APPENDIX 31: HEALTH ECONOMICS - METHODOLOGY CHECKLISTSFOR ECONOMIC EVALUATIONS

Abbreviations

EQ-5D	European Quality of Life-5 Dimensions
GDG	Guideline Development Group
HRQoL	health-related quality of life
NA	not applicable
NHS	National Health System
NICE	National Institute for Health and Care Excellence
PSS	personal social services
QALY	quality-adjusted life year
RCT	randomised controlled trial
SF-6D	Short Form Questionnaire-Six Dimensional Health State Classification
XR	extended release

1.1 CASE IDENTIFICATION AND ASSESSMENT OF ADULTS WITH BIPOLAR DISORDER

Study: Menzin J, Sussman M, Tafesse E, Duczakowski C, Neumann P, Friedman M. A model of the economic impact of a bipolar disorder screening program in primary care. Journal of Clinical Psychiatry. 2009;70:1230-36.			
Guideline topic: Case identification for adults with bipolar disorder			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults presenting for the first time with symptoms of major depressive disorder in primary care
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Partly	US study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	No	Third-party payer
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	Partly	Annual discount rate 3%
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	No	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	NA	
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	NA	
1.10	Overall judgement: **Partially applicable**		
Other comments: QALYs not estimated, but intervention dominant according to the outcome measure used			

Section 2: Study limitations (the level of methodological quality) **This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline**		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	Decision tree
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	5 years
2.3	Are all important and relevant health outcomes included?	Partly	Only number of people correctly/incorrectly identified considered
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	Literature review and further assumptions
2.5	Are the estimates of relative treatment effects from the best available source?	Partly	Literature review and further assumptions
2.6	Are all important and relevant costs included?	Yes	Direct medical costs
2.7	Are the estimates of resource use from the best available source?	Partly	Published literature
2.8	Are the unit costs of resources from the best available source?	Yes	Published cost-of-illness study
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	One-way and probabilistic analysis
2.11	Is there no potential conflict of interest?	No	Funded by pharmaceutical industry, but no apparent conflict of interest
2.12	Overall assessment: **potentially serious limitations**		
Other comments:			

1.2 PHARMACOLOGICAL INTERVENTIONS FOR MANIA, HYPOMANIA AND MIXED EPISODES IN ADULTS WITH BIPOLAR DISORDER

Study: 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 Technology Assessment. 2004;8.			
Guideline topic: Pharmacological interventions for adults with bipolar disorder in mania			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar I disorder in mania
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	UK study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	NA	Time horizon 3 weeks
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	No	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	NA	
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	NA	
1.10	Overall judgement: **Partially applicable**		
Other comments: Lack of QALYs makes judgements on relative cost effectiveness difficult			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	Decision tree
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	No	3 weeks
2.3	Are all important and relevant health outcomes included?	Partly	Side effects not considered
2.4	Are the estimates of baseline health outcomes from the best available source?	Yes	Systematic review and network meta-analysis
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	Systematic review and network meta-analysis
2.6	Are all important and relevant costs included?	Partly	Hospitalisation costs assumed to be the same in all arms; costs of side effects not considered
2.7	Are the estimates of resource use from the best available source?	No	Assumptions and information from manufacturers
2.8	Are the unit costs of resources from the best available source?	Yes	National unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11	Is there no potential conflict of interest?	Yes	
2.12	Overall assessment: **potentially serious limitations**		
Other comments: Quetiapine and olanzapine are now available in generic form			

