**Supplementary material**

**1. Interventions excluded from analysis**

A list of interventions recommended by NICE but were excluded from our analysis, and the reason for exclusion is reported in Table 1.

**Table 1. Interventions excluded from modelling and reasons for exclusion**

| **Recommended interventions** | **Reason for exclusion** |
| --- | --- |
| ***For people with possible psychosis*** |  |
| Specialist assessment | Lack of evidence about the clinical or cost impacts of specialist assessment. |
| ***For people at clinical high risk of psychosis (CHR)*** |  |
| Family intervention | Lack of evidence about the clinical or cost impacts of family intervention for people at CHR. |
| Monitoring and follow-up | Lack of evidence about the clinical or cost impacts of monitoring and follow-up for people at CHR. |
| ***For people with non-acute psychosis*** |  |
| Antipsychotic medication | Vague definitions of interventions. Although the NICE schizophrenia guideline recommends that oral antipsychotic medication should be used as the first-line treatment for patients with FEP, it did not recommend which specific oral antipsychotic medication should be used. |
| Cognitive behaviour therapy (CBT) | Lack of evidence about the clinical or cost impacts of CBT for people with non-acute psychosis. |
| Monitoring and treatment for co-existing conditions | Outside the scope of this study. |
| Occupational and educational interventions | The benefits of these interventions fall outside of the NHS and PSS – the costing perspective of this study. |
| ***For people with acute psychosis*** |  |
| Assessment at crisis resolution and home treatment team (CRHT) | Lack of evidence about the clinical or cost impacts of assessment provided by CRHT. |
| Rapid tranquillisation (optional) | Lack of evidence about the clinical or cost impacts of rapid tranquillisation. |
| Antipsychotic medication | Vague definitions of interventions. Although the NICE schizophrenia guideline recommends that antipsychotic medication should be provided to patients with acute psychosis, it did not recommend which specific oral antipsychotic medication should be used. |
| CBT | Lack of evidence about the clinical or cost impacts of CBT for patients with acute psychosis. |
| Family intervention | Lack of evidence about the clinical or cost impacts of family intervention for patients with acute psychosis. |
| Monitoring and treatment for co-existing conditions | Outside the scope of this study. |
| Occupational and educational interventions | The benefits of these interventions fall outside of the NHS and PSS – the costing perspective of this study. |

**2. Summary of key parameters**

For each intervention under assessment, the key impacts modelled in the study, including clinical benefits, clinical harms, cost and cost savings are reported in Table 2.

