1. **Title of paper**

Stratified medicine in schizophrenia — how accurate would a test of drug response need to be to achieve cost-effective improvements in quality of life?

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Supplementary material

This supplementary material contains two appendices. Online Resource 1 reports the key input data used in the model, while Online Resource 2 reports the results of sensitivity analysis.

Online Resource 1. Description of input data

This section describes the key input data used in the model, including clinical data (section 1.1), cost and resource use data (section 1.2), and health-adjusted quality of life (HRQoL) data (section 1.3). A summary of all parameters used in the model, including their fixed values, ranges, distributions and sources, is reported in Table 1.

1.1 Clinical data

Diagnostic efficacy of stratified test. In the base-case analysis, both sensitivity and specificity of the stratified test were set at 60%. A range of 0-100% was tested using one-way sensitivity analyses.

Response to different antipsychotics in misclassified individuals. It is assumed that none of the false positive patients (i.e. clozapine responders or non-responders who are wrongly predicted to respond to a second-line conventional antipsychotic), will respond to any second-line antipsychotic. For those false negative patients (those would-be AP2 responders wrongly predicted not to respond), it was estimated that they would have a 71.16% probability of responding to clozapine and therefore remain on it [1]. A range of 0-1 was tested in two-way sensitivity analysis.

Probability of non-adherence. The probabilities of non-adherence to conventional antipsychotics were obtained from a network meta-analysis conducted for the NICE schizophrenia guideline 2014 [2]. The probability of all-cause discontinuation for clozapine-takers was obtained from Legge et al [3].

Probability of relapse for patients who didn’t adhere to antipsychotics. The annual probability of relapse for patients who don’t adhere to a conventional antipsychotic treatment was obtained from Mayoral-van et al 2016 [4]. The probability of relapse for patients who don’t adhere to clozapine was obtained from Meltzer et al [5], as this paper reported separate relapse data for patients who were treatment responsive and resistant.
Baseline mortality rate. To calculate the mortality rate for people in this study, the age-specific standardised mortality ratio (SMR) observed in people with first episode psychosis [6] was multiplied by the age- and gender-specific mortality rates for the general population in England and Wales, as reported by the Office for National Statistics 2016 [7]. Mortality was calculated on the basis that the study population had a male to female ratio of 1.4 to 1 [8] and presented their first psychotic episode around 22 years of age (95% CI: 19-25 years) [9].

Impact of clozapine on mortality. Quite a few recent large-scale epidemiological studies have shown that use of clozapine is associated with reduced all-cause mortality and suicidality for schizophrenia patients [10-14]. A list of all epidemiological studies considered for this model is presented in Table 2. Although none of those studies have specified whether their patient sample is of treatment-resistant schizophrenia (TRS) or not except Wimberley et al [14], it was assumed that the vast majority of their patient sample would be TRS, as the use of clozapine is restricted to TRS in most countries. Of those epidemiological studies presented in Table 2, Wimberley’s study [14] was considered most appropriate for use in our model because firstly, it was the latest study with the longest follow-up (up to 17 years); secondly, the results of Wimberley et al is comparable to other published studies. According to Wimberley et al [14], the adjusted hazard ratio for TRS who are currently on clozapine versus TRS who are not currently on clozapine is 0.53 (0.33-0.86). However, Wimberley’s study [14] did not report separate mortality data for TRS patients who respond to clozapine, and TRS who do not respond to clozapine. For this model, it was assumed that clozapine is only effective in reducing all-cause mortality in TRS patients who respond to clozapine. Based on the assumption that 75% patients of TRS patients are clozapine responders and 25% are non-responders [15], it was calculated that the hazard ratio of all-cause mortality for clozapine responders on clozapine is 0.37 (95% CI: 0.11-0.81). Since there is a lack of evidence about the mortality rate of AP2 responders on clozapine, it is assumed that the use of clozapine does not have any impact on the all-cause mortality rate for AP2 responders.

Side effects of antipsychotics. The choice of side effects for consideration in the economic analysis was based on a number of criteria, including the number of people affected in the study population, the impact of side effects on health-related quality of life (HRQoL), the magnitude of costs incurred by their management and the availability of respective clinical data specific to the treatment options assessed. Based on the above criteria, four side effects of antipsychotics were modelled: weight gain, acute extrapyramidal symptoms (EPS), diabetes and neutropenia (for clozapine-users only). The probability data for weight gain, acute EPS and diabetes were
derived from the NICE guideline systematic review [2] and other published studies [16, 17]. The probability of developing neutropenia for patients on clozapine was obtained from Munro et al [18], which is a large-scale cohort study following 12,760 clozapine-users for up to 7.6 years.

1.2 Cost and resource use data

The model takes the perspective of the NHS and Personal Social Services (PSS), as recommended by NICE [19]. The financial year is 2016. The total costs for the treatment strategies were estimated by multiplying the unit costs with resource quantities. Unit costs were based on the NHS reference costs 2016-17 [20], prescription cost analysis (England) 2017 [21] or the Unit Costs of Health and Social Care 2017 [22]. The unit cost of the stratified test is assumed to be £500 per patient (a conservative estimate of the cost of a magnetic resonance spectroscopy scan) [23], with a range of £100-1000 tested in sensitivity analyses. Resources quantities were informed by the NICE schizophrenia guideline 2014 [2] and clinician’s estimates where these were unavailable.