Study: Caro JJ, Huybrechts KF, Xenakis JG, O'Brien JA, Rajagopalan K, Lee K. Budgetary impact of treating acute bipolar mania in hospitalized patients with quetiapine: an economic analysis of clinical trials. Current Medical Research and Opinion. 2006;22:2233-42.			
Guideline topic: Pharmacological interventions for adults with bipolar disorder in mania			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar I disorder with mania
1.2	Are the interventions and services appropriate for the guideline?	Partly	Usual care may not reflect usual care in the UK
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Partly	US study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	No	US study
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	NA	Time horizon 100 days
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	No	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	NA	
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	NA	
1.10	Overall judgement: **Partially applicable**		
Other comments:			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	Discrete event simulation
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	100 days
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	Review and administrative data
2.5	Are the estimates of relative treatment effects from the best available source?	No	Literature review
2.6	Are all important and relevant costs included?	Yes	Direct medical costs included
2.7	Are the estimates of resource use from the best available source?	No	Administrative databases
2.8	Are the unit costs of resources from the best available source?	Yes	National unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11	Is there no potential conflict of interest?	No	Funded by industry
2.12	Overall assessment: **potentially serious limitations**		
Other comments: Quetiapine is now available in generic form			

Study: Revicki DA, Paramore LC, Sommerville KW, Swann AC, Zajecka JM. Divalproex sodium versus olanzapine in the treatment of acute mania in bipolar disorder: health-related quality of life and medical cost outcomes. Journal of Clinical Psychiatry. 2003;64:288-94.			
Guideline topic: Pharmacological interventions for adults with bipolar disorder in mania			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar I disorder in mania
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Partly	US study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	No	US study
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	NA	Time horizon 12 weeks
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	No	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	NA	
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	NA	
1.10	Overall judgement: **Partially applicable**		
Other comments:			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	NA	Alongside randomised controlled trial (RCT)
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	12 weeks
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	RCT
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	RCT
2.6	Are all important and relevant costs included?	Yes	Direct medical costs included
2.7	Are the estimates of resource use from the best available source?	Partly	RCT and further assumptions
2.8	Are the unit costs of resources from the best available source?	Yes	National unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	NA	Cost consequence analysis
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Statistical analysis provided
2.11	Is there no potential conflict of interest?	No	Funded by industry
2.12	Overall assessment: **potentially serious limitations**		
Other comments: HRQoL and resource use data collected via telephone interviews. Olanzapine is now available in generic form			

Study: Zhu BT, Tunis SL, Zhao Z, Baker RW, Lage MJ, Shi L, et al. Service utilization and costs of olanzapine versus divalproex treatment for acute mania: results from a randomized, 47-week clinical trial. Current Medical Research and Opinion. 2005;21:555-64.			
Guideline topic: Pharmacological interventions for adults with bipolar disorder in mania			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar I disorder in mania
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Partly	US study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	No	US study
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	NA	Time horizon 47 weeks
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	No	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	NA	
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	NA	
1.10	Overall judgement: **Partially applicable**		
Other comments:			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	NA	Alongside RCT
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	47 weeks
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	RCT
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	RCT
2.6	Are all important and relevant costs included?	Yes	Direct medical costs included
2.7	Are the estimates of resource use from the best available source?	Partly	RCT participants who entered maintenance phase
2.8	Are the unit costs of resources from the best available source?	Yes	National unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	NA	Cost consequence analysis
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Statistical analysis provided
2.11	Is there no potential conflict of interest?	No	Funded by industry
2.12	Overall assessment: **potentially serious limitations**		
Other comments: resource use data collected only for people who entered the maintenance phase of the trial. Olanzapine is now available in generic form.			

Study: Guideline economic analysis			
Guideline topic: Pharmacological interventions for adults with bipolar disorder in mania			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar disorder in mania
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	NA	Time horizon 3 weeks
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	Yes	Cost-effectiveness analysis and cost-utility analysis
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	No	Utility data based on vignettes
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	Stable people with bipolar disorder in the US
1.10	Overall judgement: **Partially applicable**		
Other comments:			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	Decision tree
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	No	3 weeks
2.3	Are all important and relevant health outcomes included?	Partly	Side effects not considered
2.4	Are the estimates of baseline health outcomes from the best available source?	Yes	Published network meta-analysis
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	Published network meta-analysis
2.6	Are all important and relevant costs included?	Partly	Hospitalisation costs assumed to be the same in all arms; costs of side effects not considered
2.7	Are the estimates of resource use from the best available source?	Partly	Guideline Development Group (GDG) expert opinion
2.8	Are the unit costs of resources from the best available source?	Yes	National unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	
2.11	Is there no potential conflict of interest?	Yes	
2.12	Overall assessment: **potentially serious limitations**		
Other comments:			

