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The research reported in this monograph was commissioned by the HTA Programme as project number 96/19/06. The contractual start date was in May 1999. The draft report began editorial review in July 2003 and was accepted for publication in April 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment

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Objectives: To determine the clinical and cost-effectiveness of different classes of antipsychotic drug treatment in people with schizophrenia responding inadequately to, or having unacceptable side-effects from, their current medication.
Design: Two pragmatic, randomised controlled trials (RCTs) were undertaken. The first RCT (band 1) compared the class of older, inexpensive conventional drugs with the class of new atypical drugs in people with schizophrenic disorders, whose current antipsychotic drug treatment was being changed either because of inadequate clinical response or owing to side-effects. The second RCT (band 2) compared the new (non-clozapine) atypical drugs with clozapine in people whose medication was being changed because of poor clinical response to two or more antipsychotic drugs. Both RCTs were four-centre trials with concealed randomisation and three follow-up assessments over 1 year, blind to treatment.
Setting: Adult mental health settings in England.
Participants: In total, 227 participants aged 18–65 years (40% of the planned sample) were randomised to band 1 and 136 (98% of the planned sample) to band 2.
Interventions: Participants were randomised to a class of drug. The managing clinician selected the individual drug within that class, except for the clozapine arm in band 2. The new atypical drugs included risperidone, olanzapine, quetiapine and amisulpride. The conventional drugs included older drugs, including depot preparations. As in routine practice, clinicians and participants were aware of the identity of the prescribed drug, but clinicians were asked to keep their participating patient on the randomised medication for at least the first 12 weeks. If the medication needed to be changed, the clinician was asked to prescribe another drug within the same class, if possible.
Main outcome measures: The primary outcome was the Quality of Life Scale (QLS). Secondary clinical outcomes included symptoms [Positive and Negative Syndrome Scale (PANSS)], side-effects and participant satisfaction. Economic outcomes were costs of health and social care and a utility measure.
Results: Recruitment to band 1 was less than anticipated (40%) and diminished over the trial. This appeared largely due to loss of perceived clinical equipoise (clinicians progressively becoming more convinced of the superiority of new atypicals). Good follow-up rates and a higher than expected correlation between QLS score at baseline and at follow-up meant that the sample as recruited had 75% power to detect a difference in QLS score of 5 points between the two treatment arms at 52 weeks. The recruitment to band 2 was approximately as planned. Follow-up

assessments were completed at week 52 in 81% of band 1 and 87% of band 2 participants. Band 1 data showed that, on the QLS and symptom measures, those participants in the conventional arm tended towards greater improvements. This suggests that the failure to find the predicted advantage for new atypicals was not due to inadequate recruitment and statistical power in this sample. Participants reported no clear preference for either class of drug. There were no statistically significant differential outcomes for participants entering band 1 for reasons of treatment intolerance to those entering because of broadly defined treatment resistance. Net costs over the year varied widely, with a mean of £18,850 in the conventional drug group and £20,123 in the new atypical group, not a statistically significant difference. Of these costs, 2.1% and 3.8% were due to antipsychotic drug costs in the conventional and atypical group, respectively. There was a trend towards participants in the conventional drug group scoring more highly on the utility measure at 1 year. The results for band 2 showed an advantage for commencing clozapine in quality of life (QLS) at trend level ($p = 0.08$) and in symptoms (PANSS), which was statistically significant ($p = 0.01$), at 1 year. Clozapine showed approximately a 5-point advantage on PANSS total score and a trend towards having fewer total extrapyramidal side-effects. Participants reported at 12 weeks that their mental health was significantly better with clozapine than with new atypicals ($p < 0.05$). Net costs of care varied widely, but were higher than in band 1, with a mean of £33,800 in the clozapine group and £28,400 in the new atypical group. Of these costs, 4.0% and 3.3%, respectively, were due to antipsychotic drug costs. The increased costs in the clozapine group appeared to reflect the licensing requirement for inpatient admission for commencing the drug. There was a trend towards higher mean participant utility scores in the clozapine group.

Conclusions: For band 1, there is no disadvantage in terms of quality of life and symptoms, or associated costs of care, over 1 year in commencing conventional antipsychotic drugs rather than new atypical drugs. Conventional drugs were associated with non-significantly better outcomes and lower costs. Drug costs represented a small proportion of the overall costs of care (<5%). For band 2, there is a statistically significant advantage in terms of symptoms but not quality of life over 1 year in commencing clozapine rather than new atypical drugs, but with increased associated costs of care. The results suggest that conventional antipsychotic drugs, which are substantially cheaper, still have a place in the treatment of patients unresponsive to, or intolerant of, current medication. Further analyses of this data set are planned and further research is recommended into areas such as current antipsychotic treatment guidance, valid measures of utility in serious mental illness, low-dose 'conventional' treatment in first episode schizophrenia, QLS validity and determinants of QLS score in schizophrenia, and into the possible financial and other mechanisms of rewarding clinician participation in trials.

Contents

List of abbreviations

A&E	accident and emergency
AIMS	Abnormal Involuntary Movements Scale
ANCOVA	analysis of covariance
ANNSERS	Assessment of Non-Neurological Side Effects Rating Scale
BARS	Barnes Akathisia Rating Scale
BNF	British National Formulary
BPRS	Brief Psychiatric Rating Scale
CI	confidence interval
CIPFA	Chartered Institute of Public Finance and Accountancy
CPD	continuous professional development
CPMS	Clozapine Patient Monitoring Service
CRF	case-report form
CUtLASS	Cost Utility of the Latest Antipsychotics in Severe Schizophrenia
DAI	Drug Attitudes Inventory
dec.	decanoate
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
EPS	extrapyramidal side-effects
GAF	Global Assessment of Functioning
5-HT	5-hydroxytryptamine
ICC	intraclass correlation coefficient
ICD-10	International Statistical Classification of Diseases and Related Health Problems (10th revision)
ICER	incremental cost-effectiveness ratio
ICL	Imperial College London
IoP	Institute of Psychiatry
ITT	intention-to-treat
LREC	local research ethics committee
MREC	multicentre research ethics committee
NCCHTA	National Coordinating Centre for Health Technology Assessment
NICE	National Institute for Health and Clinical Excellence
NR	not reported
ns	not significant
palm.	palmitate
PANSS	Positive and Negative Syndrome Scale
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QLS	Quality of Life Scale
R&D	research and development
RCT	randomised controlled trial
SANS	Scale for the Assessment of Negative Symptoms

continued

List of abbreviations *continued*

SAPS	Scale for the Assessment of Positive Symptoms
SD	standard deviation
SE	standard error
TSC	trial support clinician
UKU	Udvalg for Kliniske Undersogelser side-effects rating scale
VA	Veterans Affairs

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Objectives

The aim of the study was to determine the clinical and cost-effectiveness of different classes of antipsychotic drug treatment in people with schizophrenia responding inadequately to, or having unacceptable side-effects from, their current medication.

Methods

Design

Two pragmatic, randomised controlled trials (RCTs) were undertaken. The first RCT (band 1) compared the class of older, inexpensive conventional drugs with the class of new atypical drugs in people with schizophrenic disorders, whose current antipsychotic drug treatment was being changed either because of inadequate clinical response or owing to side-effects. The primary hypothesis was that, in this population, the additional acquisition costs of the new atypical drugs would be offset by improvements in health-related quality of life and/or savings in the use of other health and social care services, compared with conventional drugs.

The second RCT (band 2) compared the new (non-clozapine) atypical drugs with clozapine in people whose medication was being changed because of poor clinical response to two or more antipsychotic drugs. The primary hypothesis was that, in this population, the additional acquisition costs of clozapine would be offset by improvements in health-related quality of life and/or savings in the use of other services, compared with the new atypical drugs.

Both RCTs were four-centre trials with concealed randomisation and three follow-up assessments over 1 year, blind to treatment. The trial was designed to minimise extra work for the referring clinician.

Setting

In general, the study was carried out in adult mental health settings in 14 NHS trusts in Greater Manchester, Nottingham and London.

Subjects

In total, 227 participants (40% of the planned sample) were randomised into the band 1 comparison and 136 (98% of the planned sample) were randomised into band 2. Participants were aged 18–65 years and one or more randomisations resulted from referrals by 95 general adult psychiatrists.

Interventions

Participants were randomised to a class of drug. The managing clinician selected the individual drug within that class, except for the clozapine arm in band 2. The class of new atypical drugs included risperidone, olanzapine, quetiapine and amisulpride. The class of conventional drugs included older drugs, including depot preparations. As in routine practice, clinicians and participants were aware of the identity of the prescribed drug, but clinicians were asked to try, as much as was compatible with good practice, to keep their participating patient on the randomised medication for at least the first 12 weeks. If the medication needed to be changed, the clinician was asked to prescribe another drug within the same class, if possible.

Main outcome measures

The primary outcome was the Quality of Life Scale (QLS). Secondary clinical outcomes included symptoms [Positive and Negative Syndrome Scale (PANSS)], side-effects and participant satisfaction. Economic outcomes were costs of health and social care and a utility measure.

Results

Recruitment to band 1 was less than anticipated (40%) and diminished during the course of the trial. This appeared largely to result from the loss of perceived clinical equipoise (clinicians progressively becoming more convinced of the superiority of new atypicals). Good follow-up rates and a higher than expected correlation between QLS score at baseline and at follow-up meant that the sample as recruited had 75% power to detect a difference in QLS score of 5 points between the two treatment arms at 52 weeks. The sample was recruited approximately as planned to band 2.

Follow-up assessments were completed at week 52 in 81% of band 1 and 87% of band 2 participants.

Band 1

The intention-to-treat comparison of conventional versus new atypical drugs showed that, in people with schizophrenia whose medication was being changed because of intolerance or inadequate response, there was no disadvantage in terms of quality of life or symptoms over 1 year in commencing conventional antipsychotic drugs rather than new atypical drugs. Inspection of the data showed that, on the QLS and symptom measures, those participants in the conventional arm showed a trend towards greater improvements. This suggests that the failure to find the predicted advantage for new atypicals was not due to inadequate recruitment and statistical power in this sample. Participants reported no clear preference for either class of drug. There were no statistically significant differential outcomes for participants entering band 1 for reasons of treatment intolerance to those entering because of broadly defined treatment resistance.

Net costs of care over the year varied widely, with a mean of £18,850 in the conventional drug group and £20,123 in the new atypical group, not a statistically significant difference. Of these costs, 2.1% and 3.8% were due to antipsychotic drug costs in the conventional and atypical group, respectively. There was a trend towards participants in the conventional drug group scoring more highly on the utility measure at 1 year.

Band 2

The intention-to-treat comparison of new atypicals compared with clozapine in people with more narrowly defined treatment resistance showed an advantage for commencing clozapine in quality of life (QLS) at trend level ($p = 0.08$) and in symptoms (PANSS), which was statistically significant ($p = 0.01$), at 1 year. Clozapine showed approximately a 5-point advantage on PANSS total score. Clozapine showed a trend towards having fewer total extrapyramidal side-effects. Participants reported at 12 weeks that their mental health was significantly better with clozapine than with new atypicals ($p < 0.05$).

Net costs of care varied widely, but were higher than in band 1, with a mean of £33,800 in the clozapine group and £28,400 in the new atypical group. Of these costs, 4.0% and 3.3%, respectively, were due to antipsychotic drug costs. The increased costs in the clozapine group appeared to reflect the licensing requirement for inpatient admission for commencing the drug. There was a trend towards higher mean participant utility scores in the clozapine group.

The small number of deaths in the study appeared unrelated to class of drug treatment. There were no deaths on clozapine.

Conclusions

Band 1

In people with schizophrenia whose medication is being changed because of intolerance or broadly defined treatment resistance, there is no disadvantage in terms of quality of life and symptoms, or associated costs of care, over 1 year in commencing conventional antipsychotic drugs rather than new atypical drugs. Conventional drugs were associated with non-significantly better outcomes and lower costs. A trial of a conventional drug is recommended in patients unresponsive to or intolerant of current medication. This result is not accounted for by inadequate power or by patterns of drug discontinuation. Drug costs represented a small proportion of the overall costs of care (less than 5%).

Band 2

In people with schizophrenia whose medication is being changed because of narrowly defined treatment resistance, there is a statistically significant advantage in terms of symptoms but not quality of life over 1 year in commencing clozapine rather than new atypical drugs, but with increased associated costs of care.

Implications for healthcare

This trial does not allow any statements to be made about the relative safety, efficacy and cost of new atypicals versus conventionals as first line drugs. Thus, no comment is made on National Institute for Health and Clinical Excellence (NICE) guidance as to the availability of new atypical drugs for first line treatment. The results suggest that conventionals, which are substantially cheaper, still have a place in the treatment of patients unresponsive to or intolerant of current medication.

The NICE guidance on antipsychotic drug treatment for schizophrenia recommends the wider use of clozapine in treatment-resistant schizophrenia in the NHS. The results from this non-commercially sponsored trial in clinician-defined treatment resistance in the NHS show

some advantage to clozapine over new atypical drugs and provide support to this aspect of NICE guidance, but with increased service costs. These increased costs associated with clozapine will diminish with the new licensing for outpatient initiation.

Further analysis

Further planned analyses of this data set include an examination of the effects of injectables, the impact and determinants of polypharmacy, and an examination of QLS validity and determinants of QLS score in schizophrenia.

Recommendations for research

The following areas are recommended for future research:

- a randomised trial of current antipsychotic treatment guidance using atypical versus conventional drugs in the context of careful management of schizophrenia
- the development of valid measures of utility in serious mental illness
- a randomised trial of low-dose 'conventional' treatment such as sulpiride versus a new atypical in first episode schizophrenia
- further examination of QLS validity and determinants of QLS score in schizophrenia
- an investigation into the possible financial and other mechanisms of rewarding clinician participation in trials.

Chapter 1
Introduction

Schizophrenia

Schizophrenia is a psychotic disorder of uncertain aetiology that affects about 0.5% of the population and usually has its onset in early adult life. The mainstay of treatment is antipsychotic drugs.

Symptoms and diagnostic criteria

Schizophrenia is a syndrome, a disorder for which there is no objective test or pathology, but which is identified by a characteristic cluster of symptoms that last for a certain time. Since 1994, the two main classification systems in use worldwide have been the Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM-IV), developed by the American Psychiatric Association,[1] and the International Statistical Classification of Diseases and Related Health Problems (10th revision) (ICD-10), developed by the WHO and mainly used outside North America. In their definitions of schizophrenia, the two systems are similar. Both diagnose schizophrenia with inter-rater reliabilities of at least 0.8, which compares well with medical disorders.

A large number of studies have found that the symptoms of schizophrenia usually segregate into three semi-independent symptom complexes: positive symptoms, negative symptoms and disorganisation symptoms. Positive symptoms comprise delusions and hallucinations, usually auditory. The presence and severity of negative symptoms are more critical to the prognosis than the positive symptom complex; negative symptoms include blunted, abnormally unresponsive mood, reduced willpower, reduced amount of spontaneous speech and loss of self-care skills. Negative symptoms can become progressively more severe and often persist to a degree even when positive symptoms have improved. It is important to distinguish between primary negative symptoms, which are indisputably part of the illness, and secondary negative symptoms. The latter can be similar in quality but result from a superimposed anxious or depressed mood, an impoverished, understimulating environment or the side-effects of antipsychotic medication. The third symptom complex, disorganised behaviour, comprises disrupted speech and the socially inappropriate or disorganised behaviour frequently exhibited by patients with schizophrenia.

Epidemiology

The incidence and prevalence of schizophrenia depends on whether ICD-10 or DSM-IV criteria are used. Because of the 6-month, rather than 1-month, criterion in DSM, the incidence and prevalence will be lower with DSM-IV than with ICD-10. Large, community-based surveys of geographically defined areas give prevalence estimates of between 0.2 and 0.7%. Incidence studies of epidemiological samples show that there will be about two new cases of ICD schizophrenia, or about one new case of DSM schizophrenia, per 10,000 population each year. The average GP will see one new case per four to five years and have ten to 20 established cases registered.

Schizophrenia exists in all cultures in all countries. It has long been known that rates of schizophrenia are higher in urban than in rural areas. Early surveys seemed to show that this was due to the drift of people into urban areas after the illness started, rather than to higher rates of new cases in cities. However, recent large studies have confirmed that new cases arise more commonly in cities, with the rates being proportional to the degree of urbanisation. This appears to be an unexpectedly large effect. The relative risk for large-city dwellers compared with rural residents is only two- to three-fold but, because much of the population lives in cities, the proportion of schizophrenia that can be explained on the basis of this factor is about one-third.[2] The factors associated with city life that contribute to the increased rate of schizophrenia remain to be clarified.[3]

The incidence of schizophrenia is roughly the same in men and women. Men, however, are slightly more likely to develop enduring negative symptoms than women, who have greater representation in the good prognosis group. The peak age of onset in men is 21–26 years, whereas in women it is 25–32 years.

Course and outcome

Summarising the best long-term studies available, there is a consensus that 15–20% of patients will

make a complete recovery without relapse. At the other extreme, about 15% will effectively never recover from their first episode, remaining symptomatic and needing long-term, high levels of social and medical input. Between these two poles, most patients will recover at least partly from their first episode, but will not return to their premorbid level of functioning, or will suffer future relapses, or both. Although remission from the first episode is not difficult to achieve, 50% of cases will relapse over the next 2 years and 80% over the next 5 years.[4] With each relapse, about one in six will not subsequently achieve remission.[5] Suicide occurs in 5% of patients and is difficult to predict. Young men in the first 3 years of their illness are more at risk.

Aetiology

It has long been known that there is a genetic predisposition to schizophrenia. Although genetic factors may explain over 60% of the variance, the pattern is of a polygenic or oligogenic disorder with environmental factors acting on the penetrance of several susceptibility genes.[6] The neurodevelopmental hypothesis of schizophrenia in general suggests that early neurological risk factors *in utero* and in infancy can act as risk factors whose expression is delayed until the nervous system has matured sufficiently to mediate their effects. Longitudinal studies that follow up large birth cohorts have shown that the 1–2% of the sample who go on to develop adult schizophrenia show slight delays in motor, speech and intellectual milestones, compared with the rest of the cohort.[7] These differences are subtle, such as walking delayed by 1–2 months. Certain problems, such as developmental receptive language disorders, are particularly linked to later schizophrenia. There is emerging evidence again for the role of non-biological risk factors in schizophrenia. Street drug use has long been known to be an important trigger of relapse, but was thought not to play a truly causal role in onset. New research suggests that cannabis use in adolescence increases the risk of schizophrenia at least two- to three-fold. Psychosocial explanations for the high rates of psychosis seen in black Caribbeans in the UK and other European countries appear likely.

The rationale for drug treatment: the dopamine hypothesis

Neurochemical abnormalities are the link between underlying aetiological factors, either genetic or environmental, and the overt expression of signs and symptoms of the illness. In the early 1960s, Arvid Carlsson posited the dopamine hypothesis of schizophrenia, which stated that schizophrenia was due to an excess of dopaminergic activity, either an excess of dopamine release and/or hypersensitivity of dopamine receptors. The dopamine hypothesis was refined with subsequent research. In the late 1980s, new molecular biological techniques found five dopamine receptor subtypes that differ both functionally and in their pattern of target neuron/brain region distribution. Dopamine D_2 receptor occupancy most closely correlates with the clinical potency of individual antipsychotic drugs. Studies using position emission tomography (PET) brain imaging have documented increased dopamine release in patients with schizophrenia compared with normal controls, and suggest that the extent of dopamine release is associated with the severity of positive psychotic symptoms.

Although the dopamine hypothesis remains the most salient hypothesis, there is still the issue that a significant proportion of patients with schizophrenia do not adequately respond to dopamine antagonists, which suggests that other neurotransmitters are involved in the pathophysiology of schizophrenia. The ratio of 5-hydroxytryptamine-2a (5-HT_{2a}) to D_2 blockade has been proposed as a critical distinction between conventional and new-generation antipsychotic drugs. The affinity of clozapine for the 5-HT_{2a} receptor exceeds its affinity for D_2 receptors by 20-fold, although some conventional antipsychotics, such as chlorpromazine, also have greater affinity for the 5-HT_{2a} receptor than the D_2 receptor.

Management of schizophrenia in the NHS: service models

Multidisciplinary teams are the core of community-based services for people with schizophrenia. These are effective when a case management model is used, so that one care coordinator organises the patient's full-care package. Different models of care management exist, but systematic review has shown that it is most effective when combined with assertive community treatment. This involves proactive community follow-up and delivery of as much care as possible in the patients' own settings. Getting patients back to work is important. Systematic review has shown that vocational training models, where the patient is put into a real job and supported actively, outperform traditional sheltered employment approaches. Specialist rehabilitation services aim to reduce the enduring deficits in chronic schizophrenia and improve

day-to-day social functioning. Recent mental health policy in England specifies that the delivery of care to people with psychosis should include early intervention services, assertive outreach services and home treatment teams.

First episodes of schizophrenia often go undetected and untreated for long periods. Outcome from the first episode is good in 85% of cases, with remission usually achieved within 3 months. Patients in the first episode are responsive to relatively low doses of antipsychotic drugs, and treatment should be started with the equivalent of 2 mg haloperidol daily or less. Similarly, first episode patients are sensitive to the side-effects of drugs and the new-generation antipsychotic drugs are probably to be preferred.

Psychosocial interventions have been a key part of the management of schizophrenia since the 1970s. At that time, the impact of institutionalisation on people with schizophrenia came to be realised and community-based services have increasingly developed since. More recently, specific psychological techniques aimed at improving aspects of psychotic illness have also been evaluated. Family-based interventions aimed at enhancing coping strategies with education about the illness, delivered over 6–9 months, have been shown to improve prognosis. Recent trials have shown that cognitive behaviour therapy (CBT) when given in addition to routine care and drug treatment can be effective for persistent psychotic symptoms in chronic schizophrenia.[8] Psychological treatments have not been shown to be effective in the absence of drug treatments. Their provision on the NHS is scarce.

Antipsychotic drug treatment

Efficacy and effectiveness

Specific pharmacological treatment of schizophrenia began in the early 1950s with the discovery that chlorpromazine had antipsychotic properties. The optimal maintenance treatment of schizophrenia involves the integration of physical, psychological and social care. Nevertheless, since their introduction almost 50 years ago, the conventional or typical antipsychotic drugs have formed the mainstay of both acute and long-term treatment for schizophrenia, and have been invariably used as first line therapy. The benefits of antipsychotic medication in treating acute psychotic episodes and reducing the risk of relapse in the community have been widely accepted and documented.[9,10] There is little doubt that, at least within the first 5–10 years of drug treatment, people with schizophrenia will be up to three times more likely to relapse in the subsequent year or so if their antipsychotic medication is stopped, with earlier relapse following abrupt rather than gradual withdrawal. Nevertheless, despite the administration of antipsychotic maintenance treatment, following discharge from hospital for an acute psychotic episode, between 30 and 60% of patients would be expected to relapse in the first year and between 50 and 80% in the second.[11–13] Even after hospitalisation for the first episode of schizophrenia, 80% will have a second episode within 5 years.[14]

These high incidence figures for relapse may be partly explained by the relatively high proportion of patients failing to adhere to their treatment regimen. The proportion of patients failing to adhere to their prescribed medication may be as high as 50% during the first year of treatment,[15] rising to 70% within 2 years of treatment initiation.

Limitations of conventional antipsychotics

The conventional antipsychotic drugs have several critical limitations. First, around 20–25% of people with schizophrenia treated with the conventional antipsychotics fail to show a satisfactory response, manifesting treatment-resistant or treatment-refractory schizophrenia. Second, the drugs have a limited effect on the negative symptoms of the condition. Third, these agents are associated with a wide range of unwanted effects.[16,17] These side-effects represent part of the burden on patients administered antipsychotic medication and adversely influence treatment adherence. The conventional drugs show differences in their side-effect profiles, for example, in respect of their liability for sedation and acute extrapyramidal side-effects (EPS). When weighing the risks and benefits of a particular antipsychotic for a particular individual, the side-effect profile of the drug will be a key consideration for both the patient and the prescribing clinician.

The newer, 'atypical' antipsychotics (including clozapine, risperidone, sertindole, olanzapine, quetiapine, ziprasidone, zotepine and amisulpride) are a heterogeneous group of drugs in respect of their pharmacology, side-effect profiles and efficacy, but share several characteristics. They do not produce catalepsy in animals. In patients with psychotic illness, clinical trial evidence suggests that they have a lower propensity than conventional antipsychotics to induce acute EPS such as parkinsonism, acute

akathisia and dystonia.[18] This reduced risk of EPS is a major advance, as acute EPS have undesirable motor and psychological manifestations, and often require treatment with antiparkinsonian/anticholinergic agents, which have their own side-effects and hazards. However, as discussed below, the choice of comparator antipsychotic and dose regimen means that the trial evidence supporting lower rates of side-effects is uncertain.

Claims that these newer antipsychotics also have advantages over the conventional drugs in relation to a beneficial effect on negative symptoms, improvement in cognitive function and a reduction in the risk of relapse are addressed below. Similarly, the evidence that some of the newer drugs, principally clozapine, can be effective in people whose schizophrenic illness has proved refractory to standard treatment will be reviewed.

Therapeutic efficacy

Careful reviews and meta-analyses of clinical trial data involving the atypical antipsychotic drugs testify to an equivalent efficacy with conventional antipsychotics and a lower liability for EPS.[19,20] Nevertheless, certain critical clinical issues remain uncertain. Improved tolerability with the newer drugs has been widely reported in terms of side-effects and subjective experience.[21–23] While it is reasonable to speculate that better subjective tolerability might translate into better compliance in the long term, as yet there are no convincing data to support such a view.

Geddes and colleagues[24] conducted a systematic overview and meta-regression analysis of 52 randomised trials comparing atypical antipsychotics with conventional drugs. These authors concluded that the findings of superior efficacy and tolerability with the atypical drugs were partly related to the dosage of the conventional comparator drug. Such advantages were not confirmed for those studies in which the comparison dose of haloperidol was 12 mg a day or less (or equivalent), although the lower liability for EPS was still evident. However, a variety of criticisms has been levelled at this study and its conclusions.[25–31]

Such studies tested clinical efficacy rather than effectiveness. The definition of clinical effectiveness provided by the National Institute for Health and Clinical Excellence (NICE) is "the actual or projected benefits to patients in whom the technology is used". The majority of efficacy studies of the atypical antipsychotics that have been reported relate to symptom improvement in short-term clinical trials, of less than 12 weeks in duration. However, schizophrenia is often both a chronic and recurrent disorder and hence information on efficacy and safety in long-term maintenance treatment is important. Thus far, there are only a few studies assessing longer term outcome in terms of maintaining early symptom improvement, relapse prevention, tolerability, medication compliance and quality of life. A recent systematic review suggests that the conclusions that could be drawn about the relative effectiveness of the newer antipsychotics were limited because of problems with the validity of the trials in terms of inclusion and exclusion criteria, dose used, sample size and duration of trials, outcome measures used and methods of reporting symptoms.[32] In addition, the majority of trials compare the newer atypicals to haloperidol, a drug not widely used in Europe or the UK. The side-effect profile of haloperidol, particularly used at high doses, may not be representative of that found with other typical antipsychotics.[33]

The findings of pragmatic studies of clinical effectiveness are required. These need to address some of the limitations of the clinical efficacy studies. First, there may be difficulties in interpreting the findings in terms of their clinical relevance. The outcomes are commonly mean change scores on psychiatric rating scales, such as the Brief Psychiatric Rating Scale (BPRS), the Scales for the Assessment of Positive and Negative Symptoms (SAPS, SANS), and the Positive and Negative Syndrome Scale (PANSS), while data on areas such as level of social functioning, morbidity, employment and quality of life tend not to be so commonly reported. Second, these studies are usually of short duration; schizophrenia is a lifelong disease, but drug trials with the atypical antipsychotics rarely last for more than 8 weeks. However, more trials of longer duration have been appearing recently.[34] Third, there is commonly a high dropout rate in these studies, which reduces the validity of any findings.[34] For example, in the systematic review of olanzapine by Duggan and colleagues,[35] involving 20 trials, 61% of the patients assigned to olanzapine and 73% assigned to high-dose haloperidol had dropped out by 6 weeks.

Treatment-resistant schizophrenia

Definition and prevalence

There is a general consensus in the literature that a substantial minority of patients, between one-

fifth and one-third, will derive little benefit from conventional antipsychotic drug therapy, although a smaller proportion would seem to be completely resistant,[36–38] Studies of first episode schizophrenia suggest that, even at an early stage of the illness, a small proportion of patients will show a lack of response, commonly leading to a protracted hospital admission.[38,39]

Historically, the concept of non-response to antipsychotic medication was ill defined and largely synonymous with persistent or frequent hospitalisation.[37] The use of a criterion threshold reduction in the score on a standardised psychopathology rating scale (such as 20% or 50% reduction on the BPRS total score) has allowed for more reproducible and consistent definitions of poor response to antipsychotic medication. However, such a criterion is somewhat arbitrary and may fail to take due account of the impact of symptomatology on overall functioning. Further, depending on the nature of the items that account for the reduction in scale score, a particular percentage reduction may not necessarily represent a satisfactory or substantial clinical response. This problem may be partly obviated by setting down a priori a specific level of symptomatology as the guideline for response. For example, Kane and colleagues[40] and Schulz and colleagues[41] chose a particular BPRS total score as representing a mild level of symptoms.

From a clinical perspective, treatment resistance is seen as the continuing presence of disability, encompassing vocational, social and cognitive domains, despite trials of medication that have been adequate in terms of dose, duration and compliance. This multidimensional view of treatment resistance recognises the complexity of the interrelationships between positive and negative symptomatology, cognitive deficits and behavioural disturbance[36] and their various influences on treatment outcome.[42] To assess these broader domains of the illness, some recent studies of treatment response have added clinical outcome measures such as quality of life and independent living skills.

Any expansion of the definition of treatment resistance beyond symptom scores in this way would lead to a greater proportion of patients being classified as treatment resistant.[43] However, most recent research reports on the prevalence and incidence of treatment refractory schizophrenia have used relatively stringent research criteria.[40] These figures may be considered as underestimates, in that many of the patients who would be judged clinically as showing an incomplete and unsatisfactory response to antipsychotics will not have been included.[44]

The findings in the literature thus far are compatible with the view that treatment resistance in people with schizophrenia cannot be attributed to acquired disabilities or institutionalism.[45] Rather, it appears to be a manifestation of an inherent trait that seems to be relatively consistent in individual patients over time. Further, rather than categorising patients as either good or poor responders it may be more appropriate to consider antipsychotic response as a continuum,[36] with the majority of patients showing a suboptimal response in that they continue to exhibit symptoms and functional disability.[36,44] The emergence of pharmacotherapeutic and psychological interventions that are effective treatment options in severely ill patients should be a spur to generate a valid and clinically meaningful classification of treatment resistance.

High-dose conventional antipsychotics

Controlled studies comparing very high doses of conventional antipsychotics with standard dosage regimens in treatment-resistant patients have all failed to show a statistically significant advantage for the megadose regimen.[46,47] However, there are methodological problems with these studies including small sample sizes and the lack of a consistent, valid definition of treatment resistance.[48] The latter problem is highlighted by the observation that in several of the studies a proportion of the patients on standard dose showed improvement, suggesting that their classification as treatment resistant was premature.

Combined antipsychotics

In clinical practice, the lack of a satisfactory response to a single antipsychotic often prompts the addition of another. For example, a recent multicentre audit of prescribing of antipsychotic medication for inpatients in 47 mental health services in the UK,[49,50] involving 3132 inpatients, found that 48% were receiving more than one antipsychotic drug. In the majority of cases the reason given for this polypharmacy was that a single antipsychotic had not been effective.

The particular combination of clozapine and a conventional antipsychotic has commonly been reported. There have been reports that conventional antipsychotics are used in around one-third of patients receiving clozapine in some European countries.[51,52] For example, McCarthy

and Terkelsen[53] reported that a conventional antipsychotic was added to clozapine in 30–35% of cases in Denmark. This is despite the lack of convincing research evidence to justify the addition of another antipsychotic in patients with only a partial response to clozapine monotherapy. Relevant published data are limited to a few recent case reports, case series and small studies. Adjunctive antipsychotics tested include pimozide,[54] sulpiride,[55] olanzapine,[56] loxapine[57] and amisulpride,[58] with reports of further clinical benefit. While the addition of risperidone in a couple of published cases failed to produce any improvement,[59,60] the majority of reports involving this drug have also been positive,[53,61–64] For example, in a 4-week, open study, Henderson and Goff[62] assessed the safety and efficacy of risperidone as an adjunct in 12 patients with schizophrenia who continued to show positive and negative symptoms despite treatment with clozapine. Ten of the 12 patients had a 20% or greater reduction in their total BPRS scores, and the investigators considered that controlled trials of this adjunctive therapy were warranted.

Yuzda[65] reviewed the evidence for efficacy with combined antipsychotics. She identified one randomised controlled trial (RCT),[66] two open prospective trials,[57,62] one retrospective review[54] and four anecdotal reports.[56,67] The bulk of the published data relate to combining conventional or atypical antipsychotics with clozapine. The RCT[66] involved 28 patients with a partial or unsatisfactory response to clozapine who were randomly allocated to clozapine plus sulpiride (600 mg per day) or clozapine plus placebo for 10 weeks. BPRS total score reductions were significantly greater ($p < 0.05$) in the sulpiride group, and there was a trend for younger patients to have greater than 20% BPRS reduction. Yuzda[65] identified several limitations of the study, including the small sample size and short duration, that the treatment groups were not matched for previous hospitalisation and the exclusion of complete responders to clozapine. Overall, Yuzda[65] concluded that the addition of a second antipsychotic to clozapine was an appropriate intervention, and the strongest evidence related to sulpiride. Otherwise, given the paucity of the published data, the addition of a conventional antipsychotic to an atypical could not be recommended, particularly as there was potentially an increased risk of adverse effects and non-compliance. In relation to the former, Mujica and Weiden[68] reported the development of neuroleptic malignant syndrome in a patient after haloperidol was added to their atypical antipsychotic treatment.

Chong and Remington[69] also reviewed adjunctive antipsychotics with clozapine. They considered that a limitation common to all the published studies was the lack of information regarding the previous exposure of study patients to the adjunctive antipsychotic. They argued that without such data, it remained an open question whether the responses observed could be attributed to the combination or simply to the second antipsychotic alone. Nevertheless, they concluded more positively that despite the lack of controlled data, such combinations were safe and might be efficacious for those patients for whom clozapine had produced a less than optimal improvement. Raskin and colleagues[63] questioned the safety of the combination of clozapine and risperidone, pointing to isolated references suggesting adverse reactions such as agranulocytosis[70] and marked elevation of clozapine blood levels.[60]

Clozapine

The pivotal study of clozapine in treatment-refractory schizophrenia was conducted by Kane and colleagues.[40] This was a double-blind, multicentre comparison of clozapine and chlorpromazine in 268 schizophrenic patients meeting stringent criteria for treatment resistance. These included the failure to respond to adequate trials with at least three antipsychotic drugs and a prospective single-blind trial of haloperidol, as well as no period of good functioning within the previous 5 years. By the end of the 6-week treatment period, clozapine treatment was associated with significantly greater improvement in both positive and negative symptoms. Using prospective, clinically relevant criteria of improvement, 30% of the patients receiving clozapine could be classified as responders after 6 weeks compared with only 4% of the chlorpromazine group. Subsequently, double-blind, controlled studies in patients with treatment-resistant schizophrenia have confirmed the benefit with clozapine.[71–73] There is some evidence that relatively low doses may be sufficient to achieve a response in patients showing signs of resistance to conventional antipsychotic treatment early in their illness.[74] However, Grassi and colleagues[75] raised the issue of possible loss of clinical efficacy with repeated trials of clozapine.

To evaluate the general effectiveness of clozapine in schizophrenia, Wahlbeck and colleagues[76] conducted a systematic review and meta-analysis of 31 randomised, controlled clozapine trials, involving over 2500 participants (average age 38 years), almost three-quarters of whom were men. Such demographic and clinical

characteristics are typical of those recruited into clinical trials with the new drugs, and this selection bias has been considered a limitation on the generalisability of the findings. Twenty-six of the studies were less than 13 weeks in duration, with the remainder being longer term (6 months to 2 years in length). Only seven of the studies were limited to patients with treatment-resistant schizophrenia. In comparison with conventional drugs, clinical improvement was seen more frequently in those taking clozapine both in the short and the long term. In addition, in the relatively short term, participants on clozapine had fewer relapses than those receiving conventional antipsychotic drugs. Wahlbeck and colleagues[76] noted that this "may be true" for long-term treatment as well. Symptom assessment scales consistently showed a greater reduction of symptoms in clozapine-treated patients. The authors noted the relative absence of functional and social outcomes, and called for an internationally recognised set of standard outcomes, including pragmatic assessments of functioning.

A further meta-analysis by Chakos and colleagues[77] examined the efficacy and tolerability of clozapine in treatment-resistant schizophrenia. They reviewed 12 controlled studies involving over 1900 patients. They concluded that clozapine is superior to conventional antipsychotics in terms of both efficacy and safety, although the magnitude of the treatment effect was not consistently robust. For individuals with treatment-resistant schizophrenia treated with clozapine, a 20–30% reduction in total psychopathology scores may be seen in less than half,[77,78] and a substantial proportion, perhaps 30%, have an inadequate response. However, such figures partly reflect the results of relatively short-term studies, and recent evidence from several longer term studies suggests an advantage for continued treatment with clozapine.[79]

There are other data adding to our understanding of the nature of the potential risks and benefits with clozapine. The drug may have a specific, positive effect on hostility and aggression in schizophrenia, and symptoms of disorganisation and affective symptoms in patients with schizoaffective disorder.[80,81] In addition, there is evidence that clozapine, along with certain other atypical antipsychotics, is significantly more effective than conventional antipsychotics in improving cognitive function,[82–84] one of the most consistent findings being that clozapine improves verbal fluency and attention.

The impact of clozapine on suicide has not previously been formally assessed. However, evidence from retrospective analyses of cohorts treated with clozapine and projected suicide mortality rates suggests that patients receiving this drug may have a lower rate of suicide than expected,[85–87] although one study designed to assess the impact of clozapine on suicide failed to demonstrate any positive effect. The mechanism for any such effect remains uncertain, although it has been postulated that improvement in symptoms, including depressive features, may be relevant, as might reduced extrapyramidal symptoms, better medication compliance, improved cognitive function, and greater involvement and support from the clinical team, partly related to regular blood testing.[88] A recent multicentre, randomised, international 2-year study compared the risk of suicidal behaviour in 980 patients with schizophrenia or schizoaffective disorder receiving either clozapine or olanzapine.[89] More than a quarter of the sample (26.8%) had been unresponsive to previous treatment. Clozapine was found to be significantly superior to olanzapine as a treatment for suicidality, a phenomenon assessed by variables such as suicidal behaviour, attempted suicide and requiring concomitant treatment with antidepressants.

The Cochrane systematic review comparing clozapine with new atypical medication[90] concluded that "Trials of sufficient power, with longer duration, measuring clinically important outcomes, are needed to assess the true comparative clinical effectiveness, tolerability and cost effectiveness of newer drugs in relation to clozapine".

Other atypical antipsychotic drugs

Although the efficacy of clozapine in people with rigorously treatment-refractory schizophrenia has been established, the evidence for other atypical antipsychotics is unconvincing. However, there are data suggesting that particular atypicals may have limited efficacy in more broadly defined, suboptimal responders to conventional antipsychotics.

Risperidone

Controlled trials[76,91–93] have generally failed to confirm the promise of benefit in treatment-resistant schizophrenia seen in early, uncontrolled studies. For example, Wirshing and colleagues[94] compared risperidone and haloperidol in a sample of 67 subjects with treatment-resistant schizophrenia. Over the first 4 weeks, risperidone

showed some superior efficacy, but this was not maintained over the subsequent 4 weeks of blind treatment, during which time the dosage regimens were flexible. In a controlled study by Bondolfi and colleagues,[92] 86 inpatients with chronic schizophrenia were assigned to treatment with either risperidone or clozapine for 8 weeks, in flexible dosage regimens. By the end of the study, 67% of risperidone-treated patients and 65% of those receiving clozapine were considered to be clinical responders according to a priori criteria. However, the patient sample comprised a proportion who were intolerant of, rather than unresponsive to, conventional antipsychotics, and who therefore might be expected to show a better response to an atypical drug. Bouchard and colleagues[95] examined the clinical effectiveness of risperidone over 12 months in a naturalistic study of 184 patients with chronic schizophrenia whose response to conventional antipsychotics was judged to have been 'suboptimal'. Patients were randomly assigned to be switched to risperidone or receive a conventional drug. One interpretation of the findings is that negative symptoms and general psychopathology may tend to show an early improvement with risperidone treatment, whereas the maximum improvement in positive symptoms occurs later.

Azorin and colleagues[91] noted the methodological problems with such comparative studies of risperidone and clozapine, such as small sample sizes and the use of suboptimal clozapine doses. They sought to remedy such deficiencies in their own prospective, double-blind study. They wanted to compare the two drugs in a patient sample that would be more representative of those treated with clozapine in clinical practice, and therefore applied criteria for treatment resistance that were less rigorous than those used by Kane and co-workers.[40] Over the 12-week study period, the proportion of responders (the criterion being a 20% or greater decrease in BPRS score) was 86% for clozapine patients and 70% for those treated with risperidone. These relatively high response rates may be partly explained by the broader criteria for treatment resistance that were used.

Overall, the published findings do not provide convincing evidence of equivalence between risperidone and clozapine in treatment-resistant schizophrenia.[96]

Olanzapine

Early clinical reports suggested a possible role for high-dose olanzapine in the management of treatment-resistant schizophrenia,[97–99] but the evidence from controlled studies[100,101] has not been entirely consistent. The suggestion that moderate to high doses of olanzapine (up to 40 mg per day) might be superior to standard doses for patients with treatment-resistant schizophrenia[102] remains to be tested.

Using a study design almost identical to that of Kane and colleagues,[40] Conley and co-workers[100] compared olanzapine 25 mg per day with a combination of chlorpromazine 1200 mg per day and benztropine mesylate 4 mg per day over 6 weeks. The inclusion criteria differed from those applied by Kane[40] only in the stipulation that patients should have failed to respond to two, rather than three, adequate trials of antipsychotic medication. Olanzapine showed a better side-effect profile, but no difference in efficacy between the two drug regimens emerged. Applying the response criterion for significant clinical improvement response (20% or greater improvement in total BPRS score), neither drug was associated with major symptomatic improvement. Conley and colleagues[103] included 27 of the patients who had received olanzapine but failed to fulfil the response criterion in a subsequent 8-week, open trial of clozapine (mean dose 693 mg per day). Eleven (41%) patients responded to clozapine, suggesting that a lack of response to olanzapine does not predict treatment failure with clozapine.

More recent studies have generated more positive data on the efficacy of olanzapine in treatment refractory schizophrenia. Lindenmayer and colleagues[104] reported comparable efficacy between clozapine and olanzapine in a double-blind comparative study of olanzapine, clozapine, risperidone and haloperidol in treatment-refractory schizophrenia. Tollefson and colleagues[101] conducted a 'non-inferiority' or therapeutic equivalence study comparing olanzapine (15–25 mg daily) and clozapine (200–600 mg daily) over 18 weeks, in 180 patients with schizophrenia who had failed to respond to adequate trials of at least two oral antipsychotics of different chemical classes and scored a minimum of 45 on the BPRS. Olanzapine was better tolerated, but using the response criterion of Kane and colleagues,[40] the proportion of responders in the olanzapine (38%) and clozapine (34.5%) groups was similar, suggesting comparable efficacy for the two drugs. The investigators explained the apparent discrepancy between their findings and those of Conley and colleagues[100] partly on the basis that the latter patient sample might have been especially refractory.

Quetiapine

The potential benefits offered to patients with treatment-refractory schizophrenia by quetiapine remain uncertain. The evidence from case reports[105–107] and published studies comparing quetiapine and haloperidol in people with schizophrenia showing only a partial response to standard treatment[108,109] suggests that the drug warrants further controlled trials in this area.

Relapse prevention

Given that the majority of clinical trials with atypicals thus far have been of relatively short duration, there is a lack of evidence regarding their efficacy in the prevention of relapse in the long term. Leucht and colleagues[34] carried out a meta-analysis of suitable studies to assess the potential of the new-generation antipsychotic drugs to decrease relapse rates in patients with schizophrenia. Given the very small number of trials identified for individual drugs, the atypicals were analysed as a group in an explorative manner. Analysis of six placebo comparisons (involving just over 1000 patients in total) demonstrated that these drugs are effective for relapse prevention. Ten studies (with a total of over 2000 patients) provided comparative data on relapse/treatment failure for the atypical and conventional antipsychotics (the latter being exclusively haloperidol in the trials included). Analysis of the findings revealed a modest but statistically significant reduction in relapse rates and overall treatment failure with the new drugs. The information provided in the studies did not allow any determination of whether this advantage was partly mediated by improved adherence to treatment. As mentioned above, better adherence might be expected with the greater tolerability claimed for these newer drugs, but in the meta-analysis no significant superiority was found for these agents in terms of fewer dropouts due to adverse events. Thus, the available data suggested a potential for the new drugs to reduce relapse rates. Such a conclusion is tempered by the methodological limitations of the studies, related to the choice of a suitable conventional drug comparator, appropriate dosage regimens, the application of clinically relevant relapse criteria, monitoring of adherence and the relatively high dropout rates.

Adverse effects

The side-effect profiles of the atypical antipsychotics overlap with the range of side-effects expected with conventional antipsychotic drugs, with problems such as sedation, dysphoria, sexual dysfunction, weight gain, adverse endocrine effects, autonomic and cardiovascular effects, anticholinergic effects and seizures.[110] However, a lower risk of acute EPS compared with conventional antipsychotics (principally haloperidol) has been consistently demonstrated in comparative clinical trials for drugs such as clozapine,[111,112] remoxipride,[113,114] risperidone,[115,119] sertindole,[120] olanzapine[121] and amisulpride.[122]

The safety profiles of the atypical drugs differ in respect of non-neurological side-effects. For example, clozapine may produce more fatigue, hypersalivation, nausea and orthostatic hypotension[90] whereas dizziness, dry mouth and weight gain may be more common with olanzapine.[35] However, while the relative liability of the new drugs for various side-effects is emerging for some problems, such as weight gain,[123–125] only preliminary comparative data are available for problems such as sexual dysfunction, diabetes mellitus, daytime sleepiness, and cardiovascular and gastrointestinal effects. For most side-effects, the relative liability of each of the atypical drugs, and the extent to which they are dose related, has not been systematically established. One key difference is the agranulocytosis risk with clozapine, a problem that seems to be largely absent with the other atypicals, which do not seem to show any difference from conventional drugs in this regard.

The economics of schizophrenia

The average cost per person of health and social care for people with schizophrenia has been estimated at between £2140 and £36,000 per year.[126,127] In 1992/93, the direct cost of health and social care for people with schizophrenia was approximately £810 million in England, or 3% of total health service spending. Of this, £32 million was for pharmaceutical expenditure, mainly for antipsychotic drugs.[128] Depending on dosage, the costs of clozapine are approximately £2500 per person per year, and the costs of the other newer atypicals such as amisulpride, risperidone, olanzapine and quetiapine are approximately £1400 per person per year. The cost of older, conventional antipsychotics such as haloperidol or chlorpromazine is significantly lower, at less than £100 per person per year.

It has been suggested that the new atypical antipsychotics and clozapine may lead to savings in the use of health and social care through improved symptom control, reduced side effects

and better adherence with drug therapy.[33] Several economic evaluations have been published. These have used a range of study designs such as controlled and uncontrolled cohorts[117,126,129–142] and controlled trials.[73,143–152] A large number of modelling studies has been published, based on data from a variety of sources. For the majority of these modelling studies it was not possible to verify the source or quality of the clinical or economic data. Recent models tend to be based on observed data from systematic reviews, clinical trials or large observational databases.[32,33,153–160] However, most of the studies have been limited in scale and methodology. Particular issues of concern are first, that with the exception of RCTs,[73,143–147,149,151,152] most of the studies do not use clear and adequate methods to control bias. Second, for most of the studies the sources of data and methods of data collection were potentially weak. Third, economic outcomes in terms of measures that combined the impact of symptoms and side-effects or value-based measures of utility were not included. Finally, the type and dose regimen of the comparator drug were either not typical of routine practice or outside the recommended range for routine practice. In addition, the patient populations tend to be people with a long duration of disease and severe illness. It is not clear that the data apply to a population with early disease.

Thus, the results need to be treated with caution when extrapolating to alternative time-frames, settings and patient populations. It has been suggested that the quantity and quality of clinical and economic evidence are not sufficient to enable clinical decision-makers to make treatment choices between the drugs with any certainty.[32,33,128,161] A recent economic evaluation was conducted as part of a systematic review. The study used a decision-analytic model and probabilistic sensitivity analysis to synthesise data from several sources. The probability of events was estimated from a comprehensive systematic review of the clinical literature. The use and costs of services were estimated from national statistics and databases, using conservative estimates of resource use where possible. Outcomes were converted to quality-adjusted life-years (QALYs) using data from a review of the economic and outcomes literature.[32]

The available economic evidence suggests that clozapine is associated with improved outcomes compared with conventional antipsychotics for people with severe treatment resistance and/or intolerance to conventional antipsychotics. Some studies suggest that clozapine is also associated with lower costs, primarily due to reductions in inpatient care.[126,131,151,162,163] Other economic evaluations found that clozapine was associated with a relatively small net cost, but was cost-effective on one or more measures of outcome.[33,145]

The systematic review and model by Bagnall and colleagues found that clozapine was associated with higher costs and similar or no difference in quality-adjusted outcomes compared with chlorpromazine, but was relatively cost-effective compared with haloperidol and other atypical antipsychotics.[32] In this study, clozapine was found to have a cost per QALY gained of less than £10,000 compared with ziprasidone, risperidone and amisulpride, a cost per QALY gained of less than £20,000 compared with olanzapine, and a cost per QALY gained of less than £40,000 when compared with zotepine.

Overall, the economic evidence suggests that the new atypical antipsychotics are associated with improved outcomes compared with conventional antipsychotics and with cost savings or small increases in costs. Nearly all the evaluations found that the new atypical antipsychotics were cost-effective.[32,117,130–133,135,137,139,141,146–148,150,152–155,157–160] The majority of comparisons of new atypical antipsychotics and conventional drugs considered risperidone or olanzapine. The systematic review and model by Bagnall and colleagues[32] considered a number of other new drugs in addition to these. The overall conclusion was that the following drugs were likely to be cost-effective compared with haloperidol or chlorpromazine, with a cost per QALY gained of less than £50,000: amisulpride, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine.

In summary, the published economic literature indicates that the new atypical antipsychotics including clozapine are cost-effective compared with chlorpromazine or haloperidol. However, there is little or no evidence to assess the relative cost-effectiveness of the new atypical antipsychotics compared with other conventional antipsychotics such as sulpiride. The evidence about the comparative cost-effectiveness of clozapine compared with the new atypicals is limited and uncertain, with some analyses indicating that clozapine may be more effective and less expensive, and others indicating that clozapine may be more effective and more expensive.

Chapter 2

Policy and practice prior to the trial

The commissioning brief for primary research was released in 1996. Clozapine had been licensed in 1990 and a first new atypical licensed in 1994 (risperidone). Olanzapine and sertindole were licensed in 1996; sertindole was withdrawn on safety grounds in 1999.

Clozapine was licensed for use as a third line drug only after two other drug treatments had failed inadequate trials. Long-standing familiarity with the conventional drugs meant that the claims for the improved efficacy and absent EPS for clozapine were slow to be accepted by the prescribing clinical community. In addition, clinicians were unfamiliar with and concerned by the unusual side-effect profile and the cumbersome restrictions on initiating clozapine. When risperidone and later olanzapine and sertindole appeared, it was unclear whether these were of equal effectiveness to clozapine, or more similar to the conventional drugs.

No national prescribing guidelines existed. Take-up of the new atypicals in the USA was rapid, largely owing to the medicolegal context of the probable reduced likelihood of tardive dyskinesia with the new agents. Most, if not all, local clinical guidelines for the drug treatment of schizophrenia before 1996 continued to state that conventional antipsychotic drugs were the first line agents of choice. The increased acquisition cost of new atypicals was felt not to be justified on the basis of the available evidence. Opinions differed as to whether new atypicals were second line treatments of choice, previous guidelines having stated that a second conventional drug should be tried if the patient was intolerant of or unresponsive to a first.