1.3 Health-related quality of life (HRQoL) data

HRQoL data was expressed as utilities from which quality adjusted life years (QALYs) were derived. Utility weights are usually elicited on a 0-1 ratio scale of 0 (death) to 1 (perfect health). The average utilities, for patients in different health states were taken from a UK study which reported separate utility data for stable or relapsed schizophrenia patients with or without adverse events associated with antipsychotic use [24].
Table 1. Summary of parameters used in model: base-line deterministic values, range used in one-way or two-way sensitivity analysis, distribution used in probabilistic sensitivity analysis, and references

| Parameters                                                                 | Base-line value | Range tested in one-way or two-way sensitivity analysis | Distribution                      | Source                                      |
|---------------------------------------------------------------------------|-----------------|-------------------------------------------------------|------------------------------------|---------------------------------------------|
| **Diagnostic efficacy of predictive test**                                |                 |                                                      |                                    |                                             |
| Sensitivity (proportion of second-line antipsychotic responders that are correctly identified as such) | 0.60            | 0-1.00                                                | Assumed fixed                     | Estimate of what may be achievable         |
| Specificity (proportion of second-line antipsychotic non-responders that are correctly identified as such) | 0.60            | 0-1.00                                                | Assumed fixed                     | Estimate of what may be achievable         |
| **Patient’s demographic factors**                                         |                 |                                                      |                                    |                                             |
| Gender ratio for schizophrenia patients (male to female)                  | 1.40            | N/A                                                   | Assumed fixed                     | McGrath et al [8]                           |
| Age of presentation of first psychotic episode                            |                 |                                                      |                                    |                                             |
| 18-24 years                                                               | 29.55%          | N/A                                                   | Assumed fixed                     | Coid et al [25]                              |
| 25-34 years                                                               | 42.77%          | N/A                                                   | Assumed fixed                     | As above                                    |
| 35-44 years                                                               | 16.12%          | N/A                                                   | Assumed fixed                     | As above                                    |
| 45-54 years                                                               | 8.06%           | N/A                                                   | Assumed fixed                     | As above                                    |
| 55-64 years                                                               | 3.51%           | N/A                                                   | Assumed fixed                     | As above                                    |
| **Market share of different non-clozapine antipsychotics**                |                 |                                                      |                                    |                                             |
| Olanzapine                                                                | 50.57%          | N/A                                                   | Dirichlet distribution            | Calculated from Prescription cost analysis [21] |
|                                                                           |                 |                                                      | (n=44,786,709)                    |                                             |
| Amisulpride                                                               | 7.30%           | N/A                                                   | Dirichlet distribution            | As above                                    |
|                                                                           |                 |                                                      | (n=6,463,921)                     |                                             |
| Aripiprazole                                                              | 16.12%          | N/A                                                   | Dirichlet distribution            | As above                                    |
|                                                                           |                 |                                                      | (n=14,280,763)                    |                                             |
| Paliperidone                                                              | 0.02%           | N/A                                                   | Dirichlet distribution            | As above                                    |
|                                                                           |                 |                                                      | (n=17,712)                        |                                             |
| Risperidone                                                               | 18.84%          | N/A                                                   | Dirichlet distribution            | As above                                    |
|                                                                           |                 |                                                      | (n=16,687,517)                    |                                             |
| Haloperidol                                                               | 4.27%           | N/A                                                   | Dirichlet distribution            | As above                                    |
|                                                                           |                 |                                                      | (n=3,781,443)                     |                                             |
| Flupenthixol decanoate                                                    | 2.87%           | N/A                                                   | Dirichlet distribution            | As above                                    |
|                                                                           |                 |                                                      | (n=2,541,626)                     |                                             |
| **Distribution of patients who failed a first-line antipsychotic by subsequent response/non-response** |                 |                                                      |                                    |                                             |
| Clozapine responder                                                      | 62.50%          | 0%-79.15%                                             | Dirichlet distribution            | Agid et al [15]                              |
|                                                                           |                 |                                                      | (n=21.0)                          |                                             |
| AP2 responder                                                            | 16.67%          | N/A                                                   | Dirichlet distribution            | As above                                    |
|                                                                           |                 |                                                      | (n=5.6)                           |                                             |
| Clozapine non-responder                                                   | 20.83%          | N/A                                                   | Dirichlet distribution            | As above                                    |
|                                                                           |                 |                                                      | (n=7.0)                           |                                             |
| **Response to different antipsychotics in misclassified individuals**     |                 |                                                      |                                    |                                             |
| AP2 responder’s response to clozapine                                     | 71.16%          | 0-1                                                   | Beta distribution (SD assumed to be 50% of mean value) | Calculated from Agid et al [15] and McEvoy et al [1] Estimate |
| AP2 non-responder response to second-line antipsychotics                  | 0%              | N/A                                                   | Assumed fixed                     |                                             |
| **Annual probability of discontinuing conventional antipsychotics because of non-adherence** |                 |                                                      |                                    |                                             |


