APPENDIX 33 – ECONOMIC EVIDENCE PROFILES

Case identification and assessment of adults with bipolar disorder

Clinical / economic question: MDQ versus no screening for identification of adults with bipolar disorder

Study & country	Limitations	Applicability	Other comments	Incremental cost[1]	Incremental effect	ICER (£/effect)	Uncertainty
Menzin et al., 2009 US	Potentially serious limitations[2]	Partially applicable[3]	• Time horizon: 5 years • Population: adults presenting for the first time with symptoms of major depressive disorder in primary care • Measure of outcome: number of correctly diagnosed people • Model-based	-£1,491	38 per 1000 people screened	MDQ dominant	Probability of MDQ being cost-saving: 76% Results robust under various alternative scenarios considering different prevalence of bipolar disorder, sensitivity/specificity, time horizon, treatment costs, etc.

1. Costs converted and uplifted to 2014 UK pounds, using PPP exchange rates (http://www.oecd.org/std/ppp) and the UK HCHS inflation index.
2. Measure of outcome people correctly diagnosed, efficacy data based on literature review and further assumptions, resource use based on published literature
3. US study, 3rd party payer perspective, no QALYs estimated but intervention dominant according to the outcome measure used

Pharmacological interventions for mania, hypomania and mixed episodes in adults with bipolar disorder

Clinical / economic question: olanzapine versus valproate semisodium for adults with mania

Study & country	Limitations	Applicability	Other comments	Incremental cost[1]	Incremental effect	ICER (£/effect)	Uncertainty
Revicki et al., 2003 US	Potentially serious limitations[2]	Partially applicable[3]	• Time horizon:12 weeks • Alongside RCT • Olanzapine now available in generic form • Outcomes: clinical improvement based on MRS from the SADS Change Version and the HAM-D; HRQOL based on Q-LES-Q and restricted activity days	£1,935	Similar effects between drugs	N/A	Differences in costs and outcomes not statistically significant
Zhu et al., 2005 US	Potentially serious limitations[4]	Partially applicable[5]	• Time horizon 47 weeks • Alongside RCT • Olanzapine now available in generic form • Outcomes: clinical improvement based on YMRS and rate of symptom remission (YMRS ≤12) at 3 weeks (acute phase); median time to remission of manic symptoms	-£833	Better effects for olanzapine		Difference in costs statistically non-significant; differences in outcomes statistically significant
Bridle et al., 2004 UK	Potentially serious limitations[6]	Partially applicable[7]	• Time horizon:3 weeks • Model-based analysis • Drugs included: olanzapine, haloperidol, lithium, quetiapine, valproate • Olanzapine now available in generic form • Outcome: number of responders	£32	90 per 1,000 people	≈£351/additional responder	Comparison not relevant as valproate dominated by haloperidol; Probability of cost effectiveness at WTP £20,000 per additional responder: olanzapine 0.44; valproate 0.01
Guideline economic analysis. UK	Potentially serious limitations[8]	Partially applicable[9]	• Time horizon:3 weeks • Model-based analysis • Drugs included: aripiprazole, asenapine, carbamazepine, olanzapine, risperidone, lithium, haloperidol, quetiapine, valproate • Outcomes: YRMS change scores, number of responders, QALYs	-£19	0.0008 QALYs Better effect for olanzapine in other outcomes	Olanzapine dominant	Not examined

1. Costs converted and uplifted to 2014 UK pounds, using PPP exchange rates (http://www.oecd.org/std/ppp) and the UK HCHS inflation index.
2. Resource use estimates based on RCT and further assumptions, HRQoL and resource use data collected via telephone interviews, funded by industry
3. US study, cost consequence analysis, no QALYs measured
4. Resource use estimated only for people who entered maintenance phase, funded by industry
5. US study, cost consequence analysis, no QALYs measured

