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Abstract

Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID)

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Objective(s): To assess the effects and cost-effectiveness of haloperidol, risperidone and placebo on aggressive challenging behaviour in adults with intellectual disability.
Design: A double-blind randomised controlled trial of two drugs and placebo administered in flexible dosage, with full, independent assessments of aggressive and aberrant behaviour, global improvement, carer burden, quality of life and adverse drug effects at baseline, 4, 12 and 26 weeks, and comparison of total care costs in the 6 months before and after randomisation. At 12 weeks, patients were given the option of leaving the trial or continuing until 26 weeks. Assessments of observed aggression were also carried out with key workers at weekly intervals throughout the trial.
Setting: Patients were recruited from all those being treated by intellectual disability services in eight sites in England, one in Wales and one in Queensland, Australia.
Participants: Patients from all severity levels of intellectual disability; recruitment was extended to include those who may have been treated with neuroleptic drugs in the past. Exclusion criteria: treatment with depot neuroleptics/another form of injected neuroleptic medication within the last 3 months; continuous oral neuroleptic medication within the last week; those under a section of the Mental Health Act 1983 or Queensland Mental Health Act 2000.

Interventions: Randomisation to treatment with haloperidol (a typical neuroleptic drug), risperidone (an atypical neuroleptic drug) or placebo using a permuted blocks procedure. Dosages were: haloperidol 1.25–5.0 mg daily; risperidone 0.5–2.0 mg daily.
Main outcome measures: Primary: reduction in aggressive episodes between baseline and 4 weeks using Modified Overt Aggression Scale. Secondary: Aberrant Behaviour Checklist; Uplift/Burden Scale; 40-item Quality of Life Questionnaire; Udvalg for Kliniske Undersøgelser scale; Clinical Global Impressions scale. Economic costs recorded using a modified version of Client Service Receipt Inventory for 6 months before and after randomisation.
Results: There were considerable difficulties in recruitment because of ethical and consent doubts. Twenty-two clinicians recruited a total of 86 patients. Mean daily dosages were 1.07 mg rising to 1.78 mg for risperidone and 2.54 mg rising to 2.94 mg for haloperidol. Aggression declined dramatically with all three treatments by 4 weeks, with placebo showing the greatest reduction (79%, versus 57% for combined drugs) ($p = 0.06$). Placebo-treated patients showed no evidence of inferior response in comparison to patients receiving neuroleptic drugs. An additional study found that clinicians who had not participated in clinical trials before were less likely to recruit. Mean total cost of accommodation, services, informal care and treatment over the 6 months of the trial was £16,336 for placebo, £17,626 for haloperidol and £18,954 for risperidone.
Conclusions: There were no significant important benefits conferred by treatment with risperidone or haloperidol, and treatment with these drugs was not cost-effective. While neuroleptic drugs may be of value in the treatment of aggressive behaviour in some patients with intellectual disability, the underlying pathology needs to be evaluated before these are given. The specific diagnostic indications for such treatment require further investigation. Prescription of low doses of neuroleptic drugs in intellectual disability on the grounds of greater responsiveness and greater liability to adverse effects also needs to be re-examined.
Trial registration: Current Controlled Trials ISRCTN 11736448.

Contents

List of abbreviations

ABC	Aberrant Behaviour Checklist
BALANCE	Bipolar Affective Disorder: Lithium/Anti-Convulsant Evaluation (a randomised clinical trial)
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CEAC	cost-effectiveness acceptability curve
CGI	Clinical Global Impression Scale
CSRI	Client Service Receipt Inventory
CUtLASS	Cost Utility of the Latest Antipsychotics in Severe Schizophrenia
ECG	electrocardiogram
ICER	incremental cost-effectiveness ratio
IQ	intelligence quotient
ITT	intention to treat
Mini PAS-ADD	short screening version of the PAS-ADD
MOAS	Modified Overt Aggression Scale
MRC	Medical Research Council
NACHBID	Neuroleptics in the treatment of Aggressive Challenging Behaviour for people with Intellectual Disabilities
NICE	National Institute for Health and Clinical Excellence
NOSIE	Nurse's Observation Scale for Inpatient Evaluation
OAS	Overt Aggression Scale
PAS-ADD	Psychiatric Assessment Schedule for Adults with Developmental Disability
QOL-Q	Quality of Life Questionnaire
RCT	randomised controlled trial
SPSS	Statistical Package for the Social Sciences
UKU	Udvalg for Kliniske Undersøgelser (UKU Side Effects Rating Scale)

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 in the notes at the end of the table.

Executive summary

Background

Aggressive challenging behaviour is a common symptom in adults with intellectual disability and has many different causes, ranging from antisocial personality disorder to autism, mood disturbance and simple frustration over communication. Its course is variable and it is commonly treated with neuroleptic drugs. Haloperidol and chlorpromazine are licensed for this indication, but the evidence base for treatment with neuroleptic drugs is poor.

Objectives

- To compare the effects of treatment of aggressive challenging behaviour in adults with intellectual disability with haloperidol (a typical neuroleptic drug), risperidone (an atypical neuroleptic drug) and placebo in flexible dosage on episodes of aggression from 1 to 26 weeks.
- To compare the effects of haloperidol, risperidone and placebo after 4, 12 and 26 weeks in the short- and longer-term outcome of aggressive challenging behaviour in terms of quality of life, reduction in burden of carers and other behaviour disturbance.
- To assess the adverse effects of treatment of aggressive challenging behaviour in intellectual disability with haloperidol, risperidone and placebo.
- To compare the costs of care of treatment of aggressive challenging behaviour in intellectual disability with haloperidol, risperidone and placebo over a 6-month period.

Methods

The study design was a double-blind randomised controlled trial (RCT) of haloperidol, risperidone and placebo administered in flexible dosage (haloperidol 1.25–5.0 mg daily, risperidone 0.5–2.0 mg daily), with full, independent assessments of aggressive and aberrant behaviour, global improvement, carer burden, quality of life and adverse drug effects at baseline, 4, 12 and 26 weeks, accompanied by comparison of total costs of care of the three treatments in the 6 months before and after randomisation. At 12 weeks, patients were given the option of leaving the trial or continuing until 26 weeks. Assessments of overt aggression were also carried out with key workers at weekly intervals throughout the trial.

Participants

Patients were recruited from all those being treated by intellectual disability services in eight sites in England, one in Wales and one in Queensland, Australia. We included patients from all severity levels of intellectual disability, extended recruitment to include those who may have been treated with neuroleptic drugs in the past, and excluded only those who had previously been diagnosed as having a psychosis. A diagnosis of being within the group of autistic spectrum disorders was not an exclusion criterion, provided that psychosis was absent. However, those who had taken depot neuroleptics or any other form of injected neuroleptic medication treatment within the last 3 months, or continuous oral neuroleptic medication within the last week, were excluded, as were those under a section of the Mental Health Act 1983, or the Queensland Mental Health Act 2000 in the Australian arm, at the time of assessment.

Main outcome measures

The primary outcome measure was the reduction in aggressive episodes between baseline and after 4 weeks of treatment, measured using the Modified Overt Aggression Scale (MOAS). Secondary outcome measures included the Aberrant Behaviour Checklist (ABC), the Uplift/Burden Scale, the 40-item Quality of Life Questionnaire (QOL-Q), adverse drug effects using the Udvalg for Kliniske Undersøgelser (UKU) scale and severity of illness using the Clinical Global Impressions (CGI) scale. These were all completed at baseline, 4, 12 and 26 weeks by independent researchers. Modified Overt Aggression Scale scores were also recorded at weekly intervals from key workers over the 26-week period. Full economic costs using a modified version of the Client Service

Receipt Inventory (CSRI) were recorded for the 6 months before and after randomisation.

Ethics

Written informed consent was obtained, based on information that was understandable to the individuals concerned. For those who were not able to give informed consent, relevant carers, including relatives and senior staff at supported homes or related residential settings, were approached to assent to the trial. Consent was given in writing and witnessed.

Procedure

Patients likely to be suitable for the trial were identified by referring clinicians in the areas chosen for the study, and were registered for the study if they appeared to satisfy the inclusion criteria. Once identified, a researcher from the Neuroleptics in the treatment of Aggressive Challenging Behaviour for people with Intellectual Disabilities (NACHBID) team, together with health professionals involved in care, obtained consent and assent where necessary and then completed baseline assessments. Patients were randomised to placebo, risperidone or haloperidol using a permuted blocks procedure. Patients were treated initially with 1 mg risperidone/2.5 mg haloperidol/ placebo daily, which was increased, if necessary, to 2 mg risperidone or 5 mg haloperidol daily by 4 weeks, with further treatment in flexible dosage administered for a further 8 weeks. Treatment was continued from 12 to 26 weeks using the trial medication, unless the clinician or patient felt that this was no longer necessary or unless further treatment was indicated. Because some clinicians preferred to start with a lower dose (0.5 mg risperidone or 1.25 mg haloperidol) in view of concern about extra sensitivity to adverse effects in those with intellectual disability, the protocol was subsequently changed to allow this. Doses greater than two tablets per day (> 2 mg risperidone or 5 mg haloperidol) were allowed in exceptional circumstances, and lorazepam up to 2 mg daily (but no other medication) was permitted as 'rescue' medication in emergencies.

Statistical methods

We calculated that, using a 5% significance level, we needed data on 99 patients in order to have 80% power to detect a clinically relevant reduction in MOAS score of 8 points (standard deviation 11.4) between two treatments. In anticipation of a 20% drop-out rate we therefore planned to recruit 124 patients, with 99 expected to complete. The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Version 14 and R Version 2.4.1. Univariate analyses were carried out using either the Mann–Whitney or Kruskal–Wallis test for comparing the value of continuous variables between two or more treatment groups. The Fisher exact test was used to compare the value of categorical variables between groups. Multivariate analyses of continuous outcomes were by regression, adjusting for baseline values of the response variable where appropriate. Analysis was by intention to treat, imputing missing values by last observation carried forward.

The main analysis was an intention-to-treat analysis of MOAS scores of the three treatment groups at week 4 using a quasi-likelihood approach, whereby the logarithm of mean MOAS score is assumed to be a linear function of significant predictors and where the variance is estimated from the data. We adjusted for logarithmically transformed baseline MOAS value and any other significant candidate predictors.

Results

There were considerable difficulties in recruitment because of ethical and consent doubts, but 86 patients, predominantly male (62%) (one of borderline intellectual disability, 30 with mild, 41 with moderate and 14 with severe intellectual disability), with similar distribution by randomised group, were recruited to the trial between November 2002 and July 2006. The patients were recruited from North and South London, Birmingham, Leicester, Nottingham, Newcastle, Gateshead, Cumbria, Cardiff and Brisbane, Queensland, Australia. Twenty-two clinicians recruited patients, with three (ZA, AR and SC) recruiting 40 patients between them.

The mean daily dosage for risperidone was 1.07 mg rising to 1.78 mg, and for haloperidol was 2.54 mg rising to 2.94 mg. Aggression declined dramatically with all three treatments by 4 weeks, with placebo showing the greatest reduction (79%, versus 57% for combined drugs) ($p = 0.06$). Furthermore, although there were no important differences between the treatments, including adverse effects, at any of the time points, the placebo-treated patients showed no evidence of inferior response to the patients receiving neuroleptic

drugs, either singly or together. The recruitment rate was lower than expected and an additional study investigating the problems experienced in recruiting patients was carried out. It was found that those clinicians who had not participated in clinical trials before were less likely to recruit than others, but there were no other important differences.