| Parameters                                                                 | Base-line value | Range tested in one-way or two-way sensitivity analysis | Distribution                          | Source                                             |
|---------------------------------------------------------------------------|-----------------|--------------------------------------------------------|---------------------------------------|---------------------------------------------------|
| Olanzapine                                                                | 0.2730          | 0.1761-0.3848                                          | Beta distribution (SD: 0.2140)        | Calculated from NICE schizophrenia guideline [2]   |
| Amisulpride                                                               | 0.2435          | 0.1761-0.3848                                          | Beta distribution (SD: 0.2088)        | As above                                          |
| Aripiprazole                                                              | 0.3520          | 0.1761-0.3848                                          | Beta distribution (SD: 0.2300)        | As above                                          |
| Paliperidone                                                              | 0.3848          | 0.1761-0.3848                                          | Beta distribution (SD: 0.2367)        | As above                                          |
| Risperidone                                                               | 0.1761          | 0.1761-0.3848                                          | Beta distribution (SD: 0.1799)        | As above                                          |
| Haloperidol                                                               | 0.2516          | 0.1761-0.3848                                          | Beta distribution (SD: 0.2033)        | As above                                          |
| Clozapine (year 1)                                                       | 0.0570          | 0-0.4000                                               | Beta distribution (SD assumed to be 50% of mean value) | Legge et al [3]                                   |
| Clozapine (year 2 onwards)                                               | 0.0355          | 0-0.4000                                               | As above                              | As above                                          |
| **Probability of relapse for patients discontinue antipsychotic treatment due to non-adherence** |                |                                                        |                                       |                                                   |
| Annual probability of relapse, first year following discontinuation of conventional antipsychotics | 0.5650          | 0-0.8000                                               | Beta distribution (SD assumed to be 50% of mean value) | Mayoral-van et al [4]                             |
| Annual probability of relapse, second year following discontinuation of conventional antipsychotics | 0.2000          | 0-0.8000                                               | As above                              | As above                                          |
| Annual probability of relapse, year 3 onwards following discontinuation of conventional antipsychotics | 0.0632          | 0-0.8000                                               | As above                              | As above                                          |
| Annual probability of relapse, following discontinuation of clozapine, for treatment response patients | 0.7895          | 0-0.8000                                               | Beta distribution (SD: 0.0935)         | Meltzer et al [5]                                 |
| Annual probability of relapse, following discontinuation of clozapine, for treatment resistant patients | 0.3281          | 0-0.8000                                               | Beta distribution (SD: 0.0587)         | As above                                          |
| **Annual probability of developing side effect - weight gain (assume that weight gain only happens on the first year of initiation of a particular antipsychotic)** |                |                                                        |                                       |                                                   |
| Annual probability of weight gain for patients on haloperidol             | 0.2000          | 0.1716-0.4307                                          | Beta distribution (α=31, β=124)       | Calculated from NICE schizophrenia guideline [2]   |
| Annual probability of weight gain for patients on flupentixol decanoate   | 0.2000          | 0.1716-0.4307                                          | Beta distribution (α=31, β=124)       | As above                                          |
| OR of weight gain (Olanzapine v.s Haloperidol)                           | 2.8631          | 1.7050-4.5090                                          | Triangular distribution (min=1.7050, max=4.5090) | As above                                          |
| OR of weight gain (Amisulpride v.s Haloperidol)                          | 1.8604          | 0.7345-4.0360                                          | Triangular distribution (min=0.7345, max=4.0360) | As above                                          |
| OR of weight gain (Aripiprazole v.s Haloperidol)                         | 0.7373          | 0.3498-1.3990                                          | Triangular distribution (min=0.3498, max=1.3990) | As above                                          |
| OR of weight gain (Paliperidone v.s Haloperidol)                         | 1.0779          | 0.4405-2.1640                                          | Triangular distribution (min=0.4405, max=2.1640) | As above                                          |
| Parameters                                           | Base-line value | Range tested in one-way or two-way sensitivity analysis | Distribution                          | Source                           |
|-----------------------------------------------------|-----------------|----------------------------------------------------------|---------------------------------------|----------------------------------|
| OR of weight gain (Risperidone v.s Haloperidol)     | 1.0895          | 0.5214-2.0850                                            | Triangular distribution (min=0.5214, max=2.0850) | As above                        |
| RR of weight gain (Clozapine v.s Olanzapine)        | 1.5385          | 1.0000-2.0000                                            | Triangular distribution (assumed min=1.0000, max=2.0000) | Calculated from McEvoy et al [1] |

