1.26	98.2	90.1
NCT00116259	4.11	0.18, 95.37	1.8	9.9
Pooled RR			**0.77 (0.44, 1.34)**	**0.84 (0.30, 2.37)**

p-value			**0.360**	**0.748**
Heterogeneity			**I^2=14.3%, chi-square p-value=0.280**	

Study	**RD**	**95% CI**	**Weights (%) fixed-effect meta-analysis**	**Weights (%) random-effect meta-analysis**
NCT00110461	-5.0	-13.7, 3.7	86.3	60.2
NCT00116259	5.6	-8.3, 19.4	13.7	39.8
Pooled RD			**-3.5 (-11.3, 4.2)**	**-0.8 (-11.6, 10.0)**
p-value			**0.371**	**0.885**
Heterogeneity			**I^2=48.0%, chi-square p-value=0.165**	

Extrapyramidal symptoms

There is no heterogeneity in the meta-analysis on relative risks for extrapyramidal symptoms. The fixed-effect model is therefore the preferred one. There is a moderate to high amount of heterogeneity in the meta-analysis on risk differences, but it does not come out as significant. For this reason, and because the evidence in the Tramontina study is weak (based on only a small sample of patients and a small number of events, and no events in the placebo arm), the fixed-effect model is the preferred approach.

The analyses on both RR and RD measures show that there is a significantly greater chance of experiencing extrapyramidal symptoms with aripiprazole than with placebo (Table B93).

Table B93 RR and RD for extrapyramidal symptoms

Study	**RR**	**95% CI**	**Weights (%) fixed-effect meta-analysis**	**Weights (%) random-effect meta-analysis**
NCT00110461	4.36	2.08, 9.17	94.7	93.9
NCT00116259	6.28	0.34, 115.84	5.3	6.1
Pooled RR			**4.46 (2.17, 9.16)**	**4.46 (2.17, 9.16)**
p-value			**<0.001**	**<0.001**
Heterogeneity			**I^2=0%, chi-square p-value=0.813**	

Study	**RD**	**95% CI**	**Weights (%) fixed-effect meta-analysis**	**Weights (%) random-effect meta-analysis**
NCT00110461	24.3	16.0, 32.5	83.1	56.6
NCT00116259	10.7	-2.8, 24.2	16.9	43.4
Pooled RD			**22.0 (14.7, 29.2)**	**18.4 (4.8, 32.0)**
p-value			**<0.001**	**0.008**
Heterogeneity			**I^2=68.6%, chi-square p-value=0.074**	

Somnolence

There is a very high amount of heterogeneity in the meta-analysis on relative risks for somnolence, which is highly significant. The random-effect model is therefore the preferred one. This shows that patients on aripiprazole are more likely to experience somnolence than patients on placebo (Table B94). However the precision of the estimation is poor, leading to a very wide confidence interval and a non significant difference.

There is no heterogeneity in the meta-analysis on risk differences. The fixed-effect model is therefore the preferred one, which shows that there is a significantly greater chance of experiencing somnolence with aripiprazole than with placebo (Table B94).

The discrepancy between the two measures comes from the fact that the proportions of patients experiencing somnolence greatly differ between studies: 3.1% and 22.9% for the placebo and aripiprazole arm in study NCT00110461, compared to 68% and 89% in study NCT00116259. This may be partly due to the fact that frequencies of adverse events in NCT00116259 were measured over 6 weeks, whereas in NCT00110461 they were measured over 4 weeks. Differences in the study populations (see Table B5, and also that NCT00116259 included only patients with co-morbid ADHD) may also have influenced the differing incidences of somnolence.