Cost-effectiveness

The mean total cost of accommodation, services, informal care and treatment over the 6 months of the trial was £16,336 for placebo, £17,626 for haloperidol and £18,954 for risperidone. It is concluded that placebo is the most cost-effective treatment for aggressive challenging behaviour.

Conclusions

There is no evidence from this trial that either risperidone or haloperidol, given in conventionally low doses, offers any advantages over placebo in either the short- or medium-term treatment of aggressive challenging behaviour in intellectual disability, and over 4 weeks placebo was found to be more effective in reducing aggression. Placebo treatment is also cheaper in terms of total costs than the other two treatments over a 6-month period.

Implications for health care

The current use of neuroleptic drugs for the treatment of aggressive challenging behaviour in intellectual disability needs to be reviewed. The findings suggest that much of this prescribing may be unnecessary.

Recommendations for research

While neuroleptic drugs may be of value in the treatment of aggressive behaviour in some patients with intellectual disability, the underlying pathology needs to be evaluated before neuroleptic drugs are given. The specific diagnostic indications for such treatment require further investigation. The common practice of prescribing low doses of neuroleptic drugs in intellectual disability on the grounds of greater responsiveness and greater liability to adverse effects also needs to be re-examined.

Trial registration

This trial is registered as ISRCTN 11736448.

Chapter 1

Aims of the review

The aims of this study were as follows:

- to test a set of hypotheses to establish the effectiveness of neuroleptic drugs given in the dosages used in ordinary practice in the treatment of aggressive challenging behaviour in comparison with placebo medication
- to compare the adverse effects of neuroleptic drugs and placebo in this condition
- to compare the total costs of care for neuroleptic drugs and placebo in aggressive challenging behaviour in intellectual disability
- to compare short- and long-term outcomes in terms of reduction in aggressive challenging behaviour (primary outcome) and global improvement, improved quality of life, reduction in burden of carers and cost of care (secondary outcomes) in the three arms of the trial.

Chapter 2
Background

Introduction

People with intellectual disabilities have many skills that are sometimes unacknowledged by those who think of them primarily as disabled. Despite this, their resilience to adversity is generally less than those of normal intelligence, and their repertoire of strategies of dealing with stresses is also more limited. One of the most common consequences of this limitation is the expression of what is called aggressive challenging behaviour. This can be a source of considerable distress to both subjects and their carers and is surprisingly common, although it is not easy to define and interpret.[1] For this reason, the epidemiological data concerning its lifetime prevalence in those with intellectual disability cannot be taken as definitive, but may be as high as 60%.[2] There is variation between studies, partly because of difficulties in definition, but also because the expression of disorder depends critically on the environmental and social setting. The rates are also higher, with increasing severity of intellectual disability. At the level of profound intellectual disability, the diagnosis of other mental disorder becomes problematic and it is often difficult to understand the antecedents to the behaviour.[3]

Definitions

There is some argument over the exact definition of 'challenging behaviour', but the following is near to a consensus: 'any culturally abnormal behaviour(s) of such intensity, frequency or duration that the physical safety of the person or others is likely to be placed in serious jeopardy, or behaviour which is likely to seriously limit use, or result in the person being denied access to, ordinary community facilities'.[4] This definition does not include the word 'aggressive', but, in almost all instances in which behavioural disturbance is marked, aggression is also a feature.[4] The symptoms of challenging behaviour have been emphasised by Emerson, in particular, as intrinsic to their social context. The description of the behaviour in itself can never be satisfactory, as a particular behaviour could be seen as challenging in one situation, but quite appropriate in another. Several authors have reinforced Emerson's view that the social context of challenging behaviour is vital to its understanding and treatment, and should be considered both when comparing epidemiological research and interventions[5] and when comparing it with equivalent forms of behaviour in those of normal intelligence.

This concern is of relevance in the treatment of challenging behaviour with neuroleptic drugs. These were introduced into psychiatric practice in the 1950s, and were shown unequivocally to be effective in the treatment of schizophrenia in a series of studies undertaken 10 years later.[6] Bair and Herold[7] were the first to extrapolate from these findings and to recommend the use of chlorpromazine in the treatment of people with intellectual disability who showed challenging behaviour and, following this report and those of others, the use of these drugs has become commonplace. Neuroleptic drugs are now prescribed regularly for people with intellectual disability, with up to 40% of those with intellectual disability in hospital and about 20% of those in the community being prescribed such medication.[8–12] These figures are very high when one considers that the prevalence of psychiatric illness in those with intellectual disability is only 8–15%.[11] The difference in these figures suggests that at least some of the neuroleptic medication prescribed for those with intellectual disability is given for simple behavioural disturbance that lacks underlying pathology and could possibly be regarded as superfluous or inappropriate. The putative diagnosis (or symptom cluster identification) of aggressive challenging behaviour (although it cannot formally be given a diagnostic title it is often regarded as such), is very high in people with intellectual disabilities, despite the fact that the proportion suffering from a mental illness is much smaller. Thus, for example, in one intellectual disability register in Leicestershire, the prevalence of aggressive challenging behaviour was 30% at routine interviews carried out sequentially between 2000 and 2006.[12] Most neuroleptic medication is used for management of behavioural problems. As it has been estimated that when community and hospital populations are combined, about 25–35% of the 600,000 people with intellectual disability

exhibit challenging behaviour,[9,13] the public health importance of this subject is very clear. With the relocation of this population into the community, due to the small number of beds in specialist units, the use of these drugs is now spread over a larger number of settings. In many of these, the only regular medical input is from general practitioners (GPs), and supervision from skilled staff is often lacking, so if neuroleptic drugs are to be used in treating challenging behaviour we need clear evidence of their efficacy and adverse effects in such settings.

While there have been previous studies of the use of neuroleptic medication in people with both intellectual disability and challenging behaviour, these have been unsatisfactory in terms of the establishment of efficacy and the ability to generalise to most of the settings in which neuroleptic drugs are given. A recent systematic review of neuroleptic medication in the treatment of people with both challenging behaviour and intellectual disability found eight randomised controlled trials (RCTs) of neuroleptic drugs versus placebo medication, but concluded that these 'provided no evidence of whether neuroleptic medication helps or harms adults with intellectual disability and challenging behaviour'.[5] The Neuroleptics in the treatment of Aggressive Challenging Behaviour for people with Intellectual Disabilities (NACHBID) study was designed to remedy this deficiency by comparing the effects of neuroleptic drugs with placebo in those with intellectual disability who demonstrated aggressive challenging behaviour.

Choice of neuroleptic drugs

Although the early studies were all carried out with typical neuroleptic drugs such as chlorpromazine and haloperidol, and these two drugs are licensed for the treatment of acute disturbed challenging behaviour,[14] there has been a change in practice in recent years with greater prescribing of atypical neuroleptic drugs, as these have a much lower incidence of extrapyramidal side effects. At the time the NACHBID study was mounted, the National Institute for Clinical Excellence (NICE) guidelines in the UK gave cautious approval to the use of these drugs as first-line treatments, while stopping short of giving clear advice that they should be favoured in place of the older drugs, often called 'first-generation' neuroleptic drugs.[15] It is fair to note that with two major trials, the Clinical Neuroleptic Trials in Intervention Effectiveness (CATIE)[16] and Cost–Utility of the Latest neuroleptic drugs in Schizophrenia Study (CUtLASS),[17] now suggesting that the benefits of the 'second-generation' drugs are not as great as first thought and that they may not be cost-effective,[18] the NICE advice in future is likely to be tempered in favour of the older drugs.

However, in the NACHBID trial, it was recognised that the effects of both classes of neuroleptic drug were important to clinicians when choosing a treatment for aggressive challenging behaviour. The decision was made to mount a three-arm trial in which there would be approximately equal allocation to treatment with a typical (first generation) neuroleptic drug, an atypical (second generation) neuroleptic drug and placebo. The choice of haloperidol as the typical neuroleptic drug was made as haloperidol is the most frequent comparator in trials of first- and second-generation drugs and it is licensed for the treatment of aggressive behaviour. The choice of risperidone as the representative of the second-generation drug was made on the basis of usage. In the treatment of aggressive challenging behaviour in intellectual disability, risperidone is currently the most commonly prescribed drug and its main competitor, olanzapine, is used less often because of concerns over weight gain.

Risperidone is a drug of established efficacy in chronic schizophrenia[19] and has been evaluated in the treatment of people with intellectual disability. This drug, in conjunction with behavioural interventions, was found to reduce aggression and assault, self-injury and property destruction in 33 institutionalised adults with intellectual disability in a study by Lott *et al*.,[20] and this also showed that risperidone was well tolerated in this population. In another double-blind, crossover study by Van den Borre *et al*.[21] of risperidone and placebo in six different intellectual disability centres in the treatment of behavioural disturbances in people with intellectual disability, the results suggested that risperidone was superior to placebo in reducing symptoms, but this was not clear cut and there were inadequacies in the crossover design.

Although other drugs could equally well have been chosen for the study, the choice of haloperidol, risperidone and placebo was felt to be justified on the basis of evidence and usage, and in a randomised trial there was insufficient evidence available to justify stratification of the sample by any other factor. In the absence of clear indications for efficacy, a trial with equal chances of allocation

to the three arms was considered the best option in a multicentre parallel design. The study was also planned to be a pragmatic one, in which intention-to-treat (ITT) methodology was used and all attempts were made to reduce dropout after randomisation. Because we were also interested in the cost-effectiveness of the three interventions, data were also collected on all economic costs for each of the three interventions. As aggression to self or others in intellectual disability is estimated to cost the National Health Service (NHS) and Social Services a minimum of £50–140 million per annum,[22] the achievement of even a small reduction would be of considerable economic gain, irrespective of improvement in morbidity and quality of life and a reduction in stress to staff.

The duration of treatment was also felt to be important. Active drug treatment may be effective initially or only in the longer term, or it could maintain its benefit continuously. Interpretation of previous crossover trials may have suffered because of an insufficient period of treatment or too short a period of wash-out when changing treatment, and the NACHBID team were also aware that in clinical practice in intellectual disability, it was common practice to prescribe neuroleptic drugs for long periods in the treatment of challenging behaviour. It was, therefore, considered desirable to test the effect of medication over 4 weeks in the first instance, then for a maintenance period up to 12 weeks, with the option of continuing treatment to a maximum of 26 weeks. This was felt to be important, as sometimes neuroleptic drugs show a delayed therapeutic response.

Chapter 3
Methods

Study design

The study design was a three-arm parallel design trial of placebo, haloperidol and risperidone with equal randomisation to each arm. This was selected as the most appropriate design to answer the research questions. It was also felt appropriate to mount a pragmatic rather than an explanatory trial, as the project was concerned primarily with the use of neuroleptic drugs in ordinary practice, a frequent form of management that has become hallowed by long use. For this reason we wanted as few exclusion criteria as possible. We therefore included patients from all levels of intellectual disability, with particular attention to recruiting those with moderate to profound intellectual disability, as these are more commonly treated with neuroleptic drugs. We also extended recruitment to include those who may have been treated with neuroleptic drugs in the past but were no longer taking them, and excluded only those who had previously been diagnosed clinically as having a psychotic disorder, as opposed to a present or recent diagnosis. A diagnosis of being within the group of autistic spectrum disorders was not an exclusion criterion, provided that psychosis was absent.