**Annual probability of developing side effects - acute EPS (first year of initiation of a particular antipsychotic)**

| Annual probability of EPS (Haloperidol)              | 0.5367          | 0.2366-0.5367                                            | Beta distribution (α=928, β=801)       | Calculated from NICE schizophrenia guideline [2] |
| Annual probability of EPS (Flupentixol decanoate)   | 0.4891          | 0.2366-0.5367                                            | Beta distribution (α=45, β=47)         | As above                        |
| OR of EPS (Olanzapine v.s Haloperidol)               | 0.2631          | 0.1832-0.3641                                            | Triangular distribution (min=0.1832, max=0.3641) | As above                        |
| OR of EPS (Amisulpride v.s Haloperidol)              | 0.3993          | 0.2587-0.5836                                            | Triangular distribution (min=0.2587, max=0.5836) | As above                        |
| OR of EPS (Aripiprazole v.s Haloperidol)             | 0.2517          | 0.1505-0.4002                                            | Triangular distribution (min=0.1505, max=0.4002) | As above                        |
| OR of EPS (Paliperidone v.s Haloperidol)             | 0.2983          | 0.1179-0.6214                                            | Triangular distribution (min=0.1179, max=0.6214) | As above                        |
| OR of EPS (Risperidone v.s Haloperidol)              | 0.4743          | 0.3680-0.5994                                            | Triangular distribution (min=0.3680, max=0.5994) | As above                        |
| RR of EPS (Clozapine v.s Olanzapine)                 | 0.3880          | 0.2000-0.6000                                            | Triangular distribution (assumed min=0.2, max=0.6) | Calculated from Davies et al [17] |