1.3 PHARMACOLOGICAL INTERVENTIONS FOR ACUTE DEPRESSION IN ADULTS WITH BIPOLAR DISORDER

Study: Ekman M, Lindgren P, Miltenburger C, Meier G, Locklear JC, Chatterton ML. Cost effectiveness of quetiapine in patients with acute bipolar depression and in maintenance treatment after an acute depressive episode. PharmacoEconomics. 2012;30:513-30.			
Guideline topic: Pharmacological interventions for adults with bipolar disorder in acute depression			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar I or II disorder in acute depression or in remission
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	UK study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	Yes	
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	Yes	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Yes	
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	Most utilities elicited from outpatients with bipolar disorder in the US; utility of outpatient depression based on European Quality of Life-5 Dimensions (EQ-5D) UK tariff

1.10	Overall judgement: **Directly applicable**
Other comments:	

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	Discrete event simulation
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	5 years
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Yes	Placebo arms of RCTs
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	RCTs and meta-analyses of RCTs; evidence synthesis likely inappropriate, as different populations and outcome measures across studies
2.6	Are all important and relevant costs included?	Yes	
2.7	Are the estimates of resource use from the best available source?	Partly	Published data mainly based on expert opinion
2.8	Are the unit costs of resources from the best available source?	Yes	National unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11	Is there no potential conflict of interest?	No	Funded by industry
2.12	Overall assessment: **very serious limitations**		
Other comments: Quetiapine and olanzapine are now available in generic form			

Study: Guideline economic analysis			
Guideline topic: Pharmacological interventions for adults with bipolar disorder in acute depression			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar disorder in acute depression
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	NA	Time horizon 18 weeks
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	Yes	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Yes	Utility data on depression based on patient EQ-5D; utility value for mania based on vignettes
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	Yes	EQ-5D UK tariff – vignettes valued by stable people with bipolar disorder in the US
1.10	Overall judgement: **Directly applicable**		
Other comments:			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	Decision tree
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	18 weeks
2.3	Are all important and relevant health outcomes included?	Yes	Side effects indirectly considered, through discontinuation
2.4	Are the estimates of baseline health outcomes from the best available source?	Yes	Systematic review and network meta-analysis
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	Systematic review and network meta-analysis
2.6	Are all important and relevant costs included?	Partly	costs of side effects indirectly considered, through discontinuation
2.7	Are the estimates of resource use from the best available source?	Partly	National sources, other published data and GDG expert opinion
2.8	Are the unit costs of resources from the best available source?	Yes	National unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11	Is there no potential conflict of interest?	Yes	
2.12	Overall assessment: **minor limitations**		
Other comments:			

Services for adults with bipolar disorder

Study: Kessing LV, Hansen HV, Hvenegaard A, Christensen EM, Dam H, Gluud C, et al. Treatment in a specialised out-patient mood disorder clinic v. standard out-patient treatment in the early course of bipolar disorder: randomised clinical trial. British Journal of Psychiatry. 2013;202:212-9.			
Guideline topic: Mood disorder clinics for adults with bipolar disorder			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with recently diagnosed bipolar disorder
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Partly	Danish study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	No	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	NA	Time horizon 2 years
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	No	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	NA	
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	NA	
1.10	Overall judgement: **Partially applicable**		
Other comments: QALYs not estimated, but intervention dominant according to the outcome measure used			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline.		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	NA	RCT
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	2 years
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	RCT
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	RCT
2.6	Are all important and relevant costs included?	Yes	Direct medical costs
2.7	Are the estimates of resource use from the best available source?	Partly	RCT, published literature and further assumptions
2.8	Are the unit costs of resources from the best available source?	Yes	National published data
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Statistical analysis done only for clinical outcomes; sensitivity analysis only regarding cost results
2.11	Is there no potential conflict of interest?	No	Funded by pharmaceutical industry, but no apparent conflict of interest
2.12	Overall assessment: **potentially serious limitations**		
Other comments:			