Hypotheses to be tested

The planned multicentre, RCT was set up to test the following specific null hypotheses:

1. There are no differences between the effects of a typical neuroleptic drug, haloperidol, an atypical neuroleptic drug, risperidone, and placebo in reducing aggression when given in flexible dosage in the short and medium term in non-psychotic patients presenting with aggressive challenging behaviour among those under treatment from intellectual disability services.
2. There are no differences in the short or medium term in the effects of haloperidol, risperidone and placebo in treating other aspects of aberrant behaviour, quality of life, global improvement and burden on carers in those patients with intellectual disability who have aggressive challenging behaviour.
3. The administration of risperidone and haloperidol or placebo in those with aggressive challenging behaviour in the short and medium term shows no important difference in costs or effectiveness.
4. There are no differences in the adverse effects of risperidone, haloperidol and placebo when given in flexible dosage in the treatment of aggressive challenging behaviour in those with intellectual disability.

Inclusion and exclusion criteria

Patients eligible for inclusion in the study comprised those with intellectual disability and an intelligence quotient (IQ) of less than 75, who were under the management of a service that focused specifically on intellectual disability, and were:

- aged between 18 and 65 years
- currently demonstrating challenging behaviour and aggression [defined by at least two episodes of aggressive behaviour with a total Modified Overt Aggression Scale (MOAS) score of at least 4 in the past 7 days]
- able to give written informed consent based on information understandable to the individual concerned, or, if not able to give informed consent, to obtain assent from relevant carers, including relatives and senior care staff at supported homes or related residential settings. Consent was given in writing and witnessed.

Patients excluded from the study were:

- otherwise eligible participants who had taken depot neuroleptics or any other form of injected neuroleptic medication treatment within the last 3 months, or continuous oral neuroleptic medication within the last week [however, those who had been taking an oral neuroleptic occasionally, as and when necessary (i.e. pro re nata), were eligible to be included in the study, if medication had not been taken in the past week]
- otherwise eligible participants with a clinical diagnosis of schizophrenia or another psychotic disorder

- otherwise eligible participants who were under a section of the Mental Health Act 1983 (UK) or the Queensland Mental Health Act 2000 at the time of assessment
- otherwise eligible participants who had participated in any therapeutic or non-therapeutic research study during the last 3 months.

The expectations of adopting these criteria were that most patients would qualify for inclusion if they satisfied the aggression criterion. In particular, it allowed the inclusion of those who may have taken neuroleptic medication in the past for aggressive behaviour and may still be taking this, either occasionally or continuously. There is evidence that at least one-third of this group of patients can stop their drugs without any adverse effects,[23] and so the option of patients being included after withdrawal of treatment allowed for the actual population being treated with these drugs to be involved and for the sample to become more representative.

If patients with epilepsy or other physical disorders were excluded, as many as 30% of those otherwise eligible would not have treatment available. Although there is a slight risk of cerebrovascular accidents with risperidone,[24] this was not considered sufficiently great to exclude patients. In those with known existing cardiovascular disease, baseline electrocardiogram (ECG), blood pressure, pulse and haematological investigations were planned.

Procedure

Stage 1: Initial contact and randomisation

The study began with four centres – North London (including both North West and North East London boroughs), South London, Cardiff and Birmingham – in the hope that each centre would recruit about 35–40 patients, and each centre had a separate set of permuted blocks. When other centres were recruited, they were allocated one or more numbered blocks from those other centres that had not been recruiting well.

Participants likely to be eligible were identified by the principal investigators at each centre and assessed to determine if they satisfied the criteria for inclusion. Those deemed to be eligible were registered for the trial with the study co-ordinator.

Persons with intellectual disability who were treated or supervised in all relevant settings, including the community, supported housing and NHS residential facilities including hospitals, were included in the study. Once the necessary agreement, consent and assent had been obtained, the patient was assessed by one of the research assistants in the trial using the following measures in sequence:

1. trial registration form
2. multiaxial evaluation
3. MOAS
4. Udvalg for Kliniske Undersøgelser (UKU) side effects scale
5. additional interventions record sheet
6. Carer Uplift/Burden Scale
7. Aberrant Behaviour Checklist (ABC)
8. Quality of Life Questionnaire (QOL-Q)
9. Client Service Receipt Inventory (CSRI)
10. Mini Psychiatric Assessment Schedule for Adults with Developmental Disability (PAS-ADD) diagnostic screen.

After baseline assessments were completed, the study co-ordinator was informed and the patient randomised by a research assistant independent of all members of the team. The randomisation code and its nature, known only to the independent statistician from the Medical Research Council (MRC) Complex Interventions Collaborative Group (Dr Ula Nur), used a permuted blocks technique. The part-time trial statistical assistant (Bharti Rao) recorded all data to a Statistical Package for the Social Sciences (SPSS) file that was not available to any other investigator. No analysis of any sort was carried out on the outcome data until the end of February 2007, but an audit of baseline data had been carried out earlier at the request of Dr Tony Johnson, the statistician on the Data Monitoring and Ethics Committee.

Stage 2: Administration of treatments

Once randomised, the relevant clinicians (who scored the UKU scale at baseline in the study) were responsible for the prescription of the trial medication, with all three drugs being given in the form of white tablets of identical appearance. The initial intention was for all patients to begin treatment with one tablet daily (in either single or divided dosage) of placebo, risperidone (1 mg) or haloperidol (2.5 mg). However, some clinicians prescribed lower doses, at least initially, in their

ordinary practice, and a protocol amendment was made to allow initial prescription of half a tablet (0.5 mg risperidone or 1.25 mg haloperidol) daily, and new stocks were prepared of all three treatments in lower dosage. The trial adopted a flexible dosage approach, and all clinicians could prescribe up to 2 mg risperidone or 5 mg haloperidol daily. Special dispensation was allowed to increase medication beyond this level in exceptional circumstances, but this was undertaken in less than 5% of the recruited patients. Clinicians were advised to adopt their normal practice when prescribing these drugs, but also to ensure that adverse events and symptoms (using the UKU scale) were recorded 4, 12 and 26 weeks after randomisation. Rescue medication in the form of lorazepam 0.5–2.0 mg daily was also allowed during the trial, but no other psychotropic drugs were permitted. The 4- and 12-week assessments were performed for all patients recruited to the trial; after 12 weeks the decision to continue treatment up to 26 weeks was left to the individual clinician and patient. At the end of the study, the treating clinician was given the opportunity of finding out what medication the patient had been taking as, if this was clearly successful it might well be apposite to continue it in open prescribed format.

Target population

The original study protocol intended to recruit from those people referred to intellectual disability services over a period of 2 years in four study areas, with mild, moderate or severe intellectual disability, who showed aggressive challenging behaviour in the absence of a mental state diagnosis of a psychotic disorder. The trial operation, therefore, involved centres at the four sites: Centre 1 – North London, including Brent, Ealing, Harrow, Hammersmith and Fulham, Havering, Hounslow, Kensington and Chelsea, Barnet, Enfield, Redbridge and Waltham Forest; Centre 2 – South London, including Lambeth, Lewisham and Southwark; Centre 3 – Wales and South West (SW) England, including Cardiff, South Wales and SW England; and Centre 4 – Birmingham, including South Birmingham, Warwickshire, Hereford and Worcestershire, Dudley, Walsall, Sandwell, North Birmingham, Shropshire, West Birmingham, North Staffordshire, South East Staffordshire and Mid Staffordshire. However, as, after 1 year, only five referrals had been received from the South London and Birmingham centres, the organisation of the trial changed to involve the North London and Welsh centres only. It was planned to end recruitment after 2 years, in October 2004, but at that time only 57 patients had been referred to the trial and an extension to continue recruitment was granted (and subsequently extended to July 2006). The project was helped greatly by its adoption by the Mental Health Research Network (England) in 2004, and this enabled recruitment to take place from other centres linked to the different hubs of the network, so that subsequently patients were recruited from Leicester, Newcastle and Gateshead, Cumbria and Nottingham, with research assistants travelling from London to complete assessments. The trial was also extended to Queensland, Australia in 2004 with the help of Dr David Harley of the Queensland Centre for Intellectual and Developmental Disability (QCIDD), School of Medicine, University of Queensland, Brisbane, where separate ethical approval of the study and permission for transfer of trial medication was obtained. An additional attempt to recruit a similar site in Vancouver, Canada, was not successful.

Proposed sample size

We had great difficulties in establishing an appropriate sample size for the study because no previous study with a similar design had been carried out. In particular, there had been no direct comparisons between first- and second-generation neuroleptic drugs in the treatment of challenging behaviour, so it was impossible to estimate the numbers required to test differences between these drug groups. In addition, there were too many crossover trials, which were not ideal in a population in which treatment has marked carry-over effects, and these were of little value in making reliable estimates. Initially, we decided to carry out a pilot study to help determine an appropriate sample to obtain adequate power to test the main hypothesis, and for this purpose we chose the ABC[33] in order to collect data at five centres. The ABC was completed for 55 subjects who met the eligibility criteria for the study. These data were used to estimate baseline ABC scores in the proposed trial. Scores on the ABC were normally distributed with a mean of 35 and a standard deviation (SD) of 22.8. We estimated that a difference of 12 points on the ABC between those receiving risperidone or haloperidol and those receiving placebo would be clinically significant, but the exact figure was an estimate and was based on one trial carried out by Van den Borre and colleagues;[21] however, this was a crossover trial and compared only risperidone and placebo. A sample size of 194 subjects (97 taking risperidone and 97

placebo) was found to be required to have 90% power to detect a difference of this magnitude at the 5% level of significance.[34] Extrapolation to the comparison of haloperidol and placebo would use data from the same 97 subjects taking placebo and a further 97 subjects receiving haloperidol. We therefore estimated a sample size of 291 subjects, and with a potential dropout rate of 20%, the total sample required was 363.

However, the ABC was subsequently judged to be an inappropriate measure for our study, as two of its four factors appeared to be associated with limited change and, because we wanted to perform frequent assessment of aggression, we needed a simpler and shorter measure. Our work with the MOAS scale suggested that a mean difference of 8 points was likely to be clinically significant, as aggressive behaviour is detected most easily in ordinary practice. We therefore repeated the sample size calculation using data on differences in MOAS scores between baseline and 4-week follow-up for the first 20 patients in the trial. We calculated that, using a 5% significance level, we required data on 99 patients in order to have 80% power to detect a clinically relevant reduction in MOAS score of 8 points (SD = 11.4) between two treatments. In anticipation of a 20% dropout rate, we therefore planned to recruit 124 patients, with 99 expected to complete. However, we accept that this was not an ideal calculation as (1) it compared two treatments rather than three, and (2) non-parametric statistics were chosen, in the end, rather than parametric ones. As the trial progressed and the dropout rate (see Chapter 4) was much lower than expected, this number was revised downwards, but the trial team and the Data Monitoring Ethics Committee agreed that a minimum of 100 patients should be recruited.