With respect to clozapine, the fact that it had the highest acquisition costs of all led to a situation where health authorities were reluctant to sanction and fund its use. In the mid-1990s many health authorities still exercised a policy of 'clozapine capping', which allowed a fixed number of prescriptions only to be issued by mental health providers.

A range of changes occurred between the time of the commissioning brief and the start of the trial, and also during the trial itself, which had an impact on design detail, clinical equipoise and recruitment. Many of these changes were tracked using national data sets and local (Greater Manchester) data in the context of the SiGMA audit referred to in the original protocol.

This audit was funded independently of the trial from local audit monies. The rise in prescription costs of new atypicals over a 6-year period from 1996 is illustrated in *Figure 1*, which represents primary care costs (approximately 80% of the total costs) across Greater Manchester.

The pattern was that although GPs rarely initiated treatment with new atypicals, they would be closely involved in repeat prescriptions. Discussions were often pursued between clinicians in primary and secondary care as to the rationale for this. Small amounts of new money had been made available to cover the increased costs of prescribing for these new compounds.

Although nationally, over the same 6-year period, expenditure on atypicals as a class increased from 38% of total antipsychotic spending in 1996 to 90% of total antipsychotic spending in 2002 (Prescription Cost Analysis Data, 2003) the level of expenditure per capita on atypicals varied substantially between health authorities in England for the new atypicals (*Figure 2*, data obtained from the Prescription Pricing Authority). Adjusted spending figures showed a nine-fold variation in per capita spending on atypical drugs across English health authorities.[164]

Independently validated data from the 12 original mental health providers in Greater Manchester showed a wide variation of over 30-fold in capitated prescribing rates for clozapine.[165] Tracking these rates annually has revealed that although for some providers rates of clozapine prescribing increased significantly, this was not the case for many of the providers (*Figure 3*).

Exploration of a number of possible explanations, including health commissioner restriction, led to the conclusion that the variation was due mainly to different levels of evidence-based prescribing amongst clinicians in different trusts.

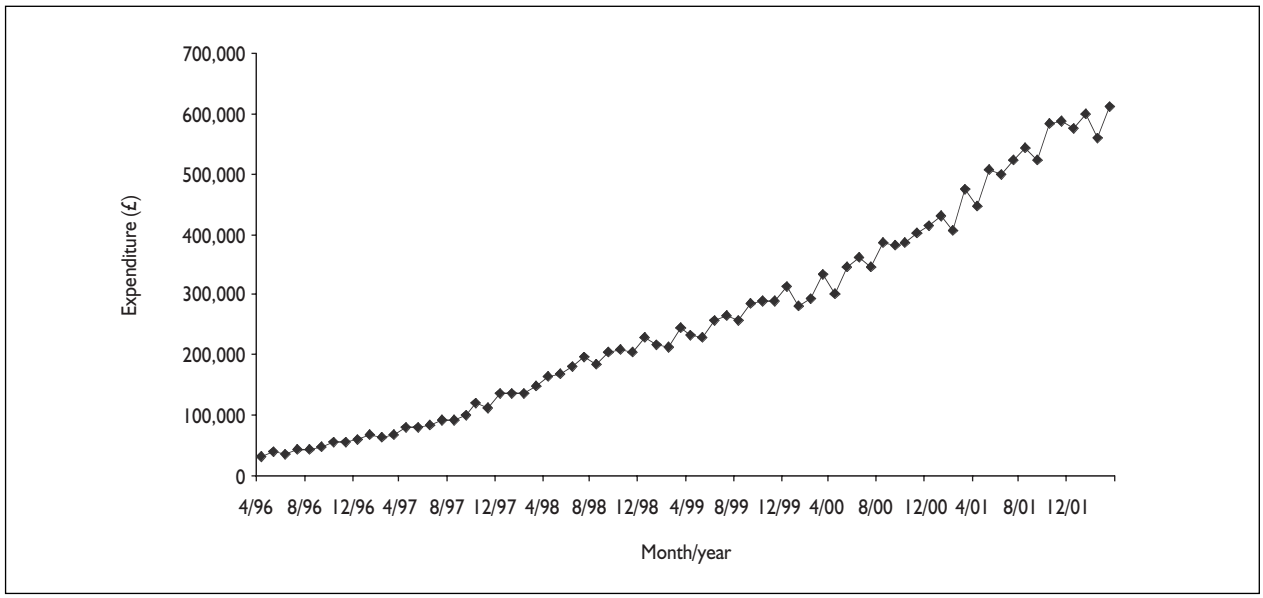

FIGURE 1 *Greater Manchester primary care atypical expenditure, 1996–2002*

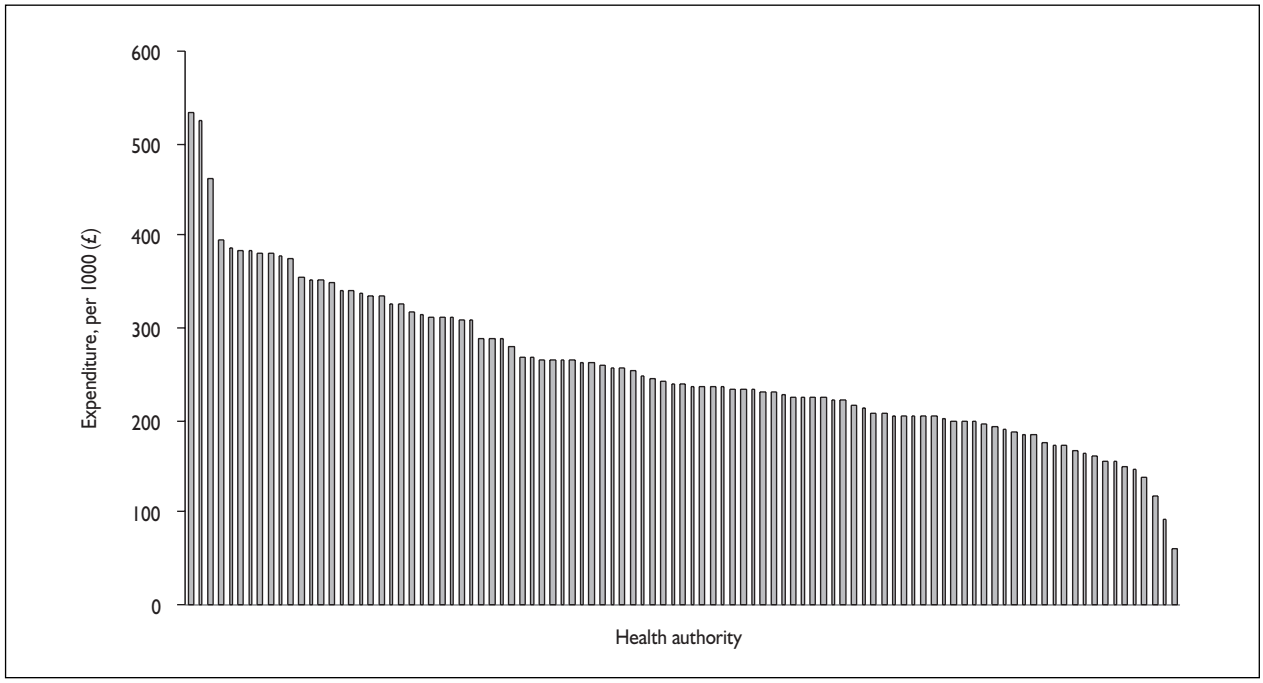

FIGURE 2 *Primary care expenditure, per capita, on all atypical antipsychotic drugs by health authority, April–June 1999*

A further SiGMA study that examined practice both before and during the trial took the form of a before-and-after, cohort-controlled, study. This indicated that for those patients who continued clozapine treatment for the whole of the 2-year period, in Greater Manchester, there was a two-thirds reduction in number of admissions and total time spent in hospital, compared with no change in the clozapine discontinuers.[166] Cost data emerged, derived from retrospective case or cohort-controlled studies, as these became more widely appreciated by commissioners, along with a climate of encouraging clozapine use to realise budgetary savings on inpatient resource use. For many clinicians using clozapine, the advantages in efficacy compared with new atypicals continued to be impressive at a day-to-day level.

Two further new atypical antipsychotics, quetiapine and amisulpride, were licensed in

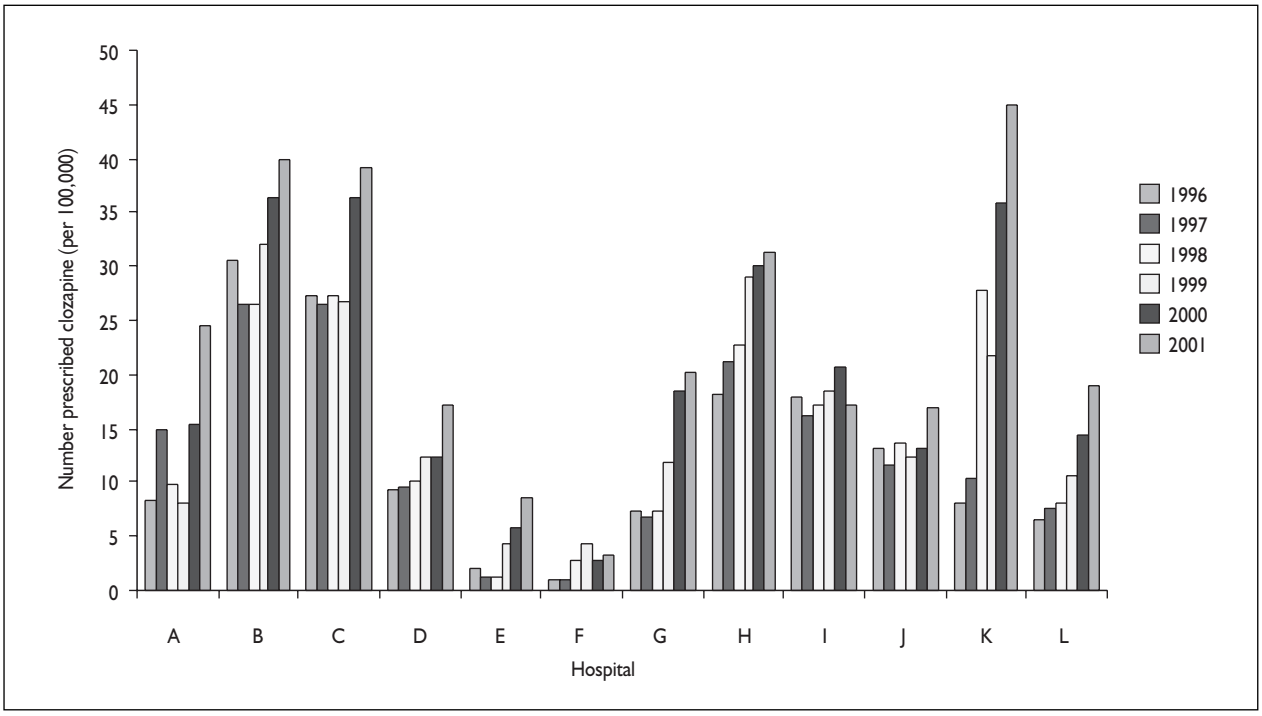

FIGURE 3 *Population-adjusted prescribing rates for clozapine across Greater Manchester, 1996–2001*

1997. Industry-sponsored, longer term Phase IV trials, in particular those using new atypicals first line, started to become available. The pharmaceutical companies involved marketed their individual products assertively.

In the absence of National Clinical Guidelines, a set of guidelines based in part on evidence was published in 1999: the Maudsley Hospital Clinical Guidelines. These recommended new atypical drugs first and second line in the treatment of schizophrenia. Pharmaceutical companies purchased a large number of copies of these and distributed them free to clinicians. The sixth edition had become available by 2001.

National drug treatment guidelines were released by NICE in mid-2002. The principal recommendations were that new atypicals should now be considered in the first line treatment of people with schizophrenia and that clozapine use should be recommended more widely in operationally defined treatment-resistant schizophrenia. The recommendations were confirmed and extended in the NICE Schizophrenia Clinical Guideline developed by the National Collaborating Centre for Mental Health, released in December 2002.

Systematic reviews and meta-analyses were published drawing, to some extent, different conclusions and giving different recommendations. Geddes and colleagues[24] took the position that there was insufficient evidence to conclude that atypical drugs offered a safety advantage, although the authors acknowledge that there appeared to be an advantage in terms of EPS. From the viewpoint of efficacy, the authors drew attention to the finding that the advantages for atypicals were present only in trials where high doses of a haloperidol comparator (>12 mg) were used. Other meta-analyses during this period[20] tended to find small but statistically significant advantages from atypical drugs. However, a more recent systematic review of all antipsychotic drugs included a range of antipsychotics not typically reported in meta-analyses and reviews. The conclusions of this report supported those of Geddes,[24] that there was insufficient high-quality evidence to indicate superior effectiveness for the atypical antipsychotics.[32]

Chapter 3

Amendments to original protocol: rationale

A set of amendments was made to details of the original protocol as funded. Each of these amendments was submitted in reports to the National Coordinating Centre for Health Technology Assessment (NCCHTA) and approved. Each was also submitted where necessary to the multicentre research ethics committee (MREC) and approved.

- Sulpiride and amisulpride were included since both these drugs appeared in clinical guidelines in several of the trusts involved. As with other drugs in the study, they were used regularly in the NHS and are fully licensed. Sulpiride has been licensed since the mid-1960s with claims, partly supported by data, that it has a reduced incidence of EPS. It has therefore been called a 'less typical' antipsychotic drug and it is included in band 1 in view of its low acquisition costs. Amisulpride is chemically unrelated to sulpiride and is a new atypical drug which was licensed in the UK shortly before the trial began. It is an atypical drug in the sense that there are good quality data to support its low incidence of EPS, although its pharmacology is slightly different from other new atypicals, its being a specific D_2 and D_3 receptor antagonist. It is priced similarly to other new atypicals.
- **Outcome measures**: the Calgary Depression Scale[167] was added since it is a brief scale validated to elicit depressive symptoms in people with schizophrenia. This was felt to be an important addition since many clinicians believe that new atypicals and clozapine may be more effective than conventional antipsychotics in reducing ancillary depressive symptoms. The side-effect evaluation was modified by adding the Abnormal Involuntary Movements Scale (AIMS) for tardive dyskinesia.[168] The Udvalg for Kliniske Undersogelser side-effects rating scale (UKU) scale had originally been proposed for the evaluation of non-neurological side-effects. However, this is not a well-validated scale and the opportunity was taken to develop a new instrument to assess the range of non-neurological side-effects important in some patients taking new atypical drugs in particular. This scale was called the Assessment of Non-Neurological Side Effects Rating Scale (ANNSERS) and details are given in Appendix 1.[169]
- **Subject eligibility**: the definition of eligible subjects was extended for band 1 from patients taking a conventional medication to include those taking a new atypical drug, who had likewise proved intolerant or unresponsive. This change was made to reflect the increasing likelihood that partly treated resistant patients may already be taking new atypical medication and the randomisation would still be to another new atypical or conventional drug subsequently. The term BDTR was replaced for simplicity by 'band 1' to denote the part of the trial contrasting conventional and new atypical drug treatments.
  Eligibility criteria were relaxed such that patients were now eligible in the context of 1 month's history, instead of 6 months, since onset of positive symptoms, as this reflects clinical practice in that patients may become intolerant to antipsychotic drugs early on in their treatment history. Clinicians felt that stipulating a 6-month history would exclude a small number of otherwise eligible patients. Similarly, the requirement that the current episode be of 6 weeks or more was removed to reflect more accurately current practice in the NHS.
- **Band 2**: narrowly defined treatment resistant. The criteria were modified to reflect current clinical practice, such that the specification that at least two drugs, one of which is a conventional, needed to be tried for a minimum of 6 weeks was relaxed.
- New logistic arrangements with the trial support clinician and clinical assessor at baseline were introduced to ensure that eligibility was checked before randomisation occurred. The consultant clinician still gave the patient the information sheet concerning the trial at least 24 hours before the trial support clinician visited and obtained informed written consent.

- The timing of blind assessments was amended to occur at 12 and 26, rather than 6 and 24 weeks, to fit in better with the logistics of the study.
- The identity of individual trial centre NHS providers was modified owing to the change in name of some of the trusts involved and further expressions of interest from NHS providers wanting to participate in the trial.

Chapter 4
Methods

Rationale of trial design

Patients will switch from one antipsychotic drug to another usually because of a lack of efficacy (treatment resistance) or the experience of unwanted adverse effects (treatment intolerance). Occasionally there may be other reasons, such as convenience of administration. The central issue for the NHS was to clarify the role of the new atypical drugs and clozapine in people with schizophrenia unresponsive or intolerant to current treatment. If the delivery of care to people with resistant or drug-intolerant schizophrenia is to be efficient, the NHS requires evidence to address the following question: How cost-effective are the new atypical antipsychotic drugs and clozapine in treatment-resistant patients? Three parts to this question were relevant: Did the atypical drugs lead to better outcomes for such patients? What is the cost of this improvement (cost–utility)? Were they cheaper for the NHS overall?

A multicentre, rater-blind RCT was the design chosen, with some features of a 'pragmatic' clinical trial to test effectiveness in routine NHS practice. The characteristics of a pragmatic trial in this context are:

- trial entry is defined by the clinician who is making a decision to change drug management
- inclusion criteria are broad, so as to best reflect normal clinical practice
- there is non-intensive follow-up with a small number of primary outcomes.

In addition, the choice of which individual drug to use within classes of treatment was made by the clinician with access to best current data. The formal RCT framework would include concealed randomisation, blind independent assessments of outcome and intention-to-treat (ITT) analysis.

In choosing this trial design, the aim was to conform to genuine clinical practice as closely as was still compatible with a randomised trial design, taking advantage of genuine nodal points of clinical uncertainty.

Treatment resistance and treatment intolerance

By the mid-1990s prescribing practices were starting to emerge, encouraged by local clinical guidelines, such that conventional antipsychotic drugs were largely used first and second line; new atypical drugs were used second and third line and clozapine was used third line and beyond. A direct comparison in a three-way treatment trial between conventionals and new atypicals and clozapine did not best represent the situation facing the NHS. Clozapine, by virtue of its licensing restrictions, could never be used first or second line and the use of conventionals third line and to some extent second line was becoming less common with the advent of the new atypicals.

Thus, two parallel trials with a common catchment area and set of clinicians and common design features including outcome assessments were proposed. 'Broadly defined treatment resistance and intolerance' would describe the patient population from which was recruited the sample going into the trial contrasting conventional and new atypical drugs ('band 1'). As previously noted, there is no single definition of treatment resistance. The pragmatic issue is the decision taken by the clinician to change antipsychotic drug treatment (not simply raise the dosage) in the face of no or partial clinical improvement, or unacceptable side-effects: thus, 'broadly (or pragmatically) defined treatment resistance or intolerance', where the decision between a conventional and new atypical drug is the most relevant.

'Narrowly defined treatment resistance' would describe the population from which was recruited the sample going into the trial contrasting new atypical drugs and clozapine ('band 2'). This distinction also reflected a distinction in comparisons between these three treatment options such that the new atypicals were believed by many prescribers to be superior to conventionals largely on the basis of tolerability, whereas clozapine was believed to be superior to new atypicals (and conventionals) in terms of efficacy.

Individual drugs or classes of drug?

Clozapine is the benchmark atypical drug. The distinction between conventional and new atypical

drugs is based on data showing, in general, that atypical drugs cause lower rates of EPS. Clinical guidelines tended to group these drugs together into the two classes. However, in terms of individual receptor pharmacology and adverse effect profile, drugs within the conventional class and the atypical class differ significantly. Some of the so-called conventional drugs, such as thioridazine and sulpiride, show features of atypicality. In view of this lack of a clear distinction, the important issue for the NHS is the relative acquisition cost. Conventional drugs are relatively inexpensive and new atypicals relatively expensive, depending on dosage. Clozapine is the most expensive. The pragmatic issue therefore is to compare classes of drugs, and this will allow the clinician natural freedom to choose drugs within a class.

Allowing clinicians and patients to choose which drug to use within a class (apart from clozapine) also best reflects normal clinical practice. This would also allow clinicians to switch to another drug within the same class without the patient being deemed to have withdrawn from allocated treatment.

Double-blind, single-blind or open treatment allocation?

Double-blind trials are the standard methodology for drug efficacy trials. Given that basic efficacy and safety data for the drugs involved are accepted, the trial seeks to test effectiveness and cost-effectiveness in the NHS. In this context, a double-blind design would be cumbersome, ethically challenging (for example, to have dummy blood tests for the haematological surveillance required for clozapine) and reduce generalisability to the NHS.

The design chosen was an open trial with outcomes assessed blind to treatment allocation. The quality of the blind needed to be high with this design.

Aims and hypotheses

The broad aim was to provide data to inform policy and treatment decision-makers about the relative clinical benefit, costs and utility of initiating treatment with conventional antipsychotics, clozapine or atypical antipsychotics in people with schizophrenia. Two broad research hypotheses were defined:

- The additional acquisition costs of the new atypical drugs over conventional drugs will be offset by improvements in patient health-related quality of life, and/or savings in the use of other health and social care services in a population with schizophrenia broadly resistant to or intolerant of their current antipsychotic drug treatment.
- The additional acquisition costs of clozapine over new atypical drugs will be offset by improvements in patient health-related quality of life and/or savings in the use of other health and social care services in a population with narrowly defined treatment-resistant schizophrenia.

The economic evaluation used the perspectives of the NHS, social support services and patients for the primary analysis. It was assumed that these represent the main stakeholders and thus approximate a societal perspective. The evaluation was designed to inform policy and treatment decisions in the practice setting of secondary and primary care in the UK for a 1-year period from the day of randomisation to the end of scheduled follow-up at 1 year. Discounting of future costs and outcomes was not necessary for this time-frame.

The economic evaluation used data collected for all the patients enrolled in the clinical trial to estimate the resource use and utilities associated with the alternative types of antipsychotic treatment. This was supplemented with unit cost data from published national databases. National average unit costs were used to approximate the relative opportunity costs of different types of resource use and service in routine primary and secondary care.

The framework of cost–utility analysis was used to compare the costs and outcomes of the two groups and estimate an incremental cost–utility ratio. Net benefit statistics were calculated and cost-effectiveness acceptability analysis used to estimate the probability that (1) initiating treatment with atypical antipsychotics was cost-effective compared with conventional antipsychotics for people with broadly defined treatment-resistant schizophrenia or intolerant of current antipsychotic therapy, and (2) initiating clozapine therapy was cost-effective compared with atypical antipsychotics for people with narrowly defined treatment-resistant schizophrenia or intolerant of current antipsychotic therapy. In addition, the cost-effectiveness acceptability analysis was used to quantify the level of uncertainty about the relative cost-effectiveness of the alternatives.

TABLE 1 *Participating Health Trusts*

Centre	Trust
Manchester	Rochdale
Manchester	Mid Cheshire
Manchester	Manchester Mental Health Partnership
Manchester	Trafford NHS Trust
Manchester	Halton Acute Services Trust
Manchester	Mental Health Services of Salford
Manchester	Bolton NHS Trust
Manchester	Stockport NHS Trust
Nottingham	Nottingham Mental Health Services NHS Trust
Institute of Psychiatry	South London & Maudsley
Imperial College	West London Mental Health Trust
Imperial College	St Mary's NHS Hospital Trust
Imperial College	Chelsea & Westminster NHS Trust
Cambridge	Cambridge & Peterborough Mental Health Partnership

Participating centres

Four centres across the UK were involved in the study: the School of Psychiatry and Behavioural Sciences of the University of Manchester, the University of Nottingham, Imperial College London and the Institute of Psychiatry London. In the last year of recruitment, the University of Cambridge (managed by the Imperial College site) became a fifth site, facilitated by the move of Professor Jones from Nottingham to Cambridge.

Participating NHS trusts across the trial centres are set out in *Table 1*, as they existed in 1999.

Recruitment of clinicians

Overall, in excess of 120 consultant grade clinicians were recruited across all centres, in that they expressed a willingness to participate by referring patients in the course of clinical practice. Of these, 95 general adult psychiatrists referred one or more patients who were successfully randomised into the study.

Excess treatment and service support costs

Arrangement for payment of legitimate NHS excess treatment and service support costs varied between centres. In the North West, agreements were reached with the regional research and development (R&D) office (Professor Maggie Pearson) for direct payments of excess treatment and service support costs to those trusts without established R&D budgets: in the terminology existing at the time, without R&D portfolio status. Excess treatment costs in band 1 were determined by agreement to be neutral, since patients currently prescribed atypicals or conventionals were randomised to either class of drug. These costs, agreed from a regional budget direct to the trust involved were pro rata, such that a fixed sum was paid for each patient recruited into the band 1 arm of the trial and the band 2 arm of the trial. The service support costs comprised £936 per patient, with an additional £700 excess treatment costs per band 2 patient.

Ethical approval

Ethical approval was sought from and granted by the North West MREC. This included approval of protocol changes. Local research ethics committee (LREC) approval was obtained for all participating districts.

Inclusion and exclusion criteria

Criteria for inclusion in or exclusion from the study are listed in *Table 2*.

Randomisation procedure

The referring clinician completed a brief, one-page demographic and clinical checklist, which was faxed or e-mailed through to the trial centre. In band 1, this included the primary reason for referral, in terms of incomplete response to current treatment or intolerance to current treatment, or both. The clinician explained verbally the nature of the trial and gave the patient a trial information sheet. The clinician also indicated in advance on the form their preferred individual drug treatment if the patient was randomised to each treatment condition.

The trial support clinician (TSC) checked eligibility from case notes and the patient was assigned a study number and visited within 3 days to obtain written consent and carry out baseline

TABLE 2 *Trial inclusion/exclusion criteria*

Inclusion criteria
DSM-4 schizophrenia, schizoaffective disorder or delusional disorder
Age 18–65 years, currently on a care programme approach
Clinician considering drug change as part of care plan

Exclusion criteria
Substance misuse or medical disorder as the major causative factor for psychotic symptoms
History of neuroleptic malignant syndrome

Band 1 (broadly defined treatment-resistant or treatment intolerant) criteria
At least one month since first onset of positive symptoms
Consultant electing to change current conventional or new atypical drug treatment because
  either poor clinical response
  or side-effects impairing global functioning

Band 2 (narrowly defined treatment-resistant) criteria
As for band 1 above, plus:
At least two previous drugs, with poor clinical response, and the clinician is considering clozapine

assessments. If confirmed as eligible and the person gave informed consent, randomisation took place.

Randomisation was undertaken via a remote telephone service provided by the Medical Statistics Unit at the Christie Hospital, Manchester. Separate randomisations were performed for each of the two bands. After stratifying by treatment centre, the method of allocation was permuted blocks within strata with block sizes varying at random between four and 12. A number of treatment centres was added during the progress of the trial (to boost recruitment) and so the number of strata ended up being larger than originally envisaged.

The randomised treatment allocation was made known to the clinician, the trial manager, local pharmacist and GP.

Individual drugs

The following drugs were considered to be conventionals and were available to prescribing clinicians for participants randomised to the conventional arm: chlorpromazine (Largactil®; Hawgreen), flupenthixol (Depixol®; Lundbeck), haloperidol (Haldol®; Janssen-Cilag), loxapine (Loxapac®; Lederle), sulpiride (Sulparex®; Bristol-Myers Squibb), trifluoperazine (Stelazine®; Goldshield), zuclopenthixol (Clopixol®; Lundbeck), as well as depot antipsychotics fluphenazine, (Modecate®; Sanofi-Synthelabo), zuclopenthixol (Clopixol®; Lundbeck), flupenthixol (Depixol®; Lundbeck) and haloperidol decanoate (Haldol®; Janssen-Cilag). Thioridazine (Melleril®; Novartis) and droperidol (Droleptan®; Janssen-Cilag) were available at the start of the trial but were removed from licence during the course of the trial. New atypical medications were risperidone (Risperdal®; Janssen-Cilag, Organon), olanzapine (Zyprexa® Lilly), amisulpride (Solian® Sanofi-Synthelabo), zotepine (Zoleptil®; Orion) and quetiapine (Seroquel® AstraZeneca).

Masking to allocation

The trial was rater-blind in nature. The clinical assessor performed all follow-up assessments blind to the treatment allocation. Measures were taken to prevent breaking the blind, both in terms of the physical location of assessors in relation to the rest of the team, with separate offices, the database, with a system of passwords, and hard copies of case-report forms (CRFs), and in terms of restrictions on discussions about individual patients within the team. Study participants were frequently reminded to avoid open discussions of treatment assignments, and randomisation lists were sent by encrypted e-mail from the randomisation centre.

Assessors reported cases where unmasking had occurred during the study to the trial manager and these were clearly documented. Details of these cases are listed in Appendix 3.

Recruitment rates

Band 1

Patients were recruited into the band 1 arm of the trial (conventional versus new atypical antipsychotics) from July 1999 in both the

Manchester and Nottingham centres. The two London centres (Institute of Psychiatry and Imperial College) experienced delays with initiating patient recruitment owing to staff recruitment difficulties. Consequently, patient recruitment started in September 1999 at the Institute of Psychiatry and November 1999 at Imperial College. Recruitment into band 1 ran from July 1999 for 30 months, with the last band 1 patient being recruited in January 2002.

Band 2

Patients were recruited into the band 2 arm of the trial (new atypical antipsychotics versus clozapine) from August 1999 in the Manchester centre and July 1999 in the Nottingham centre. Owing to the staff recruitment difficulties at the two London centres, patient recruitment started in December 1999 at the Institute of Psychiatry and October 1999 at Imperial College. Recruitment into band 2 ran from July 1999 for 33 months, with the last band 2 patient being recruited in April 2002.

Recruitment monitoring

Recruitment rates were monitored with the use of charts detailing actual patient recruitment rates by band and centre, against the projected total for all four centres (see *Figures 4* and *5*).

Recruitment initiatives and incentives to clinicians

Patient recruitment drives were initiated at each of the trial centres to maximise the number of patients referred into both bands of the study. Having a TSC focusing chiefly on patient recruitment proved important in ensuring regular referrals at both the Nottingham and Manchester sites. A suitable TSC was not appointed until January 2000 at the Imperial College site.

Raising the overall profile of the project at each centre and recruiting suitable consultants became the focus of early recruitment strategies. Study teams initiated the following activities, common to both bands of the trial, at each site:

- presentations to inpatient and outpatient clinical teams
- seminars and research meetings
- presentations at professional, academic and induction meetings
- regular face-to-face meetings with consultants, specialist registrars and senior house officers
- attendance of the TSC on ward rounds
- regular postal contact detailing the study, referral process and incentives
- creation of a Cost Utility of the Latest Antipsychotics in Severe Schizophrenia (CUtLASS) newsletter featuring relevant articles, including publicising the top referrers to the trial
- Royal College of Psychiatrists continuous professional development (CPD) accreditation for referring consultants; this was the first trial to be so accredited.
- letters to and meetings with community psychiatric nurses, nurses and locality managers
- poster and flyer campaigns
- creation of a CUtLASS website.

Recruitment rates: band 1

Despite the recruitment initiatives, only 62 patients (40% of projected recruitment) had been randomised to the band 1 arm of the trial by the end of January 2000. A number of factors influenced the low recruitment to the band 1 arm of the trial. The major issue appeared to be a lack of genuine clinical equipoise, with clinicians and patients by this time preferring atypicals over conventionals. This may have been a reflection of the widespread marketing of atypicals by the pharmaceutical industry. A further significant factor may have been the widespread use of the Maudsley Hospital prescribing guidelines, which advocate the use of atypical as opposed to conventional antipsychotics. These issues may have deterred clinicians from referring patients into the band 1 arm of the study.

During the trial, the perception grew among some clinicians that conventional antipsychotics caused more severe side-effects than atypical agents. Feedback from clinicians at local sites indicated that this was a particularly pertinent issue when considering changing the medication of patients with a previous history of side-effects. Evidence to this effect is provided by data from the clinicians' attitudes survey (see Appendix 4).

Despite later further initiatives undertaken to counter the slow recruitment to band 1, which included the widening of site catchment areas, work with local pharmacy departments to identify 'missed' patients to target non-referrers, mailshots to clinicians to investigate reasons for non-referral, the creation of a 'CUtLASS clinic' at the Institute of Psychiatry and newsletters presenting summaries of the lack of evidence regarding the superiority of atypicals over conventionals, the actual recruitment rate was 37% of that projected by August 2000 (131 recruited out of 352 projected).

Lesser issues that hampered recruitment included personnel changes at the two London sites, changes to rehabilitation services in Nottingham, the relocation of the Manchester centre and issues of research fatigue, especially pertinent at the Institute of Psychiatry, where patients and staff were frequently requested to take part in research activities. Despite the approval of a 7-month unfunded extension by the NCCHTA, recruitment to the band 1 arm of the study closed in January 2002 when 40% (n = 227) of the sample size was reached (see *Figure 4*).

Recruitment rates: band 2

Patient recruitment into the band 2 arm of the trial progressed well, reaching 86% of the projected recruitment rate by January 2000. Despite the positive recruitment rate, further recruitment initiatives were undertaken, common to both bands, as listed above, to maximise recruitment into the band 2 arm. Following the approval of a 7-month unfunded extension by the NCCHTA, recruitment to the band 2 arm of the study closed in April 2002 when 99% (n = 136) of the sample size was reached (*Figure 5*).

Reasons for non-referral to the study

Each centre carried out audits throughout the trial to establish reasons for non-referral into the study. These audits varied in their remit and size.

An audit over a 1-month period in 2000 at one referring Manchester site showed that five patients, having their antipsychotic medication changed, were eligible to enter the study. One out of five of these patients (20%) was referred into the study and subsequently randomised. Of the remaining four patients, two had consultants who were not participating in the study, one patient refused and the reason the other patient did not enter the study was not known.

Non-referral data were obtained from 30% of clinicians at the Imperial College centre. During the monitored period (October 1999 to February 2002) there were 142 changes to antipsychotic medication. Fifty-two of these patients (37%) were referred to the study. A further 11 patients (10%) did not consent to participate. The remaining 76 patients (53%) were not actually referred to the study.

These findings indicate that between 20 and 37% of eligible patients undergoing medication changes were actually referred into the study.

During an audit at the end of 2000, consultants at each participating Manchester trust were asked how many patients had been asked to participate and how many of these had refused before being referred into the study. A response rate of 62% showed that of 177 patients who had been asked to participate up to that point, 97 (55%) had refused prior to referral.

Clinician prescribing after randomisation

The TSC liaised with the consultant psychiatrist to determine whether the consultant or TSC would see the patient to initiate treatment. In most cases, this was the consultant. Attempts were made to initiate the first dose of randomised treatment within 7 days for band 1 patients. In the case of band 2 patients, where the patient could require inpatient admission and baseline haematology, attempts were made to minimise the time between randomisation and treatment initiation as much as possible. The actual mean and median times to first dose are set out in *Tables 3* and *4*.

There was a degree of variation in times to first dose and as can be seen from the patient flow section of this report (see Chapter 5: Band 1 patient flow and Chapter 6: Band 2 patient flow) a number of patients had not started treatment within their randomised arm by the end of the 12-week follow-up period. In addition to delays in instigating clozapine treatment, a number of patients assigned clozapine treatment were not given the green light to start treatment from the Clozapine Patient Monitoring Service (CPMS). In addition, some patients did not immediately commence their randomised treatment as the clinical team did not then instigate the randomised drug.

For both band 1 and band 2 patients, all efforts were made to keep the patient within the treatment arm that they were randomised to for a minimum of 12 weeks and preferably for the full year of the study. Therefore, if the consultant

TABLE 3 *Band 1: time to first dose*

Time to first dose (days)	Mean	SD	Median
Band 1	8.5	29.7	1.0

TABLE 4 *Band 2: time to first dose*

Time to first dose (days)	Mean	SD	Median
Band 2	19.31	38.1	7.0

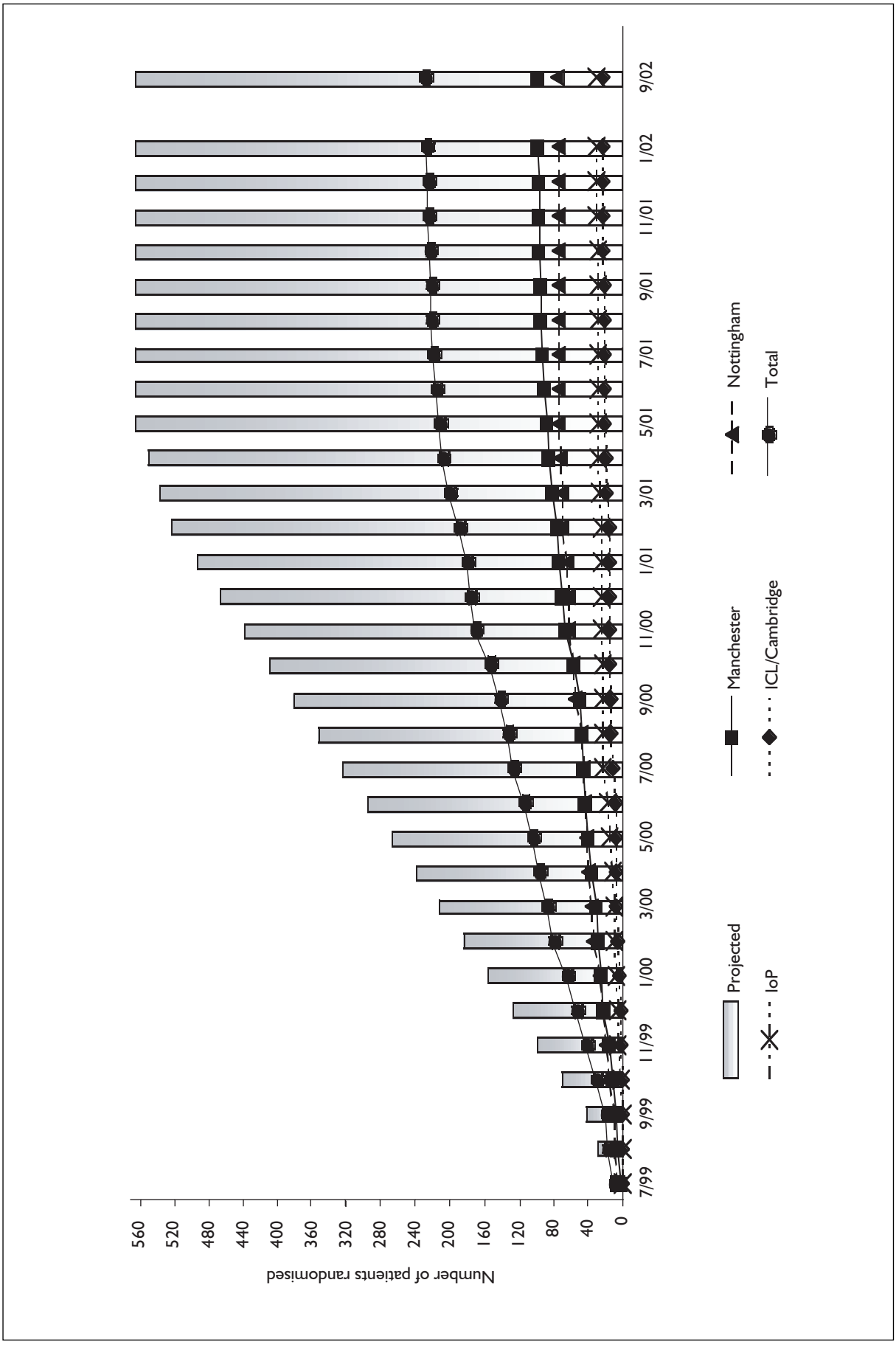

FIGURE 4 *Band 1, recruitment rates. IoP, Institute of Psychiatry; ICL, Imperial College London.*

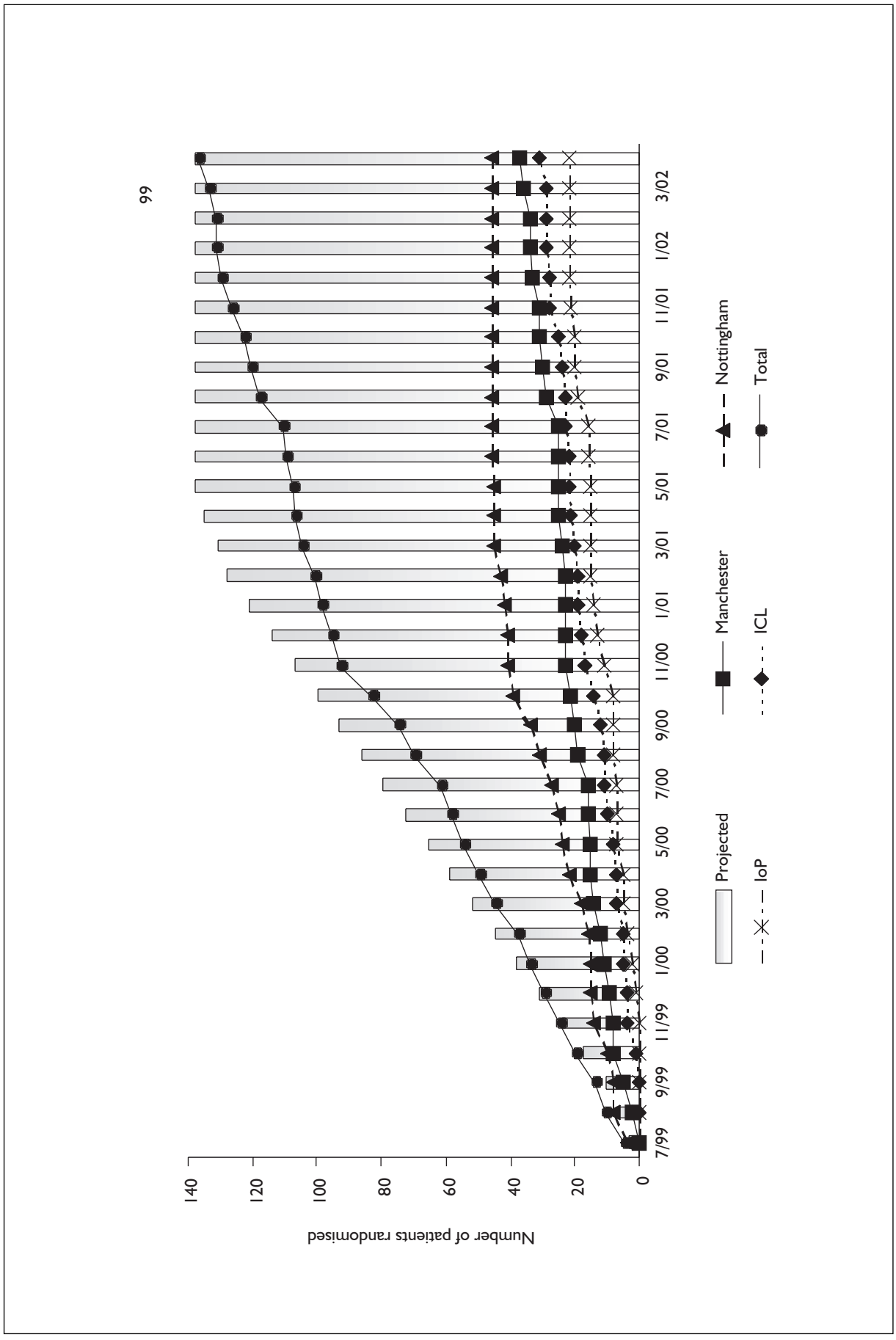

FIGURE 5 *Band 2, recruitment rates*

decided to change the antipsychotic medication, the new medication should fall within the same treatment arm. For example, a patient randomised to the new atypical arm of the study would preferably be prescribed another new atypical and not a conventional drug. Adjunctive medication was allowed and monitored, but polypharmacy of two or more antipsychotic drugs in parallel was discouraged. Clinicians had access to the desk reference best prescribing handbook written for the trial.

Baseline assessments

Baseline assessments were carried out by a TSC or clinical assessor, according to the schedule illustrated in the Gantt charts (*Tables 5* and *6*). Safety procedures for ward/home visits were adhered to (details available on request). Assessment instruments are listed below. See Appendix 1 for copies of unpublished scales (ANNSERS and patient satisfaction questionnaire).

Primary outcome measure

The primary outcome was Quality of Life Scale (QLS) score.[170] Quality of life was selected as the primary outcome variable in the trial since it is the construct that best fits the clinician's medium- and long-term treatment aim in treatment.

Quality of life consists of a sense of well-being, life satisfaction and access to resources and opportunities.[171,172] Instruments measuring quality of life may be subjective (self-completed) or objective (observer completed), generic or specific. Generic instruments measure quality of life in the general population and in any ill population, whereas specific instruments measure quality of life in a specific group, for example, those suffering from schizophrenia. There are several general considerations when using normative quality of life scales in a sample of people with schizophrenia. Floor effects may be observed particularly in role functioning domains, for example, spouse, parent and employment roles. Special attention must therefore be paid to instrument sensitivity, including sensitivity to change. Given that psychopathology affects patients' ratings of their quality of life, assessments of quality of life should be accompanied by a concomitant assessment of psychopathological symptoms.[172]

The QLS is a schizophrenia-specific quality of life measure that uses a semi-structured interview. The scale consists of 21 items with anchored ratings of 0–6, in four domains: social relationships, instrumental role functioning, intrapsychic foundations and activities of daily life. It has good inter-rater reliabilities and confirmatory factor analysis has been conducted. The QLS is the most widely used scale in the evaluation of psychopharmacological treatments for schizophrenia, predominantly in outpatients.[172] A 20% increase in total score is held to represent clinically important improvement.

Secondary outcome measures

- Cost–utility ratios: the main patient utility measure was the EuroQuol 5 Dimensions (EQ-5D).[173] This is a generic health-related quality of life scale, which has been validated in the UK.[173,174] Data confirming its concurrent validity and sensitivity to change in serious mental illness are available (P. Kind, University of York: personal communication), although none has been published. It was chosen because of its brevity and because it has been widely used in physical health. It has five items, each completed by the person on a three-point scale according to whether the problem is absent, present to some degree or severe, in terms of simple anchor points. The items are mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
- Symptoms on the PANSS[175]: the PANSS is a well-validated, widely used schizophrenia rating scale, containing 30 items divided into three subscales (positive, negative and general psychopathology). A 20% change in total score is considered clinically important.
- The Calgary Depression Scale is a widely used measure to evaluate depressive symptoms in people with schizophrenia.[167]
- Patient attitudes and compliance ratings were measured using the Drug Attitudes Inventory (DAI)[176] and the Kemp Seven-point Drug Compliance Scale.[177]
- Global functioning was measured on the Global Assessment of Functioning (GAF) scale.[1]
- Side-effects scales:
  - the Simpson and Angus scale[178] assesses pseudo-parkinsonian symptoms and signs
  - the Barnes Akathisia Rating Scale (BARS)[179] is a widely used measure of akathisia
  - the AIMs for tardive dyskinesia[168]
  - the ANNSERS, a new scale to assess the side-effects of atypicals, developed by Barnes and Kerwin. No existing scale comprehensively assessed side-effects outside the domain of

EPS and this scale was designed for this trial in an attempt to address this (see Appendix 1). The subscales examined areas of sleep disturbance, subjective experience, and cardiovascular, gastrointestinal, anticholinergic, genitourinary and sexual problems. The sexual side-effects section of the ANNSERS was validated during this trial, using the findings of an add-on study, which used the well-validated Derogatis interview for sexual functioning.[180] The Derogatis interview is a brief, self-reported, multidimensional and gender-keyed instrument designed to measure quality of current sexual functioning across five primary domains: sexual cognition/fantasy, sexual arousal, sexual behaviour/experience, orgasm and sexual drive/relationship. The aggregate total score can be used repeatedly throughout efficacy or effectiveness studies without any significant practice effects or loss of validity.[180] The Derogatis add-on study was designed to compare self-reported sexual functioning with quality of life, using the QLS[170] at baseline and 12 weeks following randomisation to either an atypical or a conventional antipsychotic. Statistically significant correlations were obtained between male scores on the Derogatis and the male sexual side-effect section of the ANNSERS ($r = –0.611$, $p < 0.01$) and between female scores on the Derogatis and the female sexual side-effect section of the ANNSERS ($r = –0.587$, $p < 0.01$). A lower score on the Derogatis indicates greater sexual dysfunction.

- Costs of health and social services were calculated from data collected on each patient's use of hospital inpatient and outpatient services, primary and community care services, social services, the criminal justice system, housing services and informal care. In addition, data were collected on employment and leisure activities for patients and carers.
- Categorical outcome variables were measured, including:
  - living in independent accommodation at the end of study
  - homelessness during the study
  - employed (sheltered, part-time, in education or full-time) at the end of study
  - admission to hospital during the study
  - loss of contact with services
  - suicide.
- Patient satisfaction rating: this questionnaire included Likert-type ratings in the areas of satisfaction with new antipsychotic drug treatment, mental health and side-effects since starting the new drug, and whether the patient would recommend their new antipsychotic drug to another person with similar mental health problems (see Appendix 1).

Follow-up assessments

On-study assessments were subsequently carried out by clinical assessors blind to treatment allocation at 12, 26 and 52 weeks following randomisation; no on-study assessment ratings were made by clinicians. Assessments were made in a range of settings, usually in the community. Often several visits were needed to secure an interview. Limited telephone interviews were performed on a small number of occasions. Participants were deemed 'lost to follow-up' only after a minimum of four failed visits. A comprehensive personal safety policy was followed (available on request). The last follow-up assessment on a band 1 patient was carried out in March 2003 and the last follow-up assessment on a band 2 patient in April 2003.

The TSC obtained information from case notes on medication and service use in order to maintain the blind. Additional information was obtained via an informal carer interview if such a carer was identified at assessment and the patient consented to their carer being contacted.

Inter-rater reliability

Inter-rater reliability was assessed using ten videotaped interviews for both the QLS and the PANSS. An initial assessment of inter-rater reliability (for $n = 9$ raters) yielded an intraclass correlation (ICC) of 0.91 for the total QLS (primary outcome measure) and 0.75 for the total PANSS (secondary outcome measure). This was followed by a period of training and a further assessment of inter-rater reliability, yielding a score of 0.99 for the total QLS and 0.84 for the total PANSS. For the QLS subscales, ICCs were 0.98 for interpersonal relations, 0.75 for role functioning and 0.99 for intra-psychic foundations. For the PANSS, the positive symptom subscale was 0.94, negative subscale 0.85 and general subscale 0.84.

Data

Study data were recorded locally on triplicated CRFs according to agreed data-editing guidelines

TABLE 5 *Study Gantt chart for band 1 patients*

Task	Screening and baseline week –12 to 0	Day 1, week 1	On-study week 12	Follow-up week 26	Follow-up week 52
Eligibility	X	X			
Prior treatment history	X				
Informed consent	X				
Administer randomised treatment		X ----------	----------	----------	X
Follow-up for prescribed medications, interventions,[a] and patient–consultant contacts		X ----------	----------	----------	X
Clinical effectiveness assessments[b]	X		X	X	X
Cost effectiveness assessments[c]	X	X ----------	----------	----------	X
Side-effect scales[d]	X		X	X	X
Patient attitudes and compliance[e]	X		X	X	X
Informal carer telephone interview	X				X

[a] Non-pharmacological interventions [e.g. laboratory tests, accident and emergency (A&E) visits].
[b] QLS, PANSS, GAF, Deliberate Self-harm Questionnaire, Calgary Depression Scale, categorical outcome variables.
[c] EQ-5D, costs of health and social services, categorical outcome variables.
[d] Simpson and Angus Scale, AIMS, BARS, ANNSERS.
[e] DAI, Kemp Seven-point Compliance Scale, patient satisfaction questionnaire (week 12 and 52 only).