**Probability of developing side effect - acute EPS (following years)**

| Probability of developing side effect - acute EPS (following years) | Assumed 10% of first year estimate | N/A | N/A (no distribution assigned) | N/A |
|--------------------------------------------------------------------|-----------------------------------|-----|--------------------------------|-----|
| Haloperidol                                                        | 0.0200                            | 0.0156-0.0417 | Beta distribution (α=2, β=98) | As above |
| Flupentixol decanoate                                              | 0.0200                            | 0.0156-0.0417 | Beta distribution (α=2, β=98) | As above |
| Olanzapine                                                         | 0.0417                            | 0.0156-0.0417 | Beta distribution (SD assumed to be 50% of mean value) | As above |
| Amisulpride                                                        | 0.0317                            | 0.0156-0.0417 | As above | As above |
| Aripiprazole                                                       | 0.0156                            | 0.0156-0.0417 | As above | As above |
| Paliperidone                                                       | 0.0212                            | 0.0156-0.0417 | As above | As above |
| Risperidone                                                        | 0.0214                            | 0.0156-0.0417 | As above | As above |
| Parameters                                      | Base-line value | Range tested in one-way or two-way sensitivity analysis | Distribution                                      | Source                                      |
|------------------------------------------------|-----------------|---------------------------------------------------------|--------------------------------------------------|--------------------------------------------|
| RR of diabetes (Clozapine vs Olanzapine)       | 1.2880          | 1.0000-2.0000                                           | Triangular distribution (assumed min=0, max=0.6000) | Calculated from Davies et al [17]          |
| Annual probability of developing side effect - neutropenia |                |                                                        |                                                  |                                            |
| Clozapine                                      | 0.0125          | 0-0.0300                                                | Triangular distribution (assumed min=0, max=0.0300) | Calculated from Munro et al [18]           |
| Annual mortality rates for male population (Death per 1,000 population) |                |                                                        |                                                  |                                            |
| 15-19 years                                    | 0.30            | N/A                                                     | Assumed fixed                                   | Office for National Statistics [7]         |
| 20-24 years                                    | 0.50            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 25-29 years                                    | 0.60            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 30-34 years                                    | 0.80            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 35-39 years                                    | 1.20            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 40-44 years                                    | 1.70            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 45-49 years                                    | 2.50            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 50-54 years                                    | 3.70            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 55-59 years                                    | 5.90            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 60-64 years                                    | 9.60            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 65-69 years                                    | 14.30           | N/A                                                     | Assumed fixed                                   | As above                                   |
| 70-74 years                                    | 24.50           | N/A                                                     | Assumed fixed                                   | As above                                   |
| 75-79 years                                    | 40.70           | N/A                                                     | Assumed fixed                                   | As above                                   |
| 80-84 years                                    | 73.20           | N/A                                                     | Assumed fixed                                   | As above                                   |
| 85 years+                                      | 162.40          | N/A                                                     | Assumed fixed                                   | As above                                   |
| Annual mortality rates for female population (Death per 1,000 population) |                |                                                        |                                                  |                                            |
| 15-19 years                                    | 0.10            | N/A                                                     | Assumed fixed                                   | Office for National Statistics [7]         |
| 20-24 years                                    | 0.20            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 25-29 years                                    | 0.30            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 30-34 years                                    | 0.40            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 35-39 years                                    | 0.70            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 40-44 years                                    | 1.00            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 45-49 years                                    | 1.60            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 50-54 years                                    | 2.50            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 55-59 years                                    | 4.00            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 60-64 years                                    | 6.10            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 65-69 years                                    | 9.40            | N/A                                                     | Assumed fixed                                   | As above                                   |
| 70-74 years                                    | 16.00           | N/A                                                     | Assumed fixed                                   | As above                                   |
| 75-79 years                                    | 28.10           | N/A                                                     | Assumed fixed                                   | As above                                   |
| 80-84 years                                    | 53.30           | N/A                                                     | Assumed fixed                                   | As above                                   |
| 85 years+                                      | 143.70          | N/A                                                     | Assumed fixed                                   | As above                                   |
| Standardized Mortality Ratios for all-cause of death (schizophrenia v.s general population) |                |                                                        |                                                  |                                            |
| 16-29 years                                    | 7.40            | N/A                                                     | Triangular distribution (min: 3.50, max: 15.50)   | Reininghaus et al [6]                      |
| 30-44 years                                    | 5.80            | N/A                                                     | Triangular distribution (min: 3.70, max: 9.20)   | As above                                   |
| Parameters                                                                 | Base-line value | Range tested in one-way or two-way sensitivity analysis | Distribution                                                                 | Source                                                                 |
|---------------------------------------------------------------------------|-----------------|---------------------------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| 45-59 years                                                               | 2.50            | N/A                                                     | Triangular distribution (min: 1.20; max: 4.90)                                | As above                                                              |
| 60-74 years                                                               | 1.70            | N/A                                                     | Triangular distribution (min: 0.80; max: 3.80)                                | As above                                                              |
| Impact of clozapine on mortality (for clozapine-responders only)          |                 |                                                         |                                                                               |                                                                       |
| Hazard ratio (HR) of all-cause mortality (clozapine v.s no clozapine)     | 0.37            | 0.11-0.81                                               | Triangular distribution (min: 0.11; max: 0.81)                                | Calculated from Wimberley et al [14] based on the assumption that of all patients on clozapine, 75% of them are clozapine responders while 25% are non-responders |
| Daily cost of antipsychotics                                             |                 |                                                         |                                                                               |                                                                       |
| Olanzapine                                                                | £0.13           | N/A                                                     | Assumed fixed                                                                | Calculated from Prescription cost analysis [21]                       |
| Amisulpride                                                               | £0.47           | N/A                                                     | Assumed fixed                                                                | As above                                                              |
| Aripiprazole                                                              | £4.08           | N/A                                                     | Assumed fixed                                                                | As above                                                              |
| Paliperidone                                                              | £6.58           | N/A                                                     | Assumed fixed                                                                | As above                                                              |
| Risperidone                                                               | £0.36           | N/A                                                     | Assumed fixed                                                                | As above                                                              |
| Haloperidol                                                               | £0.37           | N/A                                                     | Assumed fixed                                                                | As above                                                              |
| Flupentixol decanoate                                                     | £0.24           | N/A                                                     | Assumed fixed                                                                | As above                                                              |
| Clozapine                                                                 | £1.56           | N/A                                                     | Assumed fixed                                                                | As above                                                              |
| Other cost data                                                           |                 |                                                         |                                                                               |                                                                       |
| Cost of predictive test                                                   | £500.00         | £100.00-1,000.00                                        | Gamma distribution (SD assumed to be 50% of mean value)                      | Estimate                                                              |
| Cost of blood test for clozapine                                          | £2.65           | N/A                                                     | Assumed fixed                                                                | Akhtar et al [26] Resource use were obtained from the finance department of a clozapine clinic based at the South London and Maudsley NHS Foundation Trust |
| Cost of one attendance at clozapine clinic                                | £34.82          | N/A                                                     | Assumed fixed                                                                | Resource use was informed by the NICE schizophrenia guideline [2]. Unit cost was obtained from PSSRU[22] |
| Cost of switching between antipsychotics                                  | £426.00         | N/A                                                     | Gamma distribution (SD assumed to be 50% of mean value)                      |                                                                       |
| Annual cost of treating weight gain for patients adhere to antipsychotics (Year 1) | £97.20          | £0-1,000.00                                             | As above                                                                     | As above                                                              |
| Annual cost of treating weight gain for patients adhere to antipsychotics (Year 2 onwards) | £309.68         | £0-1,000.00                                             | As above                                                                     | Calculated and uplifted from                                           |
| Parameters                                                                 | Base-line value | Range tested in one-way or two-way sensitivity analysis | Distribution          | Source                                                                                     |
|---------------------------------------------------------------------------|-----------------|--------------------------------------------------------|------------------------|-------------------------------------------------------------------------------------------|
| Annual cost of treating weight gain for patients who discontinue antipsychotics due to non-adherence | 50% of original cost | 0-100% of original cost                               | As above               | Scarborough et al [27] Estimate                                                             |
| Annual cost of treating acute EPS for patients adhere to antipsychotics   | £51.95          | £0-500.00                                              | As above               | Resource use was informed by the NICE schizophrenia guideline [2]. Unit cost was obtained from PSSRU [22] Estimate |
| Annual cost of treating acute EPS for patients discontinue antipsychotics due to non-adherence | £0              | 0-100% of original cost                               | As above               | Probability of developing complications of diabetes was informed by the NICE schizophrenia guideline [2]. Cost of treating each complication was uplifted from UKPDS [28] Estimate |
| Annual cost of treating diabetes with/out complications for patients adhere to antipsychotics | £1,336.31       | £0-2,000.00                                           | As above               |                                                                                             |
| Annual cost of treating diabetes with/out complications for patients who discontinue antipsychotics due to non-adherence | 50% of original cost | 0-100% of original cost                               | As above               | NHS reference cost 2016-17 [20]                                                             |
| Cost of treating neutropenia                                              | £469.48         | £0-1,000.00                                            | Gamma distribution (SD assumed to be 50% of mean value) |                                                                           |
| Annual cost of treating patients with active psychosis                    | £39,141         | N/A                                                    | As above               | Uplifted from the NICE schizophrenia guideline [2]                                         |
| Annual cost of treating remitted patients                                 | £15,086         | £10,000-£39,141                                       | As above               |                                                                                             |
| Relapse                                                                   | 0.4790          | 0.1900-0.6040                                          | Beta distribution (SD: 0.0330) | Briggs et al [24]                                                                          |
| Stable schizophrenia without adverse events                               | 0.8650          | 0.8650-0.9190                                          | Beta distribution (SD: 0.0210) | As above                                                                                  |
| Stable schizophrenia with weight gain                                     | 0.7790          | 0.7790-0.8650                                          | Beta distribution (SD: 0.0240) | As above                                                                                  |
| Stable schizophrenia with diabetes                                        | 0.7120          | 0.7120-0.8650                                          | Beta distribution (SD: 0.0280) | As above                                                                                  |
| Stable schizophrenia with acute EPS                                        | 0.5740          | 0.5740-0.8650                                          | Beta distribution (SD: 0.0320) | As above                                                                                  |
| Other input data                                                           |                 |                                                        |                        |                                                                                             |
| Parameters                              | Base-line value | Range tested in one-way or two-way sensitivity analysis | Distribution     | Source               |
|----------------------------------------|-----------------|---------------------------------------------------------|------------------|----------------------|
| Annual discount rate for both costs and outcomes | 0.0350          | 0.0-0.050                                               | Assumed fixed    | NICE guideline manual [19] |
| Cycle length                           | 1 year          | N/A                                                     | Assumed fixed    | Estimate             |
| Number of cycles                       | 80              | 10-100                                                  | Assumed fixed    | Estimate             |