**Table 2.** **Summary of key parameters used in the schizophrenia whole disease model**

| Parameters | Base-line value | Distribution | Source |
| --- | --- | --- | --- |
| **Epidemiological data** |  |  |  |
| Mean age | 23.52 y | Normal (SE=2.85) | ([1](#_ENREF_1)) |
| Male | 60.40% | Beta (α=665.61; β=436.39) | ([1](#_ENREF_1)) |
| Starting disease status – not at risk of psychosis | 33.21% | Dirichlet (n=276) | ([1](#_ENREF_1)) |
| Starting disease status – CHR | 34.90% | Dirichlet (n=290) | ([1](#_ENREF_1)) |
| Starting disease status – FEP | 31.89% | Dirichlet (n=265) | ([1](#_ENREF_1)) |
| **Service provision data** |  |  |  |
| Provision of CBT | 41.01% | Beta (α=1,011; β=1,454) | ([2](#_ENREF_2)) |
| Take up of CBT | 51.00% | Beta (α=510; β=490) | ([2](#_ENREF_2)) |
| Provision of family intervention | 30.98% | Beta (α=589; β=1,312) | ([2](#_ENREF_2)) |
| Take up of family intervention | 38.49% | Beta (α=224; β=358) | ([2](#_ENREF_2)) |
| Provision of antipsychotic | 100.00% | Assume fixed | Expert opinion |
| Take up of antipsychotic for patients with FEP | 97.38% | Beta (α=484; β=13) | ([3](#_ENREF_3)) |
| Delay in initiation of clozapine | 3.98 years | Gamma (α=137.25; β=0.023) | ([4](#_ENREF_4)) |
| **Clinical effectiveness data** **– non-pharmacological interventions** |  |  |  |
| RR of transition to psychosis (CBT vs practice as usual) | 0.41 | Log normal (ln(SE)=0.29) | ([5](#_ENREF_5)) |
| RR of relapse (family intervention vs standard care or other control) | 0.63 | Log normal (ln(SE)=0.16) | ([6](#_ENREF_6)) |
| **Clinical effectiveness data** **– antipsychotic medication for people with TRS** |  |  |  |
| Annual probability of discontinuing clozapine due to inefficacy | 0.02 | Beta (α=4.98; β=310.02) | ([7](#_ENREF_7)) |
| OR Haloperidol vs clozapine | 5.56 | Log normal (ln(SE)= 0.35) | ([8](#_ENREF_8)) |
| OR Olanzapine vs clozapine | 1.37 | Log normal (ln(SE)=0.34) | ([8](#_ENREF_8)) |
| OR Quetiapine vs clozapine | 4.35 | Log normal (ln(SE)=0.69) | ([8](#_ENREF_8)) |
| OR Risperidone vs clozapine | 2.27 | Log normal (ln(SE)=0.40) | ([8](#_ENREF_8)) |
| **Health-related quality of life data** |  |  |  |
| People at CHR | 0.71 | Beta (α=100.22; β=40.78) | ([9](#_ENREF_9)) |
| People with psychosis in remission | 0.80 | Normal (SE=0.04) | ([10](#_ENREF_10)) |
| People with psychosis in relapse | 0.67 | Normal (SE=0.06) | ([10](#_ENREF_10)) |
| Disutility – weight gain | 0.03 | Normal (SE=0.01) | ([10](#_ENREF_10)) |
| Disutility – EPS | 0.07 | Normal (SE=0.01) | ([10](#_ENREF_10)) |
| Disutility – diabetes | 0.09 | Normal (SE=0.05) | ([11](#_ENREF_11)) |
| **Cost data** |  |  |  |
| Cost of CBT (per session) | £97.00 | Gamma (α=44.44; β=2.18) | ([12](#_ENREF_12)) |
| No. of CBT sessions | 16 | Assumed fixed | ([6](#_ENREF_6)) |
| Cost of family intervention (per session) | £112.00 | Gamma (α=44.44; β=2.52) | ([12](#_ENREF_12)) |
| No. of family intervention sessions | 20 | Assumed fixed | ([6](#_ENREF_6)) |
| Daily cost of oral antipsychotic – Amisulpride | £0.47 | Gamma (α= 22.68; β=0.02) | ([13](#_ENREF_13)) |
| Daily cost of oral antipsychotic –Aripiprazole | £4.08 | Gamma (α=23.80; β=0.17) | ([13](#_ENREF_13)) |
| Daily cost of oral antipsychotic – Haloperidol | £0.37 | Gamma (α=30.86; β=0.01) | ([13](#_ENREF_13)) |
| Daily cost of oral antipsychotic – Olanzapine | £0.13 | Gamma (α=13.72; β=0.01) | ([13](#_ENREF_13)) |
| Daily cost of oral antipsychotic – Quetiapine | £1.24 | Gamma (α=6.25; β=0.20) | ([13](#_ENREF_13)) |
| Daily cost of oral antipsychotic – Risperidone | £0.36 | Gamma (α=5.41; β=0.07) | ([13](#_ENREF_13)) |
| Daily cost of oral antipsychotic – Clozapine | £1.56 | Gamma (α=156.25; β=0.01) | ([13](#_ENREF_13)) |
| Cost of LAI antipsychotic – Haloperidol (28 days) | £6.56 | Gamma (α=13.72; β=0.48) | ([13](#_ENREF_13)) |
| Cost of LAI antipsychotic – Paliperidone (30 days) | £334.45 | Gamma (α=82.64; β=4.05) | ([13](#_ENREF_13)) |
| Attendance at clozapine clinic | £16.40 | Gamma (α=44.44; β=0.37) | ([12](#_ENREF_12)) |
| Annual cost of managing non-relapsed schizophrenia patients | £14,983.45 | Gamma (α=2.04; β=7,341.89) | ([6](#_ENREF_6)) |
| Cost of assessing an acute episode of psychosis | £507.00 | Gamma (α= 348.55; β=1.45) | ([6](#_ENREF_6)) |
| Cost per contact with CRHT team | £197.45 | Gamma (α=44.44; β=4.44) | ([14](#_ENREF_14)) |
| Average number of contacts with CRHT team | 16.3 | Gamma (α=78.32; β=0.21) | ([15](#_ENREF_15)) |
| Cost per hospital bed day | £379.00 | Gamma (α=44.44; β=8.52) | ([12](#_ENREF_12)) |
| Average number of bed days during one relapse | 138.90 | Weibull (α=0.65; β=0.61) | ([16](#_ENREF_16)) |
| Cost of adverse events – weight gain *(Year 1)* | £97.20 per year | Gamma (α=44.44; β=2.19) | ([12](#_ENREF_12)) |
| Cost of adverse events – weight gain *(Year 2 onwards)* | £309.68 per year | Gamma (α=3.77; β= 6,755.56) | ([17](#_ENREF_17)) |
| Cost of adverse events – acute EPS | £51.95 per episode | Gamma (α=44.44; β=1.17) | ([12](#_ENREF_12), [18](#_ENREF_18)) |
| Cost of adverse events – Diabetes | £1,336.31 per year | Gamma (α=124,044.44; β=0.01) | ([19](#_ENREF_19)) |
| Cost of adverse events – Neutropenia | £469.48 per episode | Gamma (α=92,802.96; β=0.01) | ([20](#_ENREF_20)) |