The sample size calculation was, therefore, estimated using a clinical measure of outcome. There are practical considerations when basing sample sizes on cost-effectiveness. Sample size calculations in economic evaluations usually require reasonable estimates of costs and their SDs and correlations between costs and effects, which may be difficult to find.[35] Furthermore, cost analyses usually require large sample sizes to detect differences in costs, and the study may have been underpowered for the economic analysis.[26] However, if the sample size were based on costs, the study would be overpowered to detect differences in outcome, and it may also have been inappropriate to continue the study beyond the point at which clinical effectiveness has been achieved.[36]

Economic evaluation

The cost-effectiveness component of the study was undertaken from the perspective of all providing agencies and informal carers. Cost-effectiveness was evaluated by comparing differences in treatment costs for patients receiving risperidone, haloperidol or placebo with differences in effectiveness as measured by the primary outcome, total MOAS score and an important secondary outcome, quality of life, using the QOL-Q, at the 4- and 26-week follow-ups. A measure of quality of life was appropriate in this case as it was recognised that trial medication not only has an impact on behaviour, but also may affect satisfaction, empowerment, competence and community integration. The total MOAS QOL-Q scores were used for this purpose.

To assess cost-effectiveness when three treatments were compared, an extended dominance approach was employed.[25] Briefly, treatments were ranked in ascending order of cost, and a treatment was eliminated from consideration if it had higher costs and worse outcomes than at least one other treatment. The remaining two treatments were compared by computing incremental cost-effectiveness ratios (ICERs) for the two outcomes and plotting cost-effectiveness acceptability curves (CEACs), to show the probability that an intervention would be seen as more cost-effective by decision-makers than its comparator(s) against a range of assumed values for the willingness to pay (λ) for an incremental gain in the given outcome.[26]

This approach assumes that there is a theoretical but unknown value (λ) that society would place on an improvement in symptoms of challenging behaviour as measured by the MOAS. Using the net benefit approach, a range of willingness-to-pay values (λ) for an improvement in challenging behaviour was mapped against the proportion of the estimates of the ICER for which haloperidol is cost-effective over placebo. These estimates were generated by selecting patients from the observed data one at a time, making replacements until a new sample the same size as the original data set was obtained. The procedure was repeated 1000 times and bootstrapped differences in effects and costs were derived, allowing the ICER for each replication to be calculated as $[(\text{cost}_b - \text{cost}_a)/(\text{effect}_b - \text{effect}_a)]$, where a and b indicate the

treatments being compared. The imputed monetary value of the outcome, computed as λ ($effect_b$ – $effect_a$), was calculated for MOAS by exploring a range from £0 to £3000 for λ, and was calculated for QOL -Q by exploring a range also from £0 to £3000 for λ. These estimated benefits were then compared with costs for each replication, and the proportion of all such comparisons for which benefits exceeded costs was calculated to indicate the probability that one treatment was more cost-effective than the other, and used to plot the CEAC. Statistical analyses were conducted using SPSS 11, Microsoft EXCEL 2000 and STATA 8.2 for Windows.

Resource use and cost data

Resource use data for each person were collected over a retrospective period of 6 months before randomisation. At 26 weeks, follow-up data were collected retrospectively for a 26-week period. Comprehensive data on all specialised accommodation, health, social care and other services (such as the number and duration of hospital inpatient bed days, outpatient and day hospital appointments, accident and emergency visits; hours per week spent in daytime activities; number of contacts with general practitioners, psychiatrists, community psychiatric nurses, district nurses, learning disability nurses, social workers, chiropodists, counsellors, psychologists, speech and language therapists, opticians, dentists, physiotherapists, home help, alternative therapists and art therapists) used by study participants and time unpaid family members and relatives spent providing care and support were recorded using the version of the CSRI modified for people with intellectual disability. The service use inventory recognises that the data needed to define an individual's care package may not be available from one source. Interviews were conducted with main carers including relatives and senior care staff at supported homes or other residential settings as appropriate.

The costs of the services used by patients were derived by combining medication, health and social care resource utilisation data with estimated unit costs. All unit costs were at 2005–6 prices and came from a variety of national sources. The costs of treatment medications were estimated on the basis of within-group average dosages in the exposed population multiplied by unit costs for those dosages obtained from the British National Formulary, March 2006.[14] Average within-group costs were then allocated to each individual patient. Unit costs for contacts with health and community professionals were taken from the most up-to-date figures.[27] National reference costs were used to estimate the cost of outpatient attendances.[28] We also collected data on care inputs by family and other unpaid carers, and costs of this informal care were also included in the analyses. A cost was imputed for these inputs by using the minimum hourly wage rate.[29] The minimum wage is a conservative valuation of a carer's time when the carer is employed and the occupation type is unknown. Sensitivity analyses were carried out to explore, inter alia, the consequences of adopting different values for the costs of informal care and the effects on the cost-effectiveness estimates.

Further details of planned interventions

The drugs for the study were provided in bulk by Janssen-Cilag plc and subsequently boxed commercially for each patient by an approved pharmacy, Manderville Medicines. The placebo, haloperidol and risperidone were all manufactured in the form of white tablets of identical appearance, so that a double-blind procedure could be used throughout, and containers for each time period (baseline for 4 weeks, then a further 8 weeks' supply to 12 weeks, and a further 14 weeks' supply to 26 weeks) were provided, with each containing the maximum number of tablets for that period. After baseline assessment and randomisation, the drugs were delivered to the clinician responsible for the patient, who decided on the initial dosage and continued to monitor the patient for the duration of the trial. The clinician, in conjunction with his or her local team, decided in advance on the threshold for use of the rescue medication (lorazepam). A detailed record of medication given was recorded and the agreement made that if lorazepam was given daily for more than 2 weeks at any one time it would be withdrawn in tapered doses over 4 days (to avoid the exhibition of withdrawal symptoms). However, the use of this option was not encouraged as, clearly, there was a danger that any additional medication would reduce the effect size of haloperidol–risperidone–placebo differences. Nevertheless it was judged to be ethical and appropriate to have this additional option that would also aid adherence to the trial. At the outset, it was expected that the likely rate of loss to follow-up would be no more than 20%. A record of all additional interventions, separated into behavioural, psychological, occupational/

training and pharmacological, was made over the 26 weeks of the trial.

Ethical issues

The development of effective treatments in those with intellectual disability has been handicapped by the failure to embrace the tenets of evidence-based medicine, which necessarily has to rely on data from well-conducted RCTs. Clinicians, carers and, to a lesser extent, the patients themselves, have tended to be wary about, or sometimes overtly hostile to, the notion of randomised trials in this population because of past ethical abuses.[30] However, the consequence of this concern is that many treatments of clear benefit are probably being denied those with intellectual disability and many others of dubious value are being given liberally. We argued that it was ethical for practitioners to take part in the trial because best practice requires a robust evidence base, and it is unethical for any group, particularly a vulnerable group such as those with intellectual disability, to be deprived of a source of knowledge that all others embrace. This view has also been made forcefully by an authoritative expert in intellectual disability.[31] To deprive patients of a technology that could be of great personal benefit is contrary to human rights within the context of equity and social inclusion. This view was endorsed by MENCAP, the largest charity concerned with intellectual disability, who consistently supported the trial.

Where possible, informed consent was obtained from all suitable eligible participants. At preliminary meetings it was agreed that the local practitioners would raise the purpose and ethical issues about this research with local interested groups, such as self-advocacy groups, parents' groups and care managers. The intention was to obtain general agreement from the local community involved with intellectual disability services that such research is necessary and that consent in writing could be given by those individuals who had the capacity to consent. A service user group for those with intellectual disability, the Harrow Forum, advised on procedure.

Where the patient was able to communicate and understand sufficiently well to make an informed decision, written consent was requested. Where possible, informed consent would be obtained based on information that was understandable to each intellectually disabled individual. Where the patient was not legally competent to make a treatment choice, they would be treated 'in their best interests', which would be defined in a manner appropriate to clinical research with special safeguards to ensure properly informed participation. This included certain safeguards: (1) the seeking of agreement of relatives and advocates at times when relevant individuals may be able to provide assent on behalf of their client/relative; (2) avoidance of the use of professional workers to act as a proxy relatives in the study; (3) obtaining the assent of the relative/primary carer in all cases, even where the patient has given consent; (4) awareness of, and response to, any objection by a relative or primary carer; and (5) where an adult patient lacking the capacity for consent indicated, for whatever reason, an unwillingness to participate in the study, he or she should not be included, even if the relatives/advocate or primary carer gave agreement/assent. We believe that these requirements adequately reflected the position in English Law regarding therapeutic research and the ethical position reflected in the MRC Ethics Series research section 7.2.1–7.2.4 on pages 17–18 in the MRC Ethics Series.[32]

All participating patients were given a NACHBID study card, and this card was carried at all times and presented at every medical consultation during their 6-month study period.

Carer issues

The Chair of the Parent's Forum of the Westminster Society for Carers' of People with Intellectual Disability (Catherine Slater) gave advice to the study team and was a member of the Steering Group throughout the trial. She was particularly helpful in drafting consent forms that would be understandable to patients in the study, although the language chosen was sometimes altered, in our view unnecessarily, by local ethical committees.

Data collection and statistical analysis

A record was kept of those eligible participants who were excluded or who dropped out of the study for any reason. The statistical analysis was performed using SPSS Version 14 and R Version 2.4.1. Most of the data were markedly skewed or kurtosed, and so non-parametric, rather than parametric, statistics were used for most of the analyses. Univariate analyses were carried out using the Mann–Whitney or Kruskal–Wallis tests for comparing the value of continuous variables between two or more than two

treatment groups. The Fisher exact test was used to compare the value of categorical variables between groups. Multivariate analyses of continuous outcomes were by regression, adjusting for baseline values of the response variable where appropriate. Analysis was by ITT, imputing missing values by last observation carried forward.

The main analysis was an ITT analysis of MOAS scores of the three treatment groups at week 4, using a quasi-likelihood approach, whereby the logarithm of mean MOAS score is assumed to be a linear function of significant predictors and where the variance is estimated from the data. We adjusted for logarithmically transformed baseline MOAS value and any other significant candidate predictors.

The main economic evaluation was a cost-effectiveness analysis from the societal perspective, comparing changes in the primary outcome (reduction in aggressive challenging behaviour) and total costs (services and carer inputs) between risperidone, haloperidol and placebo patients. This was supplemented by a cost–consequences analysis (examining total and component costs alongside all outcomes). The latter is, of course, less deterministic than the computed incremental ratio of a cost-effectiveness analysis, but provides potentially helpful additional information. Health and social care and public sector perspectives can also be explored in order to inform associated policy discussions.

Preliminary tests using ordinary least squares regression analysis were used to determine whether the group for which we had cost data at 26 weeks was different from the group for which we did not have any such data. Demographic indicators at baseline including age, gender, ABC score, MOAS score and QOL-Q were used individually as the dependent variable, and regressed against a variable which indicated 0 if the individual had no cost data at 26 weeks or 1 if the individual had any cost data at 26 weeks.

Missing values in resource use were replaced by the mean of the group to which the individual was allocated, and then costs were estimated for each treatment group by combining the unit cost of each resource with the intensity and duration of service use.

To explore if unobserved differences at baseline between the treatment groups may result in differences in cost between the treatment groups, regression analysis adjusting for baseline covariates [age, gender, ABC score, MOAS score, global assessment of functioning (GAF) score, presence of autism] was conducted.

In further analysis, CEACs were plotted for the remaining two treatments, which assumes that a societal value was placed on each additional gain in the given outcome. Regression models were used to calculate mean differences in net benefit between the two treatments. One thousand regression coefficients for the group variable were generated using bootstrapping, and the proportion of these that were greater than 0 indicated the probability that the treatment was cost-effective compared with the other. These probabilities were then used to generate CEACs.