1.4 PHARMACOLOGICAL INTERVENTIONS FOR THE LONG-TERM MANAGEMENT OF ADULTS WITH BIPOLAR DISORDER

Study: Calvert NW, Burch SP, Fu AZ, Reeves P, Thompson TR. The cost-effectiveness of lamotrigine in the maintenance treatment of adults with bipolar I disorder. Journal of Managed Care Pharmacy. 2006;12:322-30.			
Guideline topic: Pharmacological interventions for long-term management of adults with bipolar disorder			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar disorder I stabilised after resolution of a mixed/manic episode
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	No	US study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	No	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	NA	Time horizon 18 months
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	Yes	Other outcomes also considered
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Unclear	Unpublished Short Form Questionnaire-Six Dimensional Health State Classification (SF-6D) values and further assumptions
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	Yes	UK tariff
1.10	Overall judgement: **Partially applicable**		
Other comments:			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	18 months
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	Double-blind RCTs
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	Indirect comparisons using double-blind RCTs with different study designs and populations so method of analysis was inappropriate
2.6	Are all important and relevant costs included?	Partly	Costs of side effects not included
2.7	Are the estimates of resource use from the best available source?	Partly	Published data, clinical guidelines and a physician survey
2.8	Are the unit costs of resources from the best available source?	Yes	Published national unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11	Is there no potential conflict of interest?	No	Funded by industry
2.12	Overall assessment: **very serious limitations**		
Other comments: Lamotrigine and olanzapine are now available in generic form; potentially selective inclusion of trials			

Study: Ekman M, Lindgren P, Miltenburger C, Meier G, Locklear JC, Chatterton ML. Cost effectiveness of quetiapine in patients with acute bipolar depression and in maintenance treatment after an acute depressive episode. PharmacoEconomics. 2012;30:513-30.			
Guideline topic: Pharmacological interventions for adults with bipolar disorder in acute depression			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar I or II disorder in acute depression or in remission
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	UK study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	Yes	
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	Yes	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Yes	
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	Most utilities elicited from outpatients with bipolar disorder in the US; utility of outpatient depression based on EQ-5D UK tariff
1.10	Overall judgement: **Directly applicable**		
Other comments:			

Study: Fajutrao L, Paulsson B, Liu S, Locklear J. Cost-effectiveness of quetiapine plus mood stabilizers compared with mood stabilizers alone in the maintenance therapy of bipolar I disorder: results of a Markov model analysis. Clinical Therapeutics. 2009;31:1456-68.			
Guideline topic: Pharmacological interventions for long-term management of adults with bipolar disorder			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Newly stabilised adults with bipolar I disorder
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	Yes	
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	Yes	Other outcomes also considered
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Unclear	Unpublished SF-6D values and further assumptions
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	Yes	UK tariff
1.10	Overall judgement: **Directly applicable**		
Other comments:			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	2 years
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	Pooled data from two double-blind RCTs
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	Pooled data from two double-blind RCTs
2.6	Are all important and relevant costs included?	Partly	Costs of side effects not included
2.7	Are the estimates of resource use from the best available source?	Partly	Expert opinion derived from published clinical guidelines
2.8	Are the unit costs of resources from the best available source?	Yes	National unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Results inadequately reported
2.11	Is there no potential conflict of interest?	No	Funded by industry
2.12	Overall assessment: **potentially serious limitations**		
Other comments: Quetiapine and olanzapine (administered in mania) are now available in generic form; results of probabilistic safety analysis not reported for levels of willingness-to-pay			