TABLE 6 *Study Gantt chart for band 2 patients*

	Screening and baseline week –12 to 0	Day 1, week 1	On-study week 12	Follow-up week 26	Follow-up week 52
Eligibility	X				
Prior treatment history[a]	X				
Informed consent	X				
Administer randomised treatment		X ----------	----------	----------	X
Follow-up for prescribed medications, interventions,[b] and patient–consultant contacts		X ----------	----------	----------	X
Clinical effectiveness assessments[c]	X		X	X	X
Cost effectiveness assessments[d]	X	X ----------	----------	----------	X
Side-effect scales[e]	X		X	X	X
Patient attitudes and compliance[f]	X		X	X	X
Informal carer telephone interview	X				X

[a] Data on prior two antipsychotic drug treatments to be collected and all other prescribed drugs taken within 12 weeks before study day 1.
[b] Non-pharmacological interventions (e.g. laboratory tests, A&E visits).
[c] QLS, PANSS, GAF, Deliberate Self-harm Questionnaire (only to be done at weeks 12, 26 and 52), Calgary Depression Scale, categorical outcome variables.
[d] EQ-5D, costs of health and social services, categorical outcome variables.
[e] Simpson and Angus Scale, AIMS, BARS, ANNSERS.
[f] DAI, Kemp Seven-point Compliance Scale, patient satisfaction questionnaire (week 12 and 52 only).

(available on request). Two copies of the CRFs were stored locally, the top copy being sent to the Manchester centre to be stored separately and entered onto the central database.

The data were entered onto a single Microsoft Access database, with inputting conforming to data entry guidelines. The database was created and managed by the Manchester centre.

Data quality control

A variety of data quality-control measures was put in place. CRFs were completed and checked using the study's data-editing guidelines. Several CRFs from each centre were also initially double-checked to ensure consistent adherence to the data-editing guidelines. Medication details were confirmed with the patient's GP and direct contact made with other professionals involved, such as social workers, community psychiatric nurses, support workers and occupational therapists, to record number of contacts during each period.

An interim data analysis, carried out during November 2002, allowed for extensive data quality checks to be carried out. The database was exported from Microsoft Access into SPSS for Windows (Release 10.1.0; SPSS, Chicago, IL, USA). Frequency counts in SPSS facilitated checks of missing items, items recorded that were outside the assessment scale used, inconsistent spellings, and so on. The most common issues related to how data had been recorded on the database, for example inconsistent medication dose units and string variables that were not analysable.

Trial management

Management procedures

Procedures were put in place to manage patient follow-up assessments and data collection and to monitor data inputting rates. Projected dates of follow-up assessments were calculated, the aim being to carry out the assessment visit within 2 weeks either side of this date. Following the assessments at each period, the TSC reviewed the patient's case notes and recorded details of medication, services use and so on. Key workers and other professionals were contacted for details of contact visits.

All study centres had designated and trained personnel to check the data for missing, ambiguous, inconsistent and incorrect data, according to agreed data-editing guidelines. Any necessary corrections were made to the triplicated CRFs before these were separated and the top copy was sent to the Manchester centre.

Each study centre monitored details of remaining assessments and case-note reviews. Each centre also recorded numbers of data packs for each period sent to the Manchester centre. In addition, the Manchester centre kept track of remaining data from all centres. Figures were kept throughout the trial of data packs sent to the database and of data entered onto the database. This enabled plans to be put into place to speed up data collection, data editing and data inputting where necessary; for example, additional personnel were employed at the Manchester centre to meet data-inputting targets. Data were entered onto the database using the study's data-entry guidelines (available on request).

Clinical assessors blind to treatment allocation carried out follow-up assessments. Procedures were put in place to maintain the blind.

Follow-up rates

Follow-up rates for assessments performed at weeks 12, 26 and 52 by band and centre were calculated throughout the trial (see Appendix 3 for details of final follow-up rates). Overall, the follow-up rate for band 1 at 1 year (81%) was lower than that projected in the power calculations of the original trial proposal (85% at 1 year), but in band 2, at 87%, was higher than predicted. A breakdown of reasons for non-follow-up follows.

Dropout rates, including deaths

Deaths of patients while in the trial were monitored. There was a total of seven deaths: six in the band 1 arm and one in the band 2 arm (see Appendix 3 for further details). Three deaths occurred in patients randomised to a conventional antipsychotic and four deaths in patients randomised to a new atypical (not clozapine). Five deaths were due to cardiac failure, one death was due to infectious disease and one death was considered to be an open verdict (suicide or accidental death). Both the Trial Steering Committee and the Data Monitoring and Ethics Committee reviewed the study treatment allocations of these cases and no cause for concern was established.

Numbers of patients who withdrew consent or who were lost to follow-up at 1 year were also recorded (see Appendix 3). In the band 1 arm of the trial, 10% of patients withdrew from the study and 5%

were lost to follow-up at 1 year. In the band 2 arm, 7% withdrew from the study and 4% were lost to follow-up at 1 year. Incorporating the number of deaths into these figures, there was a total dropout rate of 17% in the band 1 arm and 12.5% in the band 2 arm of the trial. See Appendix 3 for the reasons given for withdrawing from the trial.

Meetings

Meetings of the Trial Management Committee took place monthly throughout the study, until May 2002, after which time they were held every 2 months. These meetings were chaired by the lead principal investigator (Professor Shôn Lewis) and comprised all principal investigators, trial managers, TSCs and clinical assessors.

Steering Committee meetings were held every 6 months, comprising all principal investigators on the trial plus three independent members: Professor Glyn Lewis (Cardiff; chairman), Dr John Geddes (Oxford) and Dr Peter Elton (Wigan and Bolton, Bury). The terms of reference of this group included confirming the protocol and any amendments to it, providing an overview of the running of the trial and recruitment, ensuring ethical standards, considering new scientific data, agreeing on the publication strategy, approving any 'add-on' studies and resolving any disputes between principal investigators.

A Data Monitoring and Ethics Committee met once formally and once informally throughout the trial. This group comprised Professor Graham Dunn (trial statistician, Manchester), the trial manager of the Manchester site and two independent members: Dr John Geddes (Oxford; chairman) and Professor Peter Diggle (independent statistician). The remit of this committee was to monitor the quality of randomisation and data and to advise on data analysis.

Local trial management subcommittees met regularly at each centre. These meetings were chaired by the local clinical principal investigator and were typically weekly for 1 hour.

Six-monthly progress reports were compiled for the NCCHTA throughout the trial. An on-site visit by NCCHTA staff also took place during 2001.

Complaints

One complaint was received throughout the life of the trial. This appeared to be a complaint about clinical trials in general rather than an actual event, and was not from a trial participant. The LREC of the hospital where the complaint originated handled this.

Data analysis

Band 1 power calculation

The principal outcome used to determine the sample size needed was the QLS total. The QLS literature was reviewed to establish clinically useful differences that it would be important to demonstrate between the two arms in the band 1 trial. Assuming a correlation of 0.5 between baseline and final (12-month) scores, a completed sample size of 245 in each arm would have had 85% power to detect a difference between 12-month–baseline change scores in the conventional and new atypical arms for band 1 of 5.0 on the QLS (difference in 12-month means of 40 versus 45), assuming a common standard deviation for both baseline and 12-month QLS scores of 18. For comparison, in the band 1 arm, 275 would be needed in each arm for 90% power. Estimating that there would be a 15% dropout rate at 12 months (based on the outcome of the SoCRATES trial[181]), it was concluded that the band 1 arm would need to recruit 564 patients in total.

Band 2 power calculation

The principal outcome used to determine the band 2 sample size needed was again the QLS total. For the band 2 comparison, 60 in each group would allow 85% power to show a difference in the change scores of 10 points (i.e. mean 12-month scores of 35 versus 45). Alternatively, 70 in each arm in band 2 would be needed for 90% power. Estimating a 15% dropout rate at 12 months (based on the outcome of the SoCRATES trial[181]), it was concluded that the band 2 arm of the trial needed to recruit 138 patients in total.

Statistical analysis strategy

The aim of the statistical analyses was to estimate the ITT (i.e. as randomised) effect, where necessary after making allowance for different patterns of loss to follow-up using multiple imputation (assuming that the missing data are ignorable, or missing at random, in the sense defined by Little and Rubin[182]).

Routine data manipulation and data exploration were carried out using SPSS for Windows 10 (Release 10.1.0; SPSS, Chicago, IL, USA). The following analysis of the outcomes was carried out using Stata version 7 (Release 7.0; StataCorp,

College Station, TX, USA) and SOLAS version 3.2 (Statistical Solutions, Cork, Ireland).

For each of the two bands, the data were analysed in the following sequence:

(a) Production of summary statistics for baseline characteristics to check the effectiveness of randomisation in balancing the two arms.
(b) Production of summary statistics for outcome measures.

In the case where QLS and PANSS assessments were available for a given patient but, because of the occasional missing item, one or more of the subscale scores and the total score were missing, then those items were imputed using the median response of the available items within the relevant subscale for that patient.

(c) An analysis based on all available data, to estimate the difference between the treatment arms in the total quality of life scores for each of the three times (12, 26 and 52 weeks) using a longitudinal analysis of covariance (ANCOVA), allowing for location and appropriate baseline score as covariates. This analysis was carried out using xtgee, the generalised estimating equations command in Stata, specifying the identity link and normally distributed errors. The choice of xtgee with an exchangeable structure (the compound symmetry assumption) is equivalent to fitting a random effects model in this case. A random effects regression model (using the exchangeable assumption for the correlations between repeated measures) was used to estimate the treatment arm effect common to each of the three follow-up times, allowing for covariates as above (with allowance for the effects of the baseline covariates to vary over time). The analysis was repeated using the unstructured assumption for the correlations between repeated outcome measurements (in case the results were sensitive to assumptions concerning the serial correlations). In all cases robust standard errors and confidence intervals were requested. Examples of the Stata commands are set out in Appendix 5.
(d) Examination of the patterns of missing data in the two arms over time and exploration of the association between patterns of missing data and baseline characteristics, and between patterns of missing data and outcome measures.

Use of multiple imputation (the propensity score method) in SOLAS version 3.2 to generate five complete data sets (i.e. with imputed missing values). Technical details of the multiple imputation methodology and how to combine estimates from the five generated data sets to produce a common estimate together with a valid confidence interval or standard error, are provided by the SOLAS manual and Rubin and Schenker.[183] Following Lavori and colleagues,[184] separate multiple imputations were carried out for each arm and the complete data from the two arms of the trial were then combined to continue the analysis. Variables used to impute missing values included non-missing QLS and PANNS total scores, location, section, prior poor clinical response, prior bad side-effects, and whether first episode, current alcohol misuse and current drug misuse. Each of the five data sets was analysed using the methods described in (c) and results were combined as described

(e) Repetition of sequence (b) and (c) for other secondary outcome measures. Serial correlations were specified as being unstructured. Sensitivity of the statistical significance of the results to non-normality (in the highly skewed secondary outcome measures) was checked using separate Mann–Whitney *U*-tests on the sum of the 12-, 26- and 52-week outcomes. The effect of missing data on the effects of treatment arm on PANSS total score was investigated by multiple imputation as described above.
(f) Treatment arm differences for non-longitudinal secondary binary outcome measures evaluated using Pearson's χ^2. Treatment arm differences in ordinal outcomes (e.g. patient satisfaction) were evaluated using the Mann–Whitney *U*-test.
(g) Informal exploration of outcomes as a function of compliance with allocated treatment arm (recorded at 12 and 52 weeks after randomisation), actual drug prescribed and other potential prognostic factors. The method of analysis was typically an ANCOVA on the change between baseline and 52 weeks, allowing for the baseline score and location. Tests were carried out for the effects of treatment arm, predictive factor and the treatment arm by predictive factor interaction.

Economic evaluation and analysis strategy

Specific research questions for the economic evaluation were:

1. Are there differences in the direct costs of initiating treatment with the alternative antipsychotics?
2. Are there differences in the health states of people treated with the alternative antipsychotics?
3. Are there differences in the utility of the health states associated with the alternative antipsychotics?
4. Are atypical antipsychotics likely to be more cost-effective than conventional antipsychotics in a population with broadly defined treatment-resistant schizophrenia and in patients intolerant to conventional drugs?
5. Is clozapine likely to be more cost-effective than atypical antipsychotics in a population with narrowly defined treatment-resistant schizophrenia?

Outcome measures

Health outcomes

Health outcomes were measured by the health states reported by patients using the EQ-5D at 12, 26 and 52 weeks from baseline randomisation. These health profiles were converted to utility values using the published utility tariffs for the EQ-5D. It was assumed that the utility values generated by the EQ-5D and population weights would be associated with QLS, PANSS and GAF scores at each assessment point.

Missing data for patients who completed scheduled follow-up but had missing observations were imputed by linear interpolation (value of previous period plus value of next period divided by 2) if observations either side of the missing item were available. This was based on the assumption that utility values and time for one assessment period were correlated with those of the previous and future assessment periods. If data for the baseline assessment were missing, but all subsequent assessments were completed, then the baseline value was imputed as the first observation carried backwards. This approach to missing observations was based on the assumption that time and utility values at each assessment were linearly related to the values in previous and future assessments. The QALYs for this group of patients were estimated as:

$$\text{QALY} = \Sigma\left(\left(U_i + U_{i+1}\right)/2\right) \times \left(t_{i+1} + t_i\right)$$

where U = utility value and t = number of days between assessments.

Linear interpolation was not used if patients did not complete follow-up. Any patients with one or more missing observations at the end of follow-up were treated as representing censored cases. For patients with censored data due to withdrawal or loss to follow-up, missing utility values and time between assessments were imputed from the mean values of those who completed scheduled follow-up or died, for each treatment allocation (i.e. shared care and hospital treatment). Cox regression was used to estimate the survival function and probability of survival at each assessment point, using patient status (alive, dead or withdrawn) and treatment allocation. The QALYs for this group were estimated as:

$$\text{QALY}_C = \Sigma\left(\left(U_i + U_{i+1}\right)/2\right)\left(\left(S_i + S_{i+1}\right)/2\right)\left(t_{i+1} + t_i\right)$$

where U = utility value, S = probability of survival and t = number of days between assessments.

Direct costs

Only direct costs of services used to produce care were included in the economic analysis. The indirect costs of lost production due to illness were excluded in line with guidelines for good practice. However, information was collected on employment status at each assessment period, and these descriptive data are presented in summary form.

Information was also collected from patients at each assessment about their type of accommodation, use of the criminal justice system and use of informal care. However, these items were excluded from the estimate of the direct costs of care for the following reasons. First, it was anticipated that, over a 12-month period, accommodation and use of informal care were determined by organisational systems and social settings more than the choice of antipsychotic medication. If the groups were unbalanced on these variables at baseline, this could introduce bias to the analysis. Second, the range of data collected meant that it was only possible to collect information about the use of the criminal justice system and informal care from patient report. There were concerns that use of criminal justice systems and of informal care may be inconsistently and inaccurately reported by patients. It was not possible to validate the use of criminal justice services from other sources. Assessment with informal carers was attempted, to validate the use of their time and services. However, it proved difficult to identify carers and obtain informed consent from both patients and carers to conduct the interviews. Descriptive summaries of the type of accommodation and use of the criminal justice system are presented to give an indication of the

extent to which they were reported, and the potential mis-estimation or bias that may have been introduced by their exclusion from the costs of care.

The direct costs were measured as resource use multiplied by the unit cost or price of the resource item. The mean cost (standard deviation) of events was estimated from the clinical trial data and published national unit cost data.

The main types of resource use were hospital inpatient and outpatient services, primary and community care services, and prescribed medications. Data on the use of psychiatric and non-psychiatric hospital care and medication were obtained by case-note review in the primary hospital or clinic where the patient was treated and any other hospitals that were reported as being used by patients and key workers. In addition, patients were asked to complete an economic questionnaire at each assessment. This was used to identify whether the patient had used any other hospital, primary or community care services since the last assessment. If services had been used patients were asked to give information about the type, name and location of the services. This information was used to identify sources of data about the frequency and intensity or service use, which were obtained from detailed review of the hospital, primary and community care records for each service reported as being used by each participant in the trial. It was anticipated that this method of data collection would minimise the extent of missing data for the key cost drivers (psychiatric inpatient and outpatient hospital care).

Examination of hospital trust financial returns data published by the Chartered Institute of Public Finance and Accountancy (CIPFA)[185] indicated a high degree of variability in the unit costs of the hospitals and trial centres included in the evaluation. This indicated that the use of hospital-specific unit costs would increase the variance in the cost estimates and mask any differences due to the treatment allocation. National average data were used to control for the differences in costs between care settings. The national reference costs data published by the UK Department of Health were used to estimate the costs of psychiatric inpatient and outpatient hospital care, by type of ward or outpatient visit. Sensitivity analysis was used to test the impact of using national unit cost data from other sources.[185,186] The hospital trust financial returns data published by the CIPFA[185] were used to estimate the cost of non-psychiatric hospital care by type of ward or admitting speciality.

Detailed information about medication included dose, duration and route of administration. This was used to calculate a daily cost for oral medication and cost per injection or dose for depot and 'as required' medicines. The daily cost was estimated from the British National Formulary (BNF). The daily cost was multiplied by the reported duration for courses of treatment completed within the study period and by the length of the study period for courses of treatment that were ongoing. The cost of medicines did not include the costs of dispensing or administration. It was assumed that these costs were included in the costs of hospital inpatient and outpatient care and/or primary and community care.

The unit costs of primary and community-based care services were derived from the costs of health and social care published by the Personal Social Services Research Unit (PSSRU), University of Kent.[186]

All missing resource-use data were treated as missing at random. This was based on the assumptions that, first, the level of missing data for psychiatric hospital care (the key cost component) would be minimal and, second, the use of other services would be determined by external factors such as the availability and organisation of services, and the patient's living situation and accommodation. Multiple imputation was used to impute values for the subsequent missing costs, by category of resource use. The multiple imputation was conducted using SOLAS for missing data analysis, version 3.0. The propensity score method was used. The model included study period (baseline to week 12, week 13 to week 26, and week 27 to week 52) and treatment allocation group as fixed covariates.

Incremental cost-effectiveness ratio

It was anticipated that there would be an association between cost and outcome, in that poorer health status will be associated with increased resource use and cost. In addition, the relevant outcome for an economic evaluation is the incremental cost of an additional unit of health gain. These factors mean that it was appropriate to relate the net costs of the strategies to patient outcomes. In the past economists have argued that if there is evidence that there are no statistically significant differences in health outcomes, the economic evaluation can be reduced to a cost-minimisation analysis. However, it is also

clear that in many cases, even if there are no statistically significant differences in effectiveness or costs, analysis of the cost-effectiveness plane indicates that a proportion of cases is less effective and/or more costly. It is argued, therefore, that cost-effectiveness acceptability analysis is a superior approach.[187–189] This can also include the possibility that an intervention is associated with no differences in effectiveness, and is cost saving.

For each comparison, the incremental cost–utility ratio was estimated as the net cost of the most effective antipsychotic treatment allocation divided by the net QALY of that treatment allocation (e.g. the cost of conventional antipsychotics minus the cost of atypical antipsychotics divided by the QALY of conventional antipsychotics minus the QALY of atypical antipsychotics). Cost-acceptability analysis was used to estimate the probability that an intervention was cost-effective.[190] The cost-effectiveness acceptability analysis was used to estimate the probability that an intervention is cost-effective using ceiling thresholds in the range £0/life-year gained to £50,000/life-year gained, in increments of £1000. Bootstrap estimates of the incremental cost-effectiveness ratio (ICER) and net benefit statistic (mean, 2.5–97.5 percentile), cost-effectiveness plane and cost acceptability curve are presented.[189,190]

Data analysis

Correlations between cost and QALY variables

The data were analysed to evaluate whether the assumptions that (1) health status, utility values and other outcome measures were associated, and that a low level of health reported in the EQ-5D and utility values was reflected in a reported low level of health in the other outcome measures; (2) estimates of QALYs in one assessment period were associated with QALY estimates in subsequent assessment periods, to test whether the assumption underlying the use of linear interpolation of missing observations was valid; (3) QALYs and costs were associated at baseline and over time, to test the assumption that these variables were correlated; (4) estimates of costs in one assessment period were associated with cost estimates in subsequent assessment periods; and (5) costs were associated with baseline characteristics such as type of accommodation and employment. Non-parametric bivariate correlations were used for analyses (1)–(4) and stepwise regression was used for analysis (5).

Stepwise regression analysis was used to assess whether total costs were predicted by the costs of care for the 3 months before entry into the trial, QALYs, accommodation status and living situation.

Primary analysis

The economic data were manipulated and analysed in SPSS version 11.5 to obtain estimates of costs and QALYs. The primary analysis estimated the mean (standard deviation) costs, utility values and QALYs associated with each intervention and the ICER.

The primary measure of interest for the economic analysis was the ICER. Bootstrapping techniques were used to derive estimates of imputed cost and QALY values, the cost-effectiveness plane of the ICER, net benefit statistic and cost acceptability curve to determine the probability that atypical antipsychotics were cost-effective compared with conventional antipsychotics and clozapine was cost-effective compared with atypical antipsychotics. The net benefit and cost acceptability analysis used a £0–50,000 range of cost per QALY threshold values, in increments of £1000 to estimate mean net benefit and the probability that an intervention was cost-effective. Microsoft Excel spreadsheets were used for the bootstrap analysis.

Each imputed dataset was bootstrapped and then averaged for use in the cost-effectiveness acceptability analysis.

Sensitivity analyses

A number of assumptions was required to deal with missing observations and censored cases, for both QALYs and costs. The impact of these assumptions on the results was tested using alternative approaches to imputation of missing data. The impact of alternative sources of unit cost data was also tested in the sensitivity analysis. Costs and QALYs were also compared with analysis of covariance using a general linear model and covariates of baseline QALYs or costs. Treatment allocation was entered as a fixed factor.

Chapter 5

Results: band 1

Recruitment and patient flow

In total, 275 patients were referred into the band 1 arm of the trial. Of these, 48 were not randomised (*Figure 6*), for the following reasons:

- ineligible: $n = 9$ (3%)
- clinician withdrew referral: $n = 2$ (1%)
- unable to give consent: $n = 1$ (0.4%)
- refused consent: $n = 36$ (13%).

A total of 73 clinicians had patients who were successfully randomised into the band 1 arm of the trial. The final numbers of patients in the study per treatment centre are set in *Table* 7.

There was one protocol violation. This patient had been randomised into the study before the consultant concluded that the individual did not have a mental health diagnosis. This case was included in the final analysis in their randomised treatment arm.

Figure 6 shows the flow of band 1 patients through the trial.

Baseline characteristics of band 1 patients

Baseline demographic characteristics of the band 1 sample are set out in *Table 8*. The mean age of the band 1 sample was 40.7 years and the majority (67.8%) were male. Just over 25% of the band 1 sample described themselves as non-white in terms of their ethnic origin. Schizophrenia was the diagnosis of the majority (74.7%) of band 1 participants and just over 57% of the sample were outpatients at baseline. Most band 1 patients (74.9%) were not defined as current drug users or current alcohol users (61.2%).

Drug treatment allocation

Of the 227 patients, 118 (52%) were randomly assigned to receive a conventional antipsychotic and 109 (48%) randomly assigned to receive an atypical antipsychotic drug (see *Figure 6* and *Table 9*).

The two randomised groups were comparable at baseline (see *Table 8*).

Follow-up rates

The final band 1 follow-up assessment rate was 81% at 1 year, lower than the projected rate of 85% (see Appendix 3 for full details of follow-up rates). Follow-up rates for band 1 at each period can also be seen in *Figure 6*.

As a result of the aim of conducting 1-year follow-up assessments with as many patients as possible, a number of patients' 52-week follow-up visits were done outside the projected assessment dates. Approximately 80% of assessments were carried out within the projected period. The most overdue assessment was carried out 287 days late. This was for a patient who had been involved in a road traffic accident requiring substantial periods of hospitalisation. However, there were no statistically significant differences in the overall number of days in the trial between the groups [mean difference conventional versus atypical = 10 days, 95% confidence interval (CI) of the difference –21 to +42].

Attrition rates

There were six deaths in the band 1 arm of the trial. Three deaths occurred in patients randomised to receive a conventional antipsychotic drug and three deaths occurred in

TABLE 7 *Band 1, randomised by treatment centre*

Trial centre	Number of patients randomised
Manchester	99
Nottingham	75
Institute of Psychiatry	30
Imperial College (includes Cambridge site)	23

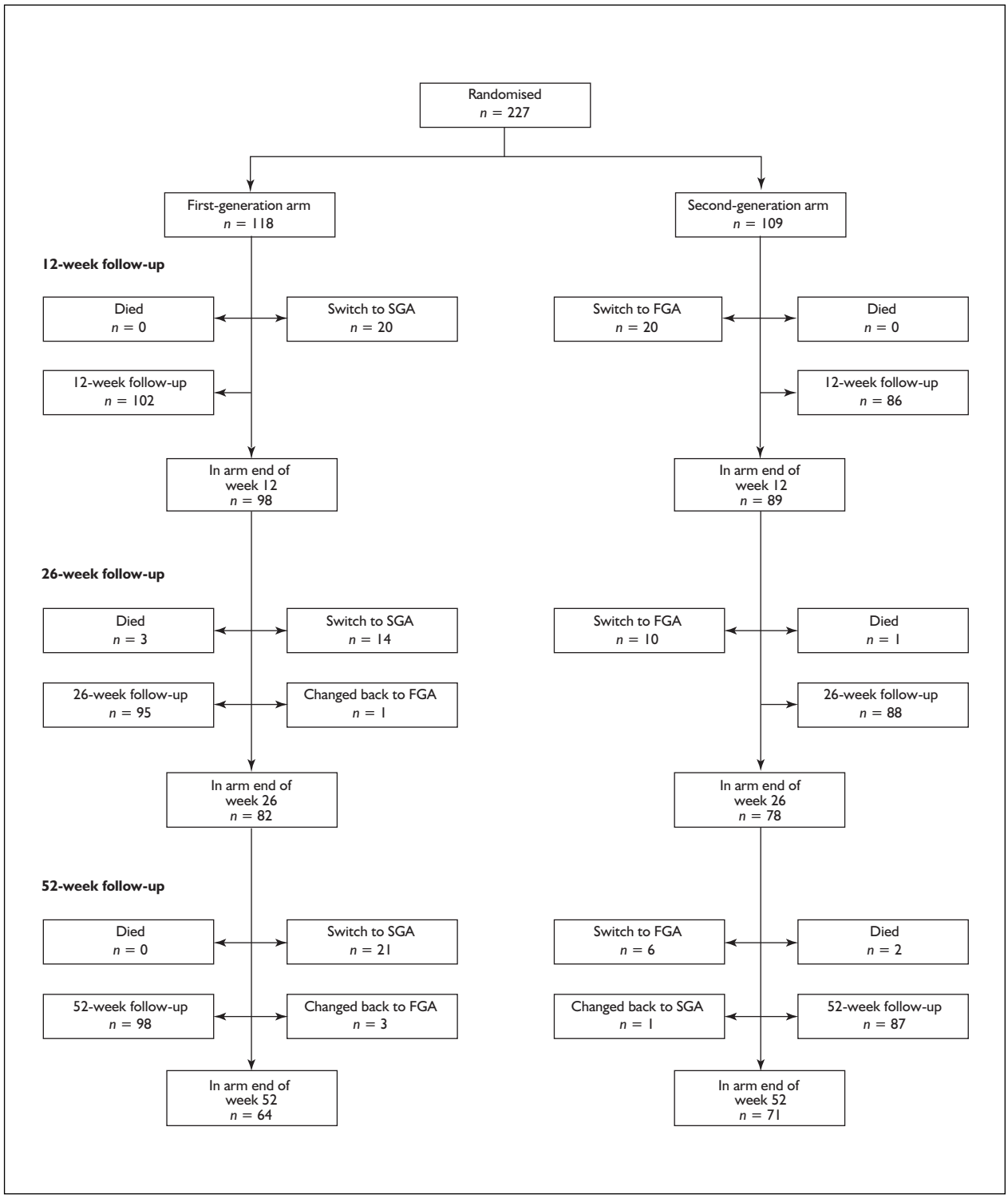

FIGURE 6 *Band 1 participant flow*

TABLE 8 *Band 1, baseline demographic characteristics*

	Conventional arm (*n* = 118)	**Atypical arm (*n* = 109)**
Age (years)		
Mean (SD)	40.5 (11.3)	40.9 (11.1)
Median (range)	40.5 (18–63)	41.6 (19–62)
Length of illness (years)		
Mean (SD)	13.3 (10.8)	14.4 (11.2)
Median (range)	11.9 (0–42)	11.6 (0–39)
Number of previous admissions		
Mean (SD)	3.4 (4.7)	3.9 (3.9)
Median (range)	2 (0–40)	3 (0–20)
Gender		
Men, *n* (%)	81 (69)	73 (67)
Women	37	36
Ethnicity		
White, *n* (%)	87 (74)	83 (76)
Black Caribbean	8	9
Black African	5	5
Black other	2	2
Indian	4	4
Pakistani	2	3
Bangladeshi	1	0
Chinese	1	1
Other Asian	2	1
Other	6	1
Diagnosis		
Schizophrenia, *n* (%)	85 (72)	83 (78)
Schizophreniform	5	3
Schizoaffective disorder	22	17
Delusional disorder	6	4
Patient status at baseline		
Inpatient	48	43
Day-patient	1	5
Outpatient, *n* (%)	69 (59)	61 (56)
First episode?		
Yes	15	11
Current drug misuse		
None	86	84
Current alcohol misuse		
None	74	65

TABLE 9 *Band 1, antipsychotic drug received*

Conventional arm[a]	***n* = 118**	**Atypical arm**[a]	***n* = 109**
Chlorpromazine	8	Amisulpride	13
Droperidol	1	Olanzapine	50
Flupenthixol	1	Quetiapine	23
Flupenthixol dec.	2	Risperidone	22
Fluphenazine dec.	3		
Haloperidol	7		
Haloperidol dec.	2		
Loxapine	3		
Pipothiazine palm.	2		
Sulpiride	58		
Thioridazine	1		
Trifluoperazine	21		
Zuclopenthixol	5		
Zuclopenthixol dec.	3		

[a] Two data points are missing.
dec., decanoate; palm., palmitate.

TABLE 10 *Band 1, median patient satisfaction scores*

	Conventional arm (*n* = 118)		Atypical arm (*n* = 109)		
	n	Median	*n*	Median	*p*
12 weeks					
Satisfaction	94	4.0	84	4.0	0.066
Mental health	94	3.0	84	2.0	0.179
Side-effects	94	2.0	82	2.0	0.671
Recommend	95	3.0	83	3.0	0.544
52 weeks					
Satisfaction	91	4.0	79	4.0	0.297
Mental health	91	2.0	78	2.0	0.958
Side-effects	90	2.0	78	2.0	0.867
Recommend	91	3.0	79	2.0	0.288

patients randomised to the new atypical arm of the trial. Of the three deaths in the conventional arm, two were due to cardiac failure and one death was considered to be an open verdict (suicide or accidental death). Of the three deaths in the new atypical arm, two were also due to cardiac failure and one death was due to septicaemia (in a quadriplegic patient). Full details of deaths during the study can be seen in Appendix 3. A further 11 patients (5%) were categorised as 'lost to follow-up' at 1 year (see Appendix 3 for these cases split by treatment centre) and 22 patients (10%) withdrew from the study. Reasons given for withdrawing from the trial are given in Appendix 3.

Including the numbers of deaths, withdrawals and lost to follow-ups, there was a total dropout rate of 39 patients (17%).

Details of unmasking

There were six cases of unmasking. Two of these cases were of patients in the atypical arm and four were patients in the conventional arm (see Appendix 3 for full details of instances of unmasking).

Patient satisfaction data

A qualitative rating of patient satisfaction was carried out at both the 12- and 52-week follow-up assessments (see Appendix 1 for this unpublished scale). This questionnaire included Likert-type ratings in the areas of satisfaction with new antipsychotic drug treatment, mental health and side-effects since starting the new drug, and whether the patient would recommend their new antipsychotic drug to another person with similar mental health problems.

In the conventional arm of band 1, the patient satisfaction questionnaire was completed by 80% of patients at the 12-week assessment and 77% at the 52-week assessment. In the atypical arm, the satisfaction questionnaire was completed by 76% of patients at the 12-week assessment and 72% at the 52-week assessment.

The findings were analysed using the non-parametric Mann–Whitney *U*-test and the results are set out in *Table 10*.

A higher score on the satisfaction scale indicates greater satisfaction and a lower score on the mental health scale indicates a rating of better mental health. A higher score on the side-effects scale indicates worse side-effects, and a lower score on the recommend scale indicates greater agreement that the patient would recommend their new treatment.

As can be seen in *Table 10*, no differences between the two treatment arms in band 1 were observable using the patient satisfaction questionnaire.

Quantitative results

Band 1 power

The band 1 trial recruited 227 patients, much lower than originally expected. After an exploration of the QLS scores, it was estimated that the correlation between baseline and 12-month total scores was a little above 0.75 (not 0.5 as used in the original power calculations). The within-group standard deviations were similar to those originally envisaged. The higher baseline–12-month correlation implies that the within-group standard deviation for the change score was about 13, not 18. The implication of this

TABLE 11 *Band 1, QLS*[170]

Variable	Conventionals			New atypicals		
	n	Mean	SD	*n*	Mean	SD
QLS total						
Baseline	118	43.29	21.65	108	43.49	20.31
12 weeks	100	49.24	19.91	87	46.55	18.95
26 weeks	93	49.22	20.50	87	50.39	18.79
52 weeks	100	53.19	21.21	85	51.34	19.59
QLS interpersonal relations subscale						
Baseline	118	15.97	9.26	108	16.56	9.53
12 weeks	100	18.09	8.75	87	16.86	8.14
26 weeks	93	18.02	9.31	87	18.01	8.10
52 weeks	100	19.37	9.03	85	18.34	8.45
QLS occupational role functioning subscale						
Baseline	118	4.97	6.85	108	4.30	5.88
12 weeks	100	5.73	6.53	87	5.00	6.26
26 weeks	93	5.25	6.23	87	6.01	6.45
52 weeks	100	6.48	6.58	85	6.32	6.57
QLS other residual symptoms subscale						
Baseline	118	22.34	8.60	108	22.64	8.68
12 weeks	100	25.42	8.25	87	24.69	8.16
26 weeks	93	25.95	8.14	87	26.37	7.63
52 weeks	100	27.34	8.87	85	26.68	7.87

TABLE 12 *Band 1, primary outcome: total quality of life scores*

Data	Estimate	SE	95% CI	
(a)	–1.67	1.43	–4.48 to 1.13	(p = 0.242)
(b)	–2.50	1.91	–6.24 to 1.24	

(a) Available data analysis; (b) mean of five multiple imputation runs.
NB. Covariates were allowed for as described previously (i.e. baseline quality of life and location).

change is that the band 1 trial would have 80% power to detect a difference of 5 points if there were about 110 patients in each of the two arms. Assuming that dropout brought the number down to 94 per arm, the resulting power would be likely to be about 75%.

Primary and secondary outcome measurements

Primary outcome

Results on the QLS are summarised in *Table 11*.

The parameter estimates given in *Table 12* are for the effect of treatment arm (randomisation) common to all three outcome times (12, 26 and 52 weeks). Two results are presented (both assuming unstructured correlations for the repeated measures): (a) an available data analysis, and (b) the mean for five multiple imputation runs to allow for missing data.

The negative parameter estimates (–1.67 and –2.50 using the two different methods of analysis) mean that, on average, the quality of life scores were about 2 points better in the conventional arm than in the new atypical arm (this follows directly from the coding of the two arms: 0 for conventionals and 1 for new atypicals). The two methods of analysis give essentially the same results. The fact that the two-sided 95% confidence intervals both include 0 means that there is no statistically significant difference between the two arms. If anything, the evidence is in favour of the conventional arm, however, and one can conclude from the upper confidence limits of 1.13 and 1.24 that even if the outcome for new atypicals were indeed better, the difference is no more than just over 1 point on the QLS. Such a difference would be clinically insignificant.

TABLE 13 *Band 1, PANSS*[175]

Variable	Conventionals			New atypicals		
	n	Mean	SD	*n*	Mean	SD
PANSS total						
Baseline	118	72.92	17.19	109	71.34	16.48
12 weeks	100	68.49	17.26	86	68.22	15.16
26 weeks	94	68.31	16.90	88	67.45	16.68
52 weeks	99	64.56	15.13	86	66.20	17.49
PANSS positive subscale						
Baseline	118	15.94	5.88	109	15.49	5.43
12 weeks	100	14.64	5.12	86	14.63	4.86
26 weeks	95	14.78	5.26	88	14.77	4.79
52 weeks	99	13.94	4.49	86	14.01	5.28
PANSS negative subscale						
Baseline	118	20.56	6.89	109	20.01	6.47
12 weeks	100	19.15	6.39	86	18.71	5.68
26 weeks	95	19.42	6.27	88	18.52	5.50
52 weeks	99	17.31	5.82	86	18.19	6.14
PANSS general subscale						
Baseline	118	36.42	8.75	109	35.84	9.48
12 weeks	100	34.70	8.64	86	34.88	8.33
26 weeks	94	34.33	8.57	88	34.16	9.48
52 weeks	99	33.30	8.08	86	34.01	9.37

Secondary outcomes

Secondary outcomes are summarised in *Tables 13–16*.

Table 17 shows the results for the complete case analysis, with the exception of the PANSS total score, which includes imputed values obtained by multiple imputation.

Supplementary analyses

Clinically significant improvement in QLS/PANSS

Supplementary analyses were carried out to examine further the change in both QLS and PANSS scores, which are considered to represent clinically significant improvement. In this trial, an increase of 8 or more units on the QLS and a decrease of 15 or more units on the PANSS represented a 20% change from mean baseline (taking both treatment bands into account).

No statistically significant relationships were found between treatment arm (conventional versus atypical drug) and 20% improvement in either QLS scores ($p = 0.187$) or PANSS scores ($p = 0.592$). In band 1, 49% of those randomised to conventionals showed a clinically significant improvement on QLS compared with 33% of those randomised to new atypical drugs. For PANSS total score, the proportions of clinically significant improvement were 24% and 18%, respectively.

Band 1: reason for referral

Patients were entered into band 1 of the trial as a result of poor clinical response to previous antipsychotic treatment (broadly defined treatment resistance) and/or as a result of side-effects from their previous antipsychotic treatment (treatment intolerance).

As can be seen from *Table 18*, there was a small imbalance in the randomised participants such that more primarily treatment-resistant, as opposed to treatment-intolerant, patients were allocated to new atypicals.

Economic results

Health status, utility values and QALYs

Table 69 in Appendix 6 indicates that there was a statistically significant association between utility values and other measures of health outcomes (QLS, PANSS, GAF), so that a low level of utility reflected a low level of health status or symptoms reported by the other outcome measures. There was also a statistically significant association

TABLE 14 *Band 1, side-effects scales*

Variable	Conventionals			New atypicals		
	n	Mean	SD	*n*	Mean	SD
Simpson–Angus Scale[178]						
Baseline	115	4.39	5.20	104	4.15	4.56
12 weeks	97	4.10	4.68	84	4.20	4.66
26 weeks	93	3.88	4.87	84	3.54	4.06
52 weeks	94	2.97	3.93	80	3.25	3.70
BARS[179]						
Baseline	118	2.35	3.00	107	3.15	3.57
12 weeks	98	1.74	2.66	85	2.21	2.76
26 weeks	93	2.03	2.68	84	1.95	2.43
52 weeks	95	1.50	2.36	81	1.98	2.71
AIMS[168]						
Baseline	118	1.71	2.92	107	1.83	3.32
12 weeks	97	1.52	3.26	85	2.04	3.31
26 weeks	94	2.29	4.40	84	1.63	3.12
52 weeks	95	2.29	4.50	81	1.79	3.28
Form 15 (total EPS side-effects score)						
Baseline	115	8.49	7.27	104	9.01	7.82
12 weeks	96	7.36	6.89	84	8.45	7.32
26 weeks	93	8.23	7.70	84	7.12	6.81
52 weeks	94	6.78	6.69	80	7.06	6.30
ANNSERS[169]						
Baseline	117	14.62	9.33	103	15.55	9.59
12 weeks	99	10.53	8.19	83	12.75	8.46
26 weeks	93	10.86	8.03	83	12.50	8.68
52 weeks	95	10.78	7.70	82	12.45	8.37

TABLE 15 *Band 1, GAF[1]*

Variable	Conventionals			New atypicals		
	n	Mean	SD	*n*	Mean	SD
GAF total						
Baseline	118	45.62	14.90	108	42.71	13.55
12 weeks	100	49.03	12.82	86	47.73	12.46
26 weeks	95	49.19	12.60	87	50.53	13.91
52 weeks	100	52.38	13.31	85	52.29	13.93
GAF symptoms						
Baseline	103	44.42	15.17	96	43.11	14.90
12 weeks	96	48.81	13.18	81	49.56	12.82
26 weeks	95	48.37	13.70	87	50.80	14.35
52 weeks	100	50.96	14.29	85	51.56	14.57
GAF disability						
Baseline	103	44.59	14.13	96	41.89	13.34
12 weeks	96	47.64	11.59	81	47.31	12.29
26 weeks	95	48.91	12.61	87	50.06	13.84
52 weeks	100	52.75	13.02	85	52.64	14.36

TABLE 16 *Band 1, remaining outcome measures*

Variable	Conventionals			New atypicals		
	n	Mean	SD	*n*	Mean	SD
Calgary Depression Scale[167]						
Baseline	118	6.58	5.00	108	6.90	5.23
12 weeks	100	4.54	4.03	86	5.12	3.82
26 weeks	95	4.56	3.97	85	5.19	4.02
52 weeks	98	4.22	3.79	83	4.96	3.86
DAI[176]						
Baseline	117	8.21	11.50	108	10.56	10.55
12 weeks	97	9.92	11.94	85	13.31	10.33
26 weeks	93	9.77	12.56	85	13.65	10.21
52 weeks	96	10.93	11.61	81	14.36	10.08
Compliance Scale[177]						
Baseline	116	5.08	1.29	108	5.08	1.35
Week 12	112	5.03	1.53	106	4.97	1.66
Week 26	110	5.05	1.50	98	4.93	1.74
Week 52	104	5.01	1.54	96	5.19	1.56

TABLE 17 *Band 1, secondary outcomes*

Variable	Estimate	SE	95% CI	*p*
PANSS total[a]	2.32	1.48	–0.58 to 5.21	0.132
After multiple imputation[a]	2.38	1.73	–1.99 to 5.44	
GAF total[b]	0.07	1.35	–2.57 to 2.71	0.961
Depression[a]	0.54	0.39	–0.22 to 1.29	0.163
Simpson–Augus[a]	0.17	0.39	–0.60 to 0.93	0.664
BARS[a]	0.01	0.26	–0.51 to 0.52	0.982
AIMS[a]	–0.19	0.39	–0.95 to 0.58	0.631
Form15 EPS total[a]	–0.16	0.68	–1.50 to 1.18	0.814
DAI[b]	1.34	1.03	–0.69 to 3.36	0.196
ANNSERS[a]	1.13	0.76	–0.35 to 2.62	0.135

[a] The positive parameter estimates (e.g. 2.32 for the PANSS total) mean that, on average, the symptom scores were better (i.e. less) in the conventional arm than in the new atypical arm (this follows directly from the coding of the two arms: 0 for conventionals and 1 for new atypicals). The two-sided 95% CIs all include 0 and mean that there are no statistically significant differences between the two arms.

[b] A high score on this item means a better outcome (as in the quality of life scores). A negative parameter estimate would imply that the conventional arm patients were doing better; a positive parameter estimate the opposite. There was, in fact, no difference between the two arms.

TABLE 18 *Band 1, reason for referral*

	Neither	Poor clinical outcome alone	Side-effects alone	Both
Conventional arm	0	52	35	31
Atypical arm	0	59	13	37

TABLE 19 *Band 1, utility and evaluation of own health, EuroQol by treatment group*

		Conventional	Atypical
Baseline		*n* = 118	*n* = 108
Utility	Mean	0.67	0.61
	SD	0.29	0.33
	Range	–0.16 to 1.00	–0.35 to 1.00
Evaluation of own health	Mean	57.40	55.27
	SD	26.83	25.33
	Range	0.00 to 100.00	0.00 to 100.00
Week 12		*n* = 102	*n* = 85
Utility	Mean	0.77	0.72
	SD	0.22	0.25
	Range	0.16 to 1.00	–0.18 to 1.00
Evaluation of own health	Mean	62.66	62.43
	SD	23.83	17.73
	Range	0.00 to 100.00	0.00 to 100.00
Week 26		*n* = 95	*n* = 86
Utility	Mean	0.82	0.75
	SD	0.18	0.25
	Range	0.11-1.00	–0.18 to 1.00
Evaluation of own health	Mean	59.47	62.36
	SD	22.72	19.68
	Range	0.00 to 100.00	20.00 to 100.00
Week 52		*n* = 98	*n* = 84
Utility	Mean	0.81	0.76
	SD	0.19	0.24
	Range	0.00 to 1.00	–0.03 to 1.00
Evaluation of own health	Mean	64.77	61.80
	SD	21.08	20.91
	Range	0.00 to 100.00	0.00 to 100.00

between utility at each assessment period suggesting that the use of linear interpolation to impute missing observations for patients with otherwise complete follow-up was valid. The linear interpolation was only used if data were available for the previous and following assessment period. If these data were not available then the data were treated as censored.

The analysis indicated that there was an improvement in health status and utility between baseline and assessment at week 12. This improvement was maintained from week 12 to week 52. *Tables 71–77* in Appendix 6 present the detailed results of the EQ-5D and utility values and the detailed results of the EQ-5D by health domain and study period, summarise these data by treatment allocation group, and present the utility values by assessment period for all patients, respectively.

Table 19 reports the utility values by treatment group and assessment period. These indicate that there was an improvement in utility in the first 12 weeks for all treatment allocations, which was maintained to week 52. This is depicted graphically in *Figure 7*.

Table 20 presents the QALY values, by treatment allocation. The results indicate that there was a trend towards higher QALYs for the group who were allocated to initiation of treatment with conventional rather than atypical antipsychotics. This applies for the primary and sensitivity analyses. In the primary analysis, although the lower end of the 2.5th percentile of the bootstrapped mean difference is negative, it is close to zero, supporting the trend towards a difference between the QALYs of patients in the conventional and atypical antipsychotic groups.

Resource use and costs

Table 21 indicates that there was no evidence of a statistically significant association between costs for the 3 months before baseline and baseline utility

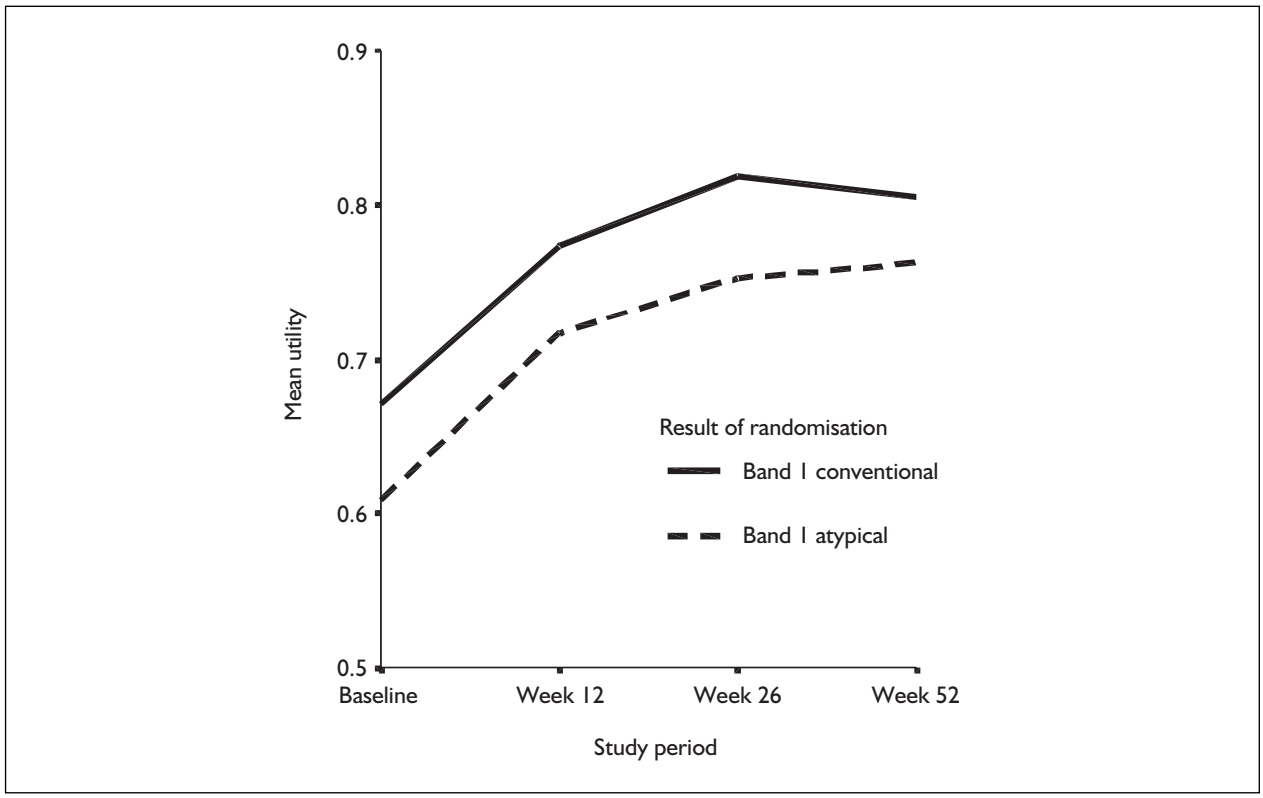

FIGURE 7 *Band 1, mean utility scores by time of follow-up*

TABLE 20 *Band 1, QALYs*

Analysis	Treatment arm	*n*	Mean	Mean difference	SE	95% CI
Primary analysis						
Bootstrapped QALYs	Conventional	118	0.74	0.08	0.00	0.01 to 0.14[a]
	Atypical	108	0.66			
Sensitivity analysis						
QALYs adjusted for covariance	Conventional	118	0.73	0.04	0.03	–0.01 to 0.10
	Atypical	108	0.68			
QALYs including imputed values for all missing data	Conventional	118	0.74	0.07	0.03	0.01 to 0.13
	Atypical	108	0.67			
QALYs, complete case analysis	Conventional	87	0.79	0.05	0.03	–0.01 to 0.11
	Atypical	70	0.74			
QALYs including imputed values for missing observations only	Conventional	101	0.77	0.06	0.03	0.00 to 0.12
	Atypical	87	0.71			

[a] 2.5th to 97.5th percentile of the bootstrapped estimates.

TABLE 21 *Band 1, stepwise regression model, dependent variable total cost baseline to week 52*

	Unstandardised coefficients	SE	Standardised coefficients	*t*	*p*-Value	95% CI for *B*	
	B		Beta			Lower bound	Upper bound
(Constant)	21,988.54	8,965.84		2.45	0.00	1.54	2.76
PREBASEC	2.72	0.31	0.83	8.66	0.00	2,197.73	5,831.44
QALYs	–25,406.99	11,595.35	–0.21	–2.19	0.00	2,962.54	11,331.88

values or between costs and QALYs at assessment periods 26 and 52. There was an association between QALYs and costs for the first 12-week period ($p = 0.03$). There was evidence of a statistically significant association between costs at each assessment period. Costs before baseline were also associated with type of accommodation ($p < 0.01$), employment status ($p = 0.03$) and living situation ($p < 0.01$) at baseline. This correlation was evident between costs and accommodation and living situation, but not employment in subsequent periods. Stepwise regression suggested that total cost over the 52-week period of the trial was dependent on the level of costs for 3 months before the trial, so that higher costs before the trial were associated with higher costs during the trial. Costs were also dependent on the total QALYs, so that improvements in health-related quality of life were associated with lower costs during the trial. Accommodation and living situation were not statistically significant and so were eliminated from the model in the stepwise process. These data support the assumption of a link between costs and QALYs. They also suggest that costs in the trial follow-up period were influenced by the patients' accommodation and employment status at baseline.

Tables 22–24 summarise the employment status, type of accommodation and use of the criminal justice system. The majority of patients were unemployed or economically inactive at baseline and throughout follow-up in both allocation groups. For both groups the majority of people lived in their own homes rather than residential accommodation or hospital facilities. Few people reported using the criminal justice system and the average use was low in both groups.

Table 25 summarises the costs by assessment period and category of service use for each treatment group, using a complete case analysis. A detailed breakdown of service use and costs is shown in Appendix 6, *Tables 75–83*. This only includes patients where complete resource use and cost data were available at each assessment point. As indicated, complete data were available for a high proportion of participants, particularly for psychiatric and non-psychiatric hospital admissions. The number of patients with recorded service use was lower for community and primary care services. In addition, *Table 82* in Appendix 6 indicates that the number of people using community-based services and the intensity of use were low.