6. Short time horizon, side effects not considered, all people assumed to be hospitalised over the time horizon of the analysis, resource use estimates based on assumptions and information from manufacturers
7. UK study, NHS & PSS perspective, but lack of QALYs makes judgements on relative cost effectiveness difficult
8. Short time horizon, side effects not considered, all people assumed to be hospitalised over the time horizon of the analysis, resource use estimates based on GDG expert opinion
9. UK analysis, NHS & PSS perspective, QALYs estimated based on vignette-based descriptions, valued by US outpatients with bipolar disorder

Clinical / economic question: quetiapine versus usual care for adults with mania

Study & country	Limitations	Applicability	Other comments	Incremental cost[1]	Incremental effect	ICER (£/effect)	Uncertainty
Caro et al., 2006 US	Potentially serious limitations[2]	Partially applicable[3]	• Time horizon:100 days • Model-based analysis • Quetiapine now available in generic form • Outcomes: % of people responding at 21 days & remitting at 84 days	-£1,157	Better effects for quetiapine	Quetiapine dominant	Results sensitive to drug prices, discharge criteria and side-effect management costs

1. Costs converted and uplifted to 2014 UK pounds, using PPP exchange rates (http://www.oecd.org/std/ppp) and the UK HCHS inflation index.
2. Clinical and resource use data based on a literature review and administrative databases, funded by industry
3. US study, cost consequence analysis, no QALYs measured, usual care may not reflect routine clinical care in the UK

Clinical / economic question: various pharmacological interventions for adults with mania

Study & country	Limitations	Applicability	Other comments	Incremental cost versus valproate[1]	Incremental effect versus valproate	ICER (£/effect)	Uncertainty
Bridle et al., 2004 UK	Potentially serious limitations[2]	Partially applicable[3]	• Time horizon:3 weeks • Model-based analysis • Olanzapine and quetiapine now available in generic form • Outcome: number of responders	Olanzapine £32 Haloperidol -£132 Lithium £33 Quetiapine £37	Extra responders per 1000 people: Olanzapine 90 Haloperidol 70 Lithium 50 Quetiapine 20	Lithium, valproate & quetiapine dominated by haloperidol Olanzapine vs.haloperidol£10,560 per extra responder	Probability of cost effectiveness at WTP £20,000 per extra responder: olanzapine 0.44; haloperidol 0.37; lithium 0.16; quetiapine 0.02; valproate 0.01 Results robust under alternative scenarios
Guideline economic analysis. UK	Potentially serious limitations[4]	Partially applicable[5]	• Time horizon:3 weeks • Model-based analysis • Outcomes: YRMS change	Carbamazepine -£14 Haloperidol -£16 Olanzapine -£19	QALYs: Carbamazepine 0.0022 Haloperidol 0.0012 Olanzapine 0.0008	(using QALYs) Carbamazepine vs. risperidone £3,842/QALY – all other drugs dominated	Not examined

			scores, number of responders, QALYs	Risperidone -£20 Quetiapine -£17 Aripiprazole £124 Lithium -£12 Asenapine £51	Risperidone 0.0006 Quetiapine 0 Aripiprazole 0 Lithium -0.0009 Asenapine -0.0016	by absolute or extended dominance Carbamazepine not cost-effective using YMRS change score	

1. Costs uplifted to 2014 UK pounds using the HCHS inflation index.
2. Short time horizon, side effects not considered, all people assumed to be hospitalised over the time horizon of the analysis, resource use estimates based on assumptions and information from manufacturers
3. UK study, NHS & PSS perspective, lack of QALYs makes judgements on relative cost effectiveness difficult
4. Short time horizon, side effects not considered, all people assumed to be hospitalised over the time horizon of the analysis, resource use estimates based on GDG expert opinion
5. UK study, NHS & PSS perspective, QALY estimates based on vignette-based descriptions valued by US outpatients with bipolar disorder

Pharmacological interventions for acute depression in adults with bipolar disorder