Outcome measures

Challenging behaviour is complex and has many possible outcomes apart from the frequency, duration and intensity of aggressive behaviour. Because such behaviour is heavily dependent on context, it is wise to take as broad a range of outcomes as possible.[5] Nevertheless, in this study we chose aggressive behaviour as our primary outcome as, in most instances, it is this symptom that is the main reason for the prescription of neuroleptic drugs. As secondary outcomes, we also measured other forms of aberrant behaviour (using the ABC), quality of life (using a special scale for those with intellectual disability,[37] reduction in burden on carers,[38] and global improvement.[39]

The ABC was developed to assess drug and other treatment effects on people with severe intellectual disability. The scale has been found to have wide generality irrespective of institutional setting and rater source.[24] This scale measures challenging behaviour and has been chosen as a main outcome in several intervention studies,[40] but after some discussion the trial team had doubts that it was sufficiently specific to measure accurately the aggressive component of challenging behaviour and instead chose the MOAS scale for this purpose.

The Overt Aggression Scale (OAS) was developed by Silver and Yudofsky[41] for the accurate documentation of aggressive episodes and to assess the effectiveness of interventions in the treatment of violent patients. The comprehensive nature of the OAS ensures that the whole range of aggressive behaviour, including self-directed aggression, is documented. The use of the OAS has particular

value in documenting and assessing individual patterns of aggression, such as verbal or physical aggression, week-to-week fluctuations in aggressive behaviours, patterns of aggression among patient groups, types of interventions utilised to control aggressive behaviours, e.g. neuroleptic medication, and the effects of pharmacological and psychosocial intervention.[21,42]

Based on experience using the Nurse's Observation Scale for Inpatient Evaluation (NOSIE), a retrospective instrument that records ward behaviour, Sorgi *et al*.[43] modified the OAS by reformatting the 16 types of aggressive behaviour into 16 scale items. This new scale included the frequency of occurrence of the 16 items rated on a five-point Likert scale. This modified instrument was easy to administer and was found to be a useful measure of both aggressive incidents and aggressiveness in a psychiatric inpatient population.[44] Ratey and Gutheil,[45] reflecting on the use of the OAS and the MOAS, found that the identification of specific acts of aggression might best be performed using the OAS, but that when frequency of episodes was important the MOAS may have the advantage. In this study, we decided to use change in the MOAS after 4 weeks of treatment as the primary outcome measure because the instrument has demonstrated good reliability, and had previously been used in an intellectually disabled population with good face validity. However, psychometric properties have only been tested in adult psychiatric populations, and so we carried out a separate study to determine its reliability and acceptability in an intellectually disabled population. This showed that inter-rater reliability was acceptable and that the measure was suitable for those with intellectual disability.[46]

The ABC – Community version was used as a secondary outcome because it is widely used as an assessment of problem behaviour and has good psychometric properties that have also been established in populations with intellectual disability. The ABC scores can be divided into four or five factors including (1) irritability, agitation, crying (15 items); (2) lethargy, social withdrawal (16 items); (3) stereotypical behaviour (7 items); (4) hyperactivity, non-compliance (16 items); and (5) inappropriate speech (4 items). We decided to use the four-factor model because of what appeared to be justified criticisms of the five-factor model, notably the fifth one of inappropriate speech.[47] The four-factor solution – revised as irritability (factor 1); lethargy and social withdrawal (factor 2), which includes the two most important components of challenging behaviour (passive–aggressive); stereotypical behaviour (factor 3); and hyperactivity (factor 4) – was used in the NACHBID study. Both MOAS and ABC assessments were felt to provide a broad-based range of assessments that would allow any significant change in aggressive challenging behaviour to be detected in the context of the trial.

Multiaxial and Mini PAS-ADD diagnostic classifications

Challenging behaviour is not a diagnosis, although it is often managed as if it were. Patients with aggressive challenging behaviour can have a range of underlying diagnostic disorders that make them vulnerable to aggressive behaviour and which may be the ultimate cause of this. For this reason, it can be important to record diagnosis formally. Both clinical and structured assessments of psychiatric diagnosis were completed for each patient in the study. The clinical assessment used the multiaxial classification DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) format with ICD-10 (International Classification of Disease) codes at baseline, and involved:

1. interview with carer
2. interview with client (where possible)
3. meeting with other relevant staff
4. review of case notes where considered necessary, in case of doubt.

For psychiatric symptoms, the Mini PAS-ADD,[48] a standardised structured instrument, was completed by interview with a key informant at baseline only. To increase reliability, this schedule uses a glossary of symptom definitions to guide the coding. The instrument has been designed so that the information collected can aid the subsequent process of diagnosis by a psychiatrist or psychologist.

The schedule produces scores relating to the following psychiatric disorders; each category has an accompanying threshold score:

- depressive disorder
- anxiety disorder
- hypomania/mania or expansive mood
- obsessive–compulsive disorder
- psychosis
- dementia or unspecified disorder
- autistic spectrum.

There was particular interest in the last of these groups, as an influential study in autistic

children has shown that the second-generation neuroleptic drug, risperidone, was effective in reducing challenging and other forms of abnormal behaviour.[38]

Other instruments used to record outcomes

Modified Overt Aggression Scale

The reasons for using this scale have already been discussed. There was unanimous agreement among the NACHBID investigators that this was the best primary outcome measure in the study. In addition to recording the MOAS scores at baseline and at the standard time points of the study (4, 12 and 26 weeks), we assessed MOAS scores weekly by telephone interview with a key informant, with the intention of obtaining information from the same informant on each occasion to limit variability in scoring. The research assistants in the study carried out all these interviews.

Aberrant Behavior Checklist – community version

This was also administered at all time points. The four-factor model was used. The ordering of these factors varies, but in our study we separated the ABC items into hyperactivity (factor 1), irritability (factor 2)(these two being the most prominent symptom of challenging behaviour), lethargy and social withdrawal (factor 3)(the passive-aggressive component of challenging behaviour), and stereotyped behaviour (factor 4)(more common in autistic spectrum disorders).

Clinical Global Impressions Scale

The Clinical Global Impressions Scale (CGI) scale measures (1) the severity of mental illness and (2) global improvement after intervention, so the severity of illness component was recorded at baseline and both severity and global improvement recorded at 4 weeks', 12 weeks' and 6 months' follow-up [37]. It is commonly used in studies despite having only a small range of options for each rating and no clear glossary of scoring instructions.

Uplift/Burden Scale

The impact of aggressive challenging behaviour on carers was measured with the Uplift/Burden Scale,[38] which was not developed specifically for populations with intellectual disability but was chosen for the NACHBID study because it was designed specifically for informants. This 23-item scale has six uplift items and 17 burden items. The scale was assessed with the primary carer at baseline, 4 weeks', 12 weeks' and 6 months' follow-up.

Quality of Life Questionnaire

The quality of life of people with intellectual disability is not as easy to measure as in those in other groups, and thus requires a measure developed for this population. We therefore used the 40-item QOL-Q,[37] and this was also assessed at all time points in the study with the patient (quality of life cannot be assessed by proxy).

UKU Side Effects Rating Scale

Extrapyramidal and related adverse effects were recorded using the UKU Side Effects Rating Scale[49] at baseline, 4 weeks', 12 weeks' and 6 months' follow-up, because it was considered valid and easy to use (i.e. it could be completed by local clinicians), and covered the main likely adverse effects of neuroleptic medication seen in this population. Although several scales are used for the assessment of extrapyramidal side effects, the UKU is well tested in populations with intellectual disability, and so was selected in favour of the better-known Simpson and Angus scale originally considered for the study.

The validity of this scale has been explored by comparing scores among people with psychosis who are and are not taking neuroleptic medication, those taking higher and lower doses and those taking different types of neuroleptic medication with different side effect profiles.

Additional interventions checklist

Because there was concern about the possible extent of need for additional treatments, these were recorded at each of the main time points of the trial. They were separated into behavioural interventions (e.g. isolation to avoid disruption and reinforcement of attention), specific therapeutic psychological interventions (e.g. counselling), drug treatments (including those for physical disorders) and occupational therapy together with speech and language therapy (SALT).

Independent supervision of trial

A Data Monitoring and Ethics Committee was established at the beginning of the trial to monitor (1) recruitment of patients to the trial, (2) ethical issues of consent, (3) quality of data (including missing data), (4) fidelity of interventions (including dosage) and (5) any other factors that might compromise the progress and satisfactory completion of the trial. This was chaired by Professor William Fraser, and included

an independent statistician, Dr Tony Johnson of the MRC Biostatistics Unit, Cambridge; Dr Deborah Rutter, Ethics Committee member; Ms Bharti Rao (trial statistical assistant); and Professor Peter Tyrer. An external steering committee was also established, chaired by Professor Sheila Hollins, and including Professor Peter Tyrer and Prof. Declan Murphy as trial working group representatives; and Dr Patricia Oliver, former trial co-ordinator, Dr Angela Hassiotis and Dr Stephen Tyrer for the monitoring of the clinical aspects of the study.

Study procedures

The procedure was carried out in the following steps:

1. Identification of a key informant for each new referral.
2. Assessment of client by referring clinician (multiaxial assessment).
3. Independent assessment of psychiatric and behavioural symptoms (Mini PAS-ADD).
4. Consent of client and assent/agreement of carer sought if patient considered eligible.
5. Independent research assessor completed baseline MOAS, ABC, UKU Side Effects Scale with key informant, CSRI, CGI (illness only), Uplift/Burden Scale, QOL-Q and additional interventions checklist.
6. Assessor telephoned randomisation database (at Chelsea and Westminster Hospital, London – a hospital where none of the NACHBID investigators had any contact) and allocation made to haloperidol, risperidone or placebo according to block design. Tablets delivered to clinician.
7. Commencement of treatment: initially with 0.5–1.0 mg risperidone/1.25–2.50 mg haloperidol/placebo daily, with increase if necessary up to 2 mg risperidone and 5 mg haloperidol daily by 4 weeks, and maintenance therapy for 8 further weeks or 6 months if necessary.
8. Further assessments – 4 weeks and 12 weeks: independent reassessment of psychiatric and MOAS (weekly by telephone with key worker), ABC, UKU Side Effects Rating Scale and CGI with key informant, Uplift/Burden Scale with primary carer, QOL-Q with patient, and completion of additional interventions checklist. Patient and carer seen at this time and decision made whether to continue with trial medication or withdraw.
9. Follow-up assessment – 6 months: independent reassessment of psychiatric and MOAS (weekly by telephone with key worker), ABC, UKU Side Effects Rating Scale, CSRI and CGI with key informant, Uplift/Burden Scale with primary carer, QOL-Q with patient, and completion of additional interventions checklist.

Pharmacy procedures

As the study was a double-blind RCT of haloperidol, risperidone and placebo, it was necessary for the research worker and clinicians to be blind to the medication taken by the patient. Therefore, an identification/randomisation number was allocated to patients for the duration of the trial. Three bottles of medication were allocated in advance for each patient. Each bottle containing the drug to which the patient had been randomised was labelled with the patient's identification number. The first bottle contained 28 tablets for the first 4 weeks; the second, 56 tablets for the next 8 weeks; and the third, 98 tablets for the next 14 weeks.