Table B94 RR and RD for somnolence

Study	RR	95% CI	Weights (%) fixed-effect meta-analysis	Weights (%) random-effect meta-analysis
NCT00110461	7.39	2.36, 23.17	18.3	47.8
NCT00116259	1.31	0.98, 1.77	81.7	52.2
Pooled RR			**2.42 (1.61, 3.64)**	**3.00 (0.22, 41.72)**
p-value			**<0.001**	**0.414**
Heterogeneity			**I^2=95.0%, chi-square p-value<0.001**	

Study	RD	95% CI	Weights (%) fixed-effect meta-analysis	Weights (%) random-effect meta-analysis
NCT00110461	19.7	13.0, 26.5	83.1	91.0
NCT00116259	21.3	-0.3, 42.9	16.9	9.0
Pooled RD			**20.0 (13.3, 26.7)**	**20.0 (13.4, 26.4)**
p-value			**<0.001**	**<0.001**
Heterogeneity			**I^2=0%, chi-square p-value=0.890**	

9.18 Appendix 18: Efficacy data from the acute and extension phases of study NCT00110461

Table B95 Mean changes from baseline in the extension phase of study NCT00110461[6, 61]

		Placebo		Aripiprazole 10 mg/day			Aripiprazole 30 mg/day			p value vs. placebo
		N	Mean change from baseline	N	Mean change from baseline	Treatment difference (95% CI)	N	Mean change from baseline	Treatment difference (95% CI)	
YMRS	Week 30	94	-8.2	96	-14.1*	[redacted]	99	-14.9*	[redacted]	*p<0.0001
CGI-BP severity	Mania – week 30	94	-0.9	96	-1.7*	[redacted]	99	-2.0**	[redacted]	*p=0.0003 **p<0.0001
	Depression – week 30	94	-0.5	96	-0.7	[redacted]	99	-0.9*	[redacted]	*p=0.0166
	Overall – week 30	94	-0.8	96	-1.6*	[redacted]	99	-1.8*	[redacted]	*p<0.0001
CGI-BP change from preceding phase	Mania – week 30	94	3.3	96	2.6*	[redacted]	99	2.5**	[redacted]	*p≤0.05 **p≤0.0001
	Depression – week 30	94	3.6	96	3.3	[redacted]	99	3.1*	[redacted]	*p≤0.05 **p≤0.0001
	Overall – week 30	94	3.4	96	2.8*	[redacted]	99	2.6**	[redacted]	*p≤0.05 **p≤0.0001
CGAS score	Week 30	94	6.8	96	16.0*	[redacted]	99	16.8*	[redacted]	*p<0.0001
GBI total scores	Parent/guardian (mania) – week 30	93	-4.3	95	-9.0*	[redacted]	96	-8.9*	[redacted]	*p<0.0001
	Parent/guardian (depression) – week 30	93	-2.8	95	-5.0*	[redacted]	96	-4.1	[redacted]	*p<0.05
	Patient (mania) – week 30	93	-5.3	96	-6.7	[redacted]	96	-7.9*	[redacted]	*p<0.05

	Patient (depression) – week 30	93	-3.2	96	-4.0	[redacted]	96	-4.4	[redacted]	N.S.
ADHD-RS-IV total score	Week 30	91	-4.6	97	-11.6**	[redacted]	97	-10.1*	[redacted]	*p≤0.05 **p≤0.0001
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to discontinuation				**			*			*p=0.0124 **p≤0.0001

N = number of subjects, with the variation reflecting that all rating scales were not completed for all subjects; NR = not reported
Positive change of the CGAS and P-QLES-Q scores signifies improvement; for all other scales, negative change signifies improvement

Table B96 Responders and patients achieving remission in the extension phase of study NCT00110461[6, 61]

		Placebo			Aripiprazole 10 mg/day			Aripiprazole 30 mg/day			p value, aripiprazole 10 mg vs. placebo	95% CI for difference (%)	p value, aripiprazole 30 mg vs. placebo	95% CI for difference (%)	Relative risk (risk difference)	
		N	n	%	N	n	%	N	n	%					Aripiprazole 10 mg	Aripiprazole 30 mg
% patients who were responders (defined as ≥50% reduction from baseline YMRS total score)	Week 30	[redacted]	[redacted]	26.60	[redacted]	[redacted]	50.00	[redacted]	[redacted]	55.56	[redacted]	[redacted]	[redacted]	[redacted]	1.88 (23.40)	2.09 (28.96)
% patients who were in remission (defined as YMRS total score ≤12 and CGI-BP severity score for mania ≤2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.63 (19.60)	8.80 (42.1)

N = number of randomized subjects with both baseline and at least one post-baseline value; n = number of responders; NR = not reported