Clinical / economic question: various drugs for adults with acute depression

Study & country	Limitations	Applicability	Other comments	Incremental cost[1]	Incremental effect (QALY)	ICER (£/QALY)	Uncertainty
Guideline economic analysis. UK	Minor limitations[2]	Directly applicable[3]	• Time horizon:18 weeks • Model-based analysis • Outcome: QALYs	Versus placebo: Valp: -£87 Fluo & Olz: -£143 Que: -£95 Olz: -£58 Lithium: £123 Lamot: -£38 Parox: -£30 Impr: £14 Moclo: £117	Versus placebo: Valp: 0.031 Fluo & Olz: 0.027 Que: 0.023 Olz: 0.020 Lithium: 0.019 Lamot: 0.018 Parox: 0.017 Impr: 0.015 Moclo: 0.010	Valproate vs. Fluo & Olz: £16,572 All other interventions dominated	Probability of valproate being cost-effective at £20,000/QALY: 0.47 After excluding valproate: probability of fluoxetine and olanzapine being cost-effective at £20,000/QALY: 0.73 Results robust under alternative scenarios

1. Costs uplifted to 2014 UK pounds using the HCHS inflation index.
2. Efficacy data based on systematic review and network meta-analysis, side effects indirectly considered through discontinuation, relatively short time horizon, resource use estimates based on national sources, other published data and GDG expert opinion
3. UK study, NHS & PSS perspective, QALYs estimated based on EQ-5D (all states except mania) and vignette-based descriptions, valued by US outpatients with bipolar disorder (mania)

Services for adults with bipolar disorder

Clinical / economic question: mood disorder clinic versus standard care for adults with bipolar disorder

Study & country	Limitations	Applicability	Other comments	Incremental cost[1]	Incremental effect	ICER (£/effect)	Uncertainty
Kessing et al., 2013 Denmark	Potentially serious limitations[2]	Partially applicable[3]	• Time horizon: 2 years • Alongside RCT • Measure of outcome: rate of first readmission to hospital	-£2,990	-18.6%	Mood disorder clinic dominant	Mood disorder clinic showed significantly better outcome Cost results sensitive to intervention costs and length of hospital re-admission

1. Costs converted and uplifted to 2014 UK pounds, using PPP exchange rates (http://www.oecd.org/std/ppp) and the UK HCHS inflation index.
2. Measure of outcome rate of first readmission to the hospital, resource use estimates based on RCT, published literature and further assumptions, statistical analysis done only for clinical outcomes; sensitivity analysis done only regarding cost results
3. Danish study, no QALYs estimated but intervention dominant according to the outcome measure used

Pharmacological interventions for the long-term management of adults with bipolar disorder

Clinical / economic question: lithium versus no pharmacological treatment for the long-term management of adults with bipolar disorder

Study & country	Limitations	Applicability	Other comments	Incremental cost[1]	Incremental effect	ICER (£/effect)	Uncertainty
Guideline economic analysis. UK	Potentially serious limitations[2]	Partially applicable[3]	• Time horizon: 1 year • Model-based analysis • Cost analysis	Intervention: £734 Savings per relapse averted: £6,714 NNT for lithium to become cost-neutral: 9	NA	NA	NNT for lithium to become cost-neutral became 15 after considering a higher preventative effect of lithium for mania

1. Costs uplifted to 2014 UK pounds using the HCHS inflation index.
2. Effects not considered due to heterogeneity across studies, side effects considered in a narrative analysis, resource use estimates based on GDG expert opinion
3. UK cost analysis, NHS & PSS perspective, threshold analysis undertaken to reveal the NNT required for lithium to be cost-neutral

Clinical / economic question: valproate semisodium versus lithium for the long-term management of adults with bipolar disorder