Study: McKendrick J, Cerri KH, Lloyd A, D'Ausilio A, Dando S, Chinn C. Cost effectiveness of olanzapine in prevention of affective episodes in bipolar disorder in the United Kingdom. Journal of Psychopharmacology. 2007;21:588-96.			
Guideline topic: Pharmacological interventions for long-term management of adults with bipolar disorder			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) This checklist should be used first to filter out irrelevant studies.		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Newly stabilised adults with bipolar I disorder
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	NA	Time horizon 12 months
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	No	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	NA	
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	NA	
1.10	Overall judgement: **Directly applicable**		
Other comments: although QALYs not considered, intervention was dominant so lack of QALYs did not affect conclusions			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	12 months
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	RCT
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	RCT
2.6	Are all important and relevant costs included?	Partly	Costs of side effects not included
2.7	Are the estimates of resource use from the best available source?	Partly	UK chart review and other published sources
2.8	Are the unit costs of resources from the best available source?	Yes	National unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11	Is there no potential conflict of interest?	No	Funded by industry
2.12	Overall assessment: **potentially serious limitations**		
Other comments: olanzapine is now available in generic form			

Study: NCCMH (2006) Bipolar Disorder: the Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary and Secondary Care. Leicester and London: The British Psychological Society and the Royal College of Psychiatrists.			
Guideline topic: Pharmacological interventions for long-term management of adults with bipolar disorder			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar I disorder in a stable state following an acute episode (that is, in a subacute or euthymic state)
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	UK study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	NHS perspective
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	Yes	
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	Yes	Other outcomes also considered
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	No	Based on vignettes
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	Valuation by stable people with bipolar disorder in the US
1.10	Overall judgement: **Partially applicable**		
Other comments: drug-specific utility values used, based on study funded by industry			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	5 years
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	Placebo arms of double-blind RCTs
2.5	Are the estimates of relative treatment effects from the best available source?	Partly	Indirect comparisons using RCTs with different study designs and populations so method of analysis was inappropriate
2.6	Are all important and relevant costs included?	Partly	Costs of side effects not included
2.7	Are the estimates of resource use from the best available source?	Partly	Expert opinion and published data
2.8	Are the unit costs of resources from the best available source?	Yes	Published national unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11	Is there no potential conflict of interest?	Yes	
2.12	Overall assessment: **very serious limitations**		
Other comments: Olanzapine is now available in generic form			

Study: Revicki DA, Hirschfeld RM, Ahearn EP, Weisler RH, Palmer C, Keck PE Jr. Effectiveness and medical costs of divalproex versus lithium in the treatment of bipolar disorder: results of a naturalistic clinical trial. Journal of Affective Disorders. 2005b;86:183-93.			
Guideline topic: Pharmacological interventions for long-term management in adults			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar I disorder following hospital discharge after a manic or mixed episode
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Partly	US study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	No	US study
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	NA	Time horizon 1 year
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	No	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	NA	
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	NA	
1.10	Overall judgement: **Partially applicable**		
Other comments:			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	NA	Alongside naturalistic trial
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	1 year
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	Pragmatic trial
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	Pragmatic trial
2.6	Are all important and relevant costs included?	Yes	Direct medical costs included
2.7	Are the estimates of resource use from the best available source?	Yes	Pragmatic trial and further assumptions
2.8	Are the unit costs of resources from the best available source?	Yes	National unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	NA	Cost consequence analysis
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Statistical analysis provided
2.11	Is there no potential conflict of interest?	No	Funded by industry
2.12	Overall assessment: **potentially serious limitations**		
Other comments: HRQoL and resource use data collected via telephone interviews			