**Note:**

1. A complete list of all parameters used in the model and their data sources are reported in a previously published study.([21](#_ENREF_21))

**Abbreviations:**

CBT: cognitive behaviour therapy; CHR: clinical high risk of psychosis; CRHT: crisis resolution and home treatment team; DUP: duration of untreated psychosis; EPS: extrapyramidal symptoms; FEP: first episode psychosis; LAI: long-acting injectable; OR: odds ratio; SE: standard error; TRS: treatment-resistant schizophrenia.

**3. Results of one-way and structural sensitivity analysis**

The results of one-way and structural sensitivity analysis for provision of CBT, family intervention and clozapine are reported in Table 3, 4 and 5, respectively.

**Table 3: Results of structural sensitivity analysis and one-way sensitivity analysis for provision of CBT for patients at CHR**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Intervention** | **Cost (£)** | **QALY** | **Incremental cost** | **Incremental QALY** | **ICER** | **Ranking of NMB**  (WTP=20,000 per QALY) | **Ranking of NMB**  (WTP=30,000 per QALY) |
| ***Base case results*** | | | | | | | |
| CBT (41.01% availability) | 168,078 | 19.1904 | – | – | Dominated | 2 | 2 |
| CBT (100.00% availability) | 167,452 | 19.1904 | -626 | 0.0000 | Dominating | 1 | 1 |
| ***SA 1: Assuming CBT can prevent transition to psychosis*** *(base case analysis assumes CBT can only delay transition to psychosis)* | | | | | | | |
| CBT (41.01% availability) | 164,100 | 19.2625 | – | – | Dominated | 2 | 2 |
| CBT (100.00% availability) | 157,913 | 19.3593 | -6,187 | 0.0968 | Dominating | 1 | 1 |
| ***SA 2: Set RR of CBT = 0.631*** | | | | | | | |
| CBT (41.01% availability) | 168,240 | 19.1904 | – | – | Dominated | 2 | 2 |
| CBT (100.00% availability) | 168,194 | 19.1904 | -46 | 0.0000 | Dominating | 1 | 1 |
| ***SA 3: Set utility of people at CHR=0.9 (baseline value:0.71)*** | | | | | | | |
| CBT (41.01% availability) | 168,078 | 19.2700 | – | – | Dominated | 2 | 2 |
| CBT (100.00% availability) | 167,452 | 19.2788 | -626 | 0.0088 | Dominating | 1 | 1 |
| ***SA 4: Brief CBT, assuming a reduced number of CBT sessions (8) and reduced effectiveness size, RR=0.71***  *(base case analysis assumes a full course of CBT with 16 sessions and a RR of 0.41)* | | | | | | | |
| CBT (41.01% availability) | 167,890 | 19.1904 | – | – | Dominated | 2 | 2 |
| CBT (100.00% availability) | 167,535 | 19.1904 | -355 | 0.0000 | Dominating | 1 | 1 |
| ***SA 5: Set unit cost of CBT = £139.832 (baseline value: £97.00)*** | | | | | | | |
| CBT (41.01% availability) | 166,211 | 19.1904 | – | – | Dominated | 2 | 2 |
| CBT (100.00% availability) | 165,022 | 19.1904 | -1,189 | 0.0000 | Dominating | 1 | 1 |