Study & country	Limitations	Applicability	Other comments	Incremental cost[1]	Incremental effect	ICER (£/effect)	Uncertainty
Revicki et al., 2005 US	Potentially serious limitations[2]	Partially applicable[3]	• Time horizon:1 year • Alongside pragmatic trial • Outcomes: Number of months without acute symptoms; MCS and PCS scores of SF-36, Mental Health Index (MHI-17), disability days; adverse events and continuation rates	-£1,935	Similar effects between drugs	N/A	Differences in costs and outcomes not statistically significant

1. Costs converted and uplifted to 2014 UK pounds, using PPP exchange rates (http://www.oecd.org/std/ppp) and the UK HCHS inflation index.
2. Pragmatic trial, resource use data based on trial and further assumptions, HRQoL and resource use data collected via telephone interviews, funded by industry
3. US study, cost consequence analysis, no QALYs measured

Clinical / economic question: olanzapine versus lithium for the long-term management of adults with bipolar disorder

Study & country	Limitations	Applicability	Other comments	Incremental cost[1]	Incremental effect	ICER (£/effect)	Uncertainty
McKendrick et al., 2007 UK	Potentially serious limitations[2]	Directly applicable[3]	• Time horizon:1 year • Model-based study • Olanzapine now available in generic form • Outcome: Number of acute episodes averted	-£1,109	0.23	Olanzapine dominant	Results most sensitive to risk, length and cost of hospitalisation for mania, and time horizon; results ranging from olanzapine being dominant to ICER of olanzapine vs. lithium £365 /acute episode avoided

1. Costs uplifted to 2014 UK pounds using the HCHS inflation index.
2. Efficacy data based on an RCT, resource use data based on UK chart review and other published sources, costs of side effects not considered, funded by industry

3. UK study, NHS & PSS perspective, QALYs not estimated but intervention was dominant so lack of QALYs did not affect conclusions

Clinical / economic question: quetiapine [XR] adjunctive to mood stabiliser versus mood stabiliser alone for the long-term management of adults with bipolar disorder

Study & country	Limitations	Applicability	Other comments	Incremental cost[1]	Incremental effect	ICER (£/effect)	Uncertainty
Fajutrao et al., 2009 UK	Potentially serious limitations[2]	Directly applicable[3]	• Time horizon:2 years • Model-based analysis • Quetiapine now available as generic • Outcome: QALY (+ other outcomes) • Comparator: mood stabiliser alone	-£601	0.07	Que + MS dominant	Results most sensitive to risk and length of hospitalisation, cost of hospital stay, and quetiapine acquisition cost
Woodward et al., 2009 US	Potentially serious limitations[4]	Partially applicable[5]	• Time horizon:2 years • Model-based analysis • Quetiapine now available as generic • Outcome: QALY (+ other outcomes) • Comparator: mood stabiliser alone	-£5	0.05	Que + MS dominant	Results most sensitive to cost of quetiapine, risk, length and cost of hospitalisation especially for mania
Woodward et al., 2010 US	Potentially serious limitations[6]	Partially applicable[7]	• Time horizon:2 years • Model-based analysis • Quetiapine XR • Comparator: mood stabiliser alone • Outcome: QALY (+ other outcomes)	£857	0.05	£16,647/QALY	Results most sensitive to efficacy, utility for euthymia, cost of quetiapine XR, risk, length and cost of hospitalisation for mania

1. Costs converted and uplifted to 2014 UK pounds, using PPP exchange rates (http://www.oecd.org/std/ppp) and the UK HCHS inflation index.
2. Efficacy data pooled from 2 RCTs, resource use estimates based on expert opinion based on published guidelines, costs of side effects not included, results of sensitivity analysis insufficiently reported, funded by industry
3. UK study, NHS & PSS perspective, QALYs estimated based on SF-36 unpublished data and using the SF-6D logarithm
4. Efficacy data pooled from 2 RCTs, resource use estimates based on published data and further assumptions, costs of side effects not included, results of sensitivity analysis insufficiently reported, funded by industry
5. US study, QALYs estimated based on SF-36 unpublished data and using the SF-6D logarithm
6. Efficacy data for quetiapine pooled from 2 RCTs for quetiapine and NOT quetiapine XR, other efficacy data from published literature identified via a non-systematic review, other comparisons available but evidence synthesis inappropriate due to different study designs, resource use estimates based on published data and further assumptions, costs of side effects not included, funded by industry
7. US study, QALYs estimated based on SF-36 unpublished data and using the SF-6D logarithm