Study: 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.			
Guideline topic: Pharmacological interventions for long-term management of adults with bipolar disorder			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with stabilised bipolar I disorder
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	Yes	
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	Yes	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Partly	Utility data on depression based on patient EQ-5D; other utility data based on vignettes
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	Partly	EQ-5D UK tariff – vignettes valued by stable people with bipolar disorder in the US
1.10	Overall judgement: **Directly applicable**		
Other comments:			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline.		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime horizon
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Yes	Systematic review and network meta-analysis
2.5	Are the estimates of relative treatment effects from the best available source?	Partly	Systematic review and network meta-analysis – RCTs had different study designs and populations so method of analysis was inappropriate
2.6	Are all important and relevant costs included?	Partly	Costs of side effects not included
2.7	Are the estimates of resource use from the best available source?	Partly	National guidelines based on expert opinion, published data and further assumptions
2.8	Are the unit costs of resources from the best available source?	Yes	National unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11	Is there no potential conflict of interest?	Yes	
2.12	Overall assessment: **very serious limitations**		
Other comments: olanzapine and lamotrigine are now available in generic form; the analysis distinguished between people with a previous manic versus depressive episod, but differential data were based on very limited evidence			

Study: Woodward TC, Tafesse E, Quon P, Kim J, Lazarus A. Cost-effectiveness of quetiapine with lithium or divalproex for maintenance treatment of bipolar I disorder. Journal of Medical Economics. 2009;12:259-68.			
Guideline topic: Pharmacological interventions for long-term management of adults with bipolar disorder			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar disorder I in a stable state
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	No	US study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	No	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	Partly	3%
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	Yes	Other outcomes also used
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Unclear	Unpublished SF-6D values and further assumptions
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	Yes	UK tariff
1.10	Overall judgement: **Partially applicable**		
Other comments:			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	2 years
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	Pooled data from two RCTs
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	Pooled data from two RCTs
2.6	Are all important and relevant costs included?	Partly	Costs of side effects not included
2.7	Are the estimates of resource use from the best available source?	Partly	Published study and further assumptions
2.8	Are the unit costs of resources from the best available source?	Yes	Published literature and national unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11	Is there no potential conflict of interest?	No	Funded by industry
2.12	Overall assessment: **potentially serious limitations**		
Other comments: Quetiapine is now available in generic form			

Study: Woodward TC, Tafesse E, Quon P, Lazarus A. Cost effectiveness of adjunctive quetiapine fumarate extended-release tablets with mood stabilizers in the maintenance treatment of bipolar I disorder. PharmacoEconomics. 2010;28:751-64.			
Guideline topic: Pharmacological interventions for long-term management of adults with bipolar disorder			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Newly stabilised adults with bipolar I disorder
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	No	US study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	No	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	Partly	3%
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	Yes	Other outcomes also used
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Unclear	Unpublished SF-6D values and further assumptions
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	Yes	UK tariff
1.10	Overall judgement: **Partially applicable**		
Other comments:			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	2 years
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	Pooled data from two RCTs
2.5	Are the estimates of relative treatment effects from the best available source?	Partly	Pooled data from two RCTs and other published data (see 'other comments')
2.6	Are all important and relevant costs included?	Partly	Costs of side effects not included
2.7	Are the estimates of resource use from the best available source?	Partly	Published study and further assumptions
2.8	Are the unit costs of resources from the best available source?	Yes	Published literature and national unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11	Is there no potential conflict of interest?	No	Funded by industry
2.12	Overall assessment: **very serious limitations**		
Other comments: Efficacy data for quetiapine extended release (XR) RCT taken from two double-blind RCTs evaluating quetiapine plus lithium or valproate versus lithium or valproate alone, but NOT quetiapine XR. Efficacy data for other treatment options were taken from a non-systematic review of RCTs with different study designs and populations, so method of analysis was inappropriate – only quetiapine XR and mood stabilisers versus mood stabilisers comparison is valid; olanzapine and lamotrigine are now available in generic form			