Table 26 summarises the costs of psychiatric hospital care by source of unit cost data, non-psychiatric hospital care, antipsychotic medication, use of other medicines, and primary and community care services. *Table 26* reports the costs for the full ITT sample of patients, including imputed values for missing observations and censored cases. *Table 27* shows the mean costs and differences in mean costs between the treatment groups.

There was a trend for the mean costs for the 52 weeks of the trial to be lower for people allocated to initiation of conventional antipsychotic therapy rather than atypical antipsychotic therapy.

Cost-effectiveness analysis

Table 28 presents point estimates of the ICER ratio. The results of the primary and sensitivity analyses suggest that conventional antipsychotics are associated with lower costs and higher QALYs than atypical antipsychotics or a cost per QALY gained of less than £5000.

The cost and effect data were bootstrapped to give pairs of mean differences for cost and QALY. For band 1, 20,000 bootstrap replicates were obtained. The bootstrap data were also used to estimate the probability that the intervention with a higher QALY value was cost-effective, the net benefit at different threshold values of cost per QALY and cost acceptability curves.

Figure 8 presents the bootstrapped data in terms of a cost-effectiveness plane for the incremental costs and QALYs of conventional antipsychotics (i.e. the costs and QALYs of conventional antipsychotics minus those of atypical antipsychotics). This shows each pair of cost and effect differences from the bootstrap replicates, and indicates that while the majority of net QALY estimates for conventional antipsychotics were higher than for atypical antipsychotics, the costs were spread between cost-saving and cost-additive.

Overall, the probability that conventional antipsychotics would be cost-effective was 0.91 if decision-makers were willing to pay up to £50,000 per QALY gained. That is, 91% of bootstrap replicates indicated that conventional antipsychotics were associated with a higher QALY value than atypical antipsychotics and a cost per QALY of less than £50,000. The analysis indicated that the probability that conventional antipsychotics were cost-effective was 0.65 at a threshold value of £0 cost per QALY. That is, if decision-makers were not prepared to pay any additional cost for an improvement in QALYs, the

TABLE 22 *Band 1, employment status by treatment group*

Current economic status		Baseline		Week 12		Week 26		Week 52	
		Conventional	Atypical	Conventional	Atypical	Conventional	Atypical	Conventional	Atypical
Employee, >30 hours per week	*n*	6	4	6	3	5	6	5	6
	%	5	4	5	3	4	6	4	6
Employee, <30 hours per week	*n*	3	1	2	1	1	2	1	2
	%	3	1	2	1	1	2	1	2
Self-employed	*n*	0	2	0	1	NR	NR	1	0
	%	0	2	0	1	NR	NR	1	0
Government-supported training	*n*	1	0	0	1	NR	NR	NR	NR
	%	1	0	0	1	NR	NR	NR	NR
Employee on sick leave	*n*	2	1	1	3	0	1	1	1
	%	2	1	1	3	0	1	1	1
Unemployed	*n*	23	19	11	5	13	2	15	2
	%	20	17	9	5	11	2	13	2
Economically inactive	*n*	77	77	78	71	71	75	72	73
	%	65	71	66	65	60	69	61	67
Other	*n*	6	5	2	2	5	2	5	1
	%	5	5	2	2	4	2	4	1
Missing	*n*	0	0	18	22	23	21	18	24
	%	0	0	15	20	20	19	15	22
Total	*n*	118	109	118	109	118	109	118	109
	%	100	100	100	100	100	100	100	100

NR, not reported.

TABLE 23 *Band 1, type of accommodation at assessment, by treatment group*

Current accommodation		Baseline		Week 12		Week 26		Week 52	
		Conventional	Atypical	Conventional	Atypical	Conventional	Atypical	Conventional	Atypical
Owner occupied	*n*	6	8	19	17	17	16	20	17
	%	5.10	7.30	16.10	15.60	14.40	14.70	16.90	15.60
Other	*n*	3	1	2	1	2	1	2	1
	%	2.50	0.90	1.70	0.90	1.70	0.90	1.70	0.90
Privately rented	*n*	1	4	6	6	6	6	9	10
	%	0.80	3.70	5.10	5.50	5.10	5.50	7.60	9.20
Rented: local authority	*n*	29	22	36	30	42	32	39	30
	%	24.60	20.20	30.50	27.50	35.6	29.40	33.10	27.50
Overnight facility 24-hour staff	*n*	4	2	8	5	5	5	7	6
	%	3.40	1.80	6.80	4.60	4.20	4.60	5.90	5.50
Overnight facility not staffed 24 hours	*n*	1	2	4	4	6	1	5	3
	%	0.80	1.80	3.40	3.70	5.10	0.90	4.20	2.80
Overnight facility unstaffed	*n*	1	0	2	0	2	1	2	1
	%	0.80	0.00	1.70	0.00	1.70	0.90	1.70	0.90
Acute psychiatric ward	*n*	2	4	2	1	5	5	1	3
	%	1.70	3.70	1.70	0.90	4.20	4.60	0.80	2.80
Psychiatric rehabilitation ward	*n*	2	0	3	5	3	5	3	4
	%	1.70	0.00	2.50	4.60	2.50	4.60	2.50	3.70
Long-stay psychiatric ward	*n*	3	1	5	2	4	2	5	2
	%	2.50	0.90	4.20	1.80	3.40	1.80	4.20	1.80
General medical ward	*n*	0	1	NR	NR	NR	NR	NR	NR
	%	0.00	0.90	NR	NR	NR	NR	NR	NR
Homeless	*n*	0	1	NR	NR	NR	NR	NR	NR
	%	0.00	0.90	NR	NR	NR	NR	NR	NR
Missing	*n*	66	63	31	38	26	35	25	32
	%	55.90	57.80	26.30	34.90	22.00	32.10	21.20	29.40
Total	*n*	118	109	118	109	118	109	118	109
	%	100	100	100	100	100	100	100	100

TABLE 24 *Band 1, average number of contacts with criminal justice system, by treatment group*

Contacts with criminal justice system	Conventional			Atypical		
	n	Mean	SD	*n*	Mean	SD
Number of police contacts	28	1	1	16	2	1
Number of probation contacts	24	1	2	16	<1	<1
Nights in cells	26	5	16	15	2	6
Number of psychiatric assessments	25	<1	1	16	1	1
Number of criminal court appearances	25	1	2	16	1	1
Number of civil court appearances	24	<1	<1	16	<1	1

TABLE 25 *Band 1, cost of services, (£, 2001–2), complete case analysis*

Study period	Allocation group		Psychiatric hospital	Non-psychiatric hospital	Anti-psychotic medicines	Other medicines	Community and primary care services	Total cost
Baseline–week 12	Conventional	Mean	5,763	172	68	41	137	5,615
		n	114	112	111	113	90	86
		SD	8,011	1,675	114	70	239	8,115
	Atypical	Mean	5,594	185	178	33	223	5,077
		n	107	97	104	102	84	75
		SD	7,347	1,745	177	50	428	6,816
Week 13–26	Conventional	Mean	4,205	73	58	43	200	4,974
		n	109	108	105	114	86	9,119
		SD	8,318	550	74	81	384	77
	Atypical	Mean	4,099	331	201	42	257	4,610
		n	101	98	93	103	83	7,702
		SD	7,493	2,591	226	62	710	72
Week 27–52	Conventional	Mean	7,181	79	240	83	292	7,455
		n	104	107	98	108	91	74
		SD	16,273	485	443	151	500	16,732
	Atypical	Mean	7,096	733	390	86	427	8,082
		n	99	93	91	101	79	69
		SD	13,368	6,834	431	132	792	15,582

TABLE 26 *Band 1, 12-month cost of services (£, 2001–2), including imputed values for missing data*

	Treatment group	*n*	Mean	SD
Psychiatric hospital	Conventional	118	17,170	28,518
	Atypical	109	16,953	24,869
Non-psychiatric hospital	Conventional	118	389	1,781
	Atypical	109	1,280	7,485
Antipsychotic medicines	Conventional	118	401	455
	Atypical	109	763	661
Other medicines	Conventional	118	172	284
	Atypical	109	166	214
Community and primary care	Conventional	118	715	860
	Atypical	109	946	1,350

TABLE 27 *Band 1, net costs of services (£, 2001–2)*

Analysis	Treatment arm	*n*	Mean	SD	Estimated difference	SE of difference
Primary analysis						
Bootstrapped imputed net costs	Conventional	118	18,849	2,637	–1,274	25
	Atypical	109	20,123	2,318		
Sensitivity analysis						
Imputed net costs, reference cost unit cost data	Conventional	118	17,555	26,840	–2,562	3,608
	Atypical	109	20,118	25,348		
Net costs, PSSRU unit cost data	Conventional	118	21,817	31,590	–1222	3,956
	Atypical	109	23,039	28,178		
Net costs, CIPFA unit cost data	Conventional	118	21,258	31,836	–1065	3994
	Atypical	109	22,322	38,456		
Net costs, complete case analysis	Conventional	96	14,766	26,809	164	3,693
	Atypical	87	14,601	22,713		

TABLE 28 *Band 1, cost per QALY gained by conventional antipsychotics (£, 2001–2)*

Analysis	Net cost	Net QALY	ICER
Primary analysis			
Bootstrapped costs and QALYs	–1,274	0.08	Conventional antipsychotics dominate
Sensitivity analysis			
QALYs adjusted for covariance, costs estimated using reference cost unit costs	–1,274	0.04	Conventional antipsychotics dominate
QALYs including imputed values for all missing data	–1,261	0.07	Conventional antipsychotics dominate
QALYs, complete case analysis	–1,261	0.05	Conventional antipsychotics dominate
QALYs including imputed values for missing observations only	–1,261	0.06	Conventional antipsychotics dominate
QALYs adjusted for covariance, costs estimated using PSSRU unit cost data	–1,222	0.04	Conventional antipsychotics dominate
QALYs adjusted for covariance, costs estimated using CIPFA unit cost data	–1,065	0.04	Conventional antipsychotics dominate
QALYs adjusted for covariance, costs estimated complete case analysis	164	0.04	4,100
QALYs, complete case analysis, costs estimated complete case analysis	164	0.05	3,280

probability that conventional antipsychotics would still be cost-effective was 65%. *Figure 9* presents the data in the form of a cost acceptability curve.

Revaluing the QALY values by ceiling thresholds of acceptable cost per QALYs from £0 to £50,000 gives an estimated net benefit. *Table 29* presents these values and they are depicted graphically in *Figure 10*. The estimated mean net benefit of conventional antipsychotics is £5008.

Band 1 patient flow

Prior drug

Prior to randomisation into the band 1 arm of the trial, 84 patients were receiving a depot drug. Conventional drugs were prescribed to 186 patients and atypical drugs were prescribed to 43 patients. One patient was prescribed clozapine immediately before randomisation. Twenty-eight patients (12%) were receiving more than one

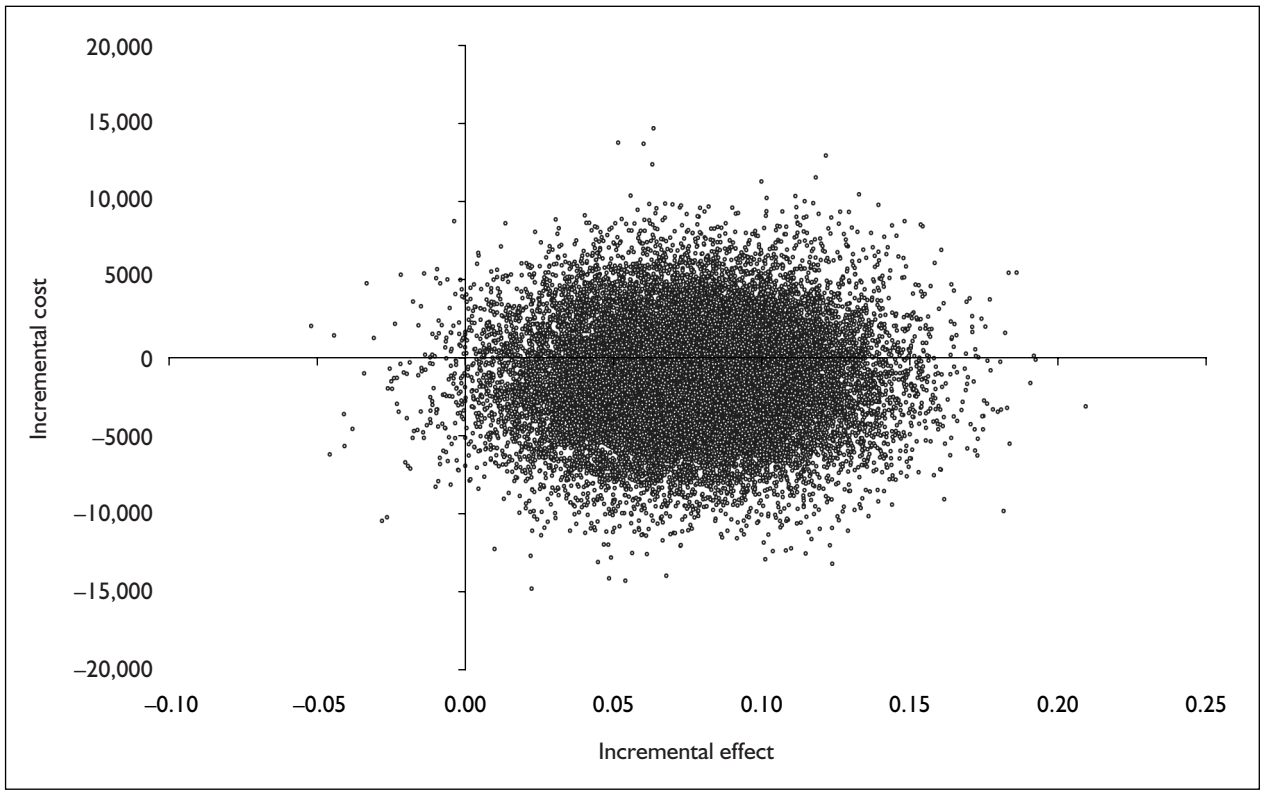

FIGURE 8 *Band 1, cost-effectiveness plane of the incremental costs and QALYs of conventional antipsychotics*

TABLE 29 *Band 1, net benefit values for conventional antipsychotics antipsychotics (£, 2001–2)*

	Net benefit of conventional antipsychotics
Mean	5,008
SD	3,966
2.5th percentile	–3,054
97.5th percentile	12,596

antipsychotic drug before randomisation into the study.

Also see *Figure 6* for band 1 patient flow details.

12-week follow-up period

Conventional arm

Twenty patients (17%) were not in the conventional arm by the end of the 12-week follow-up period, with the following reasons being given:

- ineffective: $n = 7$
- intolerable: $n = 7$
- ineffective and intolerable: $n = 1$
- other (including non-compliance): $n = 3$
- not yet started randomised arm: $n = 2$.

The seven patients who found conventionals ineffective switched to olanzapine (two patients), quetiapine, clozapine and no further antipsychotic treatment (three patients). The seven patients who found conventionals intolerable switched to risperidone (three patients), amisulpride (two patients), olanzapine and no further drug treatment. The patient who found conventional treatment both ineffective and intolerable was switched to quetiapine.

Sixteen patients (14%) switched drug within the treatment arm. Ineffectiveness was the reason cited in four cases (sulpiride to flupenthixol dec., chlorpromazine to methotrimeprazine, haloperidol to droperidol and sulpiride to pipothiazine palm.). Intolerance was cited as the reason for the switch in four cases (loxapine to sulpiride and flupenthixol dec., chlorpromazine to sulpiride, sulpiride to chlorpromazine and loxapine to flupenthixol dec.). A further four

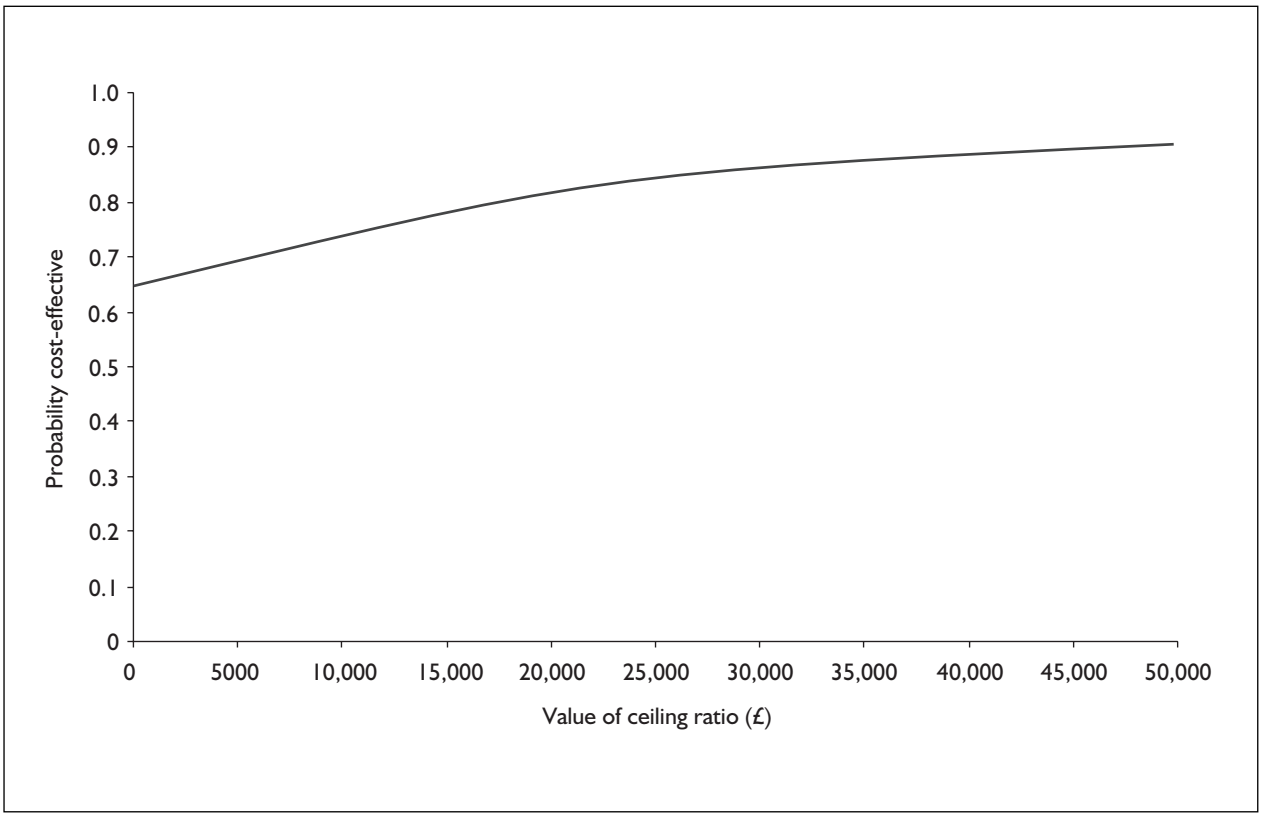

FIGURE 9 *Band 1, cost-effectiveness acceptability curve of the cost per QALY gained by conventional antipsychotics*

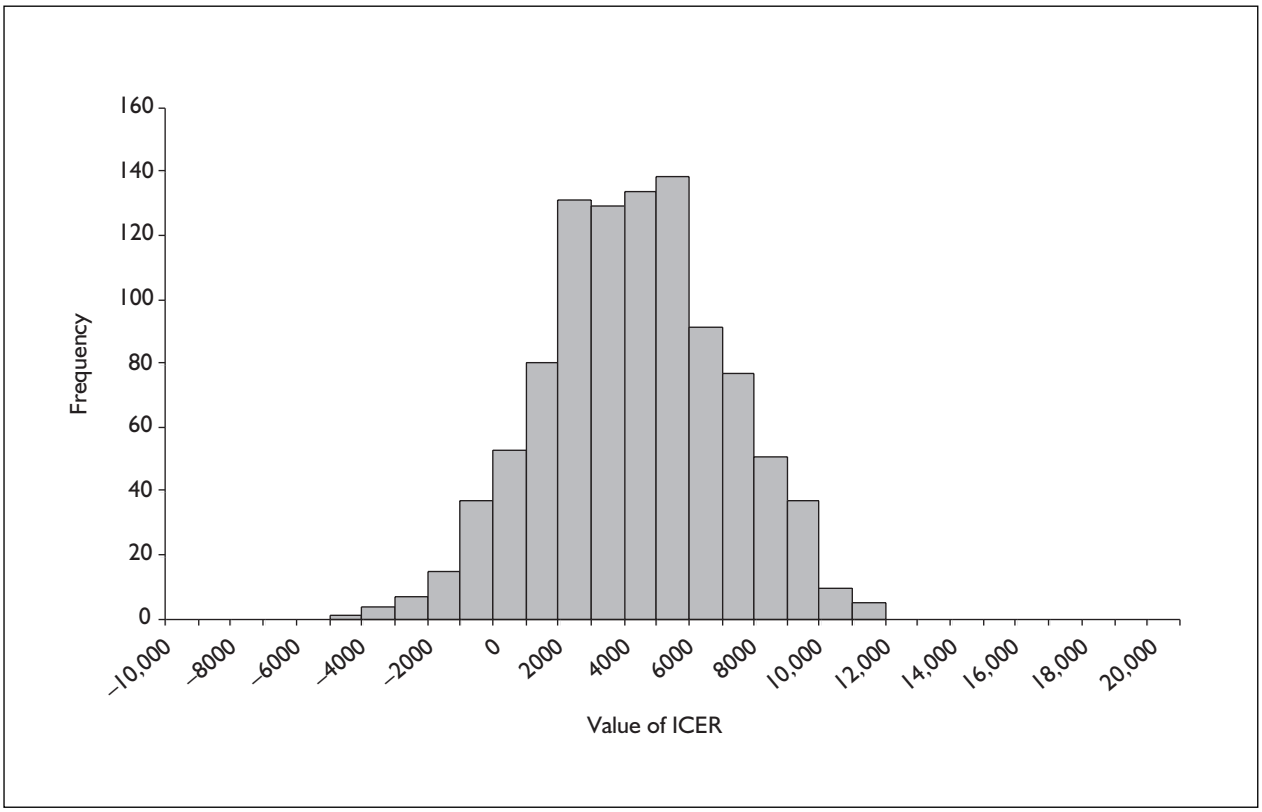

FIGURE 10 *Net benefit values of the ICER for conventional antipsychotics*

patients switched drug within the conventional arm citing other reasons including non-compliance (sulpiride to zuclopenthixol dec., sulpiride to trifluoperazine, sulpiride to flupenthixol dec. and trifluoperazine to flupenthixol dec.). Two patients (2%) had not started conventional treatment by the end of the 12-week follow-up period.

During the 12-week follow-up period, four patients in the conventional arm withdrew from the study but there were no deaths. Seventeen patients (14%) in the conventional arm were receiving more than one antipsychotic drug by the end of the 12-week follow-up period. One-hundred and two patients (86%) in the conventional arm completed their 12-week follow-up assessment and 98 patients (83%) were still in the randomised arm and receiving a conventional drug at the end of the 12-week follow-up period.

Atypical arm

Twenty patients (18%) were not in the atypical arm by the end of the 12-week follow-up period, with the following reasons being given:

- ineffective: $n = 6$
- intolerable: $n = 5$
- other (including non-compliance): $n = 5$
- not yet started atypical treatment: $n = 4$.

The six patients who found atypicals ineffective switched to clozapine (two patients), pimozide, trifluoperazine and fluphenazine dec., and one patient came off antipsychotic treatment altogether. The five patients who found atypical treatment intolerable switched to conventional drugs (trifluoperazine, pipothiazine palm., flupenthixol dec. and zuclopenthixol dec.). Of the five patients who were switched citing other reasons, two came off antipsychotics altogether, one patient switched to flupenthixol dec. and there were no available data on the other two patients.

Twelve patients switched drug within the treatment arm, four patients switching owing to ineffectiveness (risperidone to amisulpride, risperidone to quetiapine, amisulpride to risperidone and quetiapine to olanzapine). A further four patients switched drug within the arm owing to intolerance (olanzapine to risperidone, two patients, amisulpride to olanzapine and quetiapine to amisulpride). One patient switched drug owing to both ineffectiveness and intolerance, switching from amisulpride to olanzapine. The two patients who switched drug citing other reasons switched from quetiapine to olanzapine and from olanzapine to risperidone. Four patients (4%) had not started treatment in the atypical arm by the end of the 12-week follow-up period.

During the 12-week follow-up period, six patients in the atypical arm withdrew from the study but there were no deaths. Eleven patients (10%) in the atypical arm were receiving more than one antipsychotic drug, but three patients (3%) were not receiving any antipsychotic drug treatment by the end of the 12-week follow-up period. Eighty-six patients (79%) completed their 12-week follow-up assessment and 89 patients (82%) were still in the randomised arm and receiving an atypical drug at the end of the 12-week follow-up period.

26-week follow-up period

Conventional arm

A further 16 patients (14%) were not in the conventional arm by the end of the 26-week follow-up period, with the following reasons being given:

- ineffective: $n = 6$
- intolerable: $n = 3$
- other (including non-compliance): $n = 7$.

The six patients who found conventionals ineffective switched to risperidone, clozapine, olanzapine, quetiapine, amisulpride and no antipsychotic treatment at all. The three patients who found conventionals intolerable switched to olanzapine, risperidone and quetiapine. Of the further seven patients who switched citing other reasons, one went on to clozapine and there were no records available for the others. Five patients (4%) switched drug within the treatment arm. Two of these switched for reasons of ineffectiveness (sulpiride to flupenthixol), one switched because of intolerance (fluphenazine dec. to flupenthixol dec.) and one switched citing other reasons (haloperidol to trifluoperazine). One patient restarted the randomised conventional treatment during the 26-week follow-up period.

One patient in the conventional arm withdrew from the study and there were three deaths in this arm during this period. Eleven patients in the conventional arm were receiving more than one antipsychotic drug by the end of the 26-week follow-up period. Ninety-five patients (80%) completed their 26-week follow-up assessment and 83 patients (70%) were still in the randomised arm and receiving a conventional drug at the end of the 26-week follow-up period.

Atypical arm

A further 11 patients (10%) were not in the atypical arm by the end of the 26-week follow-up period, with the following reasons being given:

- ineffective: $n = 3$
- intolerable: $n = 1$
- ineffective and intolerable: $n = 2$
- other (including non-compliance): $n = 5$.

The three patients who found atypicals ineffective switched to trifluoperazine, chlorpromazine and haloperidol dec., and one patient came off antipsychotic treatment altogether. The patient who found atypical treatment intolerable switched to flupenthixol dec. and the two patients who found atypicals both ineffective and intolerable switched to clozapine. Of the five patients who were switched citing other reasons, two went on to sulpiride and fluphenazine dec. and there were no records available for the other three patients. Two patients switched drug within the treatment arm during this period because of ineffectiveness. These two patients switched from risperidone to olanzapine and from quetiapine to amisulpride.

There were no withdrawals from the study, but there was one death in the atypical arm during this period. Thirteen patients in the atypical arm were receiving more than one antipsychotic drug and one patient was not receiving any antipsychotic drug treatment by the end of the 26-week follow-up period. Eighty-eight patients (81%) in this arm completed their 26-week follow-up assessment and 78 patients (72%) were still in the randomised arm and receiving an atypical drug at the end of the 26-week follow-up period.

52-week follow-up period

Conventional arm

A further 22 patients (19%) were not in the conventional arm by the end of the 52-week follow-up period, with the following reasons being given:

- ineffective: $n = 6$
- intolerable: $n = 7$
- other (including non-compliance): $n = 9$.

The six patients who found conventionals ineffective switched to clozapine (two patients), olanzapine (two patients) and amisulpride (two patients). The seven who found conventionals intolerable switched to risperidone (two patients), olanzapine (three patients) and quetiapine (two patients). Of the further nine patients who switched citing other reasons, three went on to olanzapine and there were no records available for the others.

Four patients (3%) switched drug within the treatment arm during this period. Two switched for reasons of ineffectiveness (both sulpiride to zuclopenthixol dec.), one switched because of both ineffectiveness and intolerance (sulpiride to haloperidol) and one switched citing other reasons (sulpiride to trifluoperazine and fluphenazine dec.). Three patients were back in the conventional arm by the end of the 52-week follow-up period.

During this follow-up period, five patients in the conventional arm withdrew from the study, four patients were deemed to be lost to follow-up and there were no deaths. Ten patients in this arm were receiving more than one antipsychotic drug by the end of the study. Ninety-eight patients (83%) in the conventional arm completed their 52-week follow-up assessment and 64 patients (54%) were still in the randomised arm and receiving a conventional drug by the end of the study.

Atypical arm

A further eight patients (7%) were not in the atypical arm by the end of the 52-week follow-up period, with the following reasons being given:

- ineffective: $n = 3$
- intolerable: $n = 1$
- ineffective and intolerable: $n = 1$
- other (including non-compliance): $n = 3$.

The three who found atypicals ineffective switched to clozapine, flupenthixol dec. and pipothiazine palm. The one patient who found atypical treatment intolerable switched to trifluoperazine and the one patient who found atypicals both ineffective and intolerable switched to chlorpromazine. Of the other three patients, two died and one withdrew, with no record of subsequent drug treatment.

Five patients switched drug within the treatment arm during this period. One each switched from olanzapine to quetiapine and from olanzapine to risperidone because of ineffectiveness and the other three switched from risperidone to olanzapine, from amisulpride to risperidone and from olanzapine to risperidone.

During the 52-week follow-up period, six patients in the atypical arm withdrew from the study, seven patients were deemed to be lost to follow-up and

TABLE 30 *Band 1 conventional arm, end of study drug*

Antipsychotic drug	Number of patients
Chlorpromazine	5
Flupenthixol	4
Flupenthixol dec.	7
Fluphenazine dec.	2
Haloperidol	2
Methotrimeprazine	1
Pipothiazine palm.	1
Sulpiride	32
Trifluoperazine	12
Zuclopenthixol	3
Zuclopenthixol dec.	8
Amisulpride	5
Olanzapine	20
Quetiapine	4
Risperidone	4
Clozapine	8

TABLE 31 *Band 1 atypical arm, end of study drug*

Antipsychotic drug	Number of patients
Amisulpride	10
Olanzapine	37
Quetiapine	11
Risperidone	13
Clozapine	4
Chlorpromazine	5
Droperidol	1
Flupenthixol dec.	8
Fluphenazine dec.	3
Haloperidol	1
Haloperidol dec.	1
Pimozide	1
Pipothiazine palm.	4
Sulpiride	1
Thioridazine	1
Trifluoperazine	3
Zuclopenthixol dec	1

there were two deaths. Ten patients in the atypical arm were receiving more than one antipsychotic drug by the end of the 52-week follow-up period. Eighty-seven patients (80%) in the atypical arm completed their 52-week follow-up assessment and seventy-one patients (65%) were still in the randomised arm and receiving an atypical drug by the end of the study.

TABLE 32 *Band 1 conventional arm, end of study drug dose*

Antipsychotic drug	Mean dose (mg)	Range (mg)
Chlorpromazine	250	200–300
Flupenthixol	4	2–6
Flupenthixol dec.	142 2/52	40 4/52–250 1/52
Fluphenazine dec.	50 2/52	–
Haloperidol	22.5	20–25
Methotrimeprazine	250	–
Pipothiazine palm.	50 2/52	–
Sulpiride	813	200–2400
Trifluoperazine	15	6–30
Zuclopenthixol	37	20–50
Zuclopenthixol dec.	358 2/52	150 2/52–750 2/52

TABLE 33 *Band 1 atypical arm, end of study drug dose*

Antipsychotic drug	Mean dose (mg)	Range (mg)
Amisulpride	610	200–1200
Olanzapine	15	5–30
Quetiapine	450	200–750
Risperidone	5	2–10

Comparison of the two treatment arms

There was a non-significant trend for patients to still be in the atypical arm versus the conventional arm at 1 year (n = 71, 65% versus n = 64, 54%), taking all patients who entered the study.

End of study drug and dose

Twenty-eight of the 58 patients randomised to sulpiride (48%) were still on the drug at the end of the study, although three of these were also receiving another antipsychotic in addition to sulpiride (*Table 30*).

Thirty-seven of the 50 patients (74%) randomised to receive olanzapine were still on the drug at the end of the study (*Table 31*).

The doses of drug used at the end of the study are shown in *Tables 32* and *33*.

Chapter 6

Results: band 2

Recruitment and patient flow

In total, 168 patients were referred into the band 2 arm of the trial. Of these, 32 were not randomised (*Figure 11*) for the following reasons:

- ineligible: $n = 7$ (4%)
- refused consent: $n = 25$ (15%).

A total of 60 clinicians had patients who were successfully randomised into the band 2 arm of the trial. The final numbers of patients in the study per treatment centre are set out in *Table 34*.

There were no protocol violations in the band 2 arm of the trial.

Figure 11 shows the flow of band 2 patients through the trial.

Baseline characteristics of band 2 patients

Baseline demographic characteristics of the band 2 sample are set out in *Table 35*. The mean age of the band 2 sample was 37.6 years and the majority (68.4%) were male. Almost 30 per cent of the sample described themselves as non-white in terms of their ethnic origin. Schizophrenia was the diagnosis of the majority (86.7%) of band 2 participants and almost 56% of the sample were inpatients at baseline. Most band 2 patients (77.2%) were not defined as current drug users or current alcohol users (57.4%).

A glance at these figures reveals that the mean age of the band 2 sample was lower than that of the band 1 sample. The majority of band 2 patients were inpatients, whereas in band 1, the majority of patients were outpatients.

Drug treatment allocation

Of the 136 patients, 67 (49%) were randomly assigned to receive clozapine and 69 (51%) randomly assigned to receive an atypical antipsychotic drug (see *Figure 11* and *Table 36*).

The two randomised groups were comparable at baseline (see *Table 35*).

Follow-up rates

The final band 2 follow-up assessment rate was 87% at 1 year, higher than the projected rate of 85% (see Appendix 3 for full details of follow-up rates). Follow-up rates for band 2 at each period can also be seen in *Figure 11*.

As a result of the aim of conducting 1-year follow-up assessments with as many patients as possible, a number of patients' 52-week follow-up visits were done outside of the projected assessment dates, although approximately 80% of assessments were carried out within the projected timescale.

Attrition rates

There was one death in the band 2 arm of the trial, of a patient randomised to receive a new atypical antipsychotic. The cause of death was cardiac failure. Full details of deaths during the study can be seen in Appendix 3. A further six patients (4%) were categorised as 'lost to follow-up' at 1 year (see Appendix 3 for these cases split by treatment centre). Ten patients (7%) withdrew from the study. Reasons given for withdrawing from the trial are given in Appendix 3. Including the numbers of deaths, withdrawals and lost to follow-ups, there was a total dropout rate of 17 patients (12.5%).

TABLE 34 *Band 2, randomised by treatment centre*

Trial centre	Number of patients randomised
Manchester	37
Nottingham	46
Institute of Psychiatry	22
Imperial College (includes Cambridge site)	31

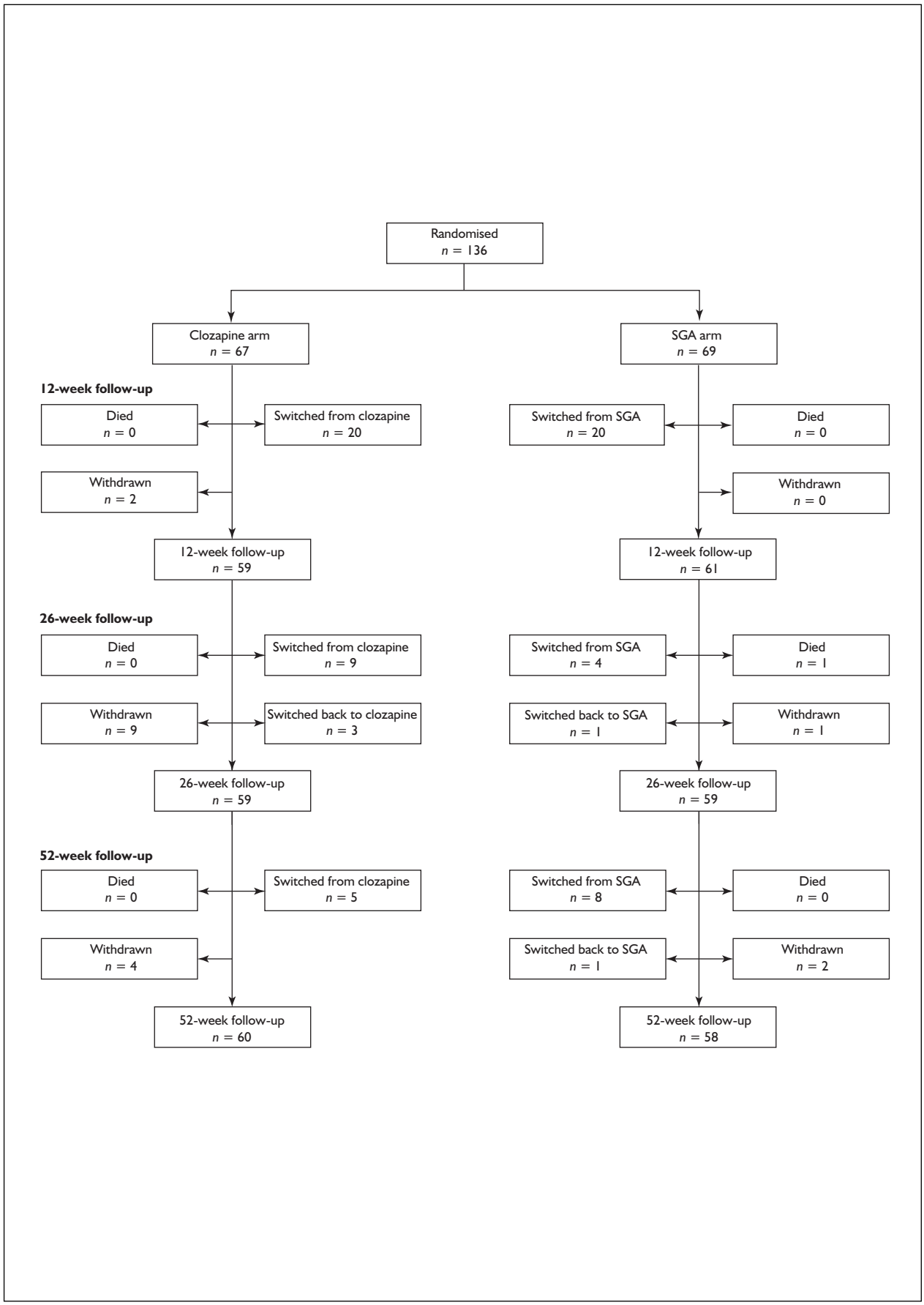

FIGURE 11 *Band 2 participant flow*

TABLE 35 *Band 2, baseline demographic characteristics*

	Clozapine arm (*n* = 67)	Atypical arm (*n* = 69)
Age (years)		
Mean (SD)	37.2 (12.2)	37.9 (10.3)
Median (range)	36.2 (18–63)	36.9 (20–65)
Length of illness (years)		
Mean (SD)	13.0 (10.5)	13.6 (10.2)
Median (range)	11.2 (0–39)	10.9 (0–46)
Number of previous admissions		
Mean (SD)	4.2 (5.0)	5.6 (5.0)
Median (range)	3.0 (0–30	5.0 (0–33)
Gender		
Men, *n* (%)	49 (73)	44 (64)
Women, *n* (%)	18 (27)	25 (36)
Ethnicity		
White, *n* (%)	45 (67)	53 (77)
Black Caribbean	9	5
Black African	2	4
Black other	3	3
Indian	3	1
Pakistani	0	0
Bangladeshi	1	1
Chinese	0	0
Other Asian	2	0
Other	2	2
Diagnosis		
Schizophrenia, *n* (%)	60 (90)	58 (84)
Schizophreniform	1	1
Schizoaffective disorder	5	9
Delusional disorder	1	1
Patient status at baseline		
Inpatient, *n* (%)	41 (61)	35 (51)
Daypatient, *n* (%)	2 (3)	2 (3)
Outpatient, *n* (%)	24 (36)	32 (46)
First episode?		
Yes, *n* (%)	8 (12)	4 (6)
Current drug misuse		
None, *n* (%)	49 (73)	56 (81)
Current alcohol misuse		
None, *n* (%)	40 (60)	38 (55)

TABLE 36 *Band 2, antipsychotic drug received*

Clozapine arm	*n* = 67	Atypical arm	*n* = 69
Clozapine	67	Amisulpride	10
		Olanzapine	31
		Quetiapine	21
		Risperidone	7

Details of unmasking

There were four cases of unmasking, where the assessor became aware of the class of drug the patient was currently receiving. One of these instances was a patient in the clozapine arm and, the other instances were of patients in the atypical arm. In two of these four cases, the patient had in fact already switched medication and, consequently, the assessor became aware of their current drug treatment and not that to which they had originally been randomised. See Appendix 3 for further details.

TABLE 37 *Band 2, median patient satisfaction scores*

	Clozapine arm (*n* = 67)		Atypical arm (*n* = 69)		
	n	**Median**	***n***	**Median**	***p***
12 weeks					
Satisfaction	53	4.0	54	3.0	0.176
Mental health	53	2.0	54	3.0	0.048
Side-effects	52	2.5	55	2.5	0.566
Recommend	53	2.5	55	3.0	0.233
52 weeks					
Satisfaction	54	4.0	55	4.0	0.668
Mental health	52	2.0	55	2.0	0.233
Side-effects	52	2.0	53	2.0	0.984
Recommend	53	2.0	54	2.0	0.794

Patient satisfaction data

A qualitative rating of patient satisfaction was carried out at both the 12- and 52-week follow-up assessments using a scale devised for the study (see Appendix 1). This questionnaire included Likert-type ratings in the areas of satisfaction with new antipsychotic drug treatment, mental health and side-effects since taking the new medication, and whether the patient would recommend their new antipsychotic drug to another person with similar mental health problems.

The patient satisfaction questionnaire was completed by 79% of patients in both treatment arms at both the 12-week and the 52-week follow-up assessments.

The findings were analysed using the non-parametric Mann–Whitney *U*-test and the results are set out in *Table 37*.

A higher score on the satisfaction scale indicates greater satisfaction and a lower score on the mental health scale indicates a rating of better mental health. A higher score on the side-effects scale indicates worse side-effects, and a lower score on the recommend scale indicates greater agreement that the patient would recommend their new treatment.

The only significant difference found between the two treatment arms in band 2, using the patient satisfaction questionnaire, was that a greater improvement in mental health at 12 weeks was reported by patients who had been randomised to receive clozapine compared with those randomised to receive a new atypical drug.

Quantitative results

Band 2 power

The band 2 arm of the trial recruited 136 patients.

Primary and secondary outcome measurements

Primary outcome

Results on the QLS are summarised in *Table 38*.

The parameter estimates given in *Table 39* are for the effect of treatment arm (randomisation) common to all three outcome times (12, 26 and 52 weeks). Two results are presented (both assuming unstructured correlations for the repeated measures): (a) an available data analysis, (b) the mean for five multiple imputation runs to allow for missing data.

The negative parameter estimates (–3.63 and –4.47 using the two different methods of analysis) mean that, on average, the quality of life scores were about 4 points better in the clozapine arm than in the new atypical arm (this follows directly from the coding of the two arms: 0 for clozapine and 1 for new atypicals). The two methods of analysis give essentially the same results. The fact that the two-sided 95% confidence intervals both just include 0 means that there is no statistically significant difference between the two arms, but the evidence is in favour of the clozapine arm.

Secondary outcomes

Secondary outcomes are summarised in *Tables 40–43*.

Table 44 shows the results for the entire case analysis, with the exception of the PANSS total score.

TABLE 38 *Band 2, QLS*[170]

Variable	Conventionals			New atypicals		
	n	Mean	SD	*n*	Mean	SD
QLS total						
Baseline	67	41.03	19.91	69	34.67	17.08
12 weeks	57	46.40	18.91	61	40.85	17.74
26 weeks	58	50.81	19.78	59	41.47	18.62
52 weeks	59	53.32	19.19	56	44.95	18.66
QLS interpersonal relations subscale						
Baseline	67	16.82	10.45	69	13.80	8.74
12 weeks	57	18.84	9.38	61	15.21	8.57
26 weeks	58	19.60	8.91	59	14.58	7.85
52 weeks	59	20.37	8.79	56	16.00	8.42
QLS occupational role functioning subscale						
Baseline	67	2.57	4.93	69	2.42	4.16
12 weeks	57	3.23	5.16	61	3.52	4.55
26 weeks	58	4.12	5.57	59	3.46	5.20
52 weeks	59	5.14	6.15	56	3.79	5.20
QLS other residual symptoms subscale						
Baseline	67	21.64	8.38	69	18.45	7.68
12 weeks	57	24.33	8.16	61	22.11	7.44
26 weeks	58	27.09	8.71	59	23.44	7.93
52 weeks	59	27.81	7.98	56	25.16	8.16

TABLE 39 *Band 2, primary outcome: total quality of life scores*

Data	Estimate	SE	95% CI	
(a)	–3.63	2.08	–7.71 to 0.46	(p = 0.082)
(b)	–4.47	2.39	–9.16 to 0.23	

(a) Available data analysis; (b) mean of five multiple imputations runs.
NB. Covariates were allowed for as described previously (i.e. baseline quality of life and location).

In terms of all side-effect ratings, there were non-significant trends for patients in the clozapine group to be doing better.

Supplementary analyses

Clinically significant improvement in QLS/PANSS

Supplementary analyses were carried out to examine further the change in both QLS and PANSS scores, considered to represent clinically significant improvement. An increase of 8 or more units on the QLS and a decrease of 15 or more units on the PANSS represented a 20% change from mean baseline in the current trial (taking both treatment bands into account).

No statistically significant relationships were found between treatment arm (clozapine versus atypical drug) and either a 20% improvement in QLS scores (p = 0.397) or PANSS scores (p = 0.987) in band 2.

Economic results

Health status, utility values and QALYs

Table 70 in Appendix 6 indicates that there was a statistically significant association between utility values and other measures of health outcomes (QLS, PANSS, GAF), so that a low level of utility reflected a low level of health status or symptoms reported by the other outcome measures. There was also a statistically significant association between utility at each assessment period, suggesting that the use of linear interpolation to impute missing observations for patients with

TABLE 40 *Band 2, PANSS*[175]

Variable	Clozapine			New atypicals		
	n	Mean	SD	*n*	Mean	SD
PANSS total						
Baseline	67	80.07	17.72	69	84.09	22.65
12 weeks	57	68.67	14.80	61	75.61	19.47
26 weeks	59	66.69	17.67	59	70.83	18.52
52 weeks	59	63.47	17.72	57	68.00	18.81
PANSS positive subscale						
Baseline	67	20.21	6.35	69	19.09	7.30
12 weeks	57	15.42	4.96	61	17.28	5.95
26 weeks	59	15.51	5.61	59	15.29	5.56
52 weeks	59	14.51	5.72	59	15.10	6.12
PANSS negative subscale						
Baseline	67	21.19	7.17	67	23.52	8.40
12 weeks	57	18.18	5.82	61	20.16	7.51
26 weeks	59	17.58	5.72	59	19.83	6.18
52 weeks	59	16.81	5.61	59	19.27	6.91
PANSS general subscale						
Baseline	67	38.67	8.70	67	41.48	11.42
12 weeks	57	35.07	7.47	61	38.16	10.02
26 weeks	59	33.61	9.13	59	35.71	9.94
52 weeks	59	32.15	8.85	57	34.00	9.81

TABLE 41 *Band 2, side-effects scales*

Variable	Clozapine			New atypicals		
	n	Mean	SD	*n*	Mean	SD
Simpson–Angus Scale[178]						
Baseline	63	5.06	5.66	64	5.44	5.48
12 weeks	57	3.37	4.39	57	3.16	3.59
26 weeks	56	3.68	4.18	56	3.46	3.17
52 weeks	56	2.84	3.72	54	3.33	3.30
BARS[179]						
Baseline	65	2.20	2.78	66	3.42	3.62
12 weeks	57	1.72	2.57	58	2.45	3.03
26 weeks	58	1.57	2.26	56	2.59	2.87
52 weeks	57	1.32	2.16	55	2.22	3.15
AIMS[168]						
Baseline	65	2.77	5.21	66	2.05	3.79
12 weeks	57	1.49	3.02	58	2.34	3.93
26 weeks	58	1.76	3.33	56	1.91	3.45
52 weeks	57	1.88	3.59	55	2.02	3.11
Form 15 (total EPS side-effects score)						
Baseline	63	10.19	10.48	64	10.97	8.49
12 weeks	57	6.58	8.28	57	7.96	7.81
26 weeks	56	7.07	7.92	56	7.96	6.69
52 weeks	56	6.09	7.32	54	7.65	6.16
ANNSERS[169]						
Baseline	66	15.15	8.80	67	15.53	9.97
12 weeks	57	13.31	8.46	59	13.58	8.68
26 weeks	58	10.67	7.04	58	12.63	9.48
52 weeks	58	10.34	8.13	56	11.60	7.45

TABLE 42 *Band 2, GAF*[1]

Variable	Clozapine			New atypicals		
	n	Mean	SD	*n*	Mean	SD
GAF total						
Baseline	65	37.25	14.06	69	35.39	13.36
12 weeks	57	44.14	12.43	61	40.90	11.96
26 weeks	59	45.53	11.18	59	43.95	12.58
52 weeks	59	49.17	12.22	59	48.05	13.69
GAF symptoms						
Baseline	59	35.08	13.23	62	36.90	13.97
12 weeks	54	44.63	12.14	58	41.95	12.32
26 weeks	59	44.97	12.63	59	44.68	13.60
52 weeks	59	48.34	13.25	59	48.95	13.09
GAF disability						
Baseline	59	37.73	13.19	62	36.32	12.75
12 weeks	54	45.41	11.21	58	41.59	11.45
26 weeks	59	46.51	11.69	59	44.58	11.70
52 weeks	59	49.46	13.11	59	47.88	13.20

TABLE 43 *Band 2, remaining outcome measures*

Variable	Clozapine			New atypicals		
	n	Mean	SD	*n*	Mean	SD
Calgary Depression Scale[167]						
Baseline	67	6.24	4.77	67	8.04	5.88
12 weeks	59	4.56	4.56	60	5.65	3.90
26 weeks	59	3.97	3.93	59	5.54	4.18
52 weeks	56	3.77	3.81	57	4.61	4.39
DAI[176]						
Baseline	66	5.59	11.78	65	6.98	10.71
12 weeks	57	10.75	10.93	59	9.78	11.57
26 weeks	57	12.23	11.32	58	10.24	9.56
52 weeks	57	12.32	11.46	56	11.80	10.79
Compliance Scale[177]						
Baseline	66	5.03	1.45	66	5.02	1.32
Week 12	66	5.09	1.45	68	4.96	1.48
Week 26	64	5.24	1.44	67	4.91	1.30
Week 52	62	5.29	1.46	64	5.16	1.34

otherwise complete follow-up was valid. The linear interpolation was only used if data were available for the previous and following assessment period. If these data were not available then the data were treated as censored.

The analysis indicated that there was an improvement in health status and utility between baseline and assessment at week 12. This improvement was maintained from week 12 to week 52. Appendix 6 presents the detailed results of the EQ-5D and utility values. *Tables 72*, *73* and *76* in Appendix 6 present the detailed results of the EQ-5D by health domain and study period, summarise these data by treatment allocation group, and present the utility values by assessment period for all patients, respectively.

Table 45 reports the utility values by treatment group and assessment period. These indicate that there was an improvement in utility in the first 12 weeks for all treatment allocations, which was maintained to week 52. This is depicted graphically in *Figure 12*.

TABLE 44 *Band 2, secondary outcomes*

Variable	Estimate	SE	95% CI	*p*
PANSS total[a]	4.93	1.98	1.05 to 8.82	0.013
After multiple imputation[a]	5.62	2.19	1.33 to 9.92	
GAF total[b]	–1.68	1.44	–4.50 to 1.13	0.242
Depression[a]	0.48	0.37	–0.40 to 1.36	0.284
Simpson–Angus[a]	0.10	0.38	–0.64 to 0.85	0.785
BARS[a]	0.55	0.35	–0.13 to 1.22	0.116
AIMS[a]	0.63	0.46	–0.28 to 1.53	0.176
Form 15 EPS total[a]	1.45	0.90	–0.30 to 3.21	0.105
DAI[a]	–1.43	1.51	–4.38 to 1.52	0.343
ANNSERS[a]	0.63	0.98	–1.28 to 2.54	0.520

[a] The positive parameter estimates for the PANSS total (4.93 and 5.62) mean that, on average, the symptom scores were about 5.5 points better (i.e. less) in the clozapine arm than in the new atypical arm (this follows directly from the coding of the two arms: 0 for clozapine and 1 for new atypicals). The two-sided 95% CIs do not include 0 and therefore the difference is statistically significant, using a 5% level of significance. There were no other statistically significant differences.
[b] A high score on this item means a better outcome (as in the quality of life scores). A negative parameter estimate implies that the conventional arm patients were doing better, but the difference failed to reach statistical significance.