**Abbreviation:**

CBT: cognitive behaviour therapy; CHR: clinical high risk of psychosis; ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; QALY:quality-adjusted life of years; RR: relative risk; WTP: willingness to pay.

**Notes:**

1. 0.63 is the RR reported by the meta-analysis conducted by the NICE schizophrenia guideline.([6](#_ENREF_6))

2. The PSSRU reports a study which compares the unit cost of CBT reported by different studies.([22](#_ENREF_22)) For patients with psychosis, the highest unit cost reported is £105.62, which is equivalent to £139.83 in 2016/2017 value.

**Table 4: Results of structural sensitivity analysis and one-way sensitivity analysis for provision of family intervention for patients with a FEP**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Intervention** | **Cost (£)** | **QALY** | **Incremental cost** | **Incremental QALY** | **ICER** | **Ranking of NMB**  (WTP=20,000 per QALY) | **Ranking of NMB**  (WTP=30,000 per QALY) |
| ***Base case results*** | | | | | | | |
| Family intervention (30.98% availability) | 168,078 | 19.1904 | – | – | Dominated | 2 | 2 |
| Family intervention (100.00% availability) | 167,905 | 19.2033 | -173 | 0.0129 | Dominating | 1 | 1 |
| ***SA 1: Set RR of family intervention=0.83***1 *(Baseline value:0.63)* | | | | | | | |
| Family intervention (30.98% availability) | 174,381 | 19.1949 | – | – | – | 1 | 1 |
| Family intervention (100.00% availability) | 169,458 | 19.2013 | 1,026 | 0.0064 | 160,313 | 2 | 2 |
| ***SA 2: Brief family intervention, assuming a shortened course with reduced number of sessions (10) and reduced effectiveness size (RR=0.82)***  *(Base case analysis assumes a full course of family intervention with 20 sessions and a RR of 0.63)* | | | | | | | |
| Family intervention (30.98% availability) | 167,539 | 19.1896 | – | – | Dominated | 2 | 2 |
| Family intervention (100.00% availability) | 167,065 | 19.1939 | -474 | 0.0042 | Dominating | 1 | 1 |
| ***SA 3: Set utility of people with acute psychosis=0.872*** *(baseline value:0.80)* | | | | | | | |
| Family intervention (30.98% availability) | 168,078 | 19.5382 | – | – | Dominated | 2 | 2 |
| Family intervention (100.00% availability) | 167,905 | 19.5509 | -173 | 0.0127 | Dominating | 1 | 1 |
| ***SA 4: Set unit cost of family intervention=£224.00*** *(Baseline value: £112.00)* | | | | | | | |
| Family intervention (30.98% availability) | 168,164 | 19.1904 | – | – | – | 2 | 2 |
| Family intervention (100.00% availability) | 168,175 | 19.2033 | 11 | 0.0129 | 828 | 1 | 1 |

**Abbreviation:**

ICER: incremental cost-effectiveness ratio; FEP: first episode psychosis; NMB: net monetary benefit; QALY: quality-adjusted life of years; RR: relative risk; WTP: willingness to pay.