Notes:
1. N refers to the number of daily doses prescribed, calculated by dividing the total amount of net ingredients prescribed by the recommended daily dose.
| Study          | Publication year | Country | Basis of analysis                                                                 | Population                                                                 | Follow-up period | Effect of clozapine on mortality                                                                 |
|---------------|------------------|---------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------|------------------|-----------------------------------------------------------------------------------------------|
| Tiihonen et al [10] | 2009             | Finland | Nationwide registers in Finland                                                   | All patients in Finland (n=66,881) who were admitted with a diagnosis of schizophrenia | 11-year          | All-cause mortality  
Clozapine v.s Perphenazine: adjusted HR for clozapine (0.74, (95% CI: 0.60–0.91)). Clozapine v.s all other antipsychotics: \( p<0.0001 \) |
| Kiviniemi et al [12] | 2013             | Finland | Four Finnish national registers.                                                 | All patients presenting with first onset of schizophrenia (n= 6,987)     | 5-year           | All-cause mortality  
Clozapine v.s no antipsychotic: adjusted odds ratio: 0.35 (95% CI: 0.21–0.58, \( p<0.001 \)) |
| Hayes et al [11]   | 2014             | UK      | A large, anonymized, electronic mental health Records database which cover 200,000 patients. | 14,754 individuals with serious mental illness including schizophrenia (n= 9437), schizoaffective (n=805) and bipolar disorders (n=4,512) aged \( \geq 15 \) years. | 5-year           | All-cause mortality  
Prescribed clozapine v.s Not prescribed clozapine: adjusted HR for clozapine (0.4; 95% CI 0.2–0.7; \( p = 0.001 \))  
Likelihood for suicide  
Prescribed clozapine v.s Not prescribed clozapine: adjusted HR for clozapine (0.29; 95% CI: 0.14–0.63; \( p = 0.002 \))  
Death by suicide  
Prescribed clozapine v.s haloperidol, adjusted odds ratio: 0.92 (95% CI: 0.70–1.22)  
Attempted suicide  
Prescribed clozapine v.s haloperidol, adjusted odds ratio: 0.45 (95% CI:0.20–0.98)  
 attempt at suicide  
Prescribed clozapine v.s haloperidol, adjusted odds ratio: 0.44 (0.28–0.70) |
| Weitoft et al [13] | 2014             | Sweden  | National Patient Register, the Swedish Prescribed Drug Register and the National Cause of Death Register. | all patients (n=26,046) in Sweden who had been treated for schizophrenia from 2006 to 2009. | 3-month          |  |
| Wimberley et al [14] | 2017             | EU      | The Danish Psychiatric Central Register, National Patient Registry, Civil Registration System and the National Prescription Registry. | 2,370 individuals meeting criteria for treatment-resistant schizophrenia after 1996 and followed until death and first episode of suicidal behaviour, emigration, or June 1, 2013. | 17-year          | All-cause mortality  
Current clozapine v.s No current clozapine, adjusted hazard ratio: 0.53 (0.33–0.86) |
Online Resource 2. Results of sensitivity analysis

This appendix reports results of one-way and two-way sensitivity analysis in Section 2.1 and 2.2, respectively.