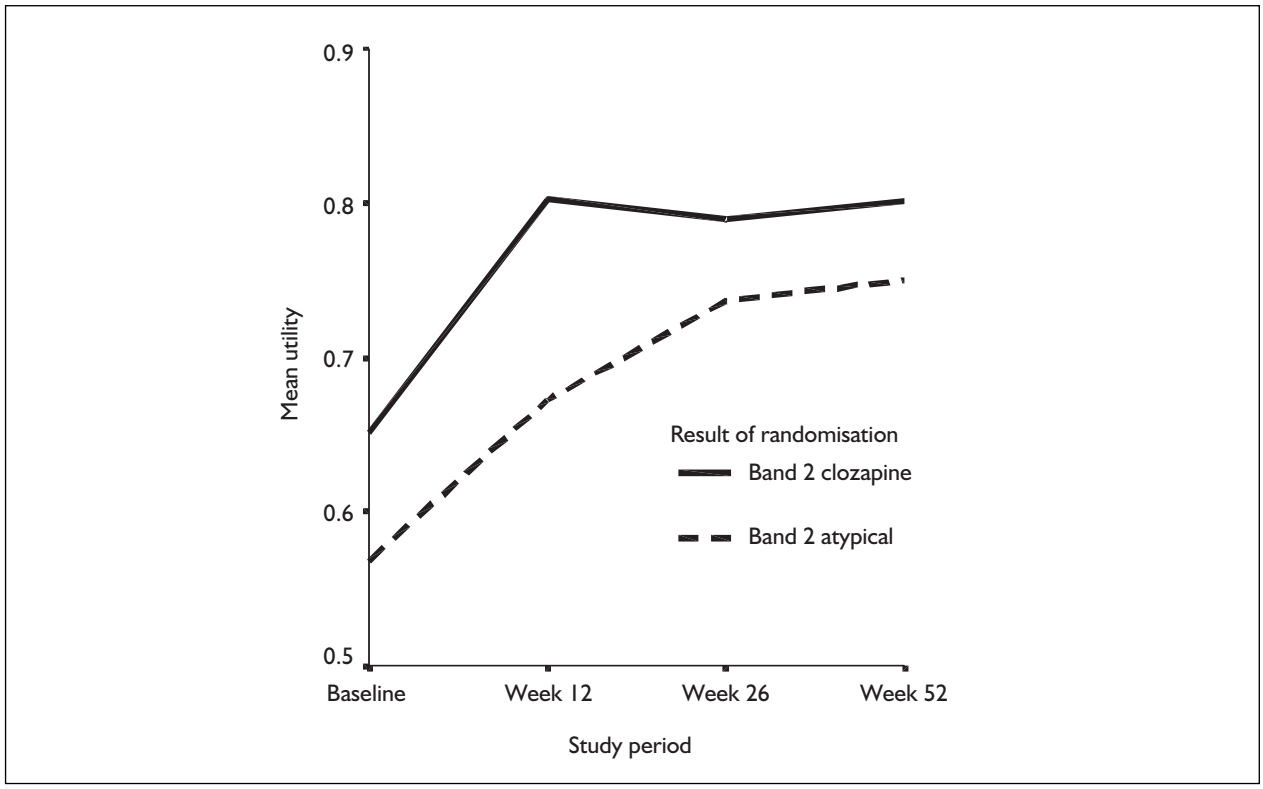

FIGURE 12 *Band 2, mean utility scores by time of follow-up*

Table 46 presents the QALY values for each band, by treatment allocation. The results indicate that there was a trend towards higher QALYs for the group who were allocated to initiation of treatment with clozapine rather than atypical antipsychotics. This applies for the primary and sensitivity analyses. In the primary analysis the 2.5th and 97.5th percentiles of the bootstrapped estimates indicate that clozapine was associated with higher QALYs than atypical antipsychotics.

Resource use and costs

Table 47 indicates that there was no evidence of a statistically significant association between costs before baseline and baseline utility values or between costs and QALYs at assessment periods 26

TABLE 45 *Band 2, utility and evaluation of own health, EuroQol by treatment group*

		Clozapine	Atypical
Baseline		*n* = 67	*n* = 69
Utility	Mean	0.65	0.57
	SD	0.26	0.38
	Range	–0.17 to 1.00	–0.24 to 1.00
Evaluation of own health	Mean	59.95	56.16
	SD	26.25	25.52
	Range	0.00 to 100.00	0.00 to 100.00
Week 12		*n* = 59	*n* = 61
Utility	Mean	0.80	0.67
	SD	0.15	0.25
	Range	0.41 to 1.00	–0.04 to 1.00
Evaluation of own health	Mean	64.76	59.75
	SD	22.81	24.69
	Range	3.00 to 100.00	0.00 to 100.00
Week 26		*n* = 59	*n* = 59
Utility	Mean	0.79	0.74
	SD	0.19	0.25
	Range	0.27 to 1.00	–0.33 to 1.00
Evaluation of own health	Mean	64.28	60.47
	SD	21.80	19.58
	Range	6.00 to 100.00	10.00 to 100.00
Week 52		*n* = 59	*n* = 59
Utility	Mean	0.80	0.75
	SD	0.19	0.21
	Range	0.19 to 1.00	0.02 to 1.00
Evaluation of own health	Mean	69.26	65.34
	SD	18.01	19.72
	Range	0.00 to 100.00	20.00 to 100.00

TABLE 46 *Band 2, QALYs*

Analysis	Treatment arm	*n*	Mean	Mean difference	SE	95% CI
Primary analysis						
Bootstrapped estimates of QALYs	Clozapine	67	0.74	0.07	0	–0.00 to 0.14[a]
	Atypical	69	0.68			
Sensitivity analysis						
QALYs adjusted for covariance	Clozapine	67	0.73	0.04	0.03	–0.023 to 0.11
	Atypical	69	0.69			
QALYs including imputed values for all missing data	Clozapine	67	0.74	0.07	0.04	–0.01 to 0.14
	Atypical	69	0.68			
QALYs, complete case analysis	Clozapine	50	0.77	0.06	0.03	–0.01 to 0.13
	Atypical	51	0.71			
QALYs including imputed values for missing observations only	Clozapine	59	0.77	0. 08	0.03	0.01 to 0.15
	Atypical	60	0.70			

[a] 2.5th and 97.5th percentiles of the bootstrapped estimates.

TABLE 47 *Band 2, stepwise regression model, dependent variable total cost baseline to week 52*

	Unstandardised coefficients	SE	Standardised coefficients	t	*p*-Value	95% CI for *B*	
	B		Beta			Lower bound	Upper bound
(Constant)	21,988.54	8,965.84		2.45	0.02	3,930.40	40,046.67
PREBASEC	2.72	0.31	0.83	8.66	0.00	2.09	3.35
QALYs	–25,406.99	11,595.35	–0.21	–2.19	0.03	–48,761.22	–2,052.76

and 52 weeks. There was an association between QALYs and costs for the first 12-week period ($p = 0.03$). There was evidence of a statistically significant association between costs at each assessment period. Costs before baseline were also associated with type of accommodation ($p < 0.01$), employment status ($p = 0.03$) and living situation ($p < 0.0.1$) at baseline. This correlation was evident between costs and accommodation and living situation, but not employment, in subsequent periods. Stepwise regression suggests that total cost over the 52-week period of the trial was dependent on the level of costs for 3 months before the trial, so that higher costs before the trial were associated with higher costs during the trial and total QALYs, and that improvements in health-related quality of life were associated with lower costs during the trial. Accommodation and living situation were eliminated from the model in the stepwise process. These data support the assumption of a link between costs and QALYs. They also suggest that costs in the trial follow-up period were influenced by the patient's accommodation and employment status at baseline.

Tables 48–50 summarise the employment status, type of accommodation and use of the criminal justice system. The majority of patients were unemployed or economically inactive at baseline and throughout follow-up in both allocation groups. For both groups the majority of people lived in their own homes rather than residential accommodation or hospital facilities. Few people reported using the criminal justice system and the average use was low in both groups.

Table 51 summarises the costs by assessment period and category of service use for each treatment group, using a complete case analysis. A detailed breakdown of service use and costs is shown in Appendix 6, *Tables 87–95*. This only includes patients where complete resource-use and cost data were available at each assessment point. As indicated, complete data were available for a high proportion of participants, particularly for psychiatric and non-psychiatric hospital admissions. The number of patients with recorded service use was lower for community and primary care services. In addition, *Table 94* in Appendix 6 indicates that the number of people using community-based services and the intensity of such use were low.

Table 52 summarises the costs of psychiatric hospital care by source of unit cost data, non-psychiatric hospital care, antipsychotic medication, use of other medicines, and primary and community care services. *Table 52* reports the costs for the full ITT sample of patients, including imputed values for missing observations and censored cases.

Table 53 shows the mean costs and differences in mean costs between the treatment groups. There was a trend for the mean costs for the 52 weeks of the trial to be higher for people allocated to initiation of clozapine therapy rather than atypical antipsychotic therapy. Again, these differences were not statistically significant.

Cost-effectiveness analysis

Table 54 presents point estimates of the ICER. The results of the primary and sensitivity analyses suggest that the cost per QALY gained by clozapine is high, at £80,000 for the primary analysis, and between £56,000 and £135,000 in the sensitivity analysis.

The cost and effect data were bootstrapped to give pairs of mean differences for cost and QALY. For band 2, 20,000 bootstrap replicates were obtained. The bootstrap data were also used to estimate the probability that the intervention with a higher QALY value was cost-effective, the net benefit at different threshold values of cost per QALY and cost acceptability curves.

Figure 13 presents the bootstrapped data in terms of a cost-effectiveness plane of the incremental

TABLE 48 *Band 2, employment status, by treatment group*

Current economic status		Baseline		Week 12		Week 26		Week 52	
		Clozapine	Atypical	Clozapine	Atypical	Clozapine	Atypical	Clozapine	Atypical
Employee, >30 hours per week	*n*	NR	NR	1.00	0.00	2.00	0.00	2	1
	%	NR	NR	1.00	0.00	3.00	0.00	3	1
Employee <30 hours per week	*n*	2	0	2.00	0.00	1.00	3.00	2	0
	%	3	0	3.00	0.00	2.00	4.00	3	0
Self-employed	*n*	NR	NR	1.00	1.00	1.00	0.00	1	1
	%	NR	NR	2.00	1.00	2.00	0.00	2	1
Government-supported training	*n*	NR	NR	NR	NR	NR	NR	NR	NR
	%	NR	NR	NR	NR	NR	NR	NR	NR
Employee on sick leave	*n*	1	0	1.00	0.00	NR	NR	NR	NR
	%	2	0	2.00	0.00	NR	NR	NR	NR
Unemployed	*n*	0	1	7.00	9.00	7.00	4.00	6	6
	%	0	1	10.00	13.00	10.00	6.00	9	9
Economically inactive	*n*	8	11	44.00	51.00	47.00	51.00	44	48
	%	12	16	66.00	74.00	70.00	74.00	66	70
Other	*n*	47	53	3.00	0.00	1.00	1.00	4	1
	%	70	77	5.00	0.00	2.00	1.00	6	1
Missing	*n*	9	3	8.00	8.00	8.00	10.00	8	12
	%	13	4	12.00	12.00	12.00	15.00	12	17
Total	*n*	0	1	67.00	69.00	67.00	69.00	67	69
	%	0	1	100.00	100.00	100.00	100.00	100	100

TABLE 49 *Band 2, type of accommodation at assessment, by treatment group*

Current accommodation		Baseline		Week 12		Week 26		Week 52	
		Clozapine	Atypical	Clozapine	Atypical	Clozapine	Atypical	Clozapine	Atypical
Owner-occupied flat or house		5 7.50	2 2.90	11 16.40	6 8.70	10 14.90	9 13.00	9 13.40	9 13.00
Other	*n* %	0 0.00	1 1.40	0 0.00	2 2.90	1 1.50	3 4.30	3 4.50	1 1.40
Privately rented flat or house	*n* %	1 1.50	0 0.00	1 1.50	1 1.40	1 1.50	2 2.90	1 1.50	1 1.40
Rented from local authority, etc.	*n* %	8 11.90	14 20.30	14 20.90	21 30.40	18 26.90	19 27.50	19 28.40	15 21.70
Overnight facility 24-hour staff	*n* %	2 3.00	3 4.30	3 4.50	6 8.70	6 9.00	5 7.20	7 10.40	9 13.00
Overnight facility not staffed 24 hours	*n* %	2 3.00	1 1.40	4 6.00	2 2.90	2 3.00	3 4.30	1 1.50	3 4.30
Overnight facility unstaffed	*n* %	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR
Acute psychiatric ward	*n* %	4 6.00	6 8.70	3 4.50	3 4.30	0 0.00	4 5.80	2 3.00	1 1.40
Psychiatric rehabilitation ward	*n* %	0 0.00	1 1.40	4 6.00	2 2.90	9 13.40	3 4.30	1 1.50	2 2.90
Long-stay psychiatric ward	*n* %	5 7.50	5 7.20	6 9.00	5 7.20	5 7.50	5 7.20	6 9.00	3 4.30
General medical ward	*n* %	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR
Homeless	*n* %	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR
Missing	*n* %	40 59.70	36 52.20	21 31.30	21 30.40	15 22.40	16 23.20	4 6.00	4 5.80
Total	*n* %	67 100.00	69 100.00	67 100.00	69 100.00	67 100.00	69 100.00	14 20.90	21 30.40

TABLE 50 *Band 2, average number of contacts with criminal justice system, by treatment group*

Contacts with criminal justice system	Clozapine			Atypical		
	n	Mean	SD	*n*	Mean	SD
Number of police contacts	14	2	1	14	2	2
Number of probation contacts	14	1	2	14	<1	<1
Nights in cells	14	8	21	14	6	17
Number of psychiatric assessments	14	1	1	14	<1	1
Number of criminal court appearances	13	2	3	14	1	1
Number of civil court appearances	14	<1	<1	14	<1	<1

TABLE 51 *Band 2, cost of services, (£, 2001–2), complete case analysis*

Study period			Psychiatric hospital	Non-psychiatric hospital	Anti-psychotic medicines	Other medicines	Community and primary care	Total cost
Baseline–week 12	Clozapine	Mean	10,083	6	221	55	147	10,307
		n	67	64	65	65	53	52
		SD	8,156	31	193	81	245	7,221
	Atypical	Mean	8,218	25	212	63	344	8,608
		n	67	65	66	66	57	9,519
		SD	8,996	130	197	96	789	51
Week 13–26	Clozapine	Mean	8,581	130	402	80	220	10,015
		n	65	64	63	64	53	49
		SD	10,509	563	295	120	290	10,930
	Atypical	Mean	7,253	3	279	72	106	7,056
		n	66	65	60	65	54	9,953
		SD	9,950	12	267	119	212	47
Week 27–52	Alozapine	Mean	12,393	347	777	152	393	12,807
		n	60	61	60	65	51	44
		SD	19,407	2462	657	235	725	19,704
	Atypical	Mean	10,579	134	470	140	430	14,382
		n	64	60	61	65	52	44
		SD	18,523	918	528	196	967	21,097

TABLE 52 *Band 2, 12-month cost of services (£, 2001–2), including imputed values for missing data*

	Treatment group	*n*	Mean	SD
Psychiatric hospital	Clozapine	67	30,761	33,497
	Atypical	69	25,961	32,917
Non-psychiatric hospital	Clozapine	67	610	2,831
	Atypical	69	347	1,043
Antipsychotic medicines	Clozapine	67	1,337	976
	Atypical	69	940	763
Other medicines	Clozapine	67	289	393
	Atypical	69	275	365
Community and primary care	Clozapine	67	798	893
	Atypical	69	884	1,288

TABLE 53 *Band 2, net costs of services (£, 2001–2)*

Analysis	Treatment arm	*n*	Mean	SD	Estimated difference	SE of difference
Primary analysis						
Bootstrapped estimates of imputed costs, reference unit cost data	Clozapine Atypical	67 69	33,781 28,431	35,716 25,765	5,350	311
Sensitivity analysis						
Imputed net costs, reference cost unit cost data	Clozapine Atypical	67 69	32,538 28,422	32,162 32,826	4,116	5,690
Net costs, PSSRU unit cost data	Clozapine Atypical	67 69	38,239 32,904	38,554 36959	5,335	6,475
Net costs, CIPFA unit cost data	Clozapine Atypical	67 69	38,456 32,819	38,357 37,004	5,636	6,462
Net costs, complete case analysis	Clozapine Atypical	59 61	26,952 23,007	30,920 31,705	3,945	5,719

TABLE 54 *Band 2, cost per QALY gained (£, 2001–2)*

Analysis	Net cost	Net QALY	ICER
Primary analysis			
Bootstrapped costs and QALYs	5,350	0.07	80,400
Sensitivity analysis			
QALYs adjusted for covariance, costs estimated using reference cost unit costs	5,388	0.04	134,700
QALYs including imputed values for all missing data	5,388	0.07	76,971
QALYs, complete case analysis	5,388	0.06	89,800
QALYs including imputed values for missing observations only	5,388	0.08	67,350
QALYs adjusted for covariance, costs estimated using PSSRU unit cost data	5,335	0.07	76,214
QALYs adjusted for covariance, costs estimated using CIPFA unit cost data	5,636	0.07	80,514
QALYs adjusted for covariance, costs estimated complete case analysis	3,945	0.07	56,357
QALYs, complete case analysis, costs estimated complete case analysis	3,945	0.06	65,750

costs and QALYs associated with clozapine. This shows each pair of cost and effect differences from the bootstrap replicates, and indicates that the majority of net QALY and cost estimates for clozapine were higher than for atypical antipsychotics.

Overall, the probability that clozapine would be cost-effective was 0.36 if decision-makers were willing to pay up to £50,000 per QALY gained. That is, 36% of bootstrap replicates indicated that clozapine was associated with a higher QALY value than atypical antipsychotics and a cost per QALY of less than £50,000. The analysis indicated that the probability that clozapine was cost-effective was 0.17 at a threshold value of £0 cost per QALY. That is, if decision-makers were not prepared to pay any additional cost for an improvement in QALYs, the probability that clozapine would still be cost-effective was 17%. *Figure 14* presents the data in the form of a cost acceptability curve. Revaluing the QALY values by ceiling thresholds

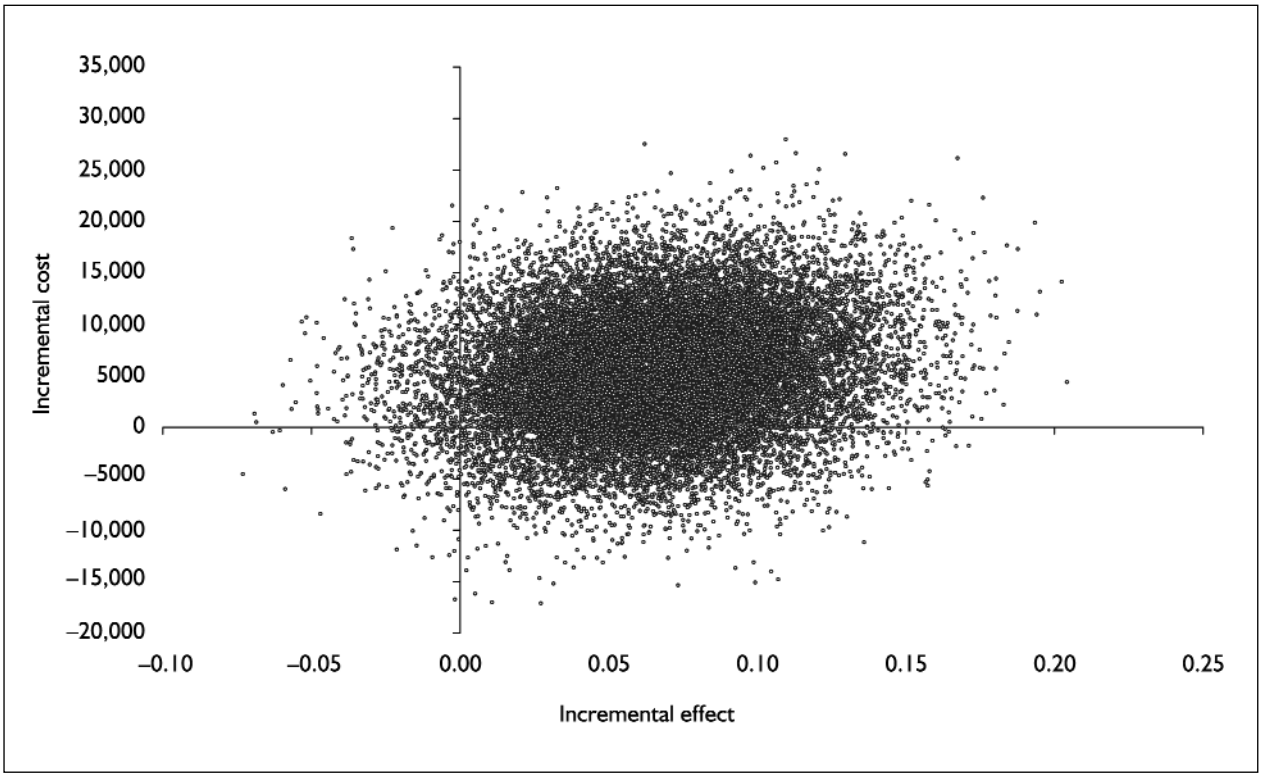

FIGURE 13 *Band 2, cost-effectiveness plane of the incremental costs and QALYs for clozapine*

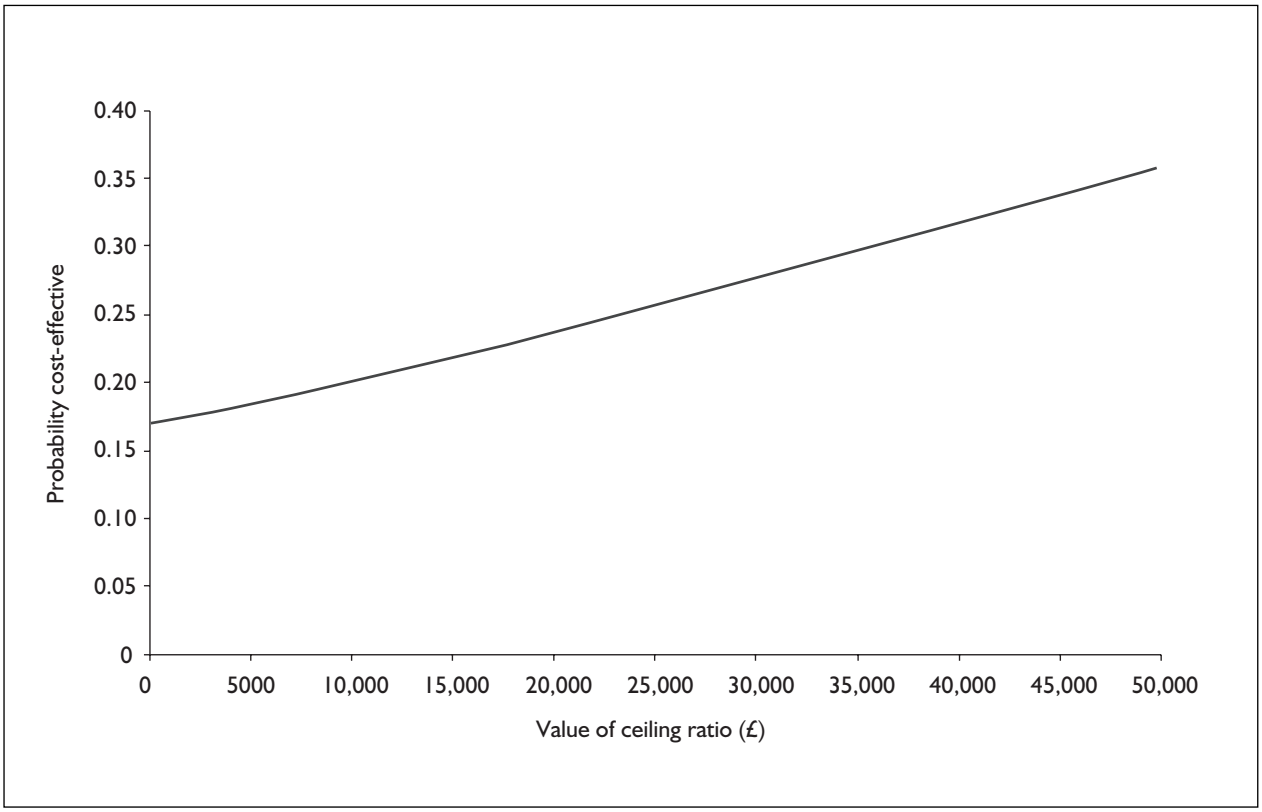

FIGURE 14 *Band 2, cost-effectiveness acceptability curve of the ICER of clozapine*

of acceptable cost per QALYs from £0 to £50,000 gives an estimated net benefit. *Table 55* presents these net benefit values and they are depicted graphically in *Figure 15*. The estimated mean net benefit of clozapine is negative, –£2145. This indicates that the monetary value of gains in QALYs is worth less to decision-makers than the costs of clozapine. However, the confidence intervals and histogram of net benefit values indicate that clozapine may be cost-effective in some cases.

Band 2 patient flow

Prior drug

Before randomisation into the two treatment arms of band 2, 59 patients were receiving a depot drug. Conventional antipsychotics were prescribed to 86 patients and atypical drugs were prescribed to 59 patients. No patients were receiving clozapine immediately before randomisation. Thirty-one patients (23%) were receiving more than one antipsychotic drug before entering the study.

See *Figure 11* for patient flow details.

TABLE 55 *Band 2, net benefit values for clozapine (£, 2001–2)*

	Net benefit of clozapine
Mean	–2,145
SD	5,810
2.5th percentile	–13,660
97.5th percentile	9,082

12-week follow-up period

Clozapine arm

Twenty patients (30%) were not in the clozapine arm by the end of the 12-week follow-up period, with the following reasons being given:

- ineffective: $n = 1$
- intolerable: $n = 2$
- amber light: $n = 1$
- not yet started clozapine: $n = 16$.

The two patients who found clozapine intolerable and the one patient who received an amber light all switched to depot conventional treatment. The patient who found clozapine ineffective switched to an atypical drug (olanzapine). A number of patients (16, 24%) had not started clozapine by the end of the 12-week follow-up period.

During this period, two patients in the clozapine arm withdrew from the study, but there were no deaths. Four patients (6%) in the clozapine arm were receiving more than one antipsychotic drug

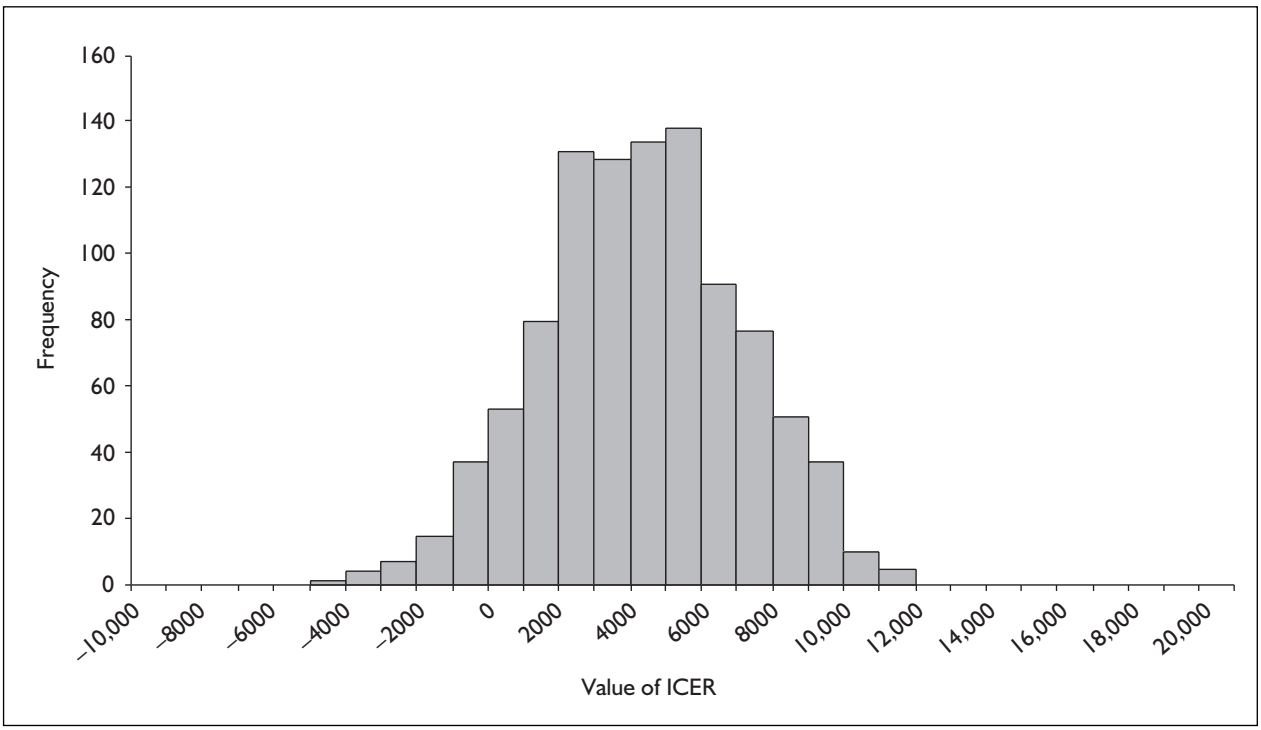

FIGURE 15 *Band 2, net benefit values of the ICER for clozapine*

by the end of the 12-week follow-up period. Fifty-nine patients (88%) in this arm completed their 12-week follow-up assessment and 47 patients (70%) were still in the randomised arm and receiving clozapine at the end of the 12-week follow-up period.

Atypical arm

Twenty patients (29%) had switched out of the atypical arm by the end of the 12-week follow-up period, with the following reasons: being given:

- ineffective: $n = 8$
- intolerable: $n = 2$
- ineffective and intolerable: $n = 1$
- other (including non-compliance): $n = 3$
- not yet started atypical treatment: $n = 6$.

Six of the eight patients who found atypicals ineffective switched to clozapine, one switched to conventional drug treatment and one patient came off antipsychotic treatment altogether. The two patients who found atypical treatment intolerable switched to clozapine and chlorpromazine. The patient who found atypical treatment both ineffective and intolerable switched to clozapine. Of the three patients who switched citing other reasons, two came off antipsychotics altogether and one switched to clozapine.

One patient switched drug within the atypical treatment arm, switching from quetiapine to risperidone owing to intolerance. Six patients (9%) had not started their randomised atypical drug treatment by the end of the 12-week follow-up period.

There were no deaths in the atypical arm during this period. Ten patients (14%) were receiving more than one antipsychotic drug by the end of the 12-week follow-up period, but four (6%) were not receiving any antipsychotic drug at all. Sixty-one patients (88%) completed their 12-week follow-up assessment and 49 patients (71%) were still in the randomised arm and receiving an atypical drug at the end of the 12-week follow-up period.

26-week follow-up period

Clozapine arm

A further nine patients (13%) were not in the clozapine arm by the end of the 26-week follow-up period, with the following reasons being given for leaving the arm:

- intolerable: $n = 4$
- other (including non-compliance): $n = 5$.

Three of the four patients who found clozapine intolerable switched to atypicals (two to risperidone and one to amisulpride) and the other patient switched to a depot conventional drug. The further five patients who switched from clozapine went on to trifluoperazine (two patients), amisulpride or no antipsychotic drug. Twelve patients (18%) had still not started treatment with clozapine by the end of the 26-week follow-up period.

During the 26-week follow-up period, one patient in the clozapine arm withdrew from the study, but there were no deaths in this arm. Three patients were receiving more than one antipsychotic drug by the end of this follow-up period. Fifty-nine patients (88%) completed their 26-week follow-up assessments and 41 (61%) were still in the randomised arm and receiving clozapine at the end of the 26-week follow-up period.

Atypical arm

A further four patients (6%) had switched out of the atypical arm by the end of the 26-week follow-up period, with the following reasons being given:

- ineffective: $n = 2$
- other (including non-compliance): $n = 2$.

The two patients who found atypicals ineffective switched to clozapine and chlorpromazine. The two patients who switched citing other reasons switched to clozapine and sulpiride.

One patient switched drug within the treatment arm, switching from olanzapine to risperidone owing to non-compliance. Six patients (9%) had still not started their randomised atypical drug treatment by the end of the 26-week follow-up period.

During this follow-up period, one patient in this arm withdrew from the study and there was one death. Eleven patients in the atypical arm were receiving more than one antipsychotic drug by the end of the 26-week follow-up period. Fifty-nine patients (86%) completed their 26-week follow-up assessment and 46 patients (67%) were still in the randomised arm and receiving an atypical drug at the end of this period.

52-week follow-up period

Clozapine arm

A further five patients (7%) were not in the clozapine arm by the end of the 52-week follow-up period, with the following reasons being given:

- ineffective: $n = 1$
- intolerable: $n = 2$
- other (including non-compliance): $n = 2$.

The one patient who found clozapine ineffective was not taking any antipsychotic treatment at the end of the study. The two patients who found clozapine intolerable switched to atypicals (quetiapine and olanzapine). Of the further two patients who switched from clozapine, one went on to an atypical (risperidone) and no record was available for the other patient. Twelve patients (18%) had still not started treatment with clozapine by the end of the 52-week follow-up period.

During the 52-week follow-up period, four patients in the clozapine arm withdrew from the study, but there were no deaths. Five patients were receiving more than one antipsychotic drug and one patient in the clozapine arm was not receiving any antipsychotic treatment by the end of the 52-week follow-up period. Sixty patients (90%) completed their 52-week follow-up assessments and 36 patients (54%) were still in the randomised arm and receiving clozapine at the end of the 52-week follow-up period.

Atypical arm

A further eight patients (12%) had switched out of the atypical arm by the end of the 52-week follow-up period, with the following reasons being given:

- ineffective: $n = 4$
- intolerable: $n = 1$
- other (including non-compliance): $n = 3$.

Two of the four patients who found atypicals ineffective switched to clozapine. There were no records for the subsequent treatment of the other two patients. The patient who found atypical treatment intolerable switched to clozapine. Two of the three patients who switched citing other reasons switched to depot conventional drugs.

Three patients switched drug within the treatment arm, switching from olanzapine to risperidone, olanzapine to amisulpride and quetiapine to risperidone because of intolerance. Five patients (7%) had still not started their randomised atypical drug treatment by the end of the 52-week follow-up period.

During this follow-up period, two patients in the atypical arm withdrew from the study, but there were no deaths. Six patients in the atypical arm were receiving more than one antipsychotic drug and two patients were not taking any antipsychotic drug by the end of the 52-week follow-up period. Fifty-eight patients (84%) in the atypical arm completed their 52-week follow-up assessment and 39 patients (57%) were still in the randomised arm and receiving an atypical drug at the end of the 52-week follow-up period.

Comparison of the two arms

There was no statistically significant advantage between the two arms of band 2 for patients to still be in their randomised arm at 1 year.

End of study drug and dose

Drugs and doses used at the end of the study are shown in *Tables 56–59*.

TABLE 56 *Band 2 clozapine arm, end of study drug*

Antipsychotic drug	Number of patients
Clozapine	37
Amisulpride	4
Olanzapine	8
Quetiapine	3
Risperidone	3
Flupenthixol dec.	4
Fluphenazine dec.	1
Haloperidol	1
Sulpiride	3
Trifluoperazine	1
Zuclopenthixol	1
Zuclopenthixol dec.	2

TABLE 57 *Band 2 atypical arm, end of study drug*

Antipsychotic drug	Number of patients
Amisulpride	7
Olanzapine	14
Quetiapine	12
Risperidone	7
Risperidone injection	1
Clozapine	15
Chlorpromazine	3
Flupenthixol dec.	2
Fluphenazine dec.	1
Haloperidol	1
Haloperidol dec.	1
Pimozide	1
Sulpiride	2
Zuclopenthixol dec.	3

TABLE 58 *Band 2 clozapine arm, end of study drug dose*

Antipsychotic drug	Mean dose (mg)	Range (mg)
Clozapine	333	100–600

TABLE 59 *Band 2 atypical arm, end of study drug dose*

Antipsychotic drug	Mean dose (mg)	Range (mg)
Amisulpride	660	600–800
Olanzapine	19	10–30
Quetiapine	521	300–750
Risperidone	6	3–8

Chapter 7
Discussion

The aim of the study was to determine the clinical and cost-effectiveness of different classes of antipsychotic drug treatment in people with schizophrenia whose current medication was associated with inadequate response and/or unacceptable side-effects. The term 'classes' is used to define groups of drugs that are not homogeneous, but are usually classed together in clinical guidelines and have similar acquisition costs.

Two pragmatic RCTs were undertaken to assess the value of the alternative classes of antipsychotic in two separate populations of people with schizophrenia. The first aimed to compare older, inexpensive conventional drugs with new atypical drugs in people whose current antipsychotic drug treatment was being changed for reasons of either inadequate clinical response to one or more drug, or of side-effects (band 1). The second compared the new atypical drugs with clozapine in people whose medication was being changed because of poor clinical response to two or more drugs (band 2). Both trials were conducted at four centres in England. Follow-up assessments over 1 year were conducted by assessors who were masked to treatment allocation. The trials were designed to keep the workload of the referring clinicians to a minimum. The primary outcome measure was the QLS. Secondary clinical outcomes included symptoms (PANSS), side-effects and participant satisfaction. Economic outcomes were direct costs of care and QALYs, a utility-based measure of health-related quality of life and survival.

Alongside these trials, three other pieces of research were conducted to inform the design and management of the trials. The first was a retrospective cohort-controlled study (mirror-image design; see Appendix 7). The second was a survey of consultant psychiatrists contacted by one of the four regional trial centres. The main objective of the survey was to investigate clinicians' attitudes about the relative benefits of conventional and atypical antipsychotic medication and the perceived validity of the study. The survey also sought to investigate a range of practical issues relating to the degree of contact that clinicians had with the study teams, and the value of RCTs in evidence-based psychiatry (see Appendix 4). The survey was prompted by a need to investigate possible reasons for low recruitment into the band 1 trial. The third study developed and validated a new instrument to assess the range of non-neurological side-effects important in some patients taking new atypical drugs in particular. This scale was called the ANNSERS,[169] and details are given in Appendix 1.

In total, 227 participants (40% of the planned sample) with a diagnosis of schizophrenic disorder were randomised into the band 1 comparison. They had all been identified by their responsible clinical team as warranting a change in antipsychotic medication because of inadequate clinical response or unacceptable side-effects. In total, 136 (98% of the planned sample) participants with clinician-defined resistance to trials of two or more antipsychotic drugs were randomised into band 2. Participants were aged 18–65 years. In total, 95 general adult psychiatrists referred one or more patients who were randomised into the trial.

In band 1, participants were randomised to the class of either conventional or new atypical drug and the managing clinician selected the individual drug within that class. In band 2, participants were randomised either to clozapine or to the class of new atypical (non-clozapine) antipsychotics. As in band 1, the managing clinician selected the individual drug within the class of new atypical antipsychotics. The class of new atypical drugs included risperidone, olanzapine, quetiapine and amisulpride. The class of conventional (or 'typical') drugs included older drugs, including depot preparations. In each case, the responsible clinician, the clinical team and the participant were aware of the identity of the prescribed drug. The operational protocol encouraged clinicians to try, as much as was compatible with good practice, to keep their participating patient on the randomised medication for at least 12 weeks. If the medication needed to be changed, the clinician was asked to prescribe another drug within the same class, if possible.

General issues

Recruitment

The rate of recruitment to band 1 diminished during the course of the trial and the final number of subjects was 40% of the anticipated figure. This appeared largely to result from a loss of clinical equipoise in referring clinicians as they became progressively more convinced of the superiority of the new atypical drugs, between planning and designing the trial and the start of patient recruitment. This notion is supported by the maintenance of an adequate recruitment rate to band 2 from the same clinicians over the same period, and by the results of a clinician survey at the close of recruitment. Slow recruitment into band 1 was despite assertive efforts to enhance recruitment, including publicity and incentives such as CPD points given to referring clinicians in a new arrangement with the Royal College of Psychiatrists. Further, demands on the referring clinician were kept to a minimum. They were not involved in obtaining written consent, or in any of the formal assessments at baseline or follow-up. In some centres, financial arrangements were agreed with regional offices for pro rata reimbursement of excess treatment and service support costs to trust mental health budgets. There was evidence to suggest that, where this was new, clearly identified money, paid from a regional ad hoc fund directly to those trusts with no history of major R&D activity (such as Rochdale or Mid-Cheshire), this arrangement provided a real incentive to management and clinicians to recruit.

The shift in equipoise in band 1 experienced by clinicians was variable and there may have been a centre effect. Some clinicians declined to take part in the trial at the outset since they believed that the new atypical antipsychotics were clearly superior in the context of the band 1 trial criteria. Others felt throughout the trial that this remained an open question and some changed their position during the course of the trial. The clinician attitudes survey (see Appendix 4) indicates that there was uncertainty about whether there were differences between typical and atypical antipsychotics in terms of efficacy. However, the survey highlighted that there was very little uncertainty that the atypical antipsychotics were associated with better side-effect profiles compared with the conventional antipsychotics.

The recruitment rate to band 2 was approximately as expected. This is notable, in that the logistics of commencing a participant on clozapine are considerable and, in the time-course of the trial, the licence required elective inpatient admission to commence the drug. In the last 6 months of the trial recruitment phase, the non-availability of acute beds for this purpose constrained recruitment in at least one centre.

Recruitment rates in both bands differed between centres. Each of the four centres received the same level of financial support.

The primary outcome: the QLS

There is no agreed scale for the assessment of quality of life in schizophrenia. The QLS has been shown to be both sensitive to change and of clinical relevance.[191] It is the most widely used quality of life or health status measure in the evaluation of psychopharmacological treatments for schizophrenia, predominantly in outpatients.[172] It is based on a semi-structured interview. The instrument consists of 21 items rated on fixed interval scales based on the interviewer's judgement of the patient's functioning in each of these 21 areas. These items cover commonplace activities: occupational role, work functioning, work level, possession of commonplace belongings, interpersonal relations (household, friends and acquaintances, social activity, social network, social withdrawal, sociosexual functioning), sense of purpose, empathy and emotional interaction; and work satisfaction. These reduce to three subscales of intrapsychic foundations, interpersonal relations and instrumental role. Inter-rater reliabilities are good and confirmatory factor analysis has been conducted.[170]

Criticisms of the QLS include the fact that, rather than being a self-report scale, it is administered by an external assessor, and that it reflects symptoms primarily, particularly negative symptoms. In the current study, PANSS total score accounted for 30% of the variance in QLS score at baseline in band 1 and 32% in band 2.

Measure of outcome for the economic analysis

The EuroQol (EQ-5D) was used to measure the self-reported health status of participants at each assessment point. The health states were valued using population tariffs of utility. The EuroQol and associated population utility values are validated measures for the estimation of QALYs. However, they are generic measures and so may not be sensitive to small but important changes in health and health-related quality of life. The differences in QALYs generated by the use of the EuroQol and associated utility values were small.

The differences were similar to those found in UK-based modelling studies that used utility-based measures to estimate QALYs.[32,33] Analysis of the trial data indicates that the utility values did correlate with other measures of outcome used and that changes in health status and in utility were detected over the 52-week follow-up period. Although statistically significant, the level of correlation between the utility values and other measures, in particular the QLS, was relatively low. Further examination of the data is required to assess whether the low correlation measure is due to a low level of association between similar domains or constructs of health-related quality of life, or whether there are other important domains that are not adequately captured by the EuroQol and associated utility values. The face validity of the scale is reasonable for this trial, since acute schizophrenia is likely to cause problems with self-care, usual activities, depression and anxiety. In addition, the side-effects associated with antipsychotic treatment are likely to affect the domains of pain or discomfort and mobility.

Use of single blinding and quality of blinded ratings

The inter-rater reliability for all the assessments at the start and during the trial was good. Steps to ensure the masking of assessments appeared to be successful: follow-up assessment was explicitly unmasked in less than 5% of cases. Overall, the use of clinical assessors who did not know the treatment allocation of participants and the high rate of success in concealing allocation suggest that the recording of clinical assessments was not biased by knowledge of treatment allocation.

However, the fact that participants and referring clinicians knew of the treatment allocation means that the subjective response of the patients to the clinical assessments may have been influenced by knowledge of treatment allocation. In addition, knowledge of the treatment allocation and drug prescribed may have influenced the assessment and interpretation of effectiveness and side-effects by the referring clinician and participant. This may be particularly important if the prior expectations of clinicians and participants did not reflect true indifference or equipoise between the classes of antipsychotics.

Discontinuations from randomly allocated treatment

As part of the operational protocol, clinicians were asked to try as hard as was compatible with good practice to keep their participating patient on the randomised medication for at least the first 12 weeks. If the medication needed to be changed, the clinician was asked to prescribe another drug within the same class, if possible.

In band 1, 72% of participants randomised to a conventional drug were still on the same drug, and 83% were still on a conventional drug of some type, at 12 weeks. In the new atypical arm, the respective percentages were identical. At 52 weeks, there was a trend for more participants to remain in the new atypical arm than in the conventional arm.

In band 2, 70% of those randomised to clozapine and 71% of those randomised to a new atypical remained in the randomised class; at 52 weeks, this was 54% and 56%, respectively.

Follow-up rates

Follow up assessments were completed at week 52 in 81% of band 1 and 87% of band 2 participants. The trial achieved a high level of follow-up and duration of follow-up in the context of trials of antipsychotic medication. The clinical and economic analyses included imputation of all missing observations to reduce the impact of bias due to loss to follow-up. Complete case analyses of those remaining in the trial were also conducted. Both analyses indicated a similar result. For the economic analyses, data to calculate utility and QALY values were available for 77–88% of patients at week 52. Data on the use of psychiatric hospital care at the 52-week follow-up were available for 90% of patients randomised to treatment (88% conventional versus 91% new atypical antipsychotics in band 1 and 89% clozapine versus 93% new atypical antipsychotics in band 2). Complete cost data were lower for other categories of cost, the lowest rate of follow-up being the use of primary and community care services at 72–77%. Overall, this meant that total cost data were only available for 65% of participants. However, the use of psychiatric hospital care comprised 92% of the total costs of care observed (92% conventional antipsychotics versus 85% atypical antipsychotics in band 1 and 91% clozapine versus 92% atypical antipsychotics in band 2). This suggests that the impact of missing data on total cost per person due to loss of follow-up is likely to be low. Nevertheless, imputation of missing data was conducted to estimate total QALYs and costs for all patients in the trial, and reduce the impact of any bias induced by missing observations or censored data. Sensitivity analysis was used to assess whether the results would differ between the full data sets, including imputed values and complete case analyses.

It was clear that the use of imputation affected the incremental cost-effectiveness analysis. For band 1 patients, conventional antipsychotics were associated with a trend towards higher QALYs and lower costs than atypical antipsychotics using the data sets with imputed values for costs and QALYs. However, the complete case analysis indicated a small net cost associated with conventional antipsychotics, giving an additional cost of up to £4100 per QALY gained. In band 2, the complete case analysis indicated a higher cost per QALY of £90,000 for clozapine compared with the cost per QALY of £75,500 indicated by the data sets including imputed values. In both cases the difference in costs per QALY between the analyses was primarily due to the differences in the estimates of costs. In this analysis missing cost data were treated as missing at random, rather than informative censoring of data. This was based on the assumption that use of services and subsequent costs was determined by a range of factors in addition to treatment allocation or previous service use. The correlational and regression analysis are indicative that this is the case, suggesting that costs are correlated with QALYs and with employment status and accommodation at baseline. Further analysis is needed to test this assumption.

Impact on clinical practice within the trial

The rate of polypharmacy (receiving more then one antipsychotic drug at the same time) in the trial at 52 weeks was about 14% (band 1), which is low compared with audit data collected in parallel in routine clinical practice outside the trial, of about 30% in Greater Manchester. Polypharmacy is recognised to be non-evidence-based practice that is proscribed in the NICE guidance. Involvement in the trial appeared to be an effective way for patients to reduce the risk of their receiving polypharmacy.

Band 1: conventional versus new atypical drugs

Baseline characteristics of sample in band 1

The demographic and clinical characteristics of participants were well balanced between the treatment allocation groups in terms of gender, ethnic group, proportion detained under a section of the Mental Health Act at the time, number in their first episode, proportion who were outpatients at the time of first randomised dose, time since first treatment for psychosis, number of previous inpatient admissions and age.

In band 1, the primary reason given by the clinician for referral to the study was intolerance in 51%, poor clinical response in 78% and both in 30%; thus, the two reasons for referral were not mutually exclusive. There was a small imbalance in the participants referred and randomised, such that more who were just treatment intolerant were allocated to conventionals (30%) than to new atypicals (12%).

In terms of the primary outcome and main secondary outcome (PANSS total score), the groups were well balanced at baseline, with similar mean scores.

Clinician choice of drug

In band 1, sulpiride was the drug selected by clinicians in 49% of cases randomised to the conventional arm, followed by trifluoperazine in 18%. In the new atypical arm, olanzapine was chosen in 46% of cases, followed by quetiapine in 19%.

Results of randomised comparison

The ITT comparison of conventional versus new atypical drugs showed that, in people with schizophrenia whose medication was being changed because of intolerance or broadly defined treatment resistance, there was no statistically significant difference in terms of quality of life or symptoms over 1 year in commencing conventional antipsychotic drugs rather than new atypical drugs. The lack of statistically significant differences in the primary outcome and the symptom measures may be due in part to inadequate power. The initial power calculation predicted that a sample size two-and-a-half times larger than that finally recruited would be needed to show with confidence a difference in QLS score between treatment groups at 1 year, should such a difference exist. However, good follow-up rates and a higher than expected correlation between QLS score at baseline and at follow-up meant that the sample as recruited actually had 75% power to detect a difference in QLS score of 5 points between the two treatment arms at 52 weeks in the sample collected. Inspection of the data showed that, on the QLS and symptom measures, those participants in the conventional arm showed a trend towards greater improvements than those on the new atypical arm, suggesting that the failure to find the hypothesised advantage for new atypicals was not simply that the accrued sample was too small.

A second reason for not finding a clear advantage in favour of atypical antipsychotics is if differential outcomes could be expected between participants

entering band 1 for reasons of treatment intolerance and those entering because of inadequate response. The most plausible source of bias would be that primarily treatment-intolerant patients would respond better to a switch to a new atypical, given that tolerability is the best established difference between the two classes of drugs. There was a non-significant trend for more participants still to be in the randomised treatment arm for new atypicals versus conventionals at 1 year. However, there were no statistically significant differential outcomes between participants entering band 1 for reasons of treatment intolerance and those entering because of broadly defined treatment resistance, and there was no significant interaction between primary reason for referral and randomised treatment. Furthermore, participants reported no clear preference for either class of drug.

Secondary categorical analysis according to an approximately 20% or more improvement in QLS and PANSS scores, taken to represent 'clinical significance', showed no significant effect of treatment in either band at 52 weeks. In band 1, 49% of those randomised to conventionals showed a clinically significant improvement on QLS compared with 33% of those randomised to new atypical drugs. For PANSS total score, the proportions were 24% and 18%, respectively.

Inspection of the subscale scores of the QLS and the PANSS in secondary analyses revealed no particular pattern of data that differed between the two classes of drug. There were no statistically significant differences between the groups over follow-up on any of the secondary outcomes. In the case of adverse effects, the relevance of examining these data in an ITT approach can be questioned if, as here, a large proportion of the sample in each randomised arm crossed to the other arm or another treatment. The planned per protocol analysis may clarify this.