Psychological and psychosocial interventions for adults with bipolar disorder

Clinical / economic question: CBT plus standard care versus standard care alone for adults with bipolar disorder

Study & country	Limitations	Applicability	Other comments	Incremental cost[1]	Incremental effect	ICER (£/effect)	Uncertainty
Lam et al., 2005 UK	Minor limitations[2]	Directly applicable[3]	• Time horizon: 30 months • Alongside RCT • Outcome: number of days free from episode	-£2,156	106	CBT plus standard care dominant	Probability of CBT being cost-effective 0.80 at WTP zero; 0.85 at WTP £10 per additional day free from episode

1. Costs uplifted to 2014 UK pounds using the HCHS inflation index.
2. Efficacy and resource use data based on RCT, resource use data taken from hospital records and self-reports, sufficient time horizon, appropriate statistical and sensitivity analysis
3. UK study, NHS & PSS perspective, no QALYs estimated but intervention dominant according to the outcome measure used

Clinical / economic question: Group psychoeducation versus unstructured group support for adults with bipolar disorder

Study & country	Limitations	Applicability	Other comments	Incremental cost[1]	Incremental effect	ICER (£/effect)	Uncertainty
Scott et al., 2009 Spain	Minor limitations[2]	Partially applicable[3]	• Time horizon: 5.5 years • Alongside RCT • Outcome: number of relapses per person and number of days free from episode per person	-£3,087	number of relapses: -2.16 number of days in episode: -432	Group psychoeducation dominant	Significant difference in outcomes Non-significant difference in costs

1. Costs converted and uplifted to 2014 UK pounds, using PPP exchange rates (http://www.oecd.org/std/ppp) and the UK HCHS inflation index.
2. Efficacy and resource use data based on RCT, resource use data taken from hospital records and self-reports, sufficient time horizon, appropriate statistical analysis
3. Spanish study, no QALYs estimated but intervention dominant according to the outcome measure used

Pharmacological interventions for mania, hypomania and mixed episodes in children and young people with bipolar disorder

Clinical / economic question: aripiprazole included in pharmacological strategies for adolescents with mania

Study & country	Limitations	Applicability	Other comments	Incremental cost[1]	Incremental effect (QALY)	ICER (£/QALY)	Uncertainty

Uttley et al., 2013 UK	Potentially serious limitations[2]	Directly applicable[3]	• Time horizon: 3 years
			• Model-based analysis
			• Outcome: QALYs
			• 4 strategies:
			  • S1: Ris-Que-Olz-Li
			  • S2: Ris-Ari-Que-Li
			  • S3: Ari-Ris-Que-Li
			  • S4: Ris-Que-Ari-Li
				Versus S1:
				S2: -£933
				S3: -£687
				S4: -£178
					Versus S1:
					S2: 0.0083
					S3: 0.0071
					S4: 0.0066
						S2 dominant	Results very sensitive to consideration of personalised medicine, reflected in small changes (1-2%) in costs and QALYs (S2 becomes dominated by all other strategies)

1. Costs uplifted to 2014 UK pounds using the HCHS inflation index.
2. Efficacy data taken from network meta-analysis of published and unpublished data, resource use estimates based mainly on expert opinion, funded by industry but reviewed by independent panel, high uncertainty of the results
3. UK study, NHS & PSS perspective, QALYs estimated based mostly on EQ-5D (outpatient depression) and vignette-based descriptions