**Notes:**

1. This is the 2-5 year RR reported by the systematic review conducted by the NICE schizophrenia GDG.([6](#_ENREF_6))

2. This is the utility value reported by a UK study based on interviewing 75 laypersons using a time trade-off instrument.([23](#_ENREF_23))

**Table 5: Results of structural sensitivity analysis and one-way sensitivity analysis for provision of clozapine for patients with TRS**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Intervention** | **Cost (£)** | **QALY** | **Incremental cost** | **Incremental QALY** | **ICER** | **Ranking of NMB**  (WTP=20,000 per QALY) | **Ranking of NMB**  (WTP=30,000 per QALY) |
| ***Basel case results*** | | | | | | | |
| Clozapine (3.98 year’s delay) | 168,078 | 19.1904 | – | – | Dominated | 2 | 2 |
| Clozapine (no delay) | 162,215 | 19.1977 | -4,486 | 0.0052 | Dominating | 1 | 1 |
| ***SA 1: Set the daily cost of all antipsychotic medication=£1***  *(Baseline value:**Clozapine=£1.56, Olanzapine=£0.13, Risperidone=£0.36, Haloperidol=£0.37, Quetiapine=£1.24)* | | | | | | | |
| Clozapine (3.98 year’s delay) | 168,198 | 19.1904 | – | – | Dominated | 2 | 2 |
| Clozapine (no delay) | 162,315 | 19.1977 | -5,883 | 0.0073 | Dominating | 1 | 1 |
| ***SA 2: Exclude the cost and health impacts of all adverse events for antipsychotic medication*** *(including weight gain, EPS, glucose intolerance, diabetes and neutropenia)* | | | | | | | |
| Clozapine (3.98 year’s delay) | 166,499 | 19.2462 | – | – | Dominated | 2 | 2 |
| Clozapine (no delay) | 161,676 | 19.2529 | -4,823 | 0.0067 | Dominating | 1 | 1 |
| ***SA 3: Exclude the cost and health impacts of weight gain*** | | | | | | | |
| Clozapine (3.98 year’s delay) | 167,881 | 19.2353 | – | – | Dominated | 2 | 2 |
| Clozapine (no delay) | 162,029 | 19.2408 | -5,852 | 0.0055 | Dominating | 1 | 1 |
| ***SA 4: Exclude the cost and health impacts of EPS*** | | | | | | | |
| Clozapine (3.98 year’s delay) | 168,073 | 19.1965 | – | – | Dominated | 2 | 2 |
| Clozapine (no delay) | 162,211 | 19.2034 | -5,863 | 0.0069 | Dominating | 1 | 1 |
| ***SA 5: Exclude the cost and health impacts of glucose intolerance and diabetes*** | | | | | | | |
| Clozapine (3.98 year’s delay) | 168,021 | 19.1934 | – | – | Dominated | 2 | 2 |
| Clozapine (no delay) | 162,179 | 19.1999 | -5,842 | 0.0065 | Dominating | 1 | 1 |
| ***SA 6: Exclude the cost and health impacts of neutropenia*** | | | | | | | |
| Clozapine (3.98 year’s delay) | 168,074 | 19.1904 | – | – | Dominated | 2 | 2 |
| Clozapine (no delay) | 162,200 | 19.1977 | -5,874 | 0.0073 | Dominating | 1 | 1 |

**Abbreviation:**

EPS=extrapyramidal symptoms; ICER=incremental cost-effectiveness ratio; NMB=net monetary benefit; QALY= quality-adjusted life of years; TRS: treatment-resistant schizophrenia; WTP=willingness to pay.

**Reference**

1. Fusar-Poli P, Byrne M, Badger S, Valmaggia LR, McGuire PK. Outreach and support in south London (OASIS), 2001-2011: ten years of early diagnosis and treatment for young individuals at high clinical risk for psychosis. European Psychiatry. 2013;28(5):315-26.