Study: Guideline economic analysis			
Guideline topic: Pharmacological interventions for long-term management of adults with bipolar disorder			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar disorder I in a stable state
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	NA	Time horizon 1 year
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	NA	Cost analysis
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?		
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?		
1.10	Overall judgement: **Partially applicable**		
Other comments:			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	1 year, but longer term considerations made
2.3	Are all important and relevant health outcomes included?	NA	Cost analysis
2.4	Are the estimates of baseline health outcomes from the best available source?	NA	
2.5	Are the estimates of relative treatment effects from the best available source?	NA	
2.6	Are all important and relevant costs included?	Partly	Costs of side effects not included, but considered separately
2.7	Are the estimates of resource use from the best available source?	Partly	Published data, and GDG expert opinion
2.8	Are the unit costs of resources from the best available source?	Yes	
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	NA	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Threshold analysis
2.11	Is there no potential conflict of interest?	yes	
2.12	Overall assessment: **potentially serious limitations**		
Other comments: Threshold analysis was carried out, to identify at which level of effectiveness lithium becomes cost-neutral			

1.5 NUTRITIONAL INTERVENTIONS FOR THE LONG-TERM MANAGEMENT OF ADULTS WITH BIPOLAR DISORDER

Study: Cheema N, Frangou S, McCrone P. Cost-effectiveness of ethyleicosapentaenoic acid in the treatment of bipolar disorder. Therapeutic Advances in Psychopharmacology. 2013; 3:73-81.			
Guideline topic: Nutritional interventions for long-term management of adults with bipolar disorder			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar I disorder in a stable (euthymic) state
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	NA	Time horizon 1 year
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	Yes	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Unclear	Unpublished SF-6D values, manic values based on vignettes
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	Yes	UK tariff; vignettes valued by stable people with bipolar disorder in the US
1.10	Overall judgement: **Directly applicable**		
Other comments:			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	1 year
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	RCT
2.5	Are the estimates of relative treatment effects from the best available source?	Unclear	Published literature, further assumptions and RCT
2.6	Are all important and relevant costs included?	Yes	
2.7	Are the estimates of resource use from the best available source?	Partly	RCT and further assumptions
2.8	Are the unit costs of resources from the best available source?	Yes	Published literature and national unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Unclear	Costs and QALYs for each intervention not reported
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11	Is there no potential conflict of interest?	Yes	
2.12	Overall assessment: **very serious limitations**		
Other comments: efficacy data for ethyl-eicosapentaenoic acid were based on a 12-week RCT of adults with bipolar depression, NOT adults in a stable state; cost and effectiveness data from the RCT were extrapolated to stable adults with bipolar disorder experiencing acute episodes, over 1 year; efficacy of ethyl-eicosapentaenoic acid in reducing depressive symptoms over 12 weeks was assumed to apply to efficacy in preventing acute manic and depressive episodes over 1 year			

1.6 PSYCHOLOGICAL AND PSYCHOSOCIAL INTERVENTIONS FOR ADULTS WITH BIPOLAR DISORDER

Study: 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. 2005;186:500-06.			
Guideline topic: Psychological and psychosocial interventions for adults with bipolar disorder			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) This checklist should be used first to filter out irrelevant studies.		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar disorder not in acute episode
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	UK study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	No	Time horizon 12 and 30 months
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	No	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	NA	
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	NA	
1.10	Overall judgement: **Directly applicable**		
Other comments: Intervention dominant and highly probable to be cost-effective, so lack of QALYs did not have a major impact on judgement of cost effectiveness			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	NA	RCT
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	12 and 30 months
2.3	Are all important and relevant health outcomes included?	Yes	Days free from acute episode
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	RCT
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	RCT
2.6	Are all important and relevant costs included?	Yes	
2.7	Are the estimates of resource use from the best available source?	Yes	Self-report and hospital records
2.8	Are the unit costs of resources from the best available source?	Yes	National unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Statistical analysis and probabilistic analysis
2.11	Is there no potential conflict of interest?	Yes	
2.12	Overall assessment: **minor limitations**		
Other comments:			