The design of the study comparing classes of drugs will serve to hide the effects of individual drugs that have particular efficacy or tolerability advantages. Of note, in contrast to published efficacy trials, sulpiride was the drug chosen by clinicians in almost half of the cases randomised to the conventional arm. The high proportion on sulpiride does not reflect the general use of this drug in the UK. Referring clinicians may have chosen it because of a belief that it shares some properties with atypical drugs. Whether it shows particular effectiveness in this group is difficult to test. Of note, however, is that only 48% of those commenced on sulpiride were still on it at 52 weeks, compared with 74% of those in the new atypical group who had been started on olanzapine. In the Cochrane review of sulpiride, Soares and colleagues[192] concluded that "sulpiride may be an effective antipsychotic drug but evidence is limited".

Haloperidol was selected by clinicians in only 8% of cases randomised to the conventional arm. This is of note, as it is has been the standard comparator in most industry-sponsored trials of new atypicals against conventionals. Audit data confirm that haloperidol is used relatively infrequently in routine clinical practice. As discussed by Geddes and colleagues,[24] haloperidol carries a high side-effect burden, particularly at the relatively high doses often selected for its role as comparator in efficacy trials. This may mean that any advantage demonstrated for the new atypicals compared with haloperidol may not hold when the new drugs are compared with other conventional antipsychotics with a lower side-effect burden.

Only three of the 21 patients commenced on trifluoperazine were still prescribed it 1 year later. The role of depots will be examined further in a secondary analysis, although only nine participants were prescribed a depot at randomisation. Other reasons why the data did not show a statistically significant advantage in favour of one class of drugs are not supported by the analyses conducted. First, the QLS may not be sensitive enough to discriminate between different profiles of side-effects or overall levels of tolerability. In simple regression analyses, total symptom score accounted for about 30% of the variance in QLS, whereas side-effects had no significant effect. In addition, there were no clear differences in the rate of side-effects measured by side-effect specific instruments.

Second, inappropriately low (or high) doses of new atypicals may have been used. Inspection of the prescribed dosages showed this not to be the case.

Third, clinicians may have failed to change new atypicals in the face of non-response during the follow-up phase of the trial, whereas they were more willing to change conventionals.

Fourth, the patient sample may have been biased to those who had failed to respond to an atypical previously. This is difficult to test, but the fact that most patients at baseline were being treated with a conventional makes this explanation unlikely. Other sources of bias may also be important.

Parallel audit in the clinical services in two of the centres suggested that only up to 30% of possibly eligible patients (those with a diagnosis of schizophrenia whose drug treatment was being changed) were randomised into the trial.

Overall, then, the data from this trial do not suggest a statistically significant advantage in favour of conventional or of atypical antipsychotic therapy. However, the data indicate that there may be a clinical advantage in favour of conventional treatment. This is in line with recently published research. Some recent reviews have noted that there may still be a place for conventional drugs. In a large-scale US audit, Leslie and Rosenheck[193] found that frequent switching occurred in clinical practice and that, of those switched, about half had been changed back to their original medication within 30 days. Compared with atypical drugs, conventional medication was more likely to be maintained for 3 months or more. The authors concluded that there still appears to be a place for conventional drugs in the management of schizophrenia.

As this report was being completed, two independent systematic reviews were published,[32,194] which converged in their conclusions that some new atypical drugs appeared to have no evidence for superiority over conventionals, and that the evidence for superiority of the new atypicals was uncertain and inconclusive.

The net costs of care over the 1 year varied widely. The mean was £18,849 in the conventional drug group and £20,123 in the new atypicals group, giving a net saving of £1274 in favour of conventional antipsychotics. Of these costs, 2.2% and 3.8% were due to antipsychotic drug costs in the conventional and atypical group, respectively. The analysis included the direct costs of psychiatric and non-psychiatric hospital admissions, hospital outpatient, day-care and clinic services, medication, community-based and primary care services. The costs of contacts with the criminal justice system, use of residential accommodation and informal care were excluded, as were the indirect costs of withdrawal from paid employment. The descriptive analysis of these variables suggests that the level of use was low and that there were few differences in the use of these services over the 12-month period of the trial. However, the total costs may be underestimated, which may bias the results if there were important differences in utilisation due to the choice of antipsychotic, rather than the use of these services at baseline and the influence of organisational and social factors. There was a trend towards participants in the conventional group scoring more highly on the utility measure at 1 year. The primary and sensitivity analyses of the economic data indicate that conventional antipsychotics were likely to be cost-saving and associated with a gain in QALYs compared with atypical antipsychotics. The cost-effectiveness acceptability analysis supported this conclusion. The analysis indicated that if the additional QALYs associated with conventional antipsychotics were valued in monetary terms, using threshold cost per QALY values between 0 and £50,000, then the probability that conventional antipsychotics were cost-effective was 0.91. In other words, for people whose treatment needed to be changed, starting the new treatment with a conventional antipsychotic would be as, or more effective than atypical antipsychotics, and the probability that they were cost-effective ranged between 0.65 and 0.91. The variance in the complete case and multiple imputation cost data was high. The use of bootstrap analysis across the distribution of cost and QALY data incorporated this variability into the estimation of cost-effectiveness and net benefit.

The economic analysis indicated an advantage to starting with conventional antipsychotic therapy if a change in drug therapy was indicated for people responding poorly to, or who were intolerant of, their current medication. This contradicts many of the findings of the clinical and economic literature to assess the value of the new atypical antipsychotics. Reasons for this difference are likely to be similar to those discussed above, in terms of the choice of conventional antipsychotic for those participants randomised to the class of conventional antipsychotics, and the effect of 'hiding' the impact of specific drugs within a class. One modelling study using UK-specific resource use and cost data indicated a potential advantage for chlorpromazine and haloperidol if they were used at lower doses than those typically used in clinical trials of atypical antipsychotics.[33] The study by Bagnall and colleagues supported this conclusion for chlorpromazine.[32]

Band 2: clozapine versus new atypical drugs

Baseline characteristics of sample in band 2

In band 2, of those randomised to clozapine or a new atypical, 67% versus 69% were male, 33%

versus 23% were from an ethnic minority, 28% versus 23% were detained under a section at baseline and 12% versus 6% were in their first episode. At the time of first dose of the randomised drug, 12% of those randomised to clozapine and 45% of those randomised to a new atypical were outpatients, the low proportion in the clozapine group reflecting the licensing indications for clozapine, where initiation of the drug had to be undertaken as an inpatient (a restriction relaxed in 2002). The mean number of prior inpatient admissions was 4.2 in the clozapine group and 5.6 in the new atypical group. The mean age at randomisation was 36.6 and 37.4 years, respectively.

The mean baseline QLS scores were not well balanced in band 2, with the clozapine group having a mean of 41.0 and the new atypical group 34.7 (a higher score reflecting a better quality of life). Presumably, this difference could only have arisen by chance. It did not seem to reflect a difference in total symptom score, since the mean PANSS total score was a little higher in the new atypical group. The proportion staying on clozapine for 1 year (54%) compares well with local audit data (56% over 2 years[166]) and with previous efficacy trials.[73] In terms of 'clinically significant improvement', 31% randomised to clozapine showed clinically significant improvement on the QLS versus 25% on new atypicals. For PANSS total score, the respective proportions were 27% and 26%.

Clinician choice of drug and dosage

In those randomised to a new atypical, olanzapine was chosen in 44% and quetiapine in 17%. The mean doses of individual new atypical drugs at the end of the trial period all appeared appropriate. The mean dose of clozapine was fairly low, however, at 333 mg. Some evidence suggests that clinical response is better above 400 mg daily.[195]

Results of randomised comparison

The ITT comparison of new atypicals with clozapine in people with more narrowly defined treatment resistance showed an advantage in commencing clozapine in quality of life (QLS) at trend level ($p = 0.08$) and in symptoms (PANSS), which was statistically significant ($p = 0.01$), at 1 year. Clozapine showed approximately a 4-point advantage (not statistically significant) on QLS score at 52 weeks, against the predicted 10 points, and approximately a 5-point advantage on PANSS total score. Clozapine showed a trend towards having lower total scores for EPS ($p = 0.1$). Participants' satisfaction with their mental health was significantly better at 12 weeks in those assigned to clozapine compared with the new atypicals ($p < 0.05$).

In general, the results from this comparison are similar to those from the large, randomised, 1-year double-blind comparative study at 15 Veterans Affairs (VA) Medical Centers,[73] generally considered to be the definitive efficacy trial thus far. The subjects in the sample in that study had a diagnosis of refractory schizophrenia and had been hospitalised by the disorder for between 30 and 264 days in the previous year. In the trial, 205 patients were randomised to clozapine and 218 to haloperidol. A total of 57% of patients in the clozapine group continued their assigned treatment for the entire year compared with 28% of the patients in the haloperidol group ($p < 0.001$). As judged according to the PANSS total score, patients in the clozapine group had 5.4% lower symptom levels than those in the haloperidol group at all follow-up evaluations ($p = 0.02$). This equated to a mean PANSS score difference of 4.5 points, very similar to the 5-point advantage to clozapine shown in the current trial.

As in the current trial, the difference on QLS at 1 year in the VA trial was not significant in the ITT analysis. It was significant among patients who did not cross over to the other treatment ($p = 0.003$). Over a 1-year period, patients assigned to clozapine had fewer mean days of hospitalisation for psychiatric reasons (143.8 versus 168.1 days, $p = 0.03$). The total per capita costs to society were US$58,151 in the clozapine group and $60,885 in the haloperidol group. Fewer EPS and dyskinesias were observed in the clozapine group. The VA study concluded that, for patients with refractory schizophrenia and high levels of hospital use, clozapine was somewhat more effective than haloperidol and had fewer side-effects and similar overall costs. This study did not consider the burden of non-neurological side-effects of antipsychotics such as weight gain. The notable difference between the two trials, apart from the double-blind design, was the choice of comparator, with haloperidol in the VA trial and new atypicals in CUtLASS band 2. The difference between clozapine and the comparator was of similar magnitude in the two trials. If the denominator for the ICER for the comparison of clozapine and new atypical antipsychotics was improvement on the PANSS score of 5 points in favour of clozapine, the cost per PANSS point gained would be £1060, which is similar to that in previous evaluations.

Net costs of care again varied widely, but were higher than in band 1, with a mean of £33,781 in the clozapine group and £28,431 in the new atypical group. This gave a net cost to clozapine of £5350. Of these costs, 4.0% and 3.3%, respectively, were due to antipsychotic drug costs.

As for band 1, the analysis included the direct costs of psychiatric and non-psychiatric hospital admissions, hospital outpatient, day-care and clinic services, medication, community-based and primary care services. The costs of contacts with the criminal justice system, use of residential accommodation and informal care were excluded, as were the indirect costs of withdrawal from paid employment. Again, the descriptive analysis of these variables suggests that the level of use was low and that there were few differences in the use of these services over the 12-month period of the trial. However, the total costs may be underestimated, which may bias the results if there were important differences in utilisation due to the choice of antipsychotic, rather than the use of these services at baseline and the influence of organisational and social factors.

There was a trend towards higher mean QALYs in the clozapine group. The incremental cost per QALY for clozapine was high at £80,000. The estimated probability that clozapine was cost-effective was low at 0.36 if decision-makers are prepared to pay up to £50,000 per QALY gained. This means that the costs outweigh the value of the benefits in more than half the cases where clozapine is used, rather than atypical antipsychotics.

The increased costs in the clozapine group appeared to reflect the licensing requirement for inpatient admission for commencing the drug. This will be explored further in secondary analyses. At the time of first dose, 84% of participants allocated to the clozapine arm were inpatients (some trusts initiated a day-case initiation policy for clozapine during the course of the trial) compared with 51% in the new atypical group. In 2002, the licensing restriction in the UK for inpatient initiation was relaxed. However, the picture painted by retrospective cohort or case-controlled studies regarding savings on inpatient days with clozapine may be misleading and has not been supported by large prospective randomised and non-randomised studies.[73,151]

There are few published economic studies that compare clozapine with atypical antipsychotics. Two recent reviews and economic models of the relative cost-effectiveness of alternative antipsychotics concluded that clozapine was both more costly and associated with higher QALYs.[32,33] The level of costs and relative difference in costs in both models were lower than those observed here. The level of QALYs was similar when adjusted to the same time-frame of 1 year used in this trial. This economic analysis used observed data to estimate QALYs and costs from a pragmatic trial in the UK. In contrast, the two modelling studies used conservative estimates of the use and the costs of health service use. Inpatient admissions and length of stay data for the models were estimated from UK Hospital Episode Statistics, for all people with schizophrenia and from a controlled trial of day and inpatient therapy for people with acute psychiatric illness. These sources may underestimate the use of psychiatric hospital care by people with schizophrenia. In addition, the use of other services in the two modelling studies was based on minimum estimates of the services required.

The NICE guidance on antipsychotic drug treatment for schizophrenia recommends the wider use of clozapine in treatment-resistant schizophrenia in the NHS. The results from this non-commercially sponsored trial in clinician-defined treatment resistance in the NHS show some advantage to clozapine over new atypical drugs and provide support to this aspect of NICE guidance. However, subject to the important caveats outlined above for the analysis of band 2 data, the economic analysis suggests that clozapine may not be cost-effective for this group of patients. This will be examined further in secondary analyses. The economic results differ from the overall literature about the cost-effectiveness of clozapine, which suggests that clozapine is cost-effective. However, the majority of these economic comparisons compare clozapine with conventional antipsychotics. The results of this economic evaluation are broadly in line with the economic studies that have compared clozapine with atypical antipsychotics in people with narrowly defined treatment resistance.

Chapter 8
Conclusions

Band 1

In people with schizophrenia whose medication is being changed because of intolerance or inadequate clinical response, there is no disadvantage in terms of quality of life and symptoms over 1 year in commencing conventional antipsychotic drugs rather than new (non-clozapine) atypical drugs. There is an economic advantage in terms of utility, QALYs and costs to changing to a conventional antipsychotic in the first instance. A trial of a conventional drug is recommended in patients unresponsive to or intolerant of current drug treatment.

This result is not accounted for by inadequate power or by patterns of drug discontinuation and is supported by data from the primary quality of life measure, symptom scales and side-effects measures. Drug costs represented a small proportion of the overall costs of care (less than 5%).

There was a non-significant trend for participants still to be in the randomised treatment arm for new atypicals versus conventionals at 1 year (65% versus 54%).

Band 2

In people with schizophrenia whose medication is being changed because of narrowly defined treatment resistance, there is a statistically significant advantage in terms of symptoms but not quality of life over 1 year in commencing clozapine rather than new (non-clozapine) atypical drugs.

The superior clinical effectiveness of clozapine over new atypicals as a class in treatment-resistant schizophrenia suggested by efficacy trials is supported for the first time in routine NHS settings. These findings support the use of clozapine in this patient population as recommended in NICE guidance. However, the change to clozapine is not supported by the economic analysis, which suggests that the small improvements in symptoms and QALYs are associated with a high cost, and may not represent value for money.

Others

The deaths in the study appeared unrelated to the assigned class of drug treatment. There were no deaths among those receiving clozapine.

This trial does not allow any statements to be made about the relative safety, efficacy and cost of new atypicals versus conventionals as first line drugs. Thus, no comment is made on NICE guidance as to the availability of new atypical drugs first line.

Further analysis

Further planned analyses of this data set include an examination of the effects of injectables, the impact and determinants of polypharmacy, and an examination of QLS validity and determinants of QLS score in schizophrenia.

Recommendations for future research

The following areas are recommended for further research:

- The validation of the EuroQol and, if needed, development of disease-specific health status measures, well-being and associated utility in serious mental illness. Qualitative work with patients and carers is required to identify the key attributes that are important to people with schizophrenia and their carers and to society as a whole. These could then be used with direct utility measurement techniques to determine the order and strength of preferences for these attributes.
- A randomised trial of depot drug treatment versus oral treatment in schizophrenia.
- A randomised trial of a low-dose 'conventional' such as sulpiride versus a new atypical in first episode schizophrenia. In view of the limited equipoise experienced by clinicians as demonstrated in band 1, and of the recent NICE guidance, the feasibility of this trial in the NHS would need to be carefully explored.
- An investigation into the possible financial and other mechanisms of rewarding clinician participation in recruitment to trials.

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Contribution of authors

Shôn Lewis (Professor of Adult Psychiatry) prepared the discussion and conclusions, and commented on drafts of the report. Linda Davies (Reader and Director) was responsible for the economics methods and results. Peter Jones (Professor of Psychiatry) prepared the discussion and conclusion. Tom Barnes (Professor of Clinical Psychiatry) prepared the introduction. Robin Murray (Head of Department) prepared the discussion and conclusion. Rob Kerwin (Professor of Clinical Neuropharmacology) and David Taylor (Chief Pharmacist and Honorary Senior Lecturer) were responsible for the mirror-image study report. Karen Hayhurst (Clinical Trial Manager) prepared the methods section, the results section and the structure of report, and organised the revisions required following referees' comments. Alison Markwick (Epidemiologist) worked on the methods section and recruitment. Helen Lloyd (Research Student) worked on the methods section, recruitment and clinicians' attitudes survey report. Graham Dunn (Professor of Biomedical Statistics) worked on the statistics, methods and results. All authors commented on drafts of the report.

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Appendix 1

Unpublished scales

CUtLASS Patient Satisfaction Questionnaire

DATE OF INTERVIEW: ☐☐☐☐☐☐☐☐ (ddmmyyyy)

STUDY PERIOD: ☐☐
12 = Week 12
52 = Week 52

PATIENT INITIALS: ☐☐☐

INITIALS of TSC who PERFORMED INTERVIEW: ☐☐☐

RANDOMISATION #: ☐_☐_☐☐_☐☐☐

Instructions: The blinded Clinical Assessor cannot perform this evaluation. Enter one of the codes listed below:

Is the patient still randomised to the original treatment arm?
1 = No
2 = Yes ☐

Is the patient still taking the original antipsychotic medication assigned on the day of randomisation?
1 = No
2 = Yes ☐

Did you have a preferred treatment prior to the beginning of the study?
1 = No
2 = Yes ☐

Were you placed on your preferred treatment at the beginning of the study?
1 = No
2 = Yes ☐

How satisfied have you been with your new antipsychotic medication?
1 = Very unsatisfied
2 = Unsatisfied
3 = Neither satisfied nor unsatisfied
4 = Satisfied
5 = Very satisfied ☐

Since taking the new medication my mental health is:
1 = Much better
2 = Better
3 = The same
4 = Worse
5 = Much worse ☐

In general compared to my previous medication the side effects I experience are:
1 = Much less
2 = Less
3 = The same
4 = Worse
5 = Much worse ☐

I would recommend my new medication to a friend with similar (mental health) problems:
1 = Definitely agree
2 = Agree
3 = Neither agree or disagree
4 = Disagree
5 = Definitely disagree ☐

List up to 3 things you like about your medication

.....
.....
.....

List up to 3 things you dislike about your medication

.....
.....
.....

CUtLASS: Antipsychotic Non-Neurological Side-Effects Rating Scale Record (ANNSERS)

DATE OF INTERVIEW: ☐☐☐☐☐☐☐☐ (ddmmyyyy)

PATIENT INITIALS: ☐☐☐

RANDOMISATION #: ☐_☐_☐☐_☐☐☐

STUDY PERIOD: ☐☐
00= Baseline
12 = Week 12
26 = Week 26
52 = Week 52

INITIALS of TSC who PERFORMED INTERVIEW: ☐☐☐

Instructions: This form should be completed by the blinded Clinical Assessor. The information should be obtained by interview with the patient. This scale pertains to events over the <u>past month</u>.
Rate each item for severity according to the following codes:
0 = absent, 1 = mild, 2 = moderate, 3 = severe, 9 = unknown.

Item	**Rating (report by patient)**
1 Sedation	☐
2 Headache	☐
SLEEP DISTURBANCE	
3 Night sleep pattern	☐
4 Daytime sleepiness/difficulty waking	☐
SUBJECTIVE EXPERIENCE	
5 Loss of energy/drive	☐

6 Problems with memory ☐
7 Problems with concentration ☐

8 Dysphoria ☐

CARDIOVASCULAR PROBLEMS **Rating (report by patient)**

9 Tachycardia ☐

10 Postural hypotension ☐

GASTROINTESTINAL PROBLEMS

12 Nausea/vomiting ☐

13 Constipation ☐

14 Diarrhoea ☐

15 Weight gain ☐

Please record body weight in kg ☐☐☐•☐

16 Hypersalivation ☐

ANTICHOLINERGIC PROBLEMS

17 Dry mouth ☐

18 Blurred vision ☐

19 Sweating ☐

GENITOURINARY PROBLEMS

20 Nocturnal enuresis ☐

21 Difficulty in passing urine ☐

FEMALE (if patient is not female record N/A) **Rating (report by patient)**

22 Loss of libido ☐

23 Problems of sexual arousal ☐

24 Orgasmic difficulties ☐

25 Change in menstruation ☐

MALE (if patient is not male record N/A)

22 Loss of libido ☐

23 Erectile difficulties ☐

24 Delayed ejaculation ☐

25 Reduction in ejaculatory volume/intensity ☐

26 Gynaecomastia/galactorrhoea ☐

OTHER

27 Confusion ☐

28 Fits ☐

Please specify and give details: _____

29 Respiratory problems ☐

33 Skin rash ☐

35 Other side-effect ☐

Please specify, and give details: _____

CUtLASS Antipsychotic Non-Neurological Side-Effects Rating Scale Record (ANNSERS)

DATE OF INTERVIEW: ☐☐☐☐☐☐☐☐ (ddmmyyyy)

PATIENT INITIALS: ☐☐☐

RANDOMISATION #: ☐_☐_☐☐_☐☐☐

STUDY PERIOD: ☐☐
00= Baseline
12 = Week 12
26 = Week 26
52 = Week 52

INITIALS of TSC who PERFORMED INTERVIEW: ☐☐☐

Instructions: This form should be completed by the unblinded Trial Support Clinician. The information should be obtained from the patient's medical records. This scale pertains to events over the past month.
Rate each item for severity according to the following codes:
0 = absent, 1 = mild, 2 = moderate, 3 = severe, 9 = unknown.

Item	**Rating (from medical records)**
CARDIOVASCULAR PROBLEMS	
11 ECG abnormality/QTc prolongation	☐
Please specify:	_____
OTHER	
28 Fits	☐
Please specify and give details:	_____
29 Respiratory problems	☐
30 Neuroleptic malignant syndrome	☐
31 Hepatic dysfunction	☐
32 Onset/worsening of diabetes mellitus	☐
34 Blood dyscrasias	☐
Please specify, and give details:	_____
35 Other side-effect	☐
Please specify, and give details:	_____

CUtLASS Economic Patient Questionnaire

DATE OF INTERVIEW: ☐☐☐☐☐☐☐☐ (ddmmyyyy)

STOP DATE OF PERIOD: ☐☐☐☐☐☐☐☐ (ddmmyyyy)

PATIENT INITIALS: ☐☐☐

STUDY PERIOD: ☐☐
00 = Baseline
12 = Week 12
26 = Week 26
52 = Week 52

RANDOMISATION #: ☐_☐_☐☐_☐☐☐

Section A: USUAL LIVING SITUATION

1. What is your usual/normal living situation now?

1 Living alone
2 Living with partner
3 Living with parents
4 Living with other relatives
5 Living with others
9 Not known ☐

2. What kind of accommodation is it?
(Refer to manual for definitions)

Domestic/family

1 Owner occupied flat or house
2 Privately rented flat or house
3 Rented from local authority/municipality or housing association/co-operative ☐☐

Community (non-hospital)

4 Overnight facility, 24-hour staffed
5 Overnight facility, staffed (not 24-hour)
6 Overnight facility, unstaffed at all times

Hospital

7 Acute psychiatric ward
8 Psychiatric rehabilitation ward
9 Long-stay psychiatric ward
10 General medical ward
11 Homeless/roofless
12 Other (*specify*) _____

3. *If domestic accommodation*

How many adults live there? *(aged 16 and over and including the patient, if applicable)*

Number of adults ☐

And how many children? *(under the age of 16)*

Number of children ☐

OR ***If hospital or community accommodation,*** *please give the name of the institution*

_____

4. Have you lived anywhere else *during the period under observation?* *(No = 1, Yes = 2)* ☐

4.1 *If Yes,* **please complete the table.**

Accommodation type *(see Q.2 for code)*	**Number of days** *(during period)*

Section B: SERVICE RECEIPT

1. Have you used any of these **inpatient hospital services** *during the period under observation?*
(Note 1: please enter '0' if service has not been used; Note 2: see manual for definitions)

Type of Inpatient Service	**Name of Hospital**	**Total number of admissions** (during period)	**Total number of inpatient days** (during period)
Acute psychiatric ward			
Psychiatric rehabilitation ward			
Long-stay psychiatric ward			
Emergency/crisis centre			
General medical ward			
Other *(specify)*			

2. Have you used any **outpatient hospital services** *during the period under observation?*
(Note 1: please enter '0' if service has not been used; Note 2: see manual for definitions)

Type of Outpatient Visit	**Name of Hospital**	**Total number of visits made** (during period)	**Total number of day attendances** (during period)
Psychiatric			
Non-psychiatric *(specify)*			
Accident and Emergency			
Day hospital			

3. Have you used any **community-based day services** *during the period under observation?*
(i.e. services that are NOT HOSPITAL-BASED, such as community mental health centre, day care centre, group therapy, sheltered workshop, specialist education)
(Note 1: please enter '0' if service has not been used; Note 2: please see manual for further details)

Name of Community-based Facility	**Total number of attendances** (during period)	**Average duration of attendance** (during period)

4. Have you had any **other primary and community-care contacts** *during the period under observation?*
(Note 1: enter '0' if service has not been used; Note 2: please record only contacts that occur OUTSIDE THE HOSPITAL; Note 3: see manual for further details)

Type of Contact	**Total number of contacts** (during period)	**Average contact time** (hours)
Psychiatrist		
Psychologist		
GP, surgery visit		
GP, home visit		
District nurse		
Community psychiatric nurse / case manager		
Social worker		
Occupational therapist		
Voluntary counsellor		
Home help / care worker		
Other *(specify)*		
Other *(specify)*		

Section C: EMPLOYMENT AND INCOME

1. What is your current economic status?

(Note: if patient currently has more than one status, please identify status with highest average income)

1 Employee, full time *(>30 hours/week)*
2 Employee, part time *(≤ 30 hours/week)*
3 Self-employed
4 Government-supported training
5 Employee on sick leave
6 **Unemployed**
7 Economically inactive *(i.e. not actively seeking employment or retired)*
8 Other ☐

2. What is your occupation?
Or
What was your last occupation?

(Refer to manual for definitions)

1 Manager or administrator
2 Professional *(e.g. scientist, solicitor)*
3 Associate professional *(e.g. nurse, lab technician)*
4 Clerical/secretarial *(e.g. receptionist)*
5 Craft and related *(e.g. plasterer, mechanic)*
6 Personal and protective *(e.g. fire officer)*
7 Sales *(e.g. buyers, brokers, sales reps)*
8 Plant and machine operative *(e.g. bus driver)*
9 Other *(e.g. coal miner, farm worker)* ☐

***If currently working** (Q1, answers 1–4)*, please complete Q2
***If currently unemployed or on sick leave** (Q1, answers 5–6)*, please go to Q3
***Otherwise**, (Q1, answers 7–8)*, please go to Q4

2.1 How many hours a week do you work? Hours/week ☐☐

2.2 How many days have you been absent from work owing to <u>any</u> illness *during the period under observation?* — Days absent from work ☐☐

3. How many weeks have you been unemployed or on sick leave *during the period under observation?* — Number of weeks ☐☐

4. Do you currently receive any social security benefits? *(No = 1, Yes = 2)* ☐

4.1 ***If Yes***, do you receive any of the following benefits? *(No = 1, Yes = 2)*

4.1.1	Attendance Allowance	☐	4.1.8	Income Support	☐
4.1.2	Child Benefit	☐	4.1.9	Invalid Care Allowance	☐
4.1.3	Council Tax Benefit	☐	4.1.10	Job Seeker's Allowance	☐
4.1.4	Disability Living Allowance	☐	4.1.11	Retirement Pension	☐
4.1.5	Working Family Tax Credit	☐	4.1.12	Severe Disablement Allowance	☐
4.1.6	Housing Benefit	☐	4.1.13	Statutory Sick Pay	☐
4.1.7	Incapacity Benefit	☐	4.1.14	Other *(specify)*	☐

_____

4.2 Total amount of benefit, paid <u>weekly</u> *(<u>Note</u>: please enter '0' if patient received nothing)* £ ☐☐☐

And Total amount of benefit, paid monthly *(<u>Note</u>: please enter '0' if patient received nothing)* £ ☐☐☐

5. What is your <u>main</u> source of income?

1 Salary/wage
2 Social security benefits
3 Self-employment
4 Pension and annuities
5 Family *(e.g. from parents or partner)*
6 Other unearned income

6. What is your **<u>total personal gross</u>** income from all sources?
(<u>Note 1</u>: if gross income not known, please give <u>net</u> income, i.e. after tax and other deductions)
(<u>Note 2</u>: please show patient income bands depicted in Appendix 3 of manual.)

	<u>Weekly</u>	**or**	<u>Monthly</u>	**or**	<u>Yearly</u>		
1	£131 and under	1	£569 and under	1	£6,831 and under	gross income	☐
2	£132–£253	2	£570–£1,099	2	£6,832–£13,192	***Or***	
3	£254–£413	3	£1,100–£1,795	3	£13,193–£21,535		
4	£414–£633	4	£1,796–£2,751	4	£21,536–£33,006		
5	£634 and over	5	£2,752 and over	5	£33,007 and over	net income	☐

Section D: EXTRA COSTS

1. *During the period under observation*, how much do you think you have spent on:
(Note: please enter'0' if patient has paid nothing)

Description of Item		Amount spent (during period, £)
1.1	Prescribed, and over-the-counter, medications	
1.2	Fines or legal fees	
1.3	Child-care *(e.g. employing a child minder while attending hospital)*	
1.4	Travel costs *(e.g., parking fees to attend any hospital, GP or day-care appointments, but NOT bus pass or travel card)*	

2. Does patient have a bus pass or travel card?
(No = 1, Yes = 2) ☐

2.1 ***If Yes,*** please specify period of validity
(number of weeks) ☐☐

3. *During the period under observation,* are there any other MAJOR (£50+) one-off expenses that you have had to meet?
(No = 1, Yes = 2) ☐

3.1 *If Yes,* **please complete Q3.**

Item No.	***Description of Item***	Amount spent (during period, £)	Q3.2 (see below)
1			
2			
3			
4			

3.2 **Do you think this item was incurred** because of your illness?
(No = 1, Yes = 2) ☐

Section E: INFORMAL CARE

1. Does anyone, such as member of your family, friend or neighbour, give you UNPAID help with paperwork, housework, or take you to the doctor's and/or on outings?
(No = 1, Yes = 2) ☐

If No, please go section F
If Yes, please complete section E

2. Is there one MAIN person who gives you this sort of help?
(No = 1, Yes = 2) ☐

2.1 ***If Yes,*** what is your relationship with the carer? ☐

1 Son/Daughter
2 Mother/Father
3 Brother/Sister
4 Friend/Neighbour

5 Spouse/Partner
6 Other relative (*specify*) _____
7 Other non relative (*specify*) _____

3. **During the period under observation, has your carer /have your carers usually given you…**
(Note: if patient has a main carer, please identify ONLY this carer's contribution.
If patient has no main carer, please identify ALL care received)

3.1	**Help with personal care?**	(e.g. dressing, bathing, washing, shaving, cutting nails, feeding, using the toilet)	☐
3.2	**Physical help?**	(e.g. with walking, getting up and down stairs, getting into/out of bed)	☐
3.3	Help with paperwork or financial matters?	(e.g. writing letters, sending cards, filling in forms, dealing with bills, banking)	☐
3.4	Practical help of any other sort?	(e.g. preparing meals, doing your shopping, laundry, housework, gardening, decorating, household repairs, taking to doctor's or hospital)	☐
3.5	Time, to keep you company?	(e.g. visiting, sitting with, reading to, talking to, playing cards or games)	☐
3.6	Trips out?	(e.g. taking out for a walk or a drive, taking to see friends or relatives)	☐
3.7	Medications?	(e.g. making sure you take pills, giving injections, changing dressings)	☐
3.8	Supervision, to see you are all right?		☐
3.9	Help of any other sort? *(specify)*	_____	☐

4. Do you need help of this kind most of the time or are there periods when you don't need help?

1 Needs help most of the time
2 Periods when doesn't need help
3 Other
(specify) _____ ☐

5. How many days a week do you usually receive this help?

Days per week ☐

(Note: if patient cannot give an average weekly figure, ask for number of days per month)

Days per month ☐☐

6. On average, how long does the main carer *(OR group of carers, if no main carer)* spend each week looking after or helping you, that is doing the things you've mentioned? ☐

1 0-2 hours/week
2 3-4 hours/week
3 5-9 hours/week
4 10-19 hours/week
5 20-29 hours/week
6 30-49 hours/week
7 50-99 hours/week
8 100 or more hours/week
9 Other
(specify) _____

7.	Do you receive more/less or about the same amount of help in these tasks as other people you live with?	1 More 2 Less 3 Equal	☐

Section F: CRIMINAL JUSTICE SERVICE

Note: please see manual for guidance with this section.

1. *During the period under observation,* has the patient been in contact with the criminal justice services? ☐
(No = 1, Yes = 2)

If Yes, please complete section F

1.1	How many contacts *(Note: contact = interview or stay of some hours, but not overnight)*	With the police? With a probation officer?	Contacts ☐ Contacts ☐
1.2	How many nights spent in a police cell or prison?		Nights ☐
1.3	How many psychiatric assessments whilst in custody?		Assessments ☐
1.4	How many (criminal or civil) court appearances?		Criminal courts ☐ Civil courts ☐

THANK YOU

INTERVIEWER COMMENTS

Before filing this questionnaire or proceeding on to the next interview, please complete the following section while your impressions of the patient's responses are still fresh in your memory.

1.	**How long did the interview take?**	Number of minutes	☐☐
2.	How reliable or unreliable do you think the patient's responses were?	1 very reliable 2 generally reliable 3 generally unreliable 4 very unreliable	☐

3. Any other comments?

CUtLASS CLINICIAN'S VIEWS QUESTIONNAIRE

Please indicate your response to the following questions:

1. New atypical antipsychotics are more clinically effective than conventional antipsychotics.
(a) Strongly agree
(b) Agree
(c) Uncertain
(d) Disagree
(e) Strongly disagree

2. New atypical antipsychotics have less severe side-effects than conventional antipsychotics.
(a) Strongly agree
(b) Agree
(c) Uncertain
(d) Disagree
(e) Strongly disagree

3. Randomised controlled clinical trials are the gold standard for providing the evidence for evidence-based medical practice.
(a) Strongly agree
(b) Agree
(c) Uncertain
(d) Disagree
(e) Strongly disagree

4. Which of the following sources primarily influences your initial clinical decisions?
(a) Review articles
(b) RCTs
(c) NHS guidelines and protocols
(d) Clinical experience
(e) Other (specify) _____

5. Do you participate in randomised clinical trials?
(a) Yes
(b) No

6. If not (see (5)) why not?
(a) Don't have the time
(b) Disagree with randomisation procedure
(c) Other (specify) _____

7. The contact that I have had with the CUtLASS team prompting me to consider referring patients is:
(a) Too much
(c) Just right
(d) Too little
(e) Have not been contacted

8. I believe that I have been fully informed about the purpose and design of the CUtLASS trial:
(a) Strongly agree
(b) Agree
(c) Uncertain
(d) Disagree
(e) Strongly disagree

9. I think that CUtLASS is an important clinical trial that may answer a clinically relevant and as yet unresolved question.

(a) Strongly agree
(b) Agree
(c) Uncertain
(d) Disagree
(e) Strongly disagree

Appendix 2

Information provided to patients

CUtLASS project band 1 (conventional versus new atypical)

Cost Utility of the Latest Antipsychotics

Patient information sheet

Symptoms of psychosis can be upsetting. Usually these symptoms will get much better with so-called antipsychotic drug treatment. However about a third of people do not get much better with this treatment and other people suffer side-effects.

We are asking you to help us test a newer kind of drug treatment called an "atypical" antipsychotic tablet. We want to see if it improves symptoms or gives less side-effects. Although quite new, these tablets have been used widely around the world in many people.

What will I have to do if I agree to take part?
We are asking over seven hundred people to take part, in the Northwest, Nottingham and London. If you agree you will have either one of the newer atypical tablets or a standard medicine. This is decided by chance. There will be a 50–50 chance whether you will be prescribed an atypical tablet or standard medicine.

To see how things are going, a member of the project team will visit you at the start to check on your symptoms. This will take about one hour. This person will visit you again after 12 weeks, 6 months and finally one year from now. Checking the symptoms takes the form of helping to fill in some questionnaires.

What are the possible risks of taking part?
All medicines have side-effects in some people. Antipsychotic medicines can cause drowsiness, stiffness and trembling in some people. The atypical tablets are less likely to cause stiffness and trembling but may have other effects such as drowsiness and putting on weight. Your doctor will be keeping an eye on side-effects. If you have any problems you should tell your doctor.

What are the possible benefits?
For some people, atypical tablets make symptoms better. Changing to another standard medicine can also make symptoms better. However, this is by no means a guarantee. This project will help us in the future care of people with symptoms.

Do I have to take part?
No, taking part is voluntary. If you do not want to take part you do not have to give a reason. Your doctor will not be upset and your treatment will not be affected. If you choose to take part but later change your mind you can do so at any time.

Your medical notes will be looked at by a member of the project team but all details will be kept confidential and anonymous. We would like your permission to let your GP know that you are taking part.

What do I do now?
After talking to your doctor, a member of the project team will visit you within a few days. He or she can answer any questions and you can let them know if you want to take part.

Contact for further information
If you have any more questions please contact the trial support clinician Dr _____ at _____

Thank you for thinking about taking part. Please discuss this with your family, friends or GP if you wish.

CUtLASS project band 2 (new atypical versus clozapine)

Cost Utility of the Latest Antipsychotics

Patient information sheet

Symptoms of psychosis can be upsetting. Usually these symptoms will get much better with so-called antipsychotic drug treatment. However about a third of people do not get much better with this treatment and other people suffer side-effects.

We are asking you to help us test one of several of the latest range of drug treatments called "atypical" compared to clozapine which was the first atypical antipsychotic drug. We want to see which improves symptoms or gives less side-effects. Although quite new, these tablets have been used widely around the world in many people.

What will I have to do if I agree to take part?
If you agree you will have either one of the newer atypical tablets or clozapine. This is decided by chance. There will be a 50-50 chance whether you will be prescribed an atypical tablet or clozapine.

To see how things are going, a member of the project team will visit you at the start to check on your symptoms. This will take about one hour. This person will visit you again after 12 weeks, 6 months and finally one year from now. Checking the symptoms takes the form of helping to fill in some questionnaires.

What are the possible risks of taking part?
All medicines have side-effects in some people. The atypical antipsychotic tablets are less likely to cause stiffness and trembling than older tablets but may have other effects such as drowsiness and putting on weight. Your doctor will be keeping an eye on side-effects. If you have any problems you should tell your doctor.

Clozapine can cause drowsiness and weight gain. Some people get more saliva. Clozapine probably works better than other antipsychotic medicine, but you need to have regular blood tests. This is because about one in every 200 people have a blood reaction. Warning signs of this are picked up by the blood test. The blood test is done once before you start the clozapine, once a week afterwards for 18 weeks, then once a fortnight for up to a year, then once a month thereafter.

What are the possible benefits?
For some people, atypical tablets make symptoms better. Clozapine often works well and more than half those who try it are much better, despite having to have blood tests.

Do I have to take part?
No, taking part is voluntary. If you do not want to take part you do not have to give a reason. Your doctor will not be upset and your treatment will not be affected. If you choose to take part but later change your mind you can do so at any time.

Your medical notes will be looked at by a member of the project team but all details will be kept confidential and anonymous. We would like your permission to let your GP know that you are taking part.

What do I do now?
After talking to your doctor, a member of the project team will visit you within a few days. He or she can answer any questions and you can let them know if you want to take part.

Contact for further information
If you have any more questions please contact the trial support clinician Dr _____ at _____

Thank you for thinking about taking part. Please discuss this with your family, friends or GP if you wish.

Appendix 3
Tables

Follow-up rates

TABLE 60 *Follow-up rates*

Centre	Week 12 assessments completed	Week 26 assessments completed	Week 52 assessments completed
Bands 1 and 2 combined			
Manchester	82% (112/136)	82% (111/136)	85% (115/136)
Nottingham	88% (107/121)	87% (105/121)	87% (105/121)
Institute of Psychiatry	85% (44/52)	75% (39/52)	71% (37/52)
Imperial College	83% (45/54)	85% (46/54)	85% (46/54)
Total	85%	83%	83%
Band 1			
Manchester	80% (79/99)	80% (79/99)	83% (82/99)
Nottingham	88% (66/75)	85% (64/75)	85% (64/75)
Institute of Psychiatry	87% (26/30)	70% (21/30)	70% (21/30)
Imperial College	74% (17/23)	83% (19/23)	78% (18/23)
Total	83%	81%	81%
Band 2			
Manchester	89% (33/37)	86% (32/37)	89% (33/37)
Nottingham	89% (41/46)	89% (41/46)	89% (41/46)
Institute of Psychiatry[a]	82% (18/22)	82% (18/22)	73% (16/22)[a]
Imperial College	90% (28/31)	87% (27/31)	90% (28/31)
Total	88%	87%	87%

[a] Plus one band 2 52-week follow-up assessment not received.

Deaths and dropout rates

TABLE 61 *Deaths*

Centre	Patient ID no./age	Cause of death	Length of time in study	Treatment group
Manchester	1-1-03-005/36	Suicide or accidental death (open verdict)	26 weeks	Conventional
Manchester	1-1-02-002/50	Septicaemia (patient was quadriplegic)	24 weeks	New atypical (band 1)
Manchester	1-1-08-024/41	Cardiac event	20 weeks	Conventional
Manchester	1-1-01-008/58	Cardiac event	13 weeks	Conventional
Nottingham	2-2-03-006/66	Cardiac event[a]	16 weeks	New atypical (band 2)
Nottingham	1-2-04-004/58	Cardiac event	28 weeks	New atypical (band 1)
Institute of Psychiatry	1-3-01-019/55	Cardiac event	52 weeks	New atypical (band 1)

[a] Band 2 patients.

TABLE 62 *Withdrawal rates*

Centre	No. of patients withdrew consent	No. of patients lost to follow-up at week 52	No. of patients died	Total estimate of withdrawal rate
Manchester	10/99 = 10% band 1 2/37 = 5% band 2	3/99 (3%) band 1 2/37 (5%) band 2	4/99 (4%) band 1 only	Band 1: 17/99 (17%) Band 2: 4/37 (11%)
Nottingham	2/75 = 3% band 1 2/46 = 4% band 2	5/75 (7%) band 1 2/46 (4%) band 2	1/75 (1%) band 1 1/46 (2%) band 2	Band 1: 8/75 (11%) Band 2: 5/46 (11%)
Institute of Psychiatry[a]	6/30 = 20% band 1 4/22 = 18% band 2	2/30 (7%) band 1 1/22 (5%) band 2	1/30 (3%) band 1 only	Band 1: 9/30 (30%) Band 2: 5/22 (23%)
Imperial College	4/23 = 17% band 1 2/31 = 6% band 2	1/23 (4%) band 1 1/31 (3%) band 2	No deaths	Band 1: 5/23 (22%) Band 2: 3/31 (10%)
Total	**32/363 (9%)**	**17/363 (5%)**	**7/363 (2%)**	**56/363 (15%)**

[a] Plus one set of week 52 CRFs not received from centre.

Reasons for withdrawals

Band 1

A total of 22 patients (10%) withdrew from the band 1 arm of the trial. Withdrawals by centre are set out in *Table 63*.

TABLE 63 *Band 1, withdrawals by centre*

Study centre	*n* (%)
Manchester (Man)	10 (10)
Nottingham (Notts)	2 (3)
Imperial College, London (ICL)	4 (17)
Institute of Psychiatry, London (IoP)	6 (20)
Total	**22 (10)**

Reasons given for withdrawing from the study are set out in *Table 64*.

TABLE 64 *Band 1, reasons for withdrawing from study*

Patient ID	Centre	Treatment arm	Stage in study	Reason given
1-1-03-004	Man	Conventional: sulpiride	Week 26	No longer wished to be in study
1-1-08-010	Man	Conventional: loxapine	Week 52	Withdrew
1-1-08-025	Man	Atypical: olanzapine	Week 12	Patient stated that assessments were too intrusive and provoked anxiety
1-1-05-005	Man	Atypical: olanzapine	Week 52	Patient said she found the questions a burden
1-1-09-001	Man	Atypical: olanzapine	Baseline	Withdrew consent to participate
1-1-08-034	Man	Atypical: amisulpride	Week 12	No reason given
1-1-08-036	Man	Conventional: sulpiride	Week 12	Did not wish to continue with study
1-1-01-009	Man	Atypical: quetiapine	Week 12	Patient wished to withdraw from the study
1-1-01-010	Man	Atypical: olanzapine	Week 52	Not specified
1-1-01-012	Man	Conventional: fluphenazine dec.	Week 52	Withdrew consent
1-2-02-001	Notts	Atypical: olanzapine	Week 52	Patient was adamant did not want to participate any further
1-2-03-042	Notts	Conventional: sulpiride	Week 52	Patient refused to be seen for assessment on numerous occasions

continued

TABLE 64 *Band 1, reasons for withdrawing from study (cont'd)*

Patient ID	Centre	Treatment arm	Stage in study	Reason given
1-4-02-001	ICL	Atypical: olanzapine	Week 12	Patient stated no longer wanted to meet and discuss what is happening; feels that it is quite hopeless
1-4-03-003	ICL	Atypical: olanzapine	Week 52	Patient refused: too anxious/worried
1-4-03-004	ICL	Conventional: sulpiride	Baseline	Patient stated did not feel needed any medication; felt medication sedated him
1-4-01-001	ICL	Convectional: trifluoperazine	Week 52	Patient refused
1-3-01-002	IoP	Atypical: risperidone	Week 12	Did not want to talk to study team
1-3-01-006	IoP	Atypical: amisulpride	Week 52	Not known
1-3-01-017	IoP	Atypical: olanzapine	Week 52	Patient refused to be seen
1-3-01-020	IoP	Conventional: sulpiride	Week 12	Patient did not want to speak to anyone other than his psychiatrist
1-3-01-028	IoP	Conventional: trifluoperazine	Week 12	Patient refused to be assessed
1-3-01-030	IoP	Conventional: loxapine	Week 52	Not known

Band 2

A total of 10 patients (7%) withdrew from the band 2 arm of the trial. Withdrawals by centre are set out in *Table 65*.

TABLE 65 *Band 2, withdrawals by centre*

Study centre	*n* (%)
Manchester	2 (5)
Nottingham	2 (4)
Imperial College, London (ICL)	2 (6)
Institute of Psychiatry, London (IoP)	4 (18)
Total	**10 (7)**

Reasons given for withdrawing from the study are set out in *Table 66*.

TABLE 66 *Band 2, reasons for withdrawing from study*

Patient ID	Centre	Treatment arm	Stage in study	Reason given
2-1-03-005	Man	Atypical: quetiapine	Week 52	Technical withdrawal: patient did not attend >4 arranged appointments
2-1-08-018	Man	Clozapine	Week 12	Patient was unable to start randomised drug owing to NHS cost constraints and withdrew from study as a result of this
2-2-02-001	Notts	Clozapine	Week 52	Patient refused to be interviewed 4 times
2-2-03-036	Notts	Atypical: olanzapine	Week 52	Patient refused to be seen for week 52 assessment
2-5-01-001	ICL	Clozapine	Week 52	Patient refused to do week 52 assessment
2-5-01-003	ICL	Clozapine	Week 12	Patient stated no longer wants to participate in study
2-3-01-001	IoP	Clozapine	Week 52	Delusional attitude towards research: no recollection of taking part
2-3-01-011	IoP	Atypical: quetiapine	Week 26	Patient refused to be interviewed throughout trial
2-3-01-012	IoP	Clozapine	Week 52	Patient refused to switch to randomised antipsychotic
2-3-01-013	IoP	Clozapine	Week 26	Patient refused

Details of unmasking

TABLE 67 *Band 1, details of unmasking*

Patient ID	Centre	Treatment arm	Randomised drug	Circumstances
1-1-08-001	Man	Conventional	Haloperidol	Week 52 (partial) assessment carried out by a member of clinical team as patient refused to see CUtLASS assessor
1-1-08-047	Man	Atypical	Amisulpride	At end of week 26 period
1-3-01-013	IoP	Conventional	Sulpiride	Mother of patient showed medications to assessor at week 12 assessment
1-4-03-005	ICL	Conventional	Sulpiride	Assessor unblinded but medications were then switched
1-4-02-012	ICL	Atypical	Quetiapine	Assessor unblinded but medications were then switched
1-4-02-011	ICL	Conventional	Fluphenazine	Assessor unblinded to treatment arm but not to randomised drug

TABLE 68 *Band 2, details of unmasking*

Patient ID	Centre	Treatment arm	Randomised drug	Circumstances
2-1-01-004	Man	Atypical	Amisulpride	Week 12: assessor realised patient on clozapine as patient said was having regular blood tests. This was not in fact randomised drug (amisulpride) as patient had switched from this during week 12 period
2-1-05-002	Man	Clozapine	Clozapine	Patient talked about blood tests at week 12 assessment
2-1-10-001	Man	Atypical	Amisulpride	Assessor unblinded at end of week 12 period
2-4-02-014	IcL	Atypical	Quetiapine	Assessor unblinded at week 12 period to clozapine (not randomised drug)

Appendix 4

Clinicians' attitudes survey

Introduction

During April and September 2002 the Imperial College site of the CUtLASS study initiated and coordinated an anonymous survey of 262 consultant psychiatrists across four regional trial centres. All consultants contacted by CUtLASS staff during the patient recruitment phase (August 1999 to April 2002) were sent a simple nine-question multiple-choice questionnaire (see Appendix 1). The main objective of the survey was to investigate clinicians' attitudes regarding conventional versus atypical antipsychotic medication and the perceived validity of the study. The survey also sought to investigate a range of practical issues relating to the degree of contact that clinicians had with the study teams, and the value of RCTs in evidence-based psychiatry. The survey was prompted by a need to investigate the above issues in light of the problems experienced in recruiting patients to the band 1 arm of the trial (conventional versus atypical antipsychotics), where only 40% of the original sample size was achieved. Early feedback from local clinicians had indicated that during the course of the study, attitudes were changing towards the use of antipsychotics, with clinicians favouring the use of atypicals over the use of conventional antipsychotics. This apparent lack of clinical equipoise regarding the efficacy of the two groups of antipsychotics was suggested as one of the problems hampering recruitment to band 1. Consequently, this survey was conducted (1) to investigate a range of other factors that may have influenced patient recruitment, and (2) to provide the trial management team with an opportunity to investigate attitudes towards the trial's operation and its perception by the clinicians involved.

Method

The survey questionnaire (designed by Alison Markwick; Trial Manager, Manchester) asked clinicians to respond to nine questions selecting the appropriate response from the set range available (see Appendix 1). The set responses 'strongly agree', 'agree', 'uncertain', 'disagree' and 'strongly disagree' were provided for the questions concerning antipsychotics (Q1 and Q2), RCTs (Q3), level of information provided to clinicians by CUtLASS staff (Q8) and the validity of the study (Q9). The responses to the questions relating to influences of clinical decisions (Q4), participation in RCTs (Q5 and Q6) and contact with CUtLASS (Q7) were tailored appropriately, i.e. yes/no, too much/too little, review articles/NHS guidelines.

The following number of questionnaires were sent to clinicians at each regional centre: Manchester $n = 52$, Nottingham $n = 50$, Imperial College (including Cambridge) $n = 83$ and the Institute of Psychiatry $n = 77$. Of the 262 questionnaires sent, 112 were returned; an overall response rate of 43%. Each questionnaire was sent with a preaddressed envelope and assigned a code specific to each regional centre. To facilitate a representative response, each questionnaire was anonymous. Since CUtLASS recruited 95 clinicians across all four sites (i.e. clinicians with patients randomised into the study) and 60% ($n = 67$) of survey respondents stated that they actively took part in RCTs, it seems fair to assume that a high proportion of those who returned questionnaires and also answered 'yes' to this question may have actively enrolled patients into the study. A simple cross-tabulation using SPSS examined the responses to all questions between two groups: those who stated that they did participate in RCTs (60%) and those who stated they did not (40%). No significant difference was found in the range of responses across both groups to all the other questions, that is, questions concerning antipsychotics, RCTs and the validity of the trial.