2. NHS England. Report of the early intervention in psychosis audit. London, UK: NHS England; 2016.

3. Whale R, Harris M, Kavanagh G, Wickramasinghe V, Jones CI, Marwaha S, et al. Effectiveness of antipsychotics used in first-episode psychosis: a naturalistic cohort study. The British Journal of Psychiatry Open. 2016;2(5):323-9.

4. Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. British Journal of Psychiatry. 2012;201(6):481-5.

5. Hutton P, Taylor PJ. Cognitive behavioural therapy for psychosis prevention: a systematic review and meta-analysis. Psychological Medicine. 2014;44(3):449-68.

6. National Collaborating Centre for Mental Health. Psychosis and schizophrenia in adults: prevention and management. NICE guideline (CG178). London, UK: The British Psychological Society and The Royal College of Psychiatrists; 2014.

7. Legge SE, Hamshere M, Hayes RD, Downs J, O'Donovan MC, Owen MJ, et al. Reasons for discontinuing clozapine: A cohort study of patients commencing treatment. Schizophrenia Research. 2016;174(1-3):113-9.

8. Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, et al. Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. JAMA Psychiatry. 2016;73(3):199-210.

9. Addington J, Penn D, Woods SW, Addington D, Perkins DO. Social functioning in individuals at clinical high risk for psychosis. Schizophrenia Research. 2008;99(1-3):119-24.

10. Lenert LA, Sturley AP, Rapaport MH, Chavez S, Mohr PE, Rupnow M. Public preferences for health states with schizophrenia and a mapping function to estimate utilities from positive and negative symptom scale scores. Schizophrenia Research. 2004;71(1):155-65.

11. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Medical Decision Making. 2002;22(4):340-9.

12. Curtis J, Burns A. Unit Costs of Health and Social Care 2016. Kent, UK: Personal Social Services Research Unit, University of Kent, Canterbury; 2016.

13. NHS Digital. Prescription Cost Analysis - England 20162017 3rd March 2016. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/prescription-cost-analysis-england-2016>.

14. Department of Health. NHS reference costs 2012 to 2013. London, UK: Department of Health; 2013. Available from: <https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013>.

15. McCrone P, Johnson S, Nolan F, Pilling S, Sandor A, Hoult J, et al. Economic evaluation of a crisis resolution service: a randomised controlled trial. Epidemiology and Psychiatric Sciences. 2009;18(1):54-8.

16. Munro J. Hospital treatment and management in relapse of schizophrenia in the UK: associated costs. The Psychiatrist. 2011;35(3):95-100.

17. Scarborough P, Bhatnagar P, Wickramasinghe KK, Allender S, Foster C, Rayner M. The economic burden of ill health due to diet, physical inactivity, smoking, alcohol and obesity in the UK: an update to 2006-07 NHS costs. Journal of Public Health. 2011;33(4):527-35.

18. Joint Formulary Committee. British National Formulary. 69 ed. London, UK: BMJ Group and Pharmaceutical Press; 2016.

19. Alva ML, Gray A, Mihaylova B, Leal J, Holman RR. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). Diabetic Medicine. 2015;32(4):459-66.

20. Department of Health. NHS reference costs 2016 to 2017. UK, London: Department of Health,; 2017. Available from: <https://www.gov.uk/government/publications/nhs-reference-costs-2016-to-2017>.

21. Jin H, Tappenden P, MacCabe JH, Robinson S, Byford S. Evaluation of the Cost-effectiveness of Services for Schizophrenia in the UK Across the Entire Care Pathway in a Single Whole-Disease Model. JAMA Network Open. 2020;3(5):e205888-e.

22. Curtis J, Burns A. Unit Costs of Health and Social Care 2013. Kent, UK: Personal Social Services Research Unit, University of Kent, Canterbury; 2013.

23. Briggs A, Wild D, Lees M, Reaney M, Dursun S, Parry D, et al. Impact of schizophrenia and schizophrenia treatment-related adverse events on quality of life: direct utility elicitation. Health and quality of life outcomes. 2008;6:105.