1. For each bottle dispensed, the centre researcher and pharmacist was responsible for completing a 'NACHBID Trial Dispensing and Returns Log'. A copy of the completed form was retained by the relevant pharmacist in the study centre and kept in the pharmacy, and a further completed copy was retained by the Trial Manager for the NACHBID team.
   - If the patient subsequently entered the trial, the research worker returned (or faxed) a copy of the 'NACHBID Trial Prescription Form' signed by the consultant psychiatrist responsible for that patient.
   - If, after assessment, the patient, for any reason, did not enter the trial, the research worker returned the bottle and the 'NACHBID Trial Dispensing and Returns Log' was destroyed. The bottle was then dispensed to the next patient.
2. In some cases the research worker organised subsequent prescriptions from the pharmacist at the relevant centre; at others they were obtained from the main trial centre. The psychiatrist remained responsible for prescribing at all stages in the trial.
3. If at any time the clinician judged that the patient needed more than the maximum number of tablets daily (in excess of 2 mg risperidone or 5 mg haloperidol), arrangements were made for the clinician

to inform the trial team immediately so that extra tablets could be made available for these patients.

4. The randomisation centre in the trial (based at the Chelsea and Westminster Hospital) posted copies of the allocated medication details to the trial pharmacists to keep them informed about patient details, randomisation group and follow-up dates for each patient, in order to facilitate planning of subsequent prescriptions over the 26-week period of the trial. If the clinician or patient decided at 12 weeks not to continue with the trial, the pharmacist was informed and subsequent bottles were destroyed.
5. Similar procedures were followed at 4 and 12 weeks. The medication was dispensed after the research worker had completed the patient 'NACHBID Trial Dispensing and Returns Log' form kept in the pharmacy. A copy was again retained by the research worker, who also returned the updated copy of the 'NACHBID Trial Prescription Form', signed by the consultant psychiatrist, to the pharmacist.
6. The 'NACHBID Trial Dispensing and Returns Log' was completed and the tablet bottles returned (even if empty) to the pharmacy after each follow up. The remaining tablets were counted and recorded on the 'NACHBID Trial Dispensing and Returns Log'. An audit of administration of the medication showed that in all centres the tablets were being given as prescribed, as in no case was the patient alone responsible for the administration of his or her drugs. The returned bottles should be kept in the pharmacy even when empty.
7. These procedures were applicable to all participating centre pharmacies for the trial. However, where there was agreement between the researcher and the pharmacist there was flexibility in relation to the timing of delivery and storage of originals/copies of the 'NACHBID Trial Dispensing and Returns Log', the 'NACHBID Trial Prescription Form' and the returned bottles for each particular study centre.
8. The same procedure was followed at the Queensland Centre, except that the assessments were carried out and prescriptions given by a public health physician (Dr David Harley), with the exception of one patient who was referred by Dr Nicholas Lennox, a general practitioner experienced in the care of those with intellectual disabilities. Randomisation used the same procedure as in the UK centres.

Chapter 4
Results

Recruitment

The study was funded in July 2002 and, following a long process of ethical committee and research and development approval it was ready to recruit its first patient at the end of October 2002. The recruitment rate, as indicated in *Figure 1*, was much slower than hoped, as the original target was to recruit 120 patients by November 2004.

Eighty-six patients were recruited to the trial between 6 November 2002 and 24 August 2006, representing a recruitment rate of 1.9 per month, with the maximum rate (2.75 per month) occurring within the first year. This represented a shortfall in our planned recruitment target of 124, but this had assumed a 20% drop-out rate so that only 99 were expected to be assessed for the primary outcome measure. As the figure of 20% proved to be entirely wrong (the drop-out rate was 0), the degree of underpower was not as great as first thought. At the beginning of the trial there were four centres in North London, South London, Birmingham and Wales, with research assistants at each centre. In May 2003 it became clear, with at that time only three patients being recruited from the Birmingham and South London centres combined, that full-time research assistants at these centres could not be justified, and the decision was made to concentrate recruitment at the North London and Welsh centres, with the Welsh-based research assistant also covering Birmingham. In June 2004, an additional centre was recruited in Leicester with a research assistant, but only two patients were recruited and so this additional resource was also abandoned. In April 2005, after 18 months of negotiation, the Brisbane centre was opened and the research assistant was supported by the University of Queensland for 1 year; six patients in all were recruited from this centre. In March 2005, the Mental Health Research Network adopted the project and this allowed widening of recruitment to include patients from Nottingham, Gateshead and Cumbria, and also allowed clinical studies officers attached to the network to help in recruitment at each of the eight hub centres of the network.

The North London centre recruited the most patients (36%) followed by Wales (31%) and Birmingham (14%). The Australian arm of the trial recruited six patients (7%) and the other centres in England recruited the remaining 12%. Forty-nine (57%) of the patients were recruited by four consultants in the North London and Welsh centres. There is no evidence of any significant association between treatment group and centre (*Table 1*).

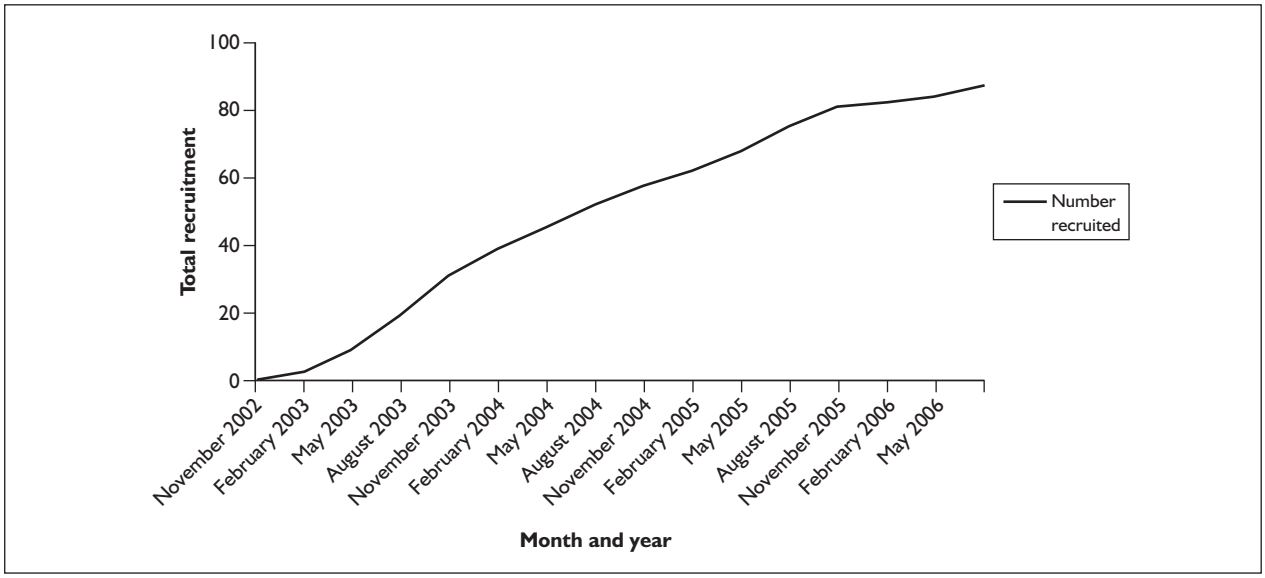

FIGURE 1 *Recruitment rate in NACHBID study between November 2002 and July 2006.*

TABLE 1 *Distribution of treatment group by centre*

Randomised treatment [*n* (%)]	North London	South East London	Wales	Birmingham	Leicester	Australia	Gateshead	Nottingham	Cumbria
Placebo, 29 (33.7)	11 (37.9)	1 (3.4)	10 (34.5)	3 (10.3)	0 (0)	2 (6.9)	1 (3.4)	1 (3.4)	0 (0)
Risperidone, 29 (33.7)	10 (34.5)	0 (0)	9 (31)	4 (13.8)	2 (6.9)	2 (6.9)	1 (3.4)	1 (3.4)	0 (0)
Haloperidol 28 (32.6)	10 (35.7)	1 (3.6)	8 (28.6)	5 (17.9)	1 (3.6)	2 (7.1)	0 (0)	0 (0)	1 (3.6)

Characteristics of population at baseline

One hundred and eighty patients were registered for the trial but only 86 took part. The main reasons for failure to take part for the remaining 94 were refusal of consent or assent (28%), patients already on neuroleptic drugs for aggressive challenging behaviour for whom it was felt too risky to withdraw the medication (32%) and refusal to consider medication in any form as a treatment option (11%). The full details are shown in *Table 2*.

Of the 86 patients, 31 (36%) had mild intellectual disability, 41 (48%) had moderate disability and 14 (16%) had severe or profound intellectual disability, with similar distribution across the randomised groups (*Table 3*). This is roughly representative of the population under the care of services for this group and is clinically relevant, as aggressive challenging behaviour is more common in those with more severe intellectual disability. Many previous trials have predominantly involved patients with borderline and mild intellectual disability who are clearly not representative. The mean age of those recruited was 40.1 years, with

TABLE 2 *Reasons for failure to recruit 94 registered and potentially eligible patients*

Problem or barrier	Number (*n*)	Percentage of total contacts
Patients and relatives refused consent/assent	26	27.7
Client non-compliant with medication to be reviewed	3	3.2
Refused study tablets/prefers liquid solution	1	1.1
Intermittent challenging behaviour	2	2.1
Against medication/refused trial medication	10	10.6
Side effects of trial medication	2	2.1
Prefers PRN medication to continuous trial medication	1	1.1
Antagonistic towards RCTs	7	7.4
Aggressive patients already taking neuroleptic medication and psychiatrist refused withdrawal of neuroleptic medication for trial washout period of 1 week	30	32.0
Patients under mental health legislation[a]	5	5.3
Other reasons (e.g. family trauma, physical illness, carer stress, physical assault)	7	7.4
Total eligible patients not entered in trial	94	100

PRN, pro re nata (as required).
a An exclusion criterion of the trial requested by the Scotland Multicentre Research Ethics Committee.

TABLE 3 *Level of intellectual disability by randomised group*

	Randomisation group			
	Risperidone [*n* (%)]	**Haloperidol [*n* (%)]**	**Placebo [*n* (%)]**	**Total (*n*)**
Total sample	29 (34)	28 (32)	29 (34)	86
Level of intellectual disability				
Borderline	0 (0)	0 (0)	1 (4)	1
Mild	11 (38)	8 (29)	11 (38)	30
Moderate	15 (52)	14 (50)	12 (41)	41
Severe	3 (10)	6 (21)	5 (17)	14

similar age distribution across all three treatment groups (*Table 4*).

The severity of illness (as opposed to level of intellectual disability) at baseline (using the CGI scale) also shows little difference between the allocated drugs. There were no patients allocated to placebo who were regarded as severely ill, but the comparison with the other groups was not significant [chi-squared 2×2 test 3.28, $p = 0.07$ ($p = 0.17$ after Yates correction)] and distribution in all other groups was even (*Table 5*). It is of interest that, despite qualifying for treatment in the trial, a total of 15 patients (17%; fewest in the placebo group) were described as 'normal' with no signs of illness.

Diagnostic status using Mini PAS-ADD

Thirty-six (42%) of the patients did not meet the threshold for consideration of a psychiatric diagnosis using the Mini PAS-ADD checklist over the first 4 weeks of the trial. The anxiety threshold was met by the highest proportion (22%), followed by the hypomanic/manic threshold (15%) (*Table 6*). Despite psychosis being a (clinical) exclusion for the trial, 11 patients (12.8%) reached the threshold for this possible diagnosis.