2.1 One-way sensitivity analysis results

The conclusion of the base case analysis (SMA being the most cost-effective strategy) was robust to all scenarios tested. The detailed results of one-way sensitivity analysis are reported in Table 3.
Table 3. One-way sensitivity analyses results

| Analysis                                                                 | Value tested | Cost savings of SMA compared to TAU (£) | QALY gains of SAM compared to TAU | Conclusion |
|--------------------------------------------------------------------------|--------------|----------------------------------------|---------------------------------|------------|
| **Clinical parameters**                                                  |              |                                        |                                 |            |
| Annual probability of discontinuing antipsychotics because of non-       | 0.1761       | 7,037                                  | 0.1008                          | SMA dominant |
| adherence, for patients on conventional antipsychotics                  | 0.3848       | 7,659                                  | 0.1064                          | SMA dominant |
| Annual probability of discontinuing antipsychotics because of non-       | 0            | 7,480                                  | 0.1053                          | SMA dominant |
| adherence, for patients on clozapine (year 1)                           | 0.40         | 6,308                                  | 0.0891                          | SMA dominant |
| Annual probability of discontinuing antipsychotics because of non-       | 0            | 8,289                                  | 0.1181                          | SMA dominant |
| adherence, for patients on clozapine (year 2 onwards)                  | 0.40         | 2,595                                  | 0.0290                          | SMA dominant |
| Probability of relapse following discontinuation of conventional        | 0            | 6,309                                  | 0.0792                          | SMA dominant |
| antipsychotics (year 1)                                                 | 0.80         | 8,146                                  | 0.1220                          | SMA dominant |
| Probability of relapse following discontinuation of conventional        | 0            | 7,122                                  | 0.0982                          | SMA dominant |
| antipsychotics (year 2)                                                 | 0.80         | 8,362                                  | 0.1270                          | SMA dominant |
| Annual probability of relapse following discontinuation of conventional | 0            | 6,490                                  | 0.0836                          | SMA dominant |
| antipsychotics (year 3 onwards)                                         | 0.80         | 8,564                                  | 0.1317                          | SMA dominant |
| Annual probability of relapse, following discontinuation of clozapine,  | 0            | 8,645                                  | 0.1404                          | SMA dominant |
| for treatment response patients                                         | 0.80         | 7,360                                  | 0.1037                          | SMA dominant |
| Annual probability of relapse, following discontinuation of clozapine,  | 0            | 7,587                                  | 0.1038                          | SMA dominant |
| for treatment resistant patients                                        | 0.80         | 7,345                                  | 0.1036                          | SMA dominant |
| Probability of developing weight gain for patients on haloperidol or    | 0.1716       | 7,383                                  | 0.1100                          | SMA dominant |
| flupentixol decanoate                                                   | 0.4307       | 7,249                                  | 0.0675                          | SMA dominant |
| OR of weight gain (Olanzapine v.s Haloperidol)                          | 1.7050       | 7,421                                  | 0.1216                          | SMA dominant |
| OR of weight gain (Amisulpride v.s Haloperidol)                         | 4.5090       | 7,307                                  | 0.0867                          | SMA dominant |
| OR of weight gain (Aripiprazole v.s Haloperidol)                        | 0.7345       | 7,361                                  | 0.1033                          | SMA dominant |
| OR of weight gain (Aripiprazole v.s Haloperidol)                        | 4.0360       | 7,365                                  | 0.1043                          | SMA dominant |
| OR of weight gain (Aripiprazole v.s Haloperidol)                        | 0.3498       | 7,361                                  | 0.1033                          | SMA dominant |
| OR of weight gain (Aripiprazole v.s Haloperidol)                        | 1.3990       | 7,365                                  | 0.1043                          | SMA dominant |
| OR of weight gain (Paliperidone v.s Haloperidol)                        | 0.4405       | 7,363                                  | 0.1038                          | SMA dominant |
| OR of weight gain (Risperidone v.s Haloperidol)                         | 2.1640       | 7,363                                  | 0.1038                          | SMA dominant |
| OR of weight gain (Risperidone v.s Haloperidol)                         | 0.5214       | 7,360                                  | 0.1030                          | SMA dominant |
| OR of weight gain (Paliperidone v.s Haloperidol)                        | 2.0850       | 7,367                                  | 0.1047                          | SMA dominant |
| RR of weight gain (Clozapine v.s Olanzapine)                           | 1.0000       | 7,449                                  | 0.1290                          | SMA dominant |
| RR of weight gain (Clozapine v.s Olanzapine)                           | 2.0000       | 7,293                                  | 0.0832                          | SMA dominant |
| Annual probability of developing acute EPS for patients on haloperidol  | 0.2366       | 7,362                                  | 0.0994                          | SMA dominant |
| or flupentixol decanoate, first year of initiation of a particular       | 0.5367       | 7,363                                  | 0.1038                          | SMA dominant |
| antipsychotic                                                           |              |                                        |                                 |            |
| OR of EPS (Olanzapine v.s Haloperidol)                                  | 0.1832       | 7,363                                  | 0.1038                          | SMA dominant |
| Statistical Parameter | OR (95% CI) | p-value | SMA Dominant |
|-----------------------|-------------|---------|--------------|
| OR of EPS (Amisulpride v.s Haloperidol) | 0.2587 (7.363) | 0.1035 | SMA dominant |
| OR of EPS (Aripiprazole v.s Haloperidol) | 0.1505 (7.363) | 0.1032 | SMA dominant |
| OR of EPS (Paliperidone v.s Haloperidol) | 0.4002 (7.363) | 0.1044 | SMA dominant |
| OR of EPS (Risperidone v.s Haloperidol) | 0.1179 (7.363) | 0.1038 | SMA dominant |
| RR of EPS (Paliperidone v.s Haloperidol) | 0.5836 (7.363) | 0.1035 | SMA dominant |
| RR of EPS (Risperidone v.s Haloperidol) | 0.4002 (7.363) | 0.1037 | SMA dominant |