9.19 Appendix 19: Quality assessment & results of studies included in the systematic review but not in the meta-analysis (see Section 5.7.2)

Table B97 Quality assessment results for RCTs included in the systematic review but not in the meta-analysis

Trial no. (acronym)	Pavuluri 2010[77]	Geller 2012[78]
Was randomisation carried out appropriately?	Randomisation performed, but no details are provided to enable an evaluation of whether the method was appropriate	Yes
Was the concealment of treatment allocation adequate?	Yes – parents, caregivers and subjects were blind to the medication received, as well as the investigational staff involved in rating efficacy and safety measures	No – only the final outcomes assessor was blinded. Knowledge of drug by the patients, carers and caregivers may have biased the results towards the newer drug, risperidone.
Were the groups similar at the outset of the study in terms of prognostic factors?	No – many baseline characteristics are similar in the two groups but there are some differences, including more patients with co-morbidities in the risperidone group (ADHD, anxiety, ODD) and fewer patients being overweight.	No – disease characteristics were similar, but mean patient age was slightly older in the risperidone group
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	No – patients, family members and treating clinicians were aware of treatment assignment. Also, non-blinded interviewers conducted the weekly assessments
Were there any unexpected imbalances in drop-outs between groups?	Yes – significantly more patients dropped out of the divalproex group compared to the risperidone group	Yes – there were fewer drop-outs in the risperidone group (this may have been biased by the open nature of the study)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were	Yes	Yes, although the ITT analysis excluded patients who did not present at first visit. This was acceptable

appropriate methods used to account for missing data?		however as these patients would not have known their drug allocation and therefore this could not have biased them to drop-out. Non-responder imputation was used.

Table B98 Relevant outcomes from Pavuluri 2010[77] and Geller 2012[78]

Pavuluri[77]		Divalproex 60-120 µg/ml daily + placebo		Risperidone 0.2-2.0 mg/day + placebo			Additional comparator		
		N	Value	N	Value	p value risperidone vs. placebo	N	Value	p value risperidone vs. placebo
YMRS response (defined as ≥50% improvement from baseline YMRS)	n (%) at Week 1	NR	NR	NR	NR	NR	-	-	-
	n (%) at Week 2	NR	NR	NR	NR	NR	-	-	-
	n (%) at Week 3	NR	NR	NR	NR	NR	-	-	-
Discontinuation rate	n (%) at Week 3	33	33.3%	33	12.1%	NR	-	-	-
Extrapyramidal symptoms	n (%) at Week 3	NR	NR	NR	NR	NR	-	-	-
Somnolence	n (%) at Week 3	NR	NR	NR	NR	NR	-	-	-
Clinically significant weight gain	n (%) at Week 3	NR	NR	NR	NR	NR	-	-	-
Clinically significant increase in prolactin	n (%) at Week 3	NR	NR	NR	NR	NR	-	-	-
Geller 2012[78]		**Risperidone 4-6 mg**		**Lithium 1.1-1.3 mEq/L**			**Divalproex sodium 111-125 µg/mL**		
		N	**Value**	**N**	**Value**	**p value lithium vs. risperidone**	**N**	**Value**	**p value vs. risperidone**
YMRS response (defined as ≥50% improvement from baseline YMRS)	n (%) at Week 1	NR	NR	NR	NR	NR	NR	NR	NR
	n (%) at Week 2	NR	NR	NR	NR	NR	NR	NR	NR
	n (%) at Week 3	NR	NR	NR	NR	NR	NR	NR	NR
Discontinuation rate	n (%) at Week 3	NR	NR	NR	NR	NR	NR	NR	NR
Extrapyramidal symptoms	n (%) at Week 3	NR	NR	NR	NR	NR	NR	NR	NR
Somnolence	n (%) at Week 3	NR	NR	NR	NR	NR	NR	NR	NR
Clinically significant weight gain	n (%) at Week 3	NR	NR	NR	NR	NR	NR	NR	NR

Clinically significant increase in prolactin	n (%) at Week 3	NR	NR	NR	NR	NR	NR	NR	NR

NR, not reported

10 Related procedures for evidence submission

10.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission.

There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential

information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been

put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

10.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including

when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).