At the beginning of the trial there was considerable discussion about the possibility that those with disorders within the autistic spectrum might

TABLE 4 *Age and gender in patients included in the trial by allocated treatment groups*

Treatment	***n***	**Age [median (IQR)]**	**Gender [*n* (% male)]**
Placebo	29	43 (34.5–55.5)	17 (58.6)
Risperidone	29	39 (28.5–44.0)	19 (65.5)
Haloperidol	28	37.5 (26.25–50.75)	17 (60.7)
Total	86	Mean 40.1	53 (61.6)

IQR, interquartile range.

TABLE 5 *Severity of illness (recorded using CGI) at baseline by treatment group*

	Severity of illness [*n* (%)]						
Treatment	**Not assessed**	**Normal**	**Borderline mentally ill**	**Mildly ill**	**Moderately ill**	**Markedly ill**	**Severely ill**
Placebo, $n = 29$	1 (3.4)	4 (13.8)	4 (13.8)	6 (20.7)	11 (37.9)	3 (10.3)	0 (0)
Risperidone, $n = 29$	1 (3.4)	6 (20.7)	3 (10.3)	6 (20.7)	8 (27.6)	1 (3.4)	4 (13.8)
Haloperidol, $n = 28$	1 (3.6)	5 (17.9)	3 (10.7)	7 (25.0)	8 (28.6)	2 (7.1)	2 (7.1)

TABLE 6 *Thresholds for likely psychiatric pathology identified with the Mini PAS-ADD checklist over the baseline to 4-week period of the trial*

Diagnostic group	No. of patients meeting threshold for diagnostic consideration	Percentage of total
Depression	8	9.3
Anxiety	19	22
Mania	13	15.1
Psychosis	11	12.8
Autism	8	9.3
No thresholds met	36	42

respond preferentially to neuroleptic drugs. It was also felt that a considerable proportion of those deemed to be suitable for the trial might show this behaviour and be included. All the diagnoses in the multiaxial classification of mental disorders within the autistic spectrum were therefore examined separately; these are shown in *Table 7*.

Baseline assessments

The baseline scores of most of the instruments used in the study were very similar in the three treatment groups. However, there was a difference in the main outcome score in those allocated to risperidone. These had a median MOAS score of 19 compared with medians of 12 and 13 for placebo and haloperidol respectively (*Table 8*). This was not a significant difference, but needs to be taken into account when viewing the visual representation of progress in the figures below. It is also relevant that the ABC total scores are similar in all three groups; the risperidone group had the lowest score (i.e. least aberrant behaviour) of the three treatments. The scores for the other secondary outcomes all had a similar distribution at baseline (*Table 9*).

TABLE 7 *Distribution of autistic disorders within the three randomised treatment groups*

Treatment	Childhood autism [*n* (%)]	Atypical autism [*n* (%)]	Unspecified pervasive developmental disorder [*n* (%)]
Placebo	1 (3.4)	0 (0)	5 (17.2)
Risperidone	1 (3.4)	2 (6.9)	2 (6.9)
Haloperidol	1 (3.6)	0 (0)	2 (7.1)

TABLE 8 *Baseline scores (MOAS and ABC) in the three treatment groups on the main measures of challenging behaviour (total and the four factors[47])*

	MOAS	ABC (total) [median (IQR)]	Hyperactivity [median (IQR)]	Irritability [median (IQR)]	Lethargy and social withdrawal [median (IQR)]	Stereotypical behaviour (median)
ABC factor	NA	NA	1	2	3	4
Placebo	12 (8–25)	51 (27.5–68)	26 (19–32)	5 (3–9)	12 (9–18)	2 (0–4)
Risperidone	19 (12.5–28)	46 (32–59)	23 (14.5–44)	5 (4–13)	11.5 (7–17)	2 (0–4)
Haloperidol	13 (8–30.75)	50 (34.25–67)	23.5 (14–33)	10.5 (5.75–13.25)	12 8 (16–25)	2.5 (1–6.25)

IQR, interquartile range; NA, not applicable.
None of the differences between the scores in each group are significant.

TABLE 9 *Mean scores for secondary outcomes of quality of life, uplift/burden and adverse drug effects (UKU scale) at baseline*

Treatment	Quality of life total score [median (IQR)]	Uplift total [median (IQR)]	Burden total [median (IQR)]	UKU total [median (IQR)]
Placebo	70 (64–72.5)	14 (11.25–16)	26 (23–29)	3 (1.5–8.5)
Risperidone	69 (57.5–82)	15 (13–16)	26 (23–29.5)	4 (1.5–8)
Haloperidol	66 (58.25–72.5)	13.5 (12–15)	27 (23.25–32.5)	5.5 (1–9.75)

IQR, interquartile range.
None of the differences between the scores in each group are significant.

Passage of patients through the trial

The proportion of patients who dropped out during the trial was much less than had been anticipated in calculating the sample size. All the patients were assessed at 4 weeks, the primary end point of the trial and, at 12 weeks, assessments were made of 21 (72%) of those allocated to placebo, 18 (62%) of those allocated to risperidone and 22 (79%) of those allocated to haloperidol. At 12 weeks, both clinician and patient had the option of withdrawing from the trial, and so it was expected that assessments at 26 weeks would be fewer. Nevertheless, at 26 weeks, full assessments were made of 18 (62%) of those allocated to placebo, 13 (45%) of those allocated to risperidone and 18 (64%) of those allocated to haloperidol. The CONSORT diagram (*Figure 2*) summarises the assessments completed at each time point.

Progress and outcome at 4 weeks

One patient allocated to haloperidol had an acute reaction to the initial dose (2.5 mg) that was clearly not dystonic or ictal, but which led to the patient discontinuing medication at that stage (although assessments continued as normal with the independent researcher). No other patient ceased to take medication in the first 4 weeks. The dosage of drugs was started at a relatively low level but increased steadily throughout the 26 weeks of the study (*Table 10*). Only four patients (allocated to risperidone) were prescribed an increased dose of medication (maximum dosage given = 4 mg) beyond the planned range for the trial (this remains a low dose compared with the usual dosage in psychotic disorders).

Primary outcome

Aggression using the MOAS scale was measured in two ways, by formal face-to-face assessment at 4 weeks and by the analysis of weekly MOAS scores carried out with the key worker at weekly intervals from baseline to 4 weeks. These showed similar findings, but it is instructive to examine the data chronologically over each week of the trial. This is summarised in *Figure 3*.

Assessments at 4 weeks (for all patients apart from one) and at 12 weeks (with dropouts, last observation carried forward) for 25 patients not assessed on the last occasion.

In the first week of the trial the three treatments all had a dramatic effect, with all three associated with a reduction in MOAS (aggression) scores of 70% or greater and with virtually no difference between them (Kruskal–Wallis test between three treatments, $p = 0.95$; Mann–Whitney test between placebo and both drug treatments combined, $p = 0.82$). Between weeks 1 and 4 the patients allocated to haloperidol and risperidone showed a slight increase in aggression, whereas those allocated to placebo maintained their week 1 improvement, so that at 4 weeks placebo was at the point of being significantly more effective. To add precision to the estimate, a quasi-distribution analysis was used with differences between the three treatment groups, using log of baseline MOAS scores, age, gender, and centre as candidate predictors, as well as examining treatment and treatment–centre interaction. At 4 weeks, placebo showed greater improvement when compared in a three-way comparison ($p = 0.078$) and against the two active groups combined ($p = 0.067$). A repeated measures analysis of variance across all weekly time points yielded similar results ($p = 0.074$ in the three group comparison, $p = 0.081$ when compared with drugs combined and $p = 0.063$ with placebo compared with risperidone). The accuracy of the MOAS data was reinforced by the fact that, in the first 4 weeks of the study, all except three of the planned 344 weekly assessments were completed.

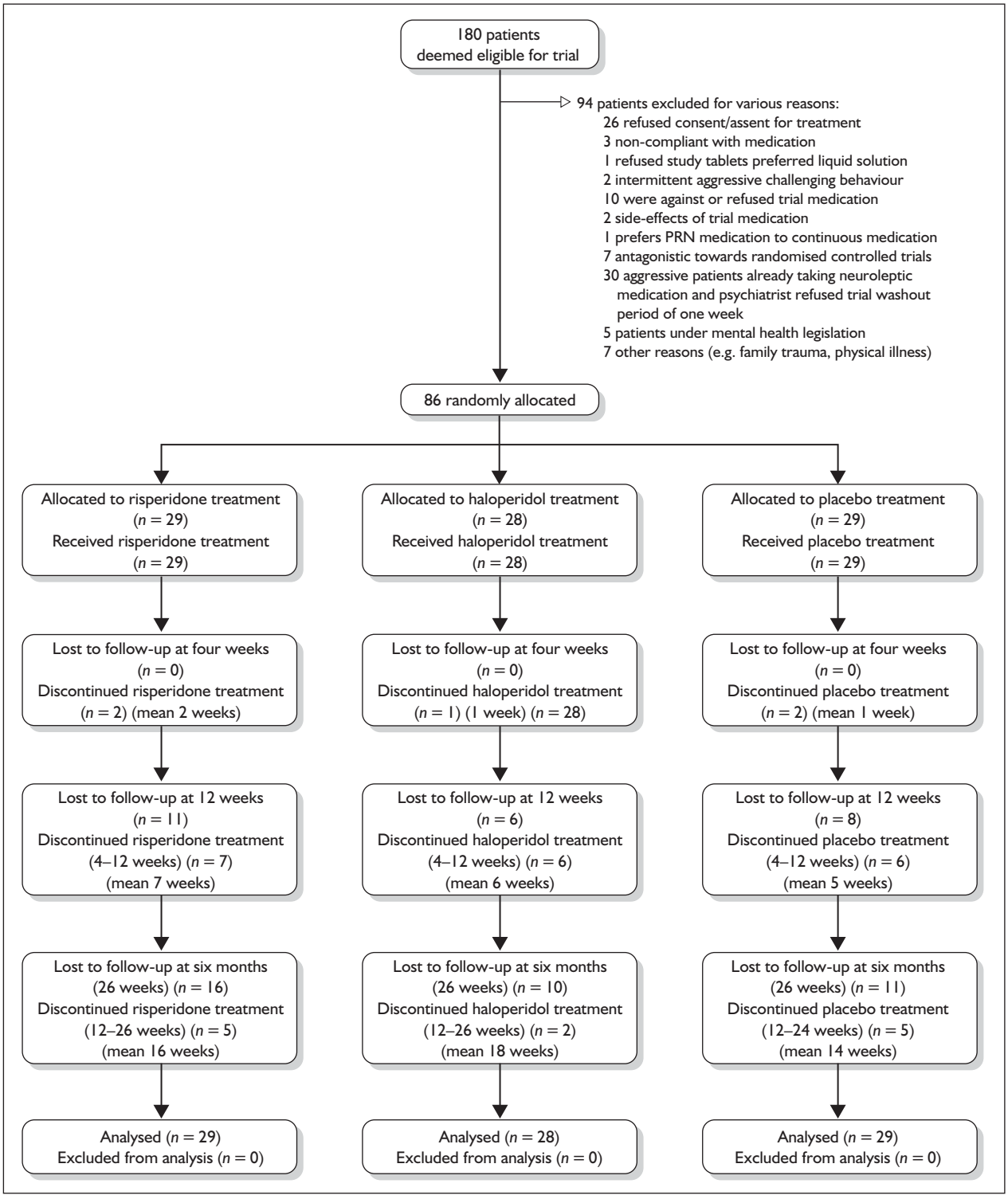

FIGURE 2 *CONSORT diagram summarising the assessments of potentially eligible patients in the trial.*

TABLE 10 *Dosage of medication used in the trial from 0 to 12 weeks*

Period in trial	Range of dosage (mg)	Mean dosage (mg)	Median dosage (mg)
Risperidone			
Initial dosage	0.5–2	1.07	1
0–4 weeks	0.5–2	1.15	1
4–12 weeks	0.5–4	1.78	2
Haloperidol			
Initial dosage	1.25–5	2.45	2.5
0–4 weeks	1.25–5	2.73	2.5
4–12 weeks	1.25–5	2.94	2.5

These data were reinforced by the formal assessment of the MOAS scores at 4 weeks, in which the benefits of placebo were very similar to those shown by the weekly MOAS scores (*Table 11*), with non-significant improvement on total ABC scores.