Data collected from each questionnaire were entered into an SPSS database, at which point certain response categories were merged to facilitate clearer analyses. For example, the categories of 'strongly agree' and 'agree' were merged, as were the categories 'strongly disagree' and 'disagree'. Responses to each question were grouped for all sites and also separated out to highlight any regional variation. Where no regional variation was present the data are presented as overall responses.

Results and discussion: efficacy and side-effects

Anonymising the questionnaires made it difficult to determine which clinicians out of those who had been originally approached had actually referred patients to the trial. With hindsight, inserting the question 'Were any of your patients actively involved in the study?' might have countered this problem. However, since no significant difference was found in the range of responses in the survey across the two groups (i.e. those clinicians who said 'yes' and those who said 'no' to participating in RCTs), this sample of respondents was treated as one group for analyses.

The responses to question 9 of the survey ('I think that CUtLASS is an important clinical trial that may answer a clinically relevant and as yet unresolved question') confirmed the general support for the study among the majority of consultants (71%) who responded to the survey (*Figure 16*). Responses to this question may also indicate that a degree of clinical equipoise was maintained among the majority of respondents, since 71% (n = 80) agreed that the clinical question regarding the use of antipsychotics was still unanswered.

There exists some regional variation in the responses to the above question (*Figure 17*). For example, a higher portion of respondents from the Institute of Psychiatry indicated that they were 'uncertain' or 'disagreed' with the above question. Explanations for this regional difference may be unclear. However, the influence of prescribing guidelines during the course of the study, such as that published by the Maudsley, may account for the higher proportion of uncertainty regarding the validity of the clinical question among clinicians based at the Institute of Psychiatry.

Despite the overall support for the study indicated by the responses to question 9, the responses to question 1 indicate that 38% of clinicians who responded to the survey held pre-existing assumptions that atypical antipsychotics are superior to conventional antipsychotics in terms of clinical efficacy (*Figure 18*). However, the NICE HTA appraisal stated that "atypical antipsychotics are at least as efficacious as the typical agents in terms of overall response rates", but not more

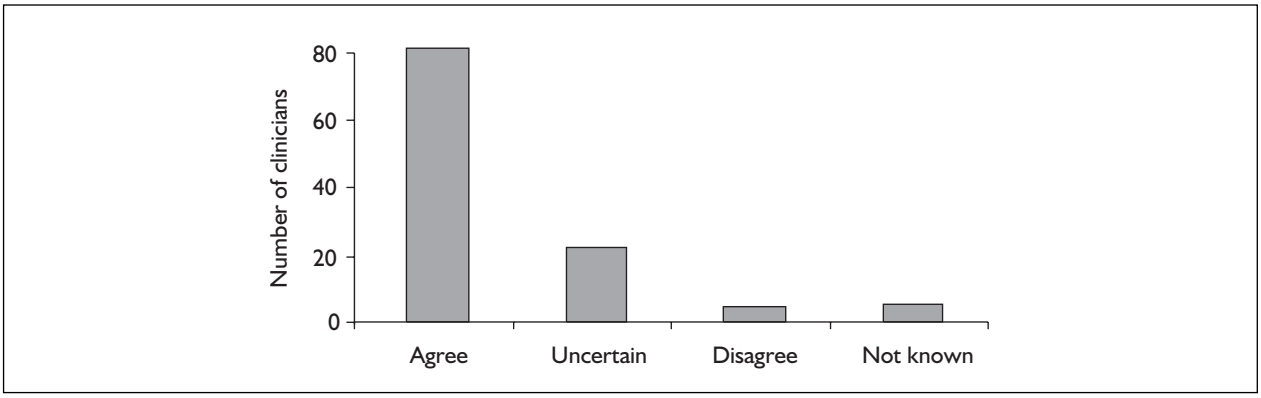

FIGURE 16 *Responses to Q9, 'I think that CUtLASS is an important clinical trial that may answer a clinically relevant and as yet unresolved question'*

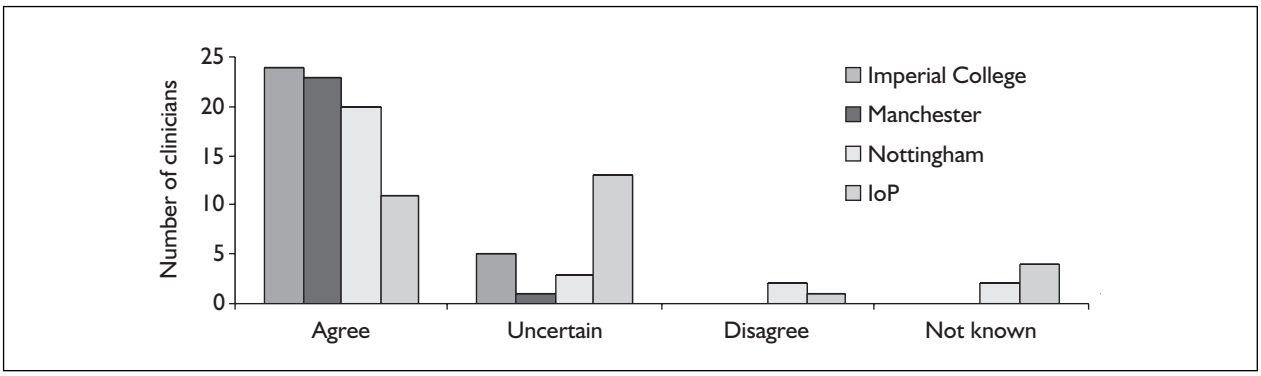

FIGURE 17 *Responses to Q9 showing regional variation*

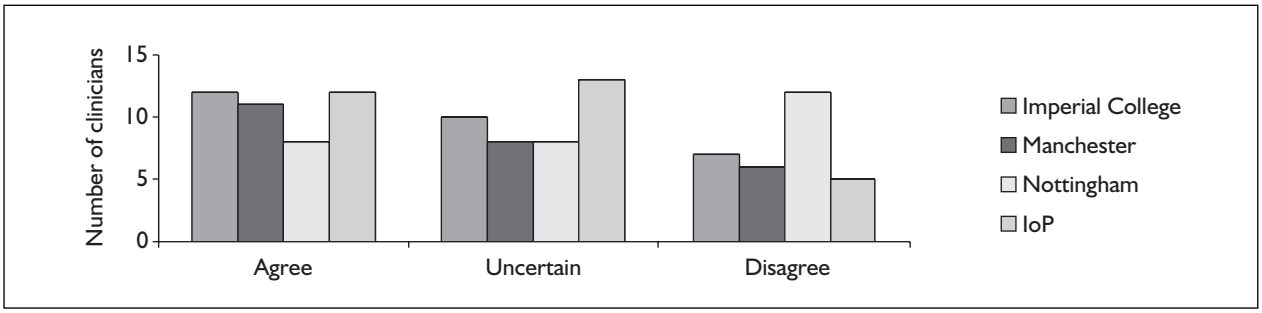

FIGURE 18 *Responses to Q1, 'New atypical antipsychotics are more clinically effective than conventional antipsychotics'*

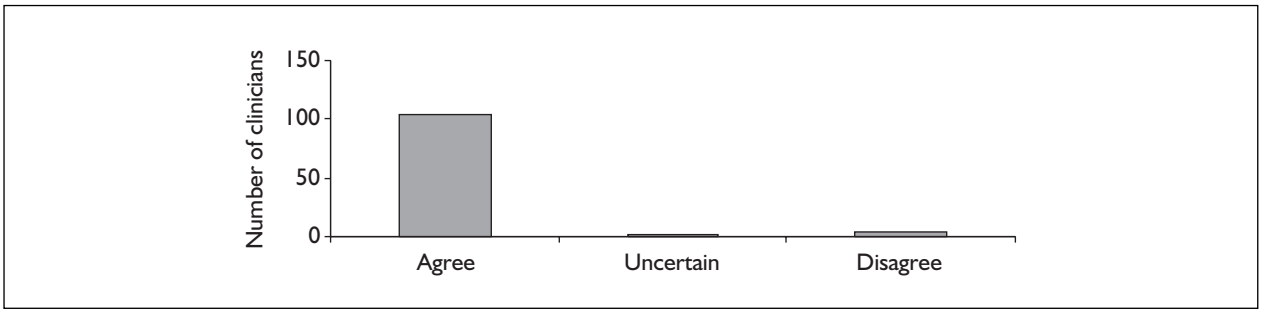

FIGURE 19 *Responses to Q2, 'New atypical antipsychotics have less severe side-effects than conventional antipsychotics'*

efficacious than conventionals. The range of responses to this question supports the need for further research on the relative clinical effectiveness of the two groups of antipsychotics.

It could be assumed that those clinicians who agreed with the statement 'New atypical antipsychotics are more clinically effective than conventional antipsychotics' would have been somewhat reluctant to refer patients to the band 1 arm of the trial, since this would have resulted in some patients being randomised to a conventional antipsychotic.

Although the main emphasis of the CUtLASS study was to investigate the perceived cost benefits associated with atypical antipsychotics, it is clear from the responses to question 2 of the survey ('New atypical antipsychotics have less severe side-effects than conventional antipsychotics') that side-effects are an important issue for prescribing clinicians. The overwhelming agreement from responding clinicians that atypicals cause less severe side-effects (90%, n = 101) (*Figure 19*) may have been a more influential factor in clinicians' overall attitude towards the clinical value of atypicals. This could be explained by the argument that a lower and less severe side-effect profile may enhance patients' adherence to their medication regimen.

The responses to this question may further illuminate some of the problems encountered recruiting patients to the band 1 arm of the study. Non-referral data collected at the Imperial College site confirmed that some clinicians were reluctant to refer patients to band 1 and risk the chance of exposing their patients to a conventional antipsychotic. This was especially relevant where patients had a past history of experiencing side-effects, since this may have affected patient adherence to medication. However, the NICE HTA appraisal guidance on the use of antipsychotics states that there are limited data to support the contention that some atypical antipsychotics prescribed over longer periods have a reduced EPS profile. In light of the difference of opinion between that held by clinicians and that stated by NICE guidance, long-term follow-up data on side-effects across a range of atypical and conventional antipsychotics at variant dosages, such as provided by CUtLASS, are necessary to provide a more informed picture.

The responses to question 3 of the survey, 'Randomised controlled clinical trials are the gold standard for providing the evidence for evidenced-based medical practice', present something of a paradox compared with the responses to questions 1 and 2. The overwhelming agreement across all four centres (89%, n = 100), that RCTs provide

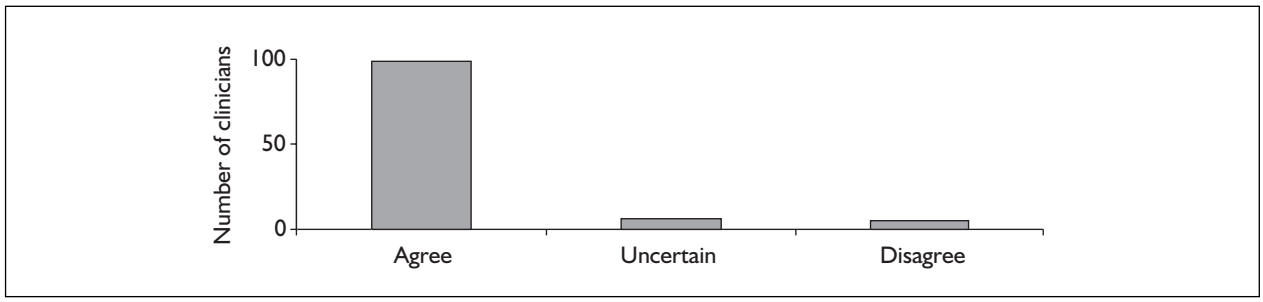

FIGURE 20 *Responses to Q3, 'Randomised controlled clinical trials are the gold standard for providing the evidence for evidence-based medical practice'*

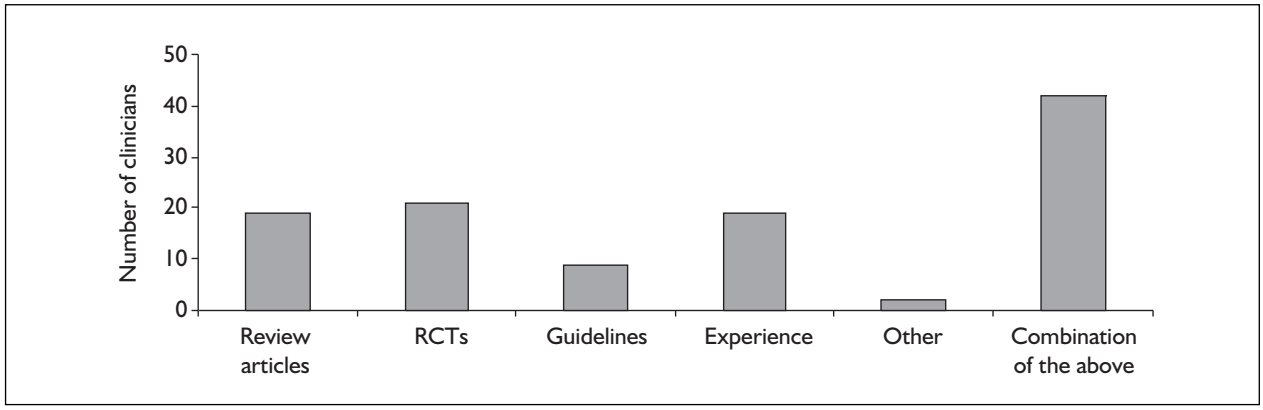

FIGURE 21 *Responses to Q4, 'Which of the following sources primarily influences your initial clinical decisions?' (overall grouped responses across all sites)*

the gold standard for evidence-based medicine (*Figure 20*), appears to contradict the pre-existing views held towards antipsychotics in light of the lack of long-term follow-up RCTs. However, many clinicians are unable to assemble and systematically review the evidence and use a number of means to gain knowledge. This includes the use of published narrative and systematic reviews as a means of summarising available evidence. As illustrated in the introduction, many of the systematic reviews focus on efficacy, and tend to suggest that atypicals are likely to have fewer side-effects.

This paradox can be partly explained by the fact that other sources influence attitudes towards the prescribing of antipsychotics. For example, 'experience' and 'review articles' appear to be as important as data generated by RCTs in influencing clinical decisions (*Figure 21*).

Discussion: study management issues

The responses to the later questions on the survey provided the study teams with an opportunity to gauge how the study had been received among the clinicians approached at each centre. Since recruitment to the band 1 arm of the study was slower than the recruitment to band 2 (atypicals versus clozapine), various initiatives were taken at each site to increase patient recruitment and clinicians were contacted regularly to encourage patient referral. However, as is the nature with medical research that relies on the referral of patients from clinical teams, study personnel felt reluctant to pursue clinicians constantly, at the risk that this may become counter-productive. This was especially true of those clinicians who had previously referred patients to the study. Nevertheless, the responses to question 7, 'The contact I have had with the CUtLASS team prompting me to refer patients is:', demonstrates that while 61% (n = 69) of respondents felt that the contact they had had with CUtLASS was 'just right', 18% (n = 20) felt that they had received 'too little' information and 17% (n = 19) stated that they had not been contacted at all (*Figure 22*). In retrospect, a simplified version of this survey conducted during the recruitment phase (including a request for contact details) might have identified clinicians who wished to be involved in the study, but were not aware that they had been contacted.

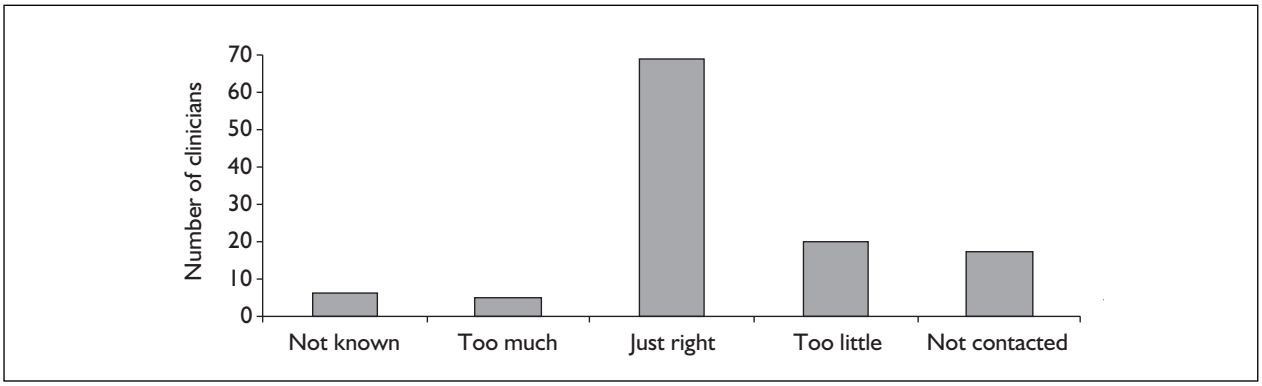

FIGURE 22 *Responses to Q7, 'The contact I have had with the CUtLASS team prompting me to refer patients is:' (grouped responses across all sites)*

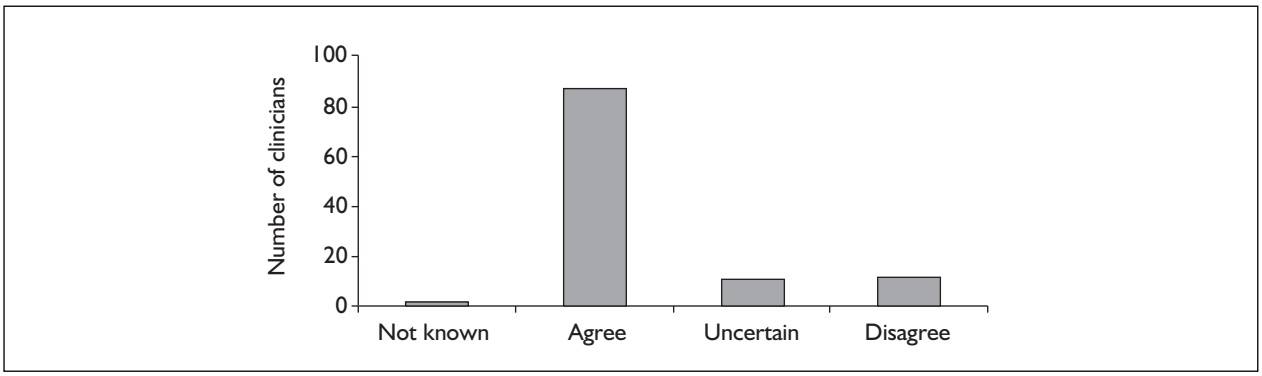

FIGURE 23 *Responses to Q8, 'I believe that I have been fully informed about the purpose and design of the CUtLASS trial' (overall grouped responses across all sites)*

Despite the responses to the above question, it was reassuring that the majority of responding clinicians (72%, $n = 81$) felt that they had been clearly informed about the purpose and design of the study (*Figure 23*). It is fair to assume that those who responded to this question as 'uncertain' (10%, $n = 11$) or 'disagree' (12%, $n = 13$) partly were 'not contacted' or had received 'too little' information.

Conclusions

This survey was designed as a tool to investigate attitudes among those clinicians approached by CUtLASS staff during the course of the study.

The results of this survey suggest that:

- Some clinicians remain unconvinced or undecided about the superiority of atypicals over conventionals. Thus, it might be assumed that patient recruitment to band 1 should not have been a problem, since 59% ($n = 66$) of clinicians who responded were either in a state of clinical equipoise (i.e. uncertain) or disagreed that atypicals are superior to conventionals.
- The responses to question 2 ('New atypical antipsychotics have less severe side-effects than conventional antipsychotics') indicate that side-effects may have been a more pertinent issue in influencing patient recruitment to band 1.

An additional benefit of this survey was that it facilitated reflexivity on the part of the study team, enabling investigation into the study management and marketing. Future trials may benefit from the instigation of similar surveys, to investigate both relevant study issues and trial management operation.

Appendix 5

Statistical analysis: example of Stata commands

Examples of the Stata commands are as follows:

```
xi: xtgee qol_total i.treat i.week*qol_base
i.location, i(pat_id) family(gaussian) link(i)
corr(exch) robust
```

or

```
xi: xtgee qol_total i.treat i.week*qol_base
i.location, i(pat_id) family(gaussian) link(i)
corr(unst) t(week) robust
```

The variables in this command are as follows:

'treat' is treatment arm (1=conventionals; 2= new atypicals)
'qol_total' is the total quality of life score at 12, 26 or 52 weeks
'qol_base' is the total quality of life score at the time of randomisation
'week' is the time since randomisation (with values 12, 26 or 52)
'location' is the academic centre (Institute of Psychiatry, Imperial College, Manchester, Nottingham or Cambridge)
'pat_id' is the patient's identification number

Appendix 6

Economic tables

TABLE 69 *Correlations between baseline outcome measures*

Measure	Spearman's rho	Utility	QLS total	PANSS total	GAF total	Evaluation of own health
Utility	Correlation coefficient	1.000	0.142**	–0.293**	0.205**	0.414**
	Significance (two-tailed)		0.007	0.000	0.000	0.000
	n	362	354	353	359	351
QLS total	Correlation coefficient	0.142**	1.000	–0.557**	0.564**	0.150**
	Significance (two-tailed)	0.007		0.000	0.000	0.005
	n	354	355	346	352	344
PANSS total	Correlation coefficient	–0.293**	–0.557**	1.000	–0.588**	–0.266**
	Significance (two-tailed)	0.000	0.000		0.000	0.000
	n	353	346	354	352	344
GAF total	Correlation coefficient	0.205**	0.564**	–0.588**	1.000	0.178**
	Significance (two-tailed)	0.000	0.000	0.000		0.001
	n	359	352	352	360	348
Evaluation of own health	Correlation coefficient	0.414**	0.150**	–0.266**	0.178**	1.000
	Significance (two-tailed)	0.000	0.005	0.000	0.001	
	n	351	344	344	348	351

**Correlation is significant at the 0.01 level (two-tailed).

TABLE 70 *Correlations between utility values over time*

			UTILITY.0: utility	UTILITY.12: utility	UTILITY.26: utility	UTILITY.52: utility
Kendall's tau_b	UTILITY.0: Utility	Correlation coefficient	1.000	0.377**	0.370**	0.321**
		Significance (two-tailed)		0.000	0.000	0.000
		n	362	307	299	362
	UTILITY.12: Utility	Correlation coefficient	0.377**	1.000	0.499**	0.454**
		Significance (two-tailed)	0.000		0.000	0.000
		n	307	307	273	307
	UTILITY.26: Utility	Correlation coefficient	0.370**	0.499**	1.000	0.567**
		Significance (two-tailed)	0.000	0.000		0.000
		n	299	273	299	299
	UTILITY.52: Utility	Correlation coefficient	0.321**	0.454**	0.567**	1.000
		Significance (two-tailed)	0.000	0.000	0.000	
		n	362	307	299	363
Spearman's rho	UTILITY.0: Utility	Correlation coefficient	1.000	0.495**	0.490**	0.436**
		Significance (two-tailed)		0.000	0.000	0.000
		n	362	307	299	362
	UTILITY.12: Utility	Correlation coefficient	0.495**	1.000	0.623**	0.576**
		Significance (two-tailed)	0.000		0.000	0.000
		n	307	307	273	307
	UTILITY.26: Utility	Correlation coefficient	0.490**	0.623**	1.000	0.684**
		Significance (two-tailed)	0.000	0.000		0.000
		n	299	273	299	299
	UTILITY.52: Utility	Correlation coefficient	0.436**	0.576**	0.684**	1.000
		Significance (two-tailed)	0.000	0.000	0.000	
		n	362	307	299	363

**Correlation is significant at the 0.01 level (two-tailed).

TABLE 71 *Correlations between utility and baseline patient characteristics*

			UTILITY.0: utility	**Age at onset**	**Age at first treatment**	**No. of hospitalisations**
Kendall's tau_b	UTILITY.0: Utility	Correlation coefficient	1.000	–0.040	–0.036	–0.063
		Significance (two-tailed)		0.285	0.330	0.102
		n	362	354	355	356
	Age at onset	Correlation coefficient	–0.040	1.000	0.889**	–0.114**
		Significance (two-tailed)	0.285		0.000	0.003
		n	354	355	353	352
	Age at first treatment	Correlation coefficient	–0.036	0.889**	1.000	–0.135**
		Significance (two-tailed)	0.330	0.000		0.000
		n	355	353	356	353
	No. of hospitalisations	Correlation coefficient	–0.063	–0.114**	–0.135**	1.000
		Significance (two-tailed)	0.102	0.003	0.000	
		n	356	352	353	357
Spearman's rho	UTILITY.0: Utility	Correlation coefficient	1.000	–0.058	–0.052	–0.092
		Significance (two-tailed)		0.273	0.326	0.083
		n	362	354	355	356
	Age at onset	Correlation coefficient	–0.058	1.000	0.923**	–0.158**
		Significance (two-tailed)	0.273		0.000	0.003
		n	354	355	353	352
	Age at first treatment	Correlation coefficient	–0.052	0.923**	1.000	–0.185**
		Significance (two-tailed)	0.326	0.000		0.000
		n	355	353	356	353
	No. of hospitalisations	Correlation coefficient	–0.092	–0.158**	–0.185**	1.000
		Significance (two-tailed)	0.083	0.003	0.000	
		n	356	352	353	357

**Correlation is significant at the 0.01 level (two-tailed).

TABLE 72 *Band 1, health status, EuroQol*

		Baseline		Week 12		Week 26		Week 52	
		n	%	*n*	%	*n*	%	*n*	%
Mobility	I have no problems in walking about	149	66	132	58	139	61	144	63
	I have some problems in walking about	72	32	54	24	42	19	38	17
	I am confined to bed	5	2	1	0				
	Missing	1	0	40	18	46	20	45	20
	n =	227	100	227	100	227	100	227	100
Self-care	I have no problems with self-care	179	79	158	70	155	68	156	69
	I have some problems with self-care	43	19	27	12	25	11	25	11
	I am unable to wash or dress myself	4	2	2	1	1	0	1	0
	Missing	1	0	40	18	46	20	45	20
	n =	227	100	227	100	227	100	227	100
Usual activities	I have no problems with performing my usual activities	102	45	103	45	100	44	99	44
	I have some problems with performing my usual activities	103	45	74	33	73	32	75	33
	I am unable to perform my usual activities	21	9	10	4	8	4	8	4
	Missing	1	0	40	18	46	20	45	20
	n =	227	100	227	100	227	100	227	100
Pain/discomfort	I have no pain or discomfort	128	56	134	59	137	60	138	61
	I have moderate pain or discomfort	83	37	47	21	41	18	40	18
	I have extreme pain or discomfort	15	7	6	3	3	1	4	2
	Missing	1	0	40	18	46	20	45	20
	n =	227	100	227	100	227	100	227	100
Anxiety/depression	I am not anxious or depressed	67	30	65	29	75	33	82	36
	I am moderately anxious or depressed	123	54	111	49	98	43	92	41
	I am extremely anxious or depressed	36	16	11	5	8	4	8	4
	Missing	1	0	40	18	46	20	45	20
	n =	227	100	227	100	227	100	227	100

TABLE 73 *Band 1, health status, EuroQol, by treatment group*

			Conventional (*n* = 118)		Atypical (*n* = 109)	
			n	**%**	***n***	**%**
Baseline	Mobility	I have no problems in walking about	85	72	64	59
		I have some problems in walking about	31	26	41	38
		I am confined to bed	2	2	3	3
		Missing	0	0	1	1
	Self-care	I have no problems with self-care	98	83	81	74
		I have some problems with self-care	20	17	23	21
		I am unable to wash or dress myself	0	0	4	4
		Missing	0	0	1	1
	Usual activities	I have no problems with performing my usual activities	53	45	49	45
		I have some problems with performing my usual activities	56	47	47	43
		I am unable to perform my usual activities	9	8	12	11
		Missing	0	0	1	1
	Pain/discomfort	I have no pain or discomfort	70	59	58	53
		I have moderate pain or discomfort	42	36	41	38
		I have extreme pain or discomfort	6	5	9	8
		Missing	0	0	1	1
	Anxiety/depression	I am not anxious or depressed	40	34	27	25
		I am moderately anxious or depressed	60	51	63	58
		I am extremely anxious or depressed	18	15	18	17
		Missing	0	0	1	1
Week 12	Mobility	I have no problems in walking about	82	69	50	46
		I have some problems in walking about	20	17	34	31
		I am confined to bed	0	0	1	1
		Missing	16	14	24	22
	Self-care	I have no problems with self-care	90	76	68	62
		I have some problems with self-care	12	10	15	14
		I am unable to wash or dress myself	0	0	2	2
		Missing	16	14	24	22
	Usual activities	I have no problems with performing my usual activities	57	48	46	42
		I have some problems with performing my usual activities	41	35	33	30
		I am unable to perform my usual activities	4	3	6	6
		Missing	16	14	24	22
	Pain/discomfort	I have no pain or discomfort	78	66	56	51
		I have moderate pain or discomfort	21	18	26	24
		I have extreme pain or discomfort	3	3	3	3
		Missing	16	14	24	22
	Anxiety/depression	I am not anxious or depressed	38	32	27	25
		I am moderately anxious or depressed	58	49	53	49
		I am extremely anxious or depressed	6	5	5	5
		Missing	16	14	24	22
Week 26	Mobility	I have no problems in walking about	78	66	61	56
		I have some problems in walking about	17	14	25	23
		I am confined to bed	0	0	0	0
		Missing	23	19	23	21
	Self-care	I have no problems with self-care	84	71	71	65
		I have some problems with self-care	10	8	15	14
		I am unable to wash or dress myself	1	1		
		Missing	23	19	23	21
	Usual activities	I have no problems with performing my usual activities	53	45	47	43
		I have some problems with performing my usual activities	39	33	34	31
		I am unable to perform my usual activities	3	3	5	5
		Missing	23	19	23	21

continued

TABLE 73 *Band 1, health status, EuroQol, by treatment group (cont'd)*

			Conventional (*n* = 118)		Atypical (*n* = 109)	
			n	**%**	***n***	**%**
	Pain/discomfort	I have no pain or discomfort	79	67	58	53
		I have moderate pain or discomfort	16	14	25	23
		I have extreme pain or discomfort	0	0	3	3
		Missing	23	19	23	21
	Anxiety/depression	I am not anxious or depressed	38	32	37	34
		I am moderately anxious or depressed	54	46	44	40
		I am extremely anxious or depressed	3	3	5	5
		Missing	23	19	23	21
Week 52	Mobility	I have no problems in walking about	80	68	64	59
		I have some problems in walking about	18	15	20	18
		I am confined to bed	0	0	0	0
		Missing	20	17	25	23
	Self-care	I have no problems with self-care	89	75	67	61
		I have some problems with self-care	9	8	16	15
		I am unable to wash or dress myself	0	0	1	1
		Missing	20	17	25	23
	Usual activities	I have no problems with performing my usual activities	56	47	43	39
		I have some problems with performing my usual activities	38	32	37	34
		I am unable to perform my usual activities	4	3	4	4
		Missing	20	17	25	23
	Pain/discomfort	I have no pain or discomfort	77	65	61	56
		I have moderate pain or discomfort	19	16	21	19
		I have extreme pain or discomfort	2	2	2	2
		Missing	20	17	25	23
	Anxiety/depression	I am not anxious or depressed	44	37	38	35
		I am moderately anxious or depressed	51	43	41	38
		I am extremely anxious or depressed	3	3	5	5
		Missing	20	17	25	23

TABLE 74 *Band 1, utility and evaluation of own health, EuroQol, all patients*

		Baseline	Week 12	Week 26	Week 52
Utility	Mean	0.64	0.75	0.79	0.79
	SD	0.31	0.24	0.22	0.22
	Range	–0.35 to 1.00	–0.18 to 1.00	–0.18 to 1.00	–0.03 to 1.00
Evaluation of own health	Mean	56.38	62.55	60.85	63.38
	SD	26.08	21.21	21.31	20.99
	Range	0.00 to 100.00	0.00 to 100.00	0.00 to 100.00	0.00 to 100.00

TABLE 75 *Band 1, use of psychiatric hospital services*

Study period	Treatment group		Inpatient stay (days)	Day-care attendances	Medical outpatient consultations, hospital visits	Medical outpatient consultations, home visits	Non-medical outpatient consultations, hospital visits	Non-medical outpatient consultations, home visits
3 months–baseline	Conventional	Mean	16	0	0	0	0	0
		n	117	117	117	117	117	117
		SD	27	2	0	0	0	1
	Atypical	Mean	17	1	0	0	0	0
		n	108	108	108	108	108	108
		SD	30	4	0	1	1	2
Baseline–week 12	Conventional	Mean	29	0	0	0	0	0
		n	115	115	115	115	115	115
		SD	37	0	0	0	0	0
	Atypical	Mean	28	0	0	0	0	0
		n	106	106	106	106	106	106
		SD	36	2	1	1	1	2
Week 13–26	Conventional	Mean	20	0	0	0	0	0
		n	111	110	111	111	110	110
		SD	36	2	0	1	0	0
	Atypical	Mean	21	0	0	0	0	0
		n	101	101	101	101	101	101
		SD	38	2	0	0	0	1
Week 27–52	Conventional	Mean	33	0	0	0	0	0
		n	107	105	107	107	106	106
		SD	66	2	0	1	0	0
	Atypical	Mean	36	1	0	0	0	0
		n	99	99	99	99	99	99
		SD	65	5	0	1	0	0

TABLE 76 *Band 1, cost of psychiatric hospital services, estimated from reference cost unit cost data (£, 2001–2)*

Study period	Treatment group		Inpatient stay	Medical and non-medical outpatient visits	Day-patient attendances	Medical home visits	Non-medical home visits	Total psychiatric hospital costs
3 months–baseline	Conventional	Mean	3,517	8	19	0	5	3,550
		n	117	117	117	117	117	117
		SD	6,631	44	136	0	55	6,629
	Atypical	Mean	3,504	19	30	20	33	3,626
		n	108	108	108	108	108	108
		SD	6,682	115	226	212	207	6,747
Baseline–week12	Conventional	Mean	5,841	0	0	0	0	5,841
		n	115	115	115	115	115	115
		SD	8,020	0	0	0	0	8,020
	Atypical	Mean	5,320	19	20	19	43	5,507
		n	106	106	106	106	106	106
		SD	7,309	93	111	110	203	7,327
Week 13–26	Conventional	Mean	4,246	4	20	20	6	4,205
		n	111	110	110	111	110	109
		SD	8,294	23	144	210	47	8,318
	Atypical	Mean	4,042	13	16	9	20	4,099
		n	101	101	101	101	101	101
		SD	7,520	61	140	92	108	7,493
Week 27–52	Conventional	Mean	7,485	3	17	26	0	7,181
		n	107	106	105	107	106	104
		SD	16,190	22	126	267	0	16,273
	Atypical	Mean	7,024	5	40	17	5	7,096
		n	99	99	99	99	99	99
		SD	13,398	30	289	166	36	13,368

TABLE 77 *Band 1, cost of psychiatric hospital services, estimated from CIPFA unit cost data (£, 2001–2)*

Study period	Treatment group		Inpatient stay	Medical and non-medical outpatient visits	Day-patient attendances	Medical home visits	Non-medical home visits	Total psychiatric hospital costs
3 months–baseline	Conventional	Mean	3,332	10	19	0	3	3,364
		n	117	117	117	117	117	117
		SD	6,154	55	136	0	37	6,153
	Atypical	Mean	3,362	23	30	13	22	3,471
		n	108	108	108	108	108	108
		SD	6,486	143	226	139	138	6,546
Baseline–week 12	Conventional	Mean	5,657	0	0	0	0	5,657
		n	115	115	115	115	115	115
		SD	7,648	0	0	0	0	7,648
	Atypical	Mean	5,098	24	20	12	29	5,269
		n	106	106	106	106	106	106
		SD	6,940	116	111	72	135	6,969
Week 13–26	Conventional	Mean	4,009	5	20	13	4	3,957
		n	111	110	110	111	110	109
		SD	7,785	29	144	137	31	7,798
	Atypical	Mean	3,810	16	16	6	13	3,861
		n	101	101	101	101	101	101
		SD	7,061	76	140	60	72	7,037
Week 27–52	Conventional	Mean	6,733	4	17	17	0	6,402
		n	107	106	105	107	106	104
		SD	14,896	27	126	174	0	14,916
	Atypical	Mean	6,508	6	40	11	3	6,574
		n	99	99	99	99	99	99
		SD	12,360	37	289	109	24	12,333

TABLE 78 *Band 1, cost of psychiatric hospital services, estimated from PSSRU unit cost data (£, 2001–2)*

Study period	Treatment group		Inpatient stay	Medical and non-medical outpatient visits	Day-patient attendances	Medical home visits	Non-medical home visits	Total psychiatric hospital costs
3 months–baseline	Conventional	Mean	3,298	10	19	0	3	3,331
		n	117	117	117	117	117	117
		SD	6,139	60	136	0	37	6,136
	Atypical	Mean	3,337	25	30	13	22	3,448
		n	108	108	108	108	108	108
		SD	6,449	156	226	139	138	6,510
Baseline–week 12	Conventional	Mean	5,550	0	0	0	0	5,550
		n	115	115	115	115	115	115
		SD	7,554	0	0	0	0	7,554
	Atypical	Mean	5,042	26	20	12	29	5,212
		n	106	106	106	106	106	106
		SD	6,887	126	111	72	135	6,908
Week 13–26	Conventional	Mean	3,960	5	20	13	4	3,907
		n	111	110	110	111	110	109
		SD	7,730	32	144	137	31	7,738
	Atypical	Mean	3,759	18	16	6	13	3,812
		n	101	101	101	101	101	101
		SD	6,983	83	140	60	72	6,958
Week 27–52	Conventional	Mean	7,032	4	17	17	0	6,703
		n	107	106	105	107	106	104
		SD	15,091	29	126	174	0	15,117
	Atypical	Mean	6,485	7	40	11	3	6,551
		n	99	99	99	99	99	99
		SD	12,352	41	289	109	24	12,325

TABLE 79 *Band 1, use and costs of non-psychiatric hospital services (£, 2001–2)*

Study period	Treatment group		Non-psychiatric inpatient stay	A&E admissions	A&E attendances	Outpatient visits	Home visits	Total cost
3 months–baseline	Conventional	Mean	1	0	0	0	0	243
		n	118	118	118	118	118	118
		SD	13	0	0	0	0	1,703
	Atypical	Mean	3	0	0	0	0	268
		n	108	109	109	109	109	108
		SD	29	0	1	0	0	1,805
Baseline–week 12	Conventional	Mean	1	0	0	0	0	172
		n	112	118	118	118	118	112
		SD	10	0	0	0	0	1,675
	Atypical	Mean	3	0	0	0	0	185
		n	97	109	109	109	109	97
		SD	29	0	0	0	0	1,745
Week 13–26	Conventional	Mean	0	0	0	0	0	73
		n	108	118	118	118	118	108
		SD	2	0	0	0	0	550
	Atypical	Mean	0	0	0	0	0	331
		n	98	109	109	109	109	98
		SD	3	0	0	0	0	2,591
Week 27–52	Conventional	Mean	0	0	0	0	0	79
		n	107	118	118	118	118	107
		SD	1	0	0	0	0	485
	Atypical	Mean	2	0	0	0	0	733
		n	93	109	109	109	109	93
		SD	19	0	0	1	0	6,834

TABLE 80 *Band 1, use and costs of drugs used for psychosis and related disorders (classified according to BNF section 4.2) (£, 2001–2)*

Drug		Conventional						Atypical					
		Daily cost		No. of days		Total cost		Daily cost		No. of days		Total cost	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Amisulpride	Base–week 12	3	2	36	31	70	43	3	1	57	39	177	133
	Week 13–26	3	1	52	42	115	64	3	2	95	25	294	204
	Week 27–52	3	1	75	72	201	213	3	2	154	66	518	354
Chlorpromazine	Base–week 12	0	0	64	37	7	5	0	0	52	47	5	7
	Week 13–26	0	0	79	39	9	6	0	0	73	49	7	9
	Week 27–52	0	0	182	100	20	13	0	0	124	88	13	16
Clozapine	Base–week 12	2	2	11	11	8	11	5	1	111		540	
	Week 13–26	4	2	46	29	188	141	8	3	43	47	337	364
	Week 27–52	6	3	161	76	1,371	862	9	3	192	74	1,758	768
Droperidol	Base–week 12	0	0	53	37	24	15	1	0	29	25	24	36
	Week 13–26	1	0	49	38	34	25	0	0	63	49	18	9
	Week 27–52	0	0	29	1	8	3	1					
Flupenthixol	Base–week 12	4	3	85	62	396	507	7	6	90	13	599	208
	Week 13–26	4	4	85	30	365	526	8	7	87	16	515	203
	Week 27–52	5	7	212	90	1,064	1,641	9	8	182		890	
Flupenthixol dec.	Base–week 12	4	2	72	18	318	207	6	5	71	40	469	449
	Week 13–26	3	2	104	14	353	191	3	2	102	8	286	156
	Week 27–52	4	2	230	88	881	616	4	2	189	47	728	413
Fluphenazine	Base–week 12	5	3	53	29	204	140						
	Week 13–26	7	3	98	0	672	310	7	2	60	54	503	550
	Week 27–52	2	0	99	21	232	49	8	1	182	0	1,470	264
Fluphenazine dec.	Base–week 12	6	6	86	29	507	514	6	3	80	8	490	248
	Week 13–26	8	7	88	57	684	758	8	3	74	42	524	338
	Week 27–52	8	7	223	70	1,853	1,295	6	4	149	67	1,064	748
Haloperidol	Base–week 12	1	2	50	38	99	182	0	0	48	41	23	28
	Week 13–26	2	3	102	49	166	203	0	0	98		65	
	Week 27–52	0	0	77	78	32	27	2	3	182	0	586	657
Haloperidol dec.	Base–week 12	6		78		450		10	6	74	17	912	573
	Week 13–26	5	1	98		565		6	1	78	65	488	428
	Week 27–52	6		182		1,050		9					

continued

TABLE 80 *Band 1, use and costs of drugs used for psychosis and related disorders (classified according to BNF section 4.2) (£, 2001–2) (cont'd)*

Drug		Conventional						Atypical					
		Daily cost		No. of days		Total cost		Daily cost		No. of days		Total cost	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Lithium	Base–week 12	0	0	81	9	8	2	0	0	82	14	5	2
	Week 13–26	0	0	105	34	9	2	0	0	102	11	8	3
	Week 27–52	0	0	216	54	22	10	0	0	252	76	20	9
Methotrimeprazine	Base–week 12	1		78		53							
	Week 13–26	1		168		186							
	Week 27–52	2		182		310							
Olanzapine	Base–week 12	4	2	71	36	336	240	4	1	67	28	281	167
	Week 13–26	4	2	55	48	228	233	5	2	100	33	460	232
	Week 27–52	5	3	124	73	773	723	5	2	189	71	923	454
Pipothiazine palm.	Base–week 12	16	10	76	32	1,071	570	17	10	87	8	1,488	911
	Week 13–26	16	14	92	19	1,529	1,427	8	0	76	86	663	706
	Week 27–52	10	4	182	1	1,736	612	9	2	177	11	1,862	252
Quetiapine	Base–week 12	4	1	39	47	178	245	3	1	65	35	247	189
	Week 13–26	3	2	44	30	190	172	4	2	82	34	397	288
	Week 27–52	4	2	106	91	536	593	4	2	154	72	710	503
Risperidone	Base–week 12	3	1	55	26	189	126	3	1	69	26	202	116
	Week 13–26	3	1	98	1	277	95	3	1	108	38	338	155
	Week 27–52	3	1	135	94	351	312	3	1	140	74	441	218
Sulpiride	Base–week 12	1	0	76	37	51	40	1	0	70	29	62	46
	Week 13–26	1	0	103	34	76	53	1	1	48	6	38	32
	Week 27–52	1	0	188	73	144	108	1		182		198	
Zuclopenthixol	Base–week 12	2	3	82	51	254	323	5	3	105	54	522	374
	Week 13–26	3	3	97	3	289	299	3		98		332	
	Week 27–52	4	4	154	78	637	715	5	2	93	78	437	195
Zuclopenthixol dec.	Base–week 12	8	4	90	71	822	991	8		84		672	
	Week 13–26	8	1	96	4	798	19	6		15		96	
	Week 27–52	8		351		2,808							

Base, baseline.

TABLE 81 *Band 1, use and costs of all other drugs used by patients in the trial (£, 2001–2)*

Study period	Treatment group		Daily cost	No. of days	Total cost
Baseline–week 12	Conventional	Mean	0	78	25
		n	238	208	203
		SD	1	31	45
	Atypical	Mean	0	72	22
		n	212	170	167
		SD	0	32	33
Week 13–26	Conventional	Mean	0	85	29
		n	205	181	178
		SD	1	32	58
	Atypical	Mean	0	83	32
		n	168	144	138
		SD	1	36	44
Week 27–52	Conventional	Mean	0	145	54
		n	213	174	172
		SD	1	70	109
	Atypical	Mean	0	153	66
		n	170	135	133
		SD	1	66	92

TABLE 82 *Band 1, use and costs of community-based and primary care services (£, 2001–2)*

Study period		*n*	Mean	SD
3 months–baseline	No. of attendances at community centre	362	9	16
	Primary care psychiatrist – contact	343	0	1
	Primary care psychiatrist – time	29	1	0
	Primary care psychology – contact	339	0	1
	Primary care psychology – time	4	1	0
	GP surgery – contact	345	1	2
	GP surgery – time	121	0	0
	GP home – contact	339	0	0
	GP home – time	4	0	0
	District nurse – contact	339	0	1
	District nurse – time	4	1	0
	Nurse – contact	342	1	5
	Nurse – time	57	1	0
	Social worker – contact	339	0	2
	Social worker – time	23	1	0
	Primary care OT – contact	340	0	2
	Primary care OT – time	12	1	1
	Primary care counsellor – contact	341	0	2
	Primary care counsellor – time	6	1	1
	Home help – contact	339	1	6
	Home help – time	7	1	1
	Other – contact	337	1	3
	Other – time	16	1	1
Baseline–week 12	No. of attendances at community centre	137	10	20
	Primary care psychiatrist – contact	291	0	0
	Primary care psychiatrist – time	11	1	0
	Primary care psychology – contacts	291	0	1
	Primary care psychology – time	6	1	0
	GP surgery – contact	294	1	2
	GP surgery – time	91	0	0
	GP home – contact	291	0	0
	GP home – time	5	0	0
	District nurse – contact	291	0	0
	District nurse – time	3	0	0
	Nurse – contact	291	1	6
	Nurse – time	40	1	0
	Social worker – contact	293	0	2
	Social worker – time	37	1	0
	Primary care OT – contact	290	0	1
	Primary care OT – time	10	1	1
	Primary care counsellor – contact	292	0	1
	Primary care counsellor – time	2	2	1
	Home help – contact	288	1	7
	Home help – time	6	2	1
	Other – contact	289	0	1
	Other – time	12	1	1
Week 13–26	No. of attendances at community centre	120	10	19
	Primary care psychiatrist – contact	286	0	0
	Primary care psychiatrist – time	16	1	0
	Primary care psychology – contact	285	0	1
	Primary care psychology – time	6	1	0
	GP surgery – contact	290	1	2
	GP surgery – time	100	0	0
	GP home – contact	285	0	0
	GP home – time	5	0	0
	District nurse – contact	285	0	1
	District nurse – time	2	0	0

continued

TABLE 82 *Band 1, use and costs of community-based and primary care services (£, 2001–2) (cont'd)*

Study period		*n*	Mean	SD
	Nurse – contact	284	1	4
	Nurse – time	37	1	0
	Social worker – contact	286	0	1
	Social worker – time	38	1	0
	Primary care OT – contact	285	0	2
	Primary care OT – time	12	1	1
	Primary care counsellor – contact	285	0	1
	Primary care counsellor – time	1	1	
	Home help – contact	284	1	4
	Home help – time	7	1	1
	Other – contact	284	1	4
	Other – time	18	1	1
Week 27–52	No. of attendances at community centre	123	19	33
	Primary care psychiatrist – contact	283	0	1
	Primary care psychiatrist – time	31	1	0
	Primary care psychology – contact	283	0	1
	Primary care psychology – time	2	1	0
	GP surgery – contact	285	1	3
	GP surgery – time	120	0	0
	GP home – contact	282	0	0
	GP home – time	2	0	0
	District nurse – contact	282	0	4
	District nurse – time	4	1	0
	Nurse – contact	281	2	5
	Nurse – time	43	1	0
	Social worker – contact	283	1	4
	Social worker – time	48	1	0
	Primary care OT – contact	282	1	3
	Primary care OT – time	18	1	1
	Primary care counsellor – contact	282	0	1
	Primary care counsellor – time	1	1	.
	Home help – contact	276	1	4
	Home help – time	8	1	1
	Other – contact	279	1	4
	Other – time	15	1	1

OT, occupational therapist.