Study: Scott J, Colom F, Popova E, Benabarre A, Cruz N, Valenti M, et al. Long-term mental health resource utilization and cost of care following group psychoeducation or unstructured group support for bipolar disorders: a cost-benefit analysis. Journal of Clinical Psychiatry. 2009;70:378-86.			
Guideline topic: Psychological and psychosocial interventions for adults with bipolar disorder			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) This checklist should be used first to filter out irrelevant studies.		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes	Adults with bipolar disorder in remission (euthymia)
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	No	Spanish study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	No	Spanish healthcare perspective
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	No	Time horizon 5.5 years
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	No	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	NA	
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	NA	
1.10	Overall judgement: **Partially applicable**		
Other comments: Intervention dominant, so lack of QALYs did not affect judgement of cost effectiveness			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	NA	RCT
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	5.5 years
2.3	Are all important and relevant health outcomes included?	Yes	Number of relapses / days in episode
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	RCT
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	RCT
2.6	Are all important and relevant costs included?	Yes	
2.7	Are the estimates of resource use from the best available source?	Yes	Self-report and hospital records
2.8	Are the unit costs of resources from the best available source?	No	Hospital costs and other published sources
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Dominance
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Statistical analysis
2.11	Is there no potential conflict of interest?	Yes	
2.12	Overall assessment: **minor limitations**		
Other comments:			

1.7 PHARMACOLOGICAL INTERVENTIONS FOR MANIA, HYPOMANIA AND MIXED EPISODES IN CHILDREN AND YOUNG PEOPLE WITH BIPOLAR DISORDER

Study: Uttley L, Kearns B, Ren S, Stevenson M. Aripiprazole for the treatment and prevention of acute manic and mixed episodes in bipolar i disorder in children and adolescents: a NICE single technology appraisal. PharmacoEconomics. 2013;31:981-90.			
Guideline topic: Pharmacological interventions for children and young people with bipolar disorder in mania			
Section 1: Applicability (relevance to specific guideline review question[s] and the NICE reference case) **This checklist should be used first to filter out irrelevant studies**		**Yes/ Partly/ No/Unclear /NA**	**Comments**
1.1	Is the study population appropriate for the guideline?	Yes(?) – see note	Young people with bipolar I disorder in an acute manic or mixed episode
1.2	Are the interventions and services appropriate for the guideline?	Yes	
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	UK study
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5	Are non-direct health effects on individuals excluded?	Yes	
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?	Likely	Not reported but NICE submission
1.7	Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	Yes	
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Yes	Mostly based on EQ-5D and vignettes
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	Yes	
1.10	Overall judgement: **Directly applicable**		
Other comments: Efficacy data on aripiprazole taken from RCT with participants potentially different from typical UK paediatric population with bipolar I disorder (US population of low mean age; high prevalence of comorbid attention deficit hyperactivity disorder; suicidal children and adolescents excluded; percentage of hospitalisation unknown)			

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline		**Yes/ Partly /No/ Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	Markov model
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	3 years
2.3	Are all important and relevant health outcomes included?	Yes	
2.4	Are the estimates of baseline health outcomes from the best available source?	Partly	Pooled RCTs
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	Network meta-analysis of published and unpublished data
2.6	Are all important and relevant costs included?	Yes	
2.7	Are the estimates of resource use from the best available source?	No	Expert opinion
2.8	Are the unit costs of resources from the best available source?	Yes	National unit costs
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11	Is there no potential conflict of interest?	Yes	
2.12	Overall assessment: **potentially serious limitations**		
Other comments: Analysis undertaken by the manufacturer of aripiprazole, but was critically appraised and replicated by an independent evidence review group			