**Cost Parameters**

| Cost Parameter | Cost (£) | 95% CI | p-value | SMA Dominant |
|----------------|----------|--------|---------|--------------|
| Cost of the stratified test | £100 | 7,763 | 0.1038 | SMA dominant |
| Annual cost of treating weight gain for patients who adhere to antipsychotics | £0 | 7,553 | 0.1038 | SMA dominant |
| Annual cost of treating weight gain for patients who discontinue antipsychotics due to non-adherence | £1,000 | 6,932 | 0.1038 | SMA dominant |
| Annual cost of treating acute EPS for patients who adhere to antipsychotics | £0 | 7,362 | 0.1038 | SMA dominant |
| Annual cost of treating acute EPS for patients who discontinue antipsychotics due to non-adherence | £500.00 | 7,373 | 0.1038 | SMA dominant |
| Annual cost of treating diabetes with/out complications for patients who adhere to antipsychotics | £0 | 7,427 | 0.1038 | SMA dominant |
| Annual cost of treating diabetes with/out complications for patients who discontinue antipsychotics due to non-adherence | £2,000.00 | 7,531 | 0.1038 | SMA dominant |
| Cost of treating neutropenia per episode | £0 | 7,357 | 0.1038 | SMA dominant |
### Annual cost of treating remitted patients

|                        | £15,656 (40% of treatment cost for relapsed patients) | £23,484 (60% of treatment cost for relapsed patients) | £31,313 (80% of treatment cost for relapsed patients) | £37,184 (100% of treatment cost for relapsed patients) |
|------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|
| **Utility**            | 7,134                                                | 3,986                                                | 837                                                  | -1,524                                               |
| **SMA dominant**       | 0.1038                                               | 0.1038                                               | 0.1038                                               | 0.1038                                               |

SMA is more cost-effective (ICER for SMA=14,683 per QALY, which is less than NICE’s threshold of £20,000 per QALY)

### Utility parameters

| Utility for schizophrenia patients in relapse | 0.1900 | 7.363 | 0.2143 | SMA dominant |
|----------------------------------------------|--------|-------|--------|--------------|
| Utility for schizophrenia patients in remission without side effects | 0.8650 | 7.363 | 0.1038 | SMA dominant |
| Utility for schizophrenia patients in remission with weight gain | 0.7790 | 7.363 | 0.1038 | SMA dominant |
| Utility for schizophrenia patients in remission with diabetes | 0.7120 | 7.363 | 0.1038 | SMA dominant |
| Utility for schizophrenia patients in remission with EPS | 0.5740 | 7.363 | 0.1038 | SMA dominant |

### Other parameters

| No. of cycles | 10 | 7.463 | 0.1076 | SMA dominant |
|---------------|----|-------|--------|--------------|
| Discount rate for both cost and QALYs | 0 | 7.391 | 0.1040 | SMA dominant |
| 0.05 | 7.287 | 0.1031 | SMA dominant |

Notes:
1. There are two scenarios under which SMA could be considered to be cost-effective:
   - Scenario 1. Compared with TAU, SMA is less costly and more clinically effective. In this case, SMA ‘dominates’ TAU and no further justification is necessary.
   - Scenario 2. Compared with TAU, SMA is more effective, but also more expensive. In this case, the decision whether to implement the SMA would depend on how much the payer of healthcare (the NHS in the UK) is prepared to pay per additional unit of QALY. The incremental cost-effectiveness ratio (ICER) is the ratio of the difference in cost divided by the difference in QALYS and is expressed in UK pounds per additional QALY. In line with the NICE reference case, a willingness-to-pay (WTP) threshold of £20,000 per additional QALY was used. Thus, if the ICER of SMA versus TAU is less than £20,000 per QALY, then SMA is more cost-effective than TAU.
2.2 Two-way sensitivity analysis results

The results of two-way sensitivity analysis are presented in Figure 1 below. Figure 1A reports the combined effects of sensitivity and specificity of the stratifier on the results. It shows that:

- If the sensitivity of the stratifier is 0%, as long as the specificity of the test is no less than 11.50%, SMA is more cost-effective than TAU
- If the sensitivity of the stratifier is 50.00%, as long as the specificity of the test is no less than 6.00%, SMA is more cost-effective than TAU

Figure 1B reports the combined effects of: proportion of clozapine responder in patients who failed a first-line antipsychotic, and proportion of AP2 responders who respond to clozapine. The results show that:

- If 50% of the AP2 responders would respond to clozapine, as long as the proportion of clozapine responder is no less than 23.75%, SMA is more cost-effective than TAU
- If none of the AP2 responders would respond to clozapine, as long as the proportion of clozapine responder is no less than 35.62%, SMA is more cost-effective than TAU
Figure 1. Two-way sensitivity analysis result showing the most cost-effective strategy.

Footnote: a: Based on a willingness-to-pay threshold of £20,000 per additional unit of QALY.

Abbreviation:
- SMA: Stratified medicine algorithm
- TAU: Treatment as usual
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