TABLE 83 *Band 1, cost of community-based and primary care services (£, 2001–2)*

		Conventional		Atypical	
		Mean	**SD**	**Mean**	**SD**
3 months–baseline	Cost of psychiatrist visits	19	78	23	85
	Cost of psychologist visits	1	6	1	5
	Cost of GP surgery visits	21	36	24	45
	Cost of GP home visits	2	12	0	5
	Cost of district nurse visits	1	5	0	0
	Cost of practice nurse visits	19	52	19	57
	Cost of social worker visits	12	68	18	102
	Cost of occupational therapist visits	1	7	35	304
	Cost of counsellor visits	8	70	2	16
	Cost of home help visits	1	12	5	28
	Cost of other primary care contacts	7	32	100	932
	Cost of community centre visits	56	180	76	200
Baseline–week 12	Cost of psychiatrist visits	2	14	11	42
	Cost of psychologist visits	4	41	1	7
	Cost of GP surgery visits	24	56	21	36
	Cost of GP home visits	0	0	8	49
	Cost of district nurse visits	0	1	0	0
	Cost of practice nurse visits	6	23	12	39
	Cost of social worker visits	22	104	16	70
	Cost of occupational therapist visits	4	23	2	18
	Cost of counsellor visits	5	46	0	0
	Cost of home help visits	16	120	2	13
	Cost of other primary care contacts	5	45	27	222
	Cost of community centre visits	59	161	118	307
Week 13–26	Cost of psychiatrist visits	6	24	11	42
	Cost of psychologist visits	2	16	3	18
	Cost of GP surgery visits	27	60	28	56
	Cost of GP home visits	2	11	6	44
	Cost of district nurse visits	0	0	2	18
	Cost of practice nurse visits	9	39	26	100
	Cost of social worker visits	7	26	27	76
	Cost of occupational therapist visits	7	64	2	19
	Cost of counsellor visits	0	0	0	0
	Cost of home help visits	19	134	6	30
	Cost of other primary care contacts	27	155	43	364
	Cost of community centre visits	89	248	104	362
Week 27–52	Cost of psychiatrist visits	13	48	33	125
	Cost of psychologist visits	13	87	0	0
	Cost of GP surgery visits	45	101	46	62
	Cost of GP home visits	0	0	1	8
	Cost of district nurse visits	1	9	17	149
	Cost of practice nurse visits	23	83	54	173
	Cost of social worker visits	10	32	60	213
	Cost of occupational therapist visits	24	177	23	136
	Cost of counsellor visits	0	0	0	0
	Cost of home help visits	7	41	5	44
	Cost of other primary care contacts	19	92	10	47
	Cost of community centre visits	130	383	165	535

TABLE 84 *Band 2, health status, EuroQol*

		Baseline		Week 12		Week 26		Week 52	
		n	%	*n*	%	*n*	%	*n*	%
Mobility	I have no problems in walking about	86	63	98	72	94	69	96	71
	I have some problems in walking about	48	35	22	16	23	17	22	16
	I am confined to bed	1	1			1	1		
	Missing	1	1	16	12	18	13	18	13
	n =	136	100	136	100	136	100	136	100
Self-care	I have no problems with self-care	96	71	97	71	97	71	99	73
	I have some problems with self-care	38	28	22	16	20	15	19	14
	I am unable to wash or dress myself	1	1	1	1	1	1		
	Missing	1	1	16	12	18	13	18	13
	n =	136	100	136	100	136	100	136	100
Usual activities	I have no problems with performing my usual activities	64	47	60	44	70	51	72	53
	I have some problems with performing my usual activities	54	40	52	38	45	33	41	30
	I am unable to perform my usual activities	17	13	8	6	3	2	5	4
	Missing	1	1	16	12	18	13	18	13
	n =	136	100	136	100	136	100	136	100
Pain/discomfort	I have no pain or discomfort	63	46	72	53	78	57	75	55
	I have moderate pain or discomfort	57	42	45	33	39	29	41	30
	I have extreme pain or discomfort	15	11	2	1	1	1	2	1
	Missing	1	1	17	13	18	13	18	13
	n =	136	100	136	100	136	100	136	100
Anxiety/depression	I am not anxious or depressed	45	33	42	31	44	32	50	37
	I am moderately anxious or depressed	68	50	70	51	65	48	63	46
	I am extremely anxious or depressed	22	16	7	5	9	7	4	3
	Missing	1	1	17	13	18	13	19	14
	n =	136	100	136	100	136	100	136	100

TABLE 85 *Band 2, health status, EuroQol, by treatment group*

			Clozapine (*n* = 67)		Atypical (*n* = 69)	
			n	**%**	***n***	**%**
Baseline	Mobility	I have no problems in walking about	46	69	40	58
		I have some problems in walking about	21	31	27	39
		I am confined to bed	0	0	1	1
		Missing	0	0	1	1
	Self-care	I have no problems with self-care	48	72	48	70
		I have some problems with self-care	18	27	20	29
		I am unable to wash or dress myself	1	1	0	0
		Missing	0	0	1	1
	Usual activities	I have no problems with performing my usual activities	37	55	27	39
		I have some problems with performing my usual activities	23	34	31	45
		I am unable to perform my usual activities	7	10	10	14
		Missing	0	0	1	1
	Pain/discomfort	I have no pain or discomfort	33	49	30	43
		I have moderate pain or discomfort	30	45	27	39
		I have extreme pain or discomfort	4	6	11	16
		Missing	0	0	1	1
	Anxiety/depression	I am not anxious or depressed	20	30	25	36
		I am moderately anxious or depressed	41	61	27	39
		I am extremely anxious or depressed	6	9	16	23
		Missing	0	0	1	1
Week 12	Mobility	I have no problems in walking about	48	72	50	72
		I have some problems in walking about	11	16	11	16
		Missing	8	12	8	12
	Self-care	I have no problems with self-care	51	76	46	67
		I have some problems with self-care	8	12	14	20
		I am unable to wash or dress myself	0	0	1	1
		Missing	8	12	8	12
	Usual activities	I have no problems with performing my usual activities	35	52	25	36
		I have some problems with performing my usual activities	22	33	30	43
		I am unable to perform my usual activities	2	3	6	9
		Missing	8	12	8	12
	Pain/discomfort	I have no pain or discomfort	43	64	29	42
		I have moderate pain or discomfort	16	24	29	42
		I have extreme pain or discomfort	0	0	2	3
		Missing	8	12	9	13
	Anxiety/depression	I am not anxious or depressed	24	36	18	26
		I am moderately anxious or depressed	34	51	36	52
		I am extremely anxious or depressed	1	1	6	9
		Missing	8	12	9	13
Week 26	Mobility	I have no problems in walking about	51	76	43	62
		I have some problems in walking about	8	12	15	22
		I am confined to bed	0	0	1	1
		Missing	8	12	10	14
	Self-care	I have no problems with self-care	50	75	47	68
		I have some problems with self-care	9	13	11	16
		I am unable to wash or dress myself	0	0	1	1
		Missing	8	12	10	14
	Usual activities	I have no problems with performing my usual activities	40	60	30	43
		I have some problems with performing my usual activities	17	25	28	41
		I am unable to perform my usual activities	2	3	1	1
		Missing	8	12	10	14

continued

TABLE 85 *Band 2, health status, EuroQol, by treatment group (cont'd)*

			Clozapine (*n* = 67)		Atypical (*n* = 69)	
			n	**%**	***n***	**%**
	Pain/discomfort	I have no pain or discomfort	42	63	36	52
		I have moderate pain or discomfort	17	25	22	32
		I have extreme pain or discomfort	0	0	1	1
		Missing	8	12	10	14
	Anxiety/depression	I am not anxious or depressed	26	39	18	26
		I am moderately anxious or depressed	28	42	37	54
		I am extremely anxious or depressed	5	7	4	6
		Missing	8	12	10	14
Week 52	Mobility	I have no problems in walking about	48	72	48	70
		I have some problems in walking about	11	16	11	16
		I am confined to bed	0	0	0	0
		Missing	8	12	10	14
	Self-care	I have no problems with self-care	51	76	48	70
		I have some problems with self-care	8	12	11	16
		I am unable to wash or dress myself	0	0	0	0
		Missing	8	12	10	14
	Usual activities	I have no problems with performing my usual activities	41	61	31	45
		I have some problems with performing my usual activities	16	24	25	36
		I am unable to perform my usual activities	2	3	3	4
		Missing	8	12	10	14
	Pain/discomfort	I have no pain or discomfort	41	61	34	49
		I have moderate pain or discomfort	17	25	24	35
		I have extreme pain or discomfort	1	1	1	1
		Missing	8	12	10	14
	Anxiety/depression	I am not anxious or depressed	26	39	24	35
		I am moderately anxious or depressed	31	46	32	46
		I am extremely anxious or depressed	1	1	3	4
		Missing	9	13	10	14

TABLE 86 *Band 2, utility and evaluation of own health, EuroQol, all patients*

		Baseline	Week 12	Week 26	Week 52
Utility	Mean	0.61	0.74	0.76	0.78
	SD	0.33	0.21	0.22	0.20
	Range	–0.24 to 1.00	–0.04 to 1.00	–0.33 to 1.00	0.02 to 1.00
Evaluation of own health	Mean	58.09	62.21	62.39	67.30
	SD	25.86	23.82	20.73	18.90
	Range	0.00 to 100.00	0.00 to 100.00	6.00 to 100.00	0.00 to 100.00

TABLE 87 *Band 2, use of psychiatric hospital services*

Study period	Treatment group		Inpatient stay (days)	Day-care attendances	Medical outpatient consultations, hospital visits	Medical outpatient consultations, home visits	Non-medical outpatient consultations, hospital visits	Non-medical outpatient consultations, home visits
3 months–baseline	Clozapine	Mean	32	0	0	0	0	0
		n	66	66	66	66	66	66
		SD	38	3	0	0	0	0
	Atypical	Mean	26	0	0	0	0	0
		n	69	69	69	69	69	69
		SD	33	1	0	0	0	2
Baseline–week 12	Clozapine	Mean	48	1	0	0	0	0
		n	67	67	67	67	67	67
		SD	35	5	1	2	0	1
	Atypical	Mean	38	1	0	0	0	0
		n	67	67	67	67	67	67
		SD	39	8	2	0	0	2
Week 13–26	Clozapine	Mean	39	1	0	0	0	0
		n	65	65	65	65	65	65
		SD	43	3	1	1	3	1
	Atypical	Mean	33	1	0	0	0	0
		n	67	67	67	67	66	66
		SD	43	8	1	0	0	3
Week 27–52	Clozapine	Mean	48	1	0	0	0	0
		n	62	61	62	62	61	61
		SD	70	3	1	1	1	1
	Atypical	Mean	44	2	0	0	0	0
		n	64	64	64	64	64	64
		SD	72	16	1	0	0	1

TABLE 88 *Band 2, cost of psychiatric hospital services, estimated from reference cost unit cost data (£, 2001–2)*

Study period	Treatment group		Inpatient stay	Medical and non-medical outpatient visits	Day-patient attendances	Medical home visits	Non-medical home visits	Total psychiatric hospital costs
3 months–baseline	Clozapine	Mean	6,936	5	20	0	0	6,975
		n	66	66	66	66	66	66
		SD	9,030	37	164	0	0	9,016
	Atypical	Mean	5,871	3	11	0	19	5,921
		n	69	69	69	69	69	69
		SD	8,531	17	84	0	155	8,540
Baseline–week 12	Clozapine	Mean	9,630	18	57	41	13	10,083
		n	67	67	67	67	67	67
		SD	7,943	103	292	337	109	8,156
	Atypical	Mean	7,978	25	83	0	30	8,218
		n	67	67	67	67	67	67
		SD	9,027	196	483	0	242	8,996
Week 13–26	Clozapine	Mean	8,440	55	45	17	17	8,581
		n	65	65	65	65	65	65
		SD	10,587	387	178	137	135	10,509
	Atypical	Mean	6,986	27	79	0	47	7,253
		n	67	66	67	67	66	66
		SD	9,956	132	486	0	266	9,950
Week 27–52	Clozapine	Mean	11,213	34	33	15	26	12,393
		n	62	61	61	62	61	60
		SD	18,655	194	173	117	143	19,407
	Atypical	Mean	10,262	17	131	0	12	10,579
		n	64	64	64	64	64	64
		SD	18,556	106	911	0	99	18,523

TABLE 89 *Band 2, cost of psychiatric hospital services, estimated from CIPFA unit cost data (£, 2001–2)*

Study period	Treatment group		Inpatient stay	Medical and non-medical outpatient visits	Day-patient attendances	Medical home visits	Non-medical home visits	Total psychiatric hospital costs
3 months–baseline	Clozapine	Mean	6,494	6	20	0	0	6,534
		n	66	66	66	66	66	66
		SD	8,387	46	164	0	0	8,372
	Atypical	Mean	5,598	4	11	0	12	5,643
		n	69	69	69	69	69	69
		SD	7,975	21	84	0	103	7,984
Baseline–week 12	Clozapine	Mean	9,127	22	57	27	9	9,542
		n	67	67	67	67	67	67
		SD	7,498	129	292	220	73	7,687
	Atypical	Mean	7,718	32	83	0	20	7,954
		n	67	67	67	67	67	67
		SD	8,562	245	483	0	161	8,538
Week 13–26	Clozapine	Mean	7,841	69	45	11	11	7,984
		n	65	65	65	65	65	65
		SD	9,818	484	178	89	90	9,744
	Atypical	Mean	6,642	34	79	0	31	6,895
		n	67	66	67	67	66	66
		SD	9,407	165	486	0	178	9,412
Week 27–52	Clozapine	Mean	10,428	43	33	10	17	11,573
		n	62	61	61	62	61	60
		SD	17,294	242	173	76	96	17,966
	Atypical	Mean	9,647	21	131	0	8	9,963
		n	64	64	64	64	64	64
		SD	17,828	133	911	0	66	17,805

TABLE 90 *Band 2, cost of psychiatric hospital services, estimated from PSSRU unit cost data (£, 2001–2)*

Study period	Treatment group		Inpatient stay	Medical and non-medical outpatient visits	Day-patient attendances	Medical home visits	Non-medical home visits	Total psychiatric hospital costs
3 months–baseline	Clozapine	Mean	6,468	6	20	0	0	6,508
		n	66	66	66	66	66	66
		SD	8,374	50	164	0	0	8,359
	Atypical	Mean	5,569	4	11	0	12	5,613
		n	69	69	69	69	69	69
		SD	7,955	23	84	0	103	7,962
Baseline–week 12	Clozapine	Mean	9,042	24	57	27	9	9,459
		n	67	67	67	67	67	67
		SD	7,453	140	292	220	73	7,648
	Atypical	Mean	7,660	35	83	0	20	7,900
		n	67	67	67	67	67	67
		SD	8,524	266	483	0	161	8,503
Week 13–26	Clozapine	Mean	7,810	75	45	11	11	7,959
		n	65	65	65	65	65	65
		SD	9,799	526	178	89	90	9,724
	Atypical	Mean	6,626	37	79	0	31	6,881
		n	67	66	67	67	66	66
		SD	9,397	179	486	0	178	9,403
Week 27–52	Clozapine	Mean	10,436	47	33	10	17	11,540
		n	62	61	61	62	61	60
		SD	17,282	264	173	76	96	17,908
	Atypical	Mean	9,651	23	131	0	8	9,971
		n	64	64	64	64	64	64
		SD	17,830	144	911	0	66	17,808

TABLE 91 *Band 2, use and cost of non-psychiatric hospital services (£, 2001–2)*

Study period	Treatment group		Non-psychiatric inpatient stay	A&E admissions	A&E attendances	Outpatient visits	Home visits	Total cost
3 months–baseline	Clozapine	Mean	0	0	0	0	0	75
		n	66	67	67	67	67	67
		SD	0	0	1	0	0	250
	Atypical	Mean	0	0	0	0	0	154
		n	69	69	69	69	69	69
		SD	1	0	1	0	0	611
Baseline–week 12	Clozapine	Mean	0	0	0	0	0	6
		n	63	67	67	67	67	64
		SD	0	0	0	0	0	31
	Atypical	Mean	0	0	0	0	0	25
		n	65	69	69	69	69	65
		SD	0	0	0	0	0	130
Week 13–26	Clozapine	Mean	0	0	0	0	0	130
		n	64	67	67	67	67	64
		SD	1	0	0	0	0	563
	Atypical	Mean	0	0	0	0	0	3
		n	65	69	69	69	69	65
		SD	0	0	0	0	0	12
Week 27–52	Clozapine	Mean	1	0	0	0	0	347
		n	61	67	67	67	67	61
		SD	11	0	0	0	0	2,462
	Atypical	Mean	0	0	0	1	0	134
		n	60	69	69	69	69	60
		SD	1	0	0	4	0	918

TABLE 92 *Band 2, use and costs of drugs used for psychosis and related disorders (classified according to BNF section 4.2) (£, 2001–2)*

		Clozapine						Atypical					
		Daily cost		Number of days		Total cost		Daily cost		Number of days		Total cost	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Amisulpride	Base–week 12	4	2	66	25	249	170	4	1	61	31	290	148
	Week 13–26	3	2	41	36	128	172	4	2	88	53	396	287
	Week 27–52	3	1	140	115	537	602	4	1	192	71	748	427
Benperidol	Base–week 12	1		84		66							
	Week 13–26	1		98		77							
	Week 27–52	1		182		143							
Chlorpromazine	Base–week 12	0	0	69	24	6	3	0	0	89	32	11	11
	Week 13–26	0	0	51	66	4	5	0	0	86	24	8	8
	Week 27–52	0		18		1		0	0	158	60	13	14
Clozapine	Base–week 12	4	2	56	36	274	207	4	2	41	30	242	211
	Week 13–26	6	2	92	28	542	279	6	3	112	51	784	533
	Week 27–52	6	2	211	70	1,320	695	6	3	165	106	1,329	1,058
Droperidol	Base–week 12	1		44		33		0					
	Week 13–26	0											
	Week 27–52	0						1		159		161	
Flupenthixol	Base–week 12	11	11	71	24	582	236	7	4	84	0	545	428
	Week 13–26	4	2					2		98		160	
	Week 27–52	3						4	4	182	0	760	655
Flupenthixol dec.	Base–week 12	12	14	81	30	825	505	12	14	83	2	1,015	1,148
	Week 13–26	7	3	98	0	692	311	5		98		479	
	Week 27–52	7	3	199	29	1,353	486	6	1	52	55	637	812
Fluphenazine	Base–week 12	9	0	84	0	764	0	6	2	84	0	505	165
	Week 13–26	9	0	98	0	892	0						
	Week 27–52	9		182		1,656							
Fluphenazine dec.	Base–week 12	7	3	84	0	576	266	6	3	53	34	381	334
	Week 13–26							7	3	98	0	672	310
	Week 27–52							5		182		841	
Haloperidol	Base–week 12	0	0	59	30	22	20	0	0	80	48	23	17
	Week 13–26	0	0	70	30	30	13	0	0	58	57	14	13
	Week 27–52	0		273		76		0	0	117	45	28	11
Haloperidol dec.	Base–week 12	9		71		615		12		84		969	
	Week 13–26							8	1	73	102	482	669

continued

TABLE 92 *Band 2, use and costs of drugs used for psychosis and related disorders (classified according to BNF section 4.2) (£, 2001–2) (cont'd)*

		Clozapine						Atypical					
		Daily cost		Number of days		Total cost		Daily cost		Number of days		Total cost	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Lithium	Week 27–52	0	0	112	48	11	7	0	0	61	38	6	4
	Base–week 12	0	0	98	0	8	1	0	0	139	41	14	6
	Week 13–26	0	0	136	74	12	7	0	0	182	0	17	3
Methotrimeprazine	Week 27–52												
Olanzapine	Base–week 12	5	1	72	24	368	166	5	2	76	22	416	214
	Week 13–26	6	1	125	41	676	112	6	2	101	27	548	186
	Week 27–52	6	1	112	69	656	424	6	2	181	71	1,034	452
Pipothiazine palm.	Base–week 12	11		11		124		22	9	77	13	1,970	486
Quetiapine	Base–week 12	4	1	74	38	333	186	4	2	79	32	370	227
	Week 13–26	4	0	111	18	474	148	4	2	110	40	509	235
	Week 27–52	4	2	100	94	460	481	5	2	165	86	864	578
Risperidone	Base–week 12	3	1	66	43	261	179	4	1	53	33	208	159
	Week 13–26	3	1	67	38	235	217	3	1	90	32	283	118
	Week 27–52	3	0	130	89	427	305	3	1	169	89	612	419
Sulpiride	Base–week 12							1	0	85	41	67	47
	Week 13–26							1	0	122	33	63	12
	Week 27–52	0	0	111	87	39	33	1	0	182		132	
Zuclopenthixol	Base–week 12	3	2	83	22	248	180	6	2	72	24	450	260
	Week 13–26	8		133		1,030		10		24		230	
	Week 27–52	8		182		1,456		10		182		1,747	
Zuclopenthixol dec.	Base–week 12	6	2	84	0	538	190	7	3	45	46	320	343
	Week 13–26	4	1	69	42	358	159	5		88		422	
	Week 27–52	6	1	182	0	1,019	206	5	2	154	130	974	988

TABLE 93 *Band 2, use and costs of all other drugs used by patients in the trial (£, 2001–2)*

Study period	Treatment group		Daily cost	No. of days	Total cost
Baseline–week 12	Clozapine	Mean	<0.5	72	33
		n	137	114	112
		SD	1	29	58
	Atypical	Mean	0	72	33
		n	147	132	129
		SD	1	34	66
Week 13–26	Clozapine	Mean	1	87	57
		n	118	93	92
		SD	1	36	83
	Atypical	Mean	1	83	47
		n	119	105	102
		SD	1	36	92
Week 27–52	Clozapine	Mean	1	157	105
		n	112	96	95
		SD	1	59	156
	Atypical	Mean	0	153	82
		n	129	120	113
		SD	1	73	134

TABLE 94 *Band 2, use and costs of community-based and primary care services (£, 2001–2)*

Study period		*n*	Mean	SD
3 months–baseline	No. of attendances at community centre	48	12	21
	Primary care psychiatrist – contact	129	0	1
	Primary care psychiatrist – time	15	1	0
	Primary care psychology – contact	128	0	1
	Primary care psychology – time	3	1	0
	GP surgery – contact	129	1	2
	GP surgery – time	45	0	0
	GP home – contact	128	0	0
	GP home – time	1	0	
	District nurse – contact	128	0	1
	District nurse – time	2	1	0
	Nurse – contact	129	2	4
	Nurse – time	27	1	0
	Social worker – contact	128	1	3
	Social worker – time	13	1	0
	Primary care OT – contact	129	0	2
	Primary care OT – time	6	1	1
	Primary care counsellor – contact	129	0	0
	Primary care counsellor – time	1	0	
	Home help – contact	128	1	9
	Home help – time	2	1	0
	Other – contact	128	1	4
	Other – time	5	1	1
Baseline–week 12	No. of attendances at community centre	47	11	25
	Primary care psychiatrist – contact	114	0	0
	Primary care psychiatrist – time	4	1	0
	Primary care psychology – contact	114	0	1
	Primary care psychology – time	3	1	0
	GP surgery – contact	115	1	2
	GP surgery – time	25	0	0
	GP home – contact	114	0	0
	GP home – time	1	1	
	District nurse – contact	114	0	1
	District nurse – time	2	1	1
	Nurse – contact	113	2	9
	Nurse – time	17	1	0
	Social worker – contact	114	1	2
	Social worker – time	17	1	0
	Primary care OT – contact	114	0	1
	Primary care OT – time	3	2	2
	Primary care counsellor – contact	114	0	0
	Primary care counsellor – time	1	2	
	Home help – contact	113	1	10
	Home help – time	1	2	
	Other – contact	113	0	1
	Other – time	6	1	1
Week 13–26	No. of attendances at community centre	40	6	9
	Primary care psychiatrist – contact	113	0	0
	Primary care psychiatrist – time	5	1	0
	Primary care psychology – contact	113	0	1
	Primary care psychology – time	2	0	0
	GP surgery – contact	113	1	2
	GP surgery – time	31	0	0
	GP home – contact	113	0	0
	GP home – time	1	1	
	District nurse – contact	113	0	1
	District nurse – time	1	0	

continued

TABLE 94 *Band 2, use and costs of community-based and primary care services (£, 2001–2) (cont'd)*

Study period		*n*	Mean	SD
	Nurse – contact	112	1	3
	Nurse – time	16	1	0
	Social worker – contact	112	0	1
	Social worker – time	14	1	0
	Primary care OT – contact	113	1	3
	Primary care OT – time	8	1	1
	Primary care counsellor – contact	113	0	1
	Primary care counsellor – time	1	1	
	Home help – contact	112	0	1
	Home help – time	0		
	Other – contact	112	1	5
	Other – time	6	1	0
Week 27–52	No. of attendances at community centre	49	19	32
	Primary care psychiatrist – contact	110	0	2
	Primary care psychiatrist – time	14	1	0
	Primary care psychology – contact	110	0	0
	Primary care psychology – time	0		
	GP surgery – contact	111	1	3
	GP surgery – time	36	0	0
	GP home – contact	110	0	0
	GP home – time	0		
	District nurse – contact	110	0	0
	District nurse – time	2	1	0
	Nurse – contact	110	2	5
	Nurse – time	17	1	0
	Social worker – contact	111	1	5
	Social worker – time	19	1	0
	Primary care OT – contact	109	1	3
	Primary care OT – time	9	1	1
	Primary care counsellor – contact	110	0	1
	Primary care counsellor – time	1	1	
	Home help – contact	105	1	6
	Home help – time	2	2	0
	Other – contact	108	0	3
	Other – time	4	1	2

TABLE 95 *Band 2, cost of community-based and primary care services (£, 2001–2)*

		Clozapine		Atypical	
		Mean	**SD**	**Mean**	**SD**
3 months–baseline	Cost of psychiatrist visits	62	268	27	78
	Cost of psychologist visits	14	83	2	13
	Cost of GP surgery visits	26	61	16	31
	Cost of GP home visits	0	0	2	12
	Cost of district nurse visits	1	9	2	15
	Cost of practice nurse visits	23	54	30	113
	Cost of social worker visits	43	174	20	74
	Cost of occupational therapist visits	17	99	23	105
	Cost of counsellor visits	2	13	0	0
	Cost of home help visits	6	36	27	153
	Cost of other primary care contacts	2	11	15	66
	Cost of community centre visits	82	271	92	279
Baseline–week 12	Cost of psychiatrist visits	0	0	13	55
	Cost of psychologist visits	17	89	1	6
	Cost of GP surgery visits	22	103	23	71
	Cost of GP home visits	2	13	0	0
	Cost of district nurse visits	0	0	4	32
	Cost of practice nurse visits	11	37	71	252
	Cost of social worker visits	27	107	54	159
	Cost of occupational therapist visits	0	0	17	81
	Cost of counsellor visits	2	13	0	0
	Cost of home help visits	16	122	23	170
	Cost of other primary care contacts	0	1	8	33
	Cost of community centre visits	46	158	121	435
Week 13–26	Cost of psychiatrist visits	6	31	7	32
	Cost of psychologist visits	17	92	0	0
	Cost of GP surgery visits	25	74	17	48
	Cost of GP home visits	0	0	2	13
	Cost of district nurse visits	2	12	0	0
	Cost of practice nurse visits	18	47	12	41
	Cost of social worker visits	35	100	19	81
	Cost of occupational therapist visits	35	133	13	59
	Cost of counsellor visits	5	38	0	0
	Cost of home help visits	2	11	3	24
	Cost of other primary care contacts	20	110	5	37
	Cost of community centre visits	51	133	31	103
Week 27–52	Cost of psychiatrist visits	27	94	73	262
	Cost of psychologist visits	0	0	0	0
	Cost of GP surgery visits	41	121	30	71
	Cost of GP home visits	0	0	0	0
	Cost of district nurse visits	0	3	0	3
	Cost of practice nurse visits	23	78	41	126
	Cost of social worker visits	54	159	141	671
	Cost of occupational therapist visits	25	138	36	162
	Cost of counsellor visits	5	40	0	0
	Cost of home help visits	28	152	2	11
	Cost of other primary care contacts	18	124	0	0
	Cost of community centre visits	187	531	114	327

Appendix 7

A controlled, mirror-image study of atypical antipsychotics in the treatment of schizophrenia; designed to complement the main randomised controlled trial

Executive summary

Objectives
To compare hospital stay and admissions to hospital in subjects switching from conventional to atypical antipsychotics with subjects switching from one conventional drug to another.

Design
Retrospective, 6-year, controlled mirror-image study.

Setting
Acute general psychiatry services in an inner-city area.

Subjects
Patients diagnosed with schizophrenia or schizoaffective disorder receiving a continuous prescription of antipsychotics over at least a 6-year period between 1994 and 2002.

Interventions
None.

Main outcome measures
Number of days spent in hospital; number of admissions to hospital.

Results
In subjects who switched from conventional to atypical antipsychotics, the number of days spent in hospital increased from a mean of 90 days in the 3 years before switching to a mean of 200 days in the 3 years after switching ($p < 0.005$). The mean number of admissions did not change significantly (1.61 before versus 1.41 after, $p > 0.05$). In those switching between conventional drugs, the mean number of days in hospital fell from 64 to 50 ($p > 0.05$) and the number of admissions was virtually unchanged (1.36 before versus 1.32 after, $p > 0.05$). Mean days in hospital were significantly increased in the atypical group compared with the conventional (control) group ($p < 0.05$).

Conclusion
Switching from conventional antipsychotics to atypical antipsychotics appears to result in an important increase in number of days spent in hospital. This finding has considerable implications for healthcare providers and funders. Further research should examine a larger cohort of patients in other settings.

Introduction

Atypical antipsychotics are now widely used throughout the Western world and are largely preferred to older, conventional antipsychotics. The basis for this preference is several-fold: atypicals are considered to be better tolerated than older drugs; some (clozapine and perhaps others) are held to be more effective; and lastly, atypicals have been shown to be cost-effective, despite their increased purchase cost. This cost-effectiveness has been demonstrated, using a variety of methods, for most available atypicals.

The uniformity of the findings of studies so far conducted is compelling, but reservations have been expressed.[196] Almost all studies have been funded, conducted and published by manufacturers of atypical antipsychotics. Moreover, only a minority of studies (e.g. Rosenheck[73]) might be considered methodologically sound.

The CUtLASS programme was designed in response to clear and reasonable reservations about the cogency, applicability and overall value of trials so far conducted and published. Funding was independent of atypical manufacturers and the main CUtLASS investigation was a randomised, controlled comparison of different atypical and conventional drugs, properly powered to reveal differences in resource use should they exist.

The CUtLASS controlled, mirror-image study was intended to complement the main randomised

controlled trial (RCT). While RCTs are considered the most robust method of assessment, they cannot exactly replicate a normal clinical environment. Mirror-image studies, although retrospective, do examine real-life outcomes in normal clinical practice.

The basis of mirror-image studies is to compare outcomes (usually hospitalisations) before and after a clinical intervention; in this case a switch to atypical drugs. A great many of such studies have been conducted.[126,197]

To a large extent, the value of these studies is dependent on the inclusion of a control group of patients who either do not change drugs or who switch from one conventional drug to another. This allows a clearer view of the influence of factors that may affect rates of hospitalisation, but which are divorced from clinical effectiveness (e.g. changes in demographics, changes in bed availability and changes in admissions policy). Relatively few controlled mirror-image studies have been conducted,[163,201] and almost all have been manufacturer sponsored.

This study independently evaluated outcome in patients switched to atypical antipsychotics and compared this with outcome in a matched group of patients who switched from one conventional drug to another.

Method

Design

This was a retrospective, controlled, 6-year mirror-image analysis. Subject outcomes 3 years before and 3 years after change from conventional to atypical treatment were compared. The control group consisted of patients switched from one conventional antipsychotic to another.

Ethics and permissions

Ethical approval for the study was obtained from the local research ethics committee. Written permission was obtained from responsible consultants to allow search of case notes and recording and analysis of data.

Location and time

The study was conducted at the Maudsley hospital in south-west London. Subjects were patients under the care of five consultant psychiatrist teams covering Camberwell, Norwood, Peckham, East Dulwich and Brixton. Data were gathered during 2000, 2001 and 2002.

Subjects

All case notes for patients in included teams were searched to identify patients who:

- had a diagnosis of schizophrenia or schizoaffective disorder
- had switched antipsychotic drug treatment at least 3 years before the date of analysis
- had received a continuous prescription for antipsychotic treatment for 3 years before and 3 years after switching
- had remained under the care of the same team throughout the 6-year period analysed.

Demographic data

The following demographic data were collected for all patients: age, gender, ethnicity, diagnosis, age at diagnosis, team location and all drugs (doses and durations) prescribed during the 6-year period of analysis.

Outcome measures

Main outcome measures were number of days spent in hospital and number of admissions to hospital during the period of analysis. These data were collected from case notes, but were verified against trust computer records. All anomalies were resolved by careful scrutiny of case notes.

Results

Case notes of 287 patients were examined. One-hundred and forty-four met the inclusion criteria and were analysed. Of these 144, 108 formed the 'control' group and 36 the 'atypical' group.

Atypical group

Demographic details are shown in *Table 96*.

Details of switching

Twenty-one (58%) were inpatients at the time of switching.

The drugs switched from and to are shown in *Table 97*.

Number of admissions

Table 98 shows the number of admissions to hospital and the number of days spent in hospital for those switching to atypical antipsychotics (see also *Figures 24* and *25*).

Statistical analysis

The number of days before and after the switch and the number of admissions before and after the switch were positively skewed with positive

TABLE 96 *Demographic details*

	Mean	SD	Median	Range
Gender, *n* (%)				
Female	15 (42)			
Male	21 (58)			
Age (years)	43.58	11.46	43.00	54
Race, *n* (%)				
Caucasian	14 (39)			
African/Caribbean	21 (58)			
Asian	1 (3)			

TABLE 97 *Drug treatment*

Drugs before	*n*	Drugs after	*n*
Flupenthixol dec.	9	Olanzapine	15
Haloperidol	7	Risperidone	14
Trifluoperazine	7	Clozapine	7
Zuclopenthixol dec.	5		
Sulpiride	3		
Fluphenazine	2		
Haloperidol dec.	1		
Pipothiazine palm.	1		
Chlorpromazine	1		

TABLE 98 *Hospital admission details*

	Mean	SD	Median	Range
Number of admissions before switch	1.61	1.78	1.00	8
Number of days before switch	89.53	144.53	33.00	619
Number of admissions after switch	1.44	1.52	1.00	6
Number of days after switch	199.97	228.02	114.50	929

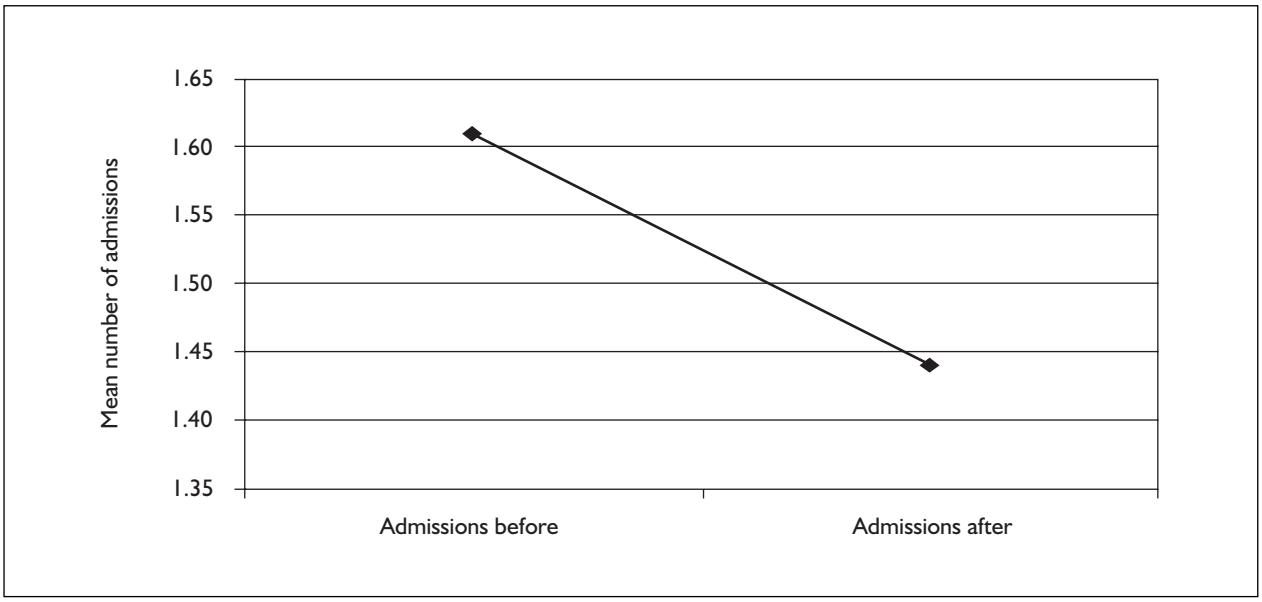

FIGURE 24 *Atypical group, mean number of admissions before and after switch*

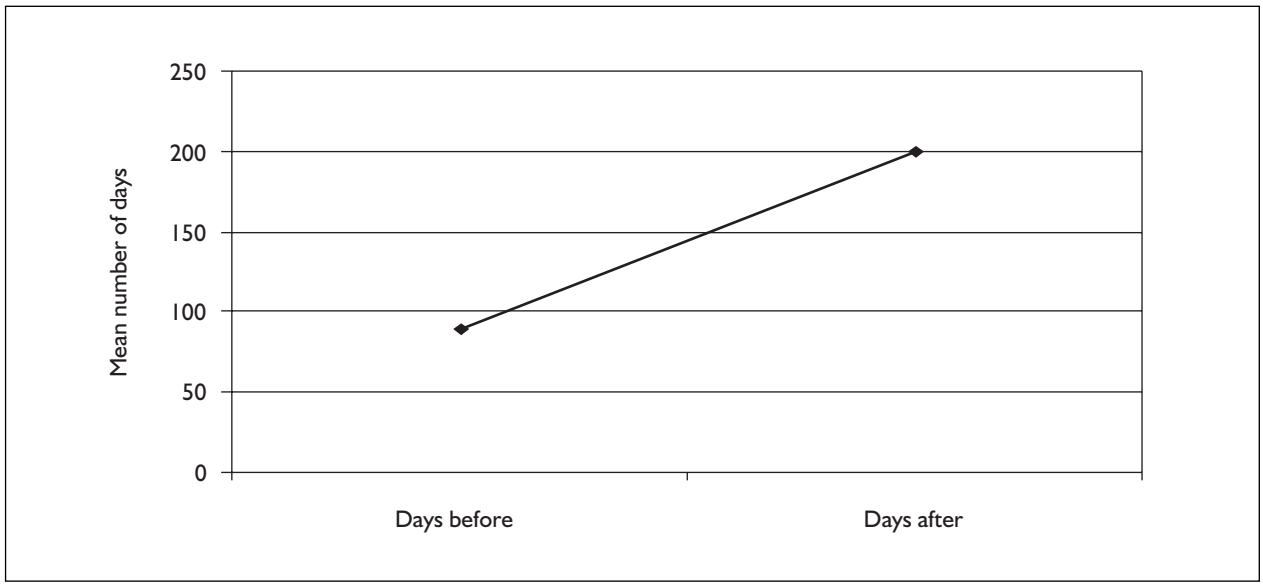

FIGURE 25 *Atypical group, mean number of hospital days before and after switch*

kurtosis. Data were therefore subjected to a square-root transformation to give data with skewness and kurtosis within acceptable levels before using *t*-tests. Non-parametric tests were also used.

In the atypical group, there was a statistically significant difference between the number of days after the switch compared with the number of days before (on both a non-parametric Wilcoxon test and a *t*-test on square-root-transformed data, $p < 0.005$).

There was no significant difference between the number of admissions before and after the switch in medication (*Table 99*).

Data were also subanalysed by atypical, as summarised in *Table 100*.

Clozapine group (*n* = 7)

All those switching to clozapine were in hospital after 1 year. At this point, five remained on clozapine at 1 year, one had switched to olanzapine and one was receiving no treatment.

In the clozapine subgroup there were no significant differences between either the number of admissions before, compared with after, the switch in medication or the number of days before compared with after (on both a non-parametric Wilcoxon test and a *t*-test on square-root-transformed data, $p < 0.05$) (*Table 101*).

Olanzapine group (*n* = 15)

Nine out of 15 (60%) starting on olanzapine were out of hospital at 1 year. All except one were still prescribed olanzapine at 1 year (one had switched to risperidone).

In the olanzapine subgroup there was no significant difference between the number of admissions before compared with after the switch in medication. There was a significant difference between the number of days before compared

TABLE 99 *Statistical analysis*

Test	Measure	*p*
Wilcoxon	Days before/days after	<0.005*
	Admissions before/admissions after	>0.05 ns
Paired *t*-test (square root transformation)	Days before/days after	<0.005*
	Admissions before/admissions after	>0.05 ns

* $p < 0.05$, ns, not significant.

TABLE 100 *Statistical analysis, individual atypical drugs*

	Clozapine (n = 7)				Olanzapine (n = 15)				Risperidone (n = 14)			
	Mean	**SD**	**Median**	**Range**	**Mean**	**SD**	**Median**	**Range**	**Mean**	**SD**	**Median**	**Range**
Gender, *n*, (%)												
Female	3 (43)				6 (40)				6 (43)			
Male	4 (57)				9 (60)				8 (57)			
Age (years)	37.71	9.36	37.00	29	47.60	11.76	44.00	42	42.21	11.17	42.00	37
Admissions before	2.86	2.41	2.00	7	1.27	1.71	1.00	7	1.36	1.28	1.00	4
Days before	248.86	244.92	113.00	594	29.00	34.39	12.00	98	74.71	95.66	54.50	342
Admissions after	2.29 ns	2.36	2.00	6	1.27 ns	1.16	1.00	3	1.21 ns	1.31	1.00	3
Days after	418.43 ns	337.92	263.00	889	117.20*	118.36	92.00	393	179.43	195.28	114.50	560

* $p < 0.05$.

TABLE 101 *Statistical analysis, clozapine subgroup*

Test	**Measure**	***p***
Wilcoxon	Days before/days after	>0.05 ns
	Admissions before/admissions after	>0.05 ns
Paired *t*-test (square root transformation)	Days before/days after	>0.05 ns
	Admissions before/admissions after	>0.05 ns

TABLE 102 *Statistical analysis, olanzapine subgroup*

Test	Measure	*p*
Wilcoxon	Days before/days after	<0.05*
	Admissions before/admissions after	>0.05 ns
Paired *t*-test	Days before/days after	<0.05*
Paired *t*-test (square root transformation)	Admissions before/admissions after	>0.05 ns

*$p < 0.05$.

TABLE 103 *Statistical analysis, risperidone subgroup*

Test	Measure	*p*
Wilcoxon	Days before/days after	<0.05*
	Admissions before/admissions after	>0.05 ns
Paired *t*-test (square root transformation)	Days before/days after	<0.05*
Paired *t*-test	Admissions before/admissions after	>0.05 ns

*$p < 0.05$.

TABLE 104 *Depot versus oral treatment*

	Depot group ($n = 16$)				Non-depot group ($n = 19$)			
	Mean	SD	Median	Range	Mean	SD	Median	Range
Gender, *n* (%)								
Female	6 (38)				8 (42)			
Male	10 (62)				11 (58)			
Age (years)	44.88	13.64	43.50	50	42.68	9.86	42.00	41
Admissions before	1.75	1.73	1.00	7	1.53	1.90	1.00	8
Days before	68.94	79.38	53.00	298	107.42	186.14	24.00	619
Admissions after	1.63	1.54	2.00	5	1.37	1.54	1.00	6
Days after	186.63	219.57	154.00	929	215.53	245.22	86.00	732

with after (on both a non-parametric Wilcoxon test and a *t*-test; $p < 0.05$) (*Table 102*).

Risperidone group ($n = 14$)

Of the risperidone group, nine were still on risperidone at 1 year, two were not receiving prescribed treatment, two had switched to olanzapine and one had switched to clozapine. Eight (57%) were in hospital at 1 year.

In the risperidone subgroup there was no significant difference between the number of admissions before compared with after the switch to risperidone. There was a significant difference between the number of days before compared with after (on both a non-parametric Wilcoxon test and a *t*-test on square-root-transformed data, $p < 0.05$) (*Table 103*).

Atypicals: between-drug comparisons

The different drugs were not statistically comparable; subject numbers were too small and baseline data differed substantially.

Switching from depot versus oral

In the atypical group, 16 switched from depot antipsychotic and 19 from oral antipsychotic (*Table 104*).

In the atypical group switched from depots, there was a statistically significant difference between the number of hospital days after the switch compared with the number of days before (on both a non-parametric Wilcoxon test and a *t*-test on square-root-transformed data, $p < 0.05$). There was no significant difference between the number of admissions before and after the switch in drugs.

TABLE 105 *Control (typical) group, details of drug treatment switches*

Drugs before	*n*	Drugs after	*n*
Chlorpromazine	7	Flupenthixol dec.	9
Haloperidol	6	Sulpiride	8
Trifluoperazine	5	Fluphenazine	5
Flupenthixol dec.	5	Zuclopenthixol dec.	5
Sulpiride	4	Trifluoperazine	3
Haloperidol dec.	3	Droperidol	2
Fluphenazine	2	Pipothiazine palm.	2
Pimozide	1	Haloperidol dec.	1
Droperidol	1	Chlorpromazine	1
Thioridazine	1		
Zuclopenthixol dec	1		

In the atypical group switched from oral drugs (non-depot group), there was also a statistically significant difference between the number of days after the switch compared with the number of days before (on both a non-parametric Wilcoxon test and a *t*-test on square-root-transformed data, $p < 0.05$). There was no significant difference between the number of admissions before and after the switch in medication.

An analysis of these two groups (depot versus non-depot) revealed no significant differences in terms of age, gender, number of admissions and number of days before index date, indicating that the two groups were comparable in terms of previous inpatient usage.

There were no statistically significant differences between these two groups in terms of the number of admissions and days in hospital after the switch in medication (using both a non-parametric Mann–Whitney test and a *t*-test on square-root-transformed data).

Atypical group versus control group

The atypical group was matched (1:1) on a 'blind' case-by-case basis on gender, age (within 10 years), race, number of admissions and number of days before the index date, without knowledge of the outcomes.

Details of switching: typicals

Three patients (8%) were in hospital at the time of switching.

Table 105 shows the drugs switched from and to (all subjects switched drugs).

In the atypical group, 21 (58%) of the group were in hospital at 1 year. In the control group, three (8%) of the group were in hospital at 1 year.

An analysis of these two groups revealed no significant differences in terms of age, gender, number of admissions and number of days before the index date (*Table 106*).

There were no statistically significant differences between 'before and after' measures in the control group.

Comparing the control group and the atypical group, there was a statistically significant difference between the number of days after the switch compared with the number of days before (on both a non-parametric Wilcoxon test and a *t*-test on square-root-transformed data, $p < 0.05$) (*Table 107*). That is, a switch to atypical antipsychotics significantly increased the number of days spent in hospital compared with typical antipsychotics. There was no significant difference between the two groups in their number of admissions before and after the switch in drugs (see *Figures 26* and *27*).

Conclusions

- A switch from conventional antipsychotics to atypical antipsychotics led to a significant increase in days spent in hospital in the 3 years after switching compared with the 3 years before. Number of admissions was not significantly different.
- Olanzapine and risperidone, but not clozapine, were associated with a significant increase in days spent in hospital.
- There was no difference in outcome for those switched from depot typical compared with

TABLE 106 *Atypical versus control group, demographic details*

	Atypical group				Control group			
	Mean	**SD**	**Median**	**Range**	**Mean**	**SD**	**Median**	**Range**
Gender, *n* (%)								
Female	15 (42)				15 (42)			
Male	21 (58)				21 (58)			
Race, *n* (%)								
Caucasian	14 (39)				12 (33)			
African/Caribbean	21 (58)				23 (64)			
Asian	1 (3)				1 (3)			
Age (years)	43.58	11.46	43.00	54	43.94	9.69	43.00	42
Admissions before	1.61	1.78	1.00	8	1.42	1.36	1.00	4
Days before	89.53	144.53	33.00	619	63.56	85.57	31.00	380
Admissions after	1.44	1.52	1.00	6	1.03	1.32	0.50	4
Days after	199.97	228.02	114.50	929	50.44	83.88	3.50	330

TABLE 107 *Atypical versus control group, statistical analysis*

Test	**Measure**	***p***
Mann–Whitney *U*-test	Days after	<0.05*
	Admissions after	>0.05 ns
Paired *t*-test (square root transformation)	Days after	<0.05*
	Admissions after	>0.05 ns

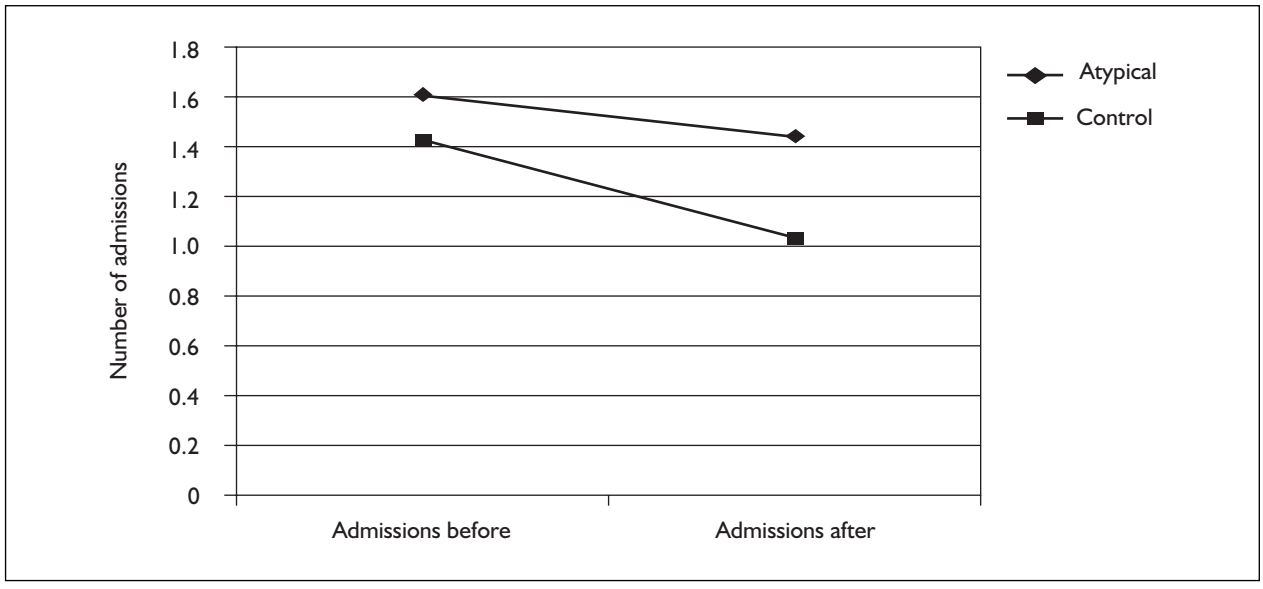

FIGURE 26 *Atypical group versus control group, total number of admissions before and after switch*

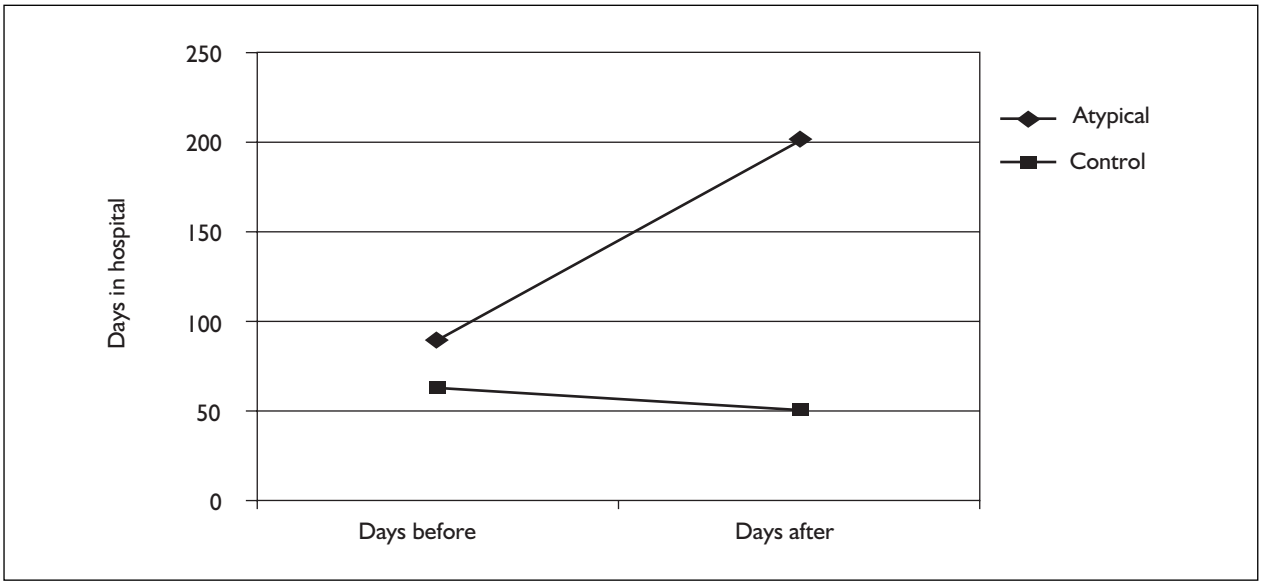

FIGURE 27 *Atypical group versus control group, total number of days in hospital before and after switch*

those switched from oral antipsychotics.
- In a matched control group, a switch from one conventional drug to another did not significantly increase days spent in hospital or number of admissions to hospital.
- A switch to atypical antipsychotics significantly increased the number of days spent in hospital compared with switching between conventional antipsychotics.

Discussion

In this patient cohort it would appear that changing to atypical antipsychotics was associated with worsened outcome, in both absolute and relative terms. This finding is in some contrast to almost all previously published mirror-image analyses (the single exception is Coley[117]).

Care was taken to control for other, non-drug influences on patient outcome by studying patients from the same clinical environment, treated by the same clinicians over the same period. Subjects in the study group were closely matched to similar subjects in the control group, to reduce the influence of various patient-related factors. The two groups for comparison were shown to be similar in most important respects.

The only striking difference between the two groups was the proportion of patients who switched drugs while inpatients (58% in the atypical group; 8% in the control group). This difference may have had an important influence on outcome, but it is noteworthy that many authors have suggested that inpatient status at index date predicts a lower use of resources in the following period.

The finding of increased healthcare utilisation following a switch to atypicals is clearly disappointing with regard to expectations that atypicals should improve these aspects of care, and is also at odds with some of the literature, particularly for clozapine. It is possible that one should conclude that switching/mirror-image studies do not represent the ideal methodology for assessing healthcare utilisation. Many switch patients may be on a deteriorating path and this cannot be corrected for in mirror-image methodology (although the use of a control group goes some way towards this). In addition, the deteriorating paucity of community placements is a problem in this trust and these results may simply reflect reduced placement options. Therefore, it may be concluded that this study emphasises the probable need for prospective parallel studies when assessing healthcare utilisation. However, this is impractical as it would be virtually impossible to set up a typical parallel group of any size in the modern naturalistic prescribing environment. It may therefore ultimately be that economic modelling is the best way forward for determining the economic benefits of atypical antipsychotics.

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We look forward to hearing from you.

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