Additional treatments

The only 'rescue medication' permitted in the trial was lorazepam. This was given to 11 (12.8%) of all patients in the trial in the first 4 weeks with an even distribution between the groups. Thus in the first 4 weeks, three patients (10.3%) allocated to placebo, six (21%) allocated to risperidone, and two (7%) allocated to haloperidol took the drug at some time, and similar proportions [nine (31%) placebo, seven (24%) risperidone and seven (25%) haloperidol] took lorazepam between weeks 4 and 26.

The other additional treatments received by the patients in the study are summarised in *Table 12*. There were no differences in the number of additional treatments, with the exception that those allocated to haloperidol had more occupational therapy and speech and language training in the first 4 weeks.

Secondary outcomes

No differences were found between the three interventions for severity of illness (*Table 13*), global improvement (*Table 14*) (both using the CGI) and Quality of Life, Uplift/Burden and UKU scales (*Table 15*). However, it is worthy of note that at 4 weeks a higher proportion of the patients allocated to placebo were graded as free from illness (38%), than the 31% on risperidone and 11% on haloperidol. There was also a greater impact of placebo on raising uplift and reducing burden, but

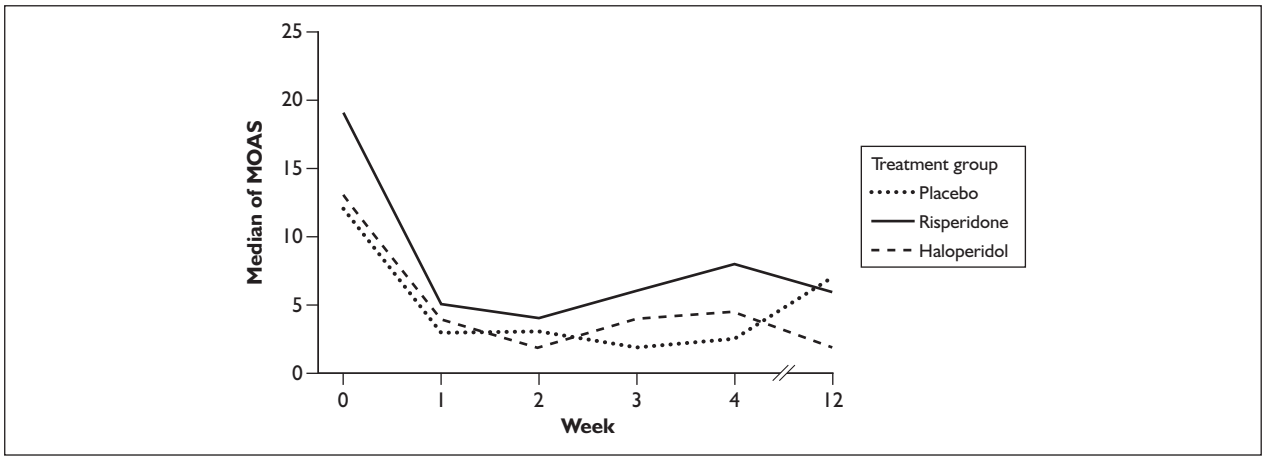

FIGURE 3 *Median weekly aggression scores using MOAS in patients allocated to placebo (n = 29), risperidone (n = 29) and haloperidol (n = 28) at weekly intervals to 12 weeks.*

TABLE 11 *Differences in MOAS (primary outcome) and ABC scores at 4 weeks*

	MOAS [median (IQR)]	ABC (total) [median (IQR)]	Hyperactivity [median (IQR)]	Irritability [median (IQR)]	Lethargy and social withdrawal [median (IQR)]	Stereotypical behaviour [median (IQR)]
ABC factor	NA	NA	1	2	3	4
Placebo	2.5 (0–6.5)	21.5 (11–45)	12.0 (7–22)	2.0 (1–7)	5.0 (4–12)	0 (0–4)
Risperidone	8 (2–22.5)	25 (16–45.5)	11.0 (6.5–26)	3.0 (2–10.25)	8.0 (4–10.25)	0 (0–3.25)
Haloperidol	4.5 (0–19)	35 (20.75–47.5)	16.5 (10.25–26.5)	5.0 (0.75–7.25)	6.5 (1.75–9.25)	1.5 (0–2)
p-value	0.06	0.48	0.523	0.60	0.52	0.95
p-value[a]	0.06	0.27	0.80	0.77	0.35	0.59

IQR, interquartile range; NA, not applicable.
a Placebo versus combined group of risperidone and haloperidol.

this only approached significance (*Table 15*). An interesting non-significant difference was shown with the UKU scores. Placebo scores increased slightly while those of risperidone and haloperidol decreased.

Results at 12 weeks and 26 weeks

The results at 12 and 26 weeks, with a reduced number of patients, showed no important differences between the three interventions. These are summarised in *Figures 4–14*. They show a general trend towards improvement over the full 26 weeks of the trial, but this is not dramatic and the gains made by week 4 are not always maintained at 12 weeks.

Economic analysis of data

The economic analyses were based on data from the CSRI. This instrument was modified slightly for use in a population with intellectual disability, but, as most of the data were obtained from carers and others rather than from the patients themselves, we feel that the data are less subject to bias than is

TABLE 12 *Additional treatments given to patients in the 26 weeks*

Study period (weeks)	Behavioural intervention	Therapeutic sessions	Occupational therapy and speech and language training	Additional medication	Significant differences
Placebo					Only one significant difference: occupational therapy and speech and language training given more often to haloperidol group (0–4 weeks) ($p < 0.01$)
0–4	7	2	0	16	
4–12	5	13	3	11	
12–26	6	1	0	14	
Risperidone					
0–4	6	2	1	16	
4–12	9	18	2	12	
12–26	6	1	2	7	
Haloperidol					
0–4	11	5	6	13	
4–12	7	22	1	14	
12–26	5	3	2	10	

TABLE 13 *Severity of illness at 4 weeks by treatment group*

	Severity of illness [*n* (%)]						
Treatment	**Not assessed**	**Normal**	**Borderline mentally ill**	**Mildly ill**	**Moderately ill**	**Markedly ill**	**Severely ill**
Placebo, *n* = 29	0 (0)	11 (37.9)	5 (17.2)	7 (24.1)	3 (10.3)	3 (10.3)	0 (0)
Risperidone, *n* = 29	1 (3.4)	9 (31.0)	6 (20.7)	6 (20.7)	4 (13.8)	1 (3.4)	2 (6.9)
Haloperidol, *n* = 27	0 (0)	3 (11.1)	9 (33.3)	7 (25.9)	6 (22.2)	1 (3.7)	1 (3.7)
There is no evidence of an association between treatment group and severity of illness at 4 weeks ($p = 0.41$).							

TABLE 14 *Degree of global improvement at 4 weeks by treatment group*

Treatment	Degree of improvement [*n* (%)]							
	Not assessed	**Very much improved**	**Much improved**	**Minimally improved**	**No change**	**Minimally worse**	**Much worse**	**Very much worse**
Placebo, *n* = 29	1	2	6	9	6	1	3	1
	(3.4)	(6.9)	(20.7)	(31.0)	(20.7)	(3.4)	(10.3)	(3.4)
Risperidone, *n* = 29	2	2	5	9	10	1	0	0
	(6.9)	(6.9)	(17.2)	(31.0)	(34.5)	(3.4)	(0)	(0)
Haloperidol, *n* = 27	0	1	6	11	7	2	0	0
	(0)	(3.7)	(22.2)	(40.7)	(25.9)	(7.4)	(0)	(0)
There is no evidence of an association between treatment group and global improvement at 4 weeks ($p = 0.63$).								

TABLE 15 *Change in quality of life, uplift and burden and UKU (adverse effects score) at 4 weeks by treatment group*

	Quality of life total score [median (IQR)]	**Uplift total score [median (IQR)]**	**Burden total score [median (IQR)]**	**UKU total score [median (IQR)]**
Placebo	72 (65.75–77.75)	15.5 (12.25–17)	24 (21–27.75)	4 (1–6.5)
Risperidone	70 (60–78)	15 (13–16.5)	24 (21.5–30)	3 (0–8)
Haloperidol	66 (59.5–75.5)	14 (12.25–16)	27.5 (22.25–31)	3.5 (0.25–8.75)
p-value	0.33	0.44	0.18	0.76
p-value[a]	0.24	0.41	0.15	0.64

IQR, interquartile range.
a Placebo versus combined group of risperidone and haloperidol.

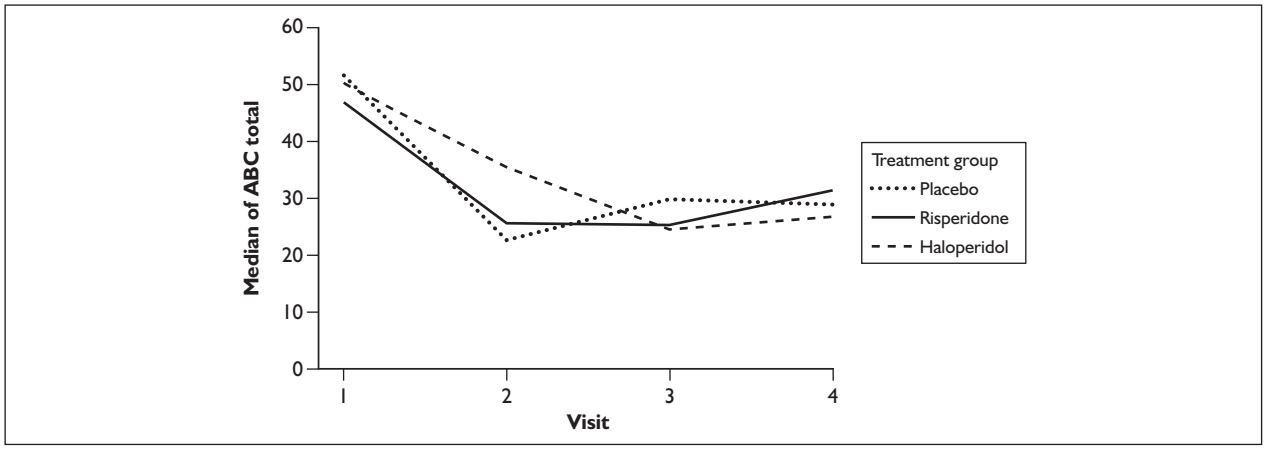

FIGURE 4 *Change in scores on ABC from baseline to 26 weeks by treatment group. Plot based on patients with complete data and compromised by some missing data, particularly for the last two visits (one patient missing week 4 ABC data, six at week 12 and 25 at week 26). Differences between ABC scores at 12 weeks adjusted for baseline differences: placebo vs risperidone* p = *0.453, vs haloperidol* p = *0.418, vs both active drugs,* p = *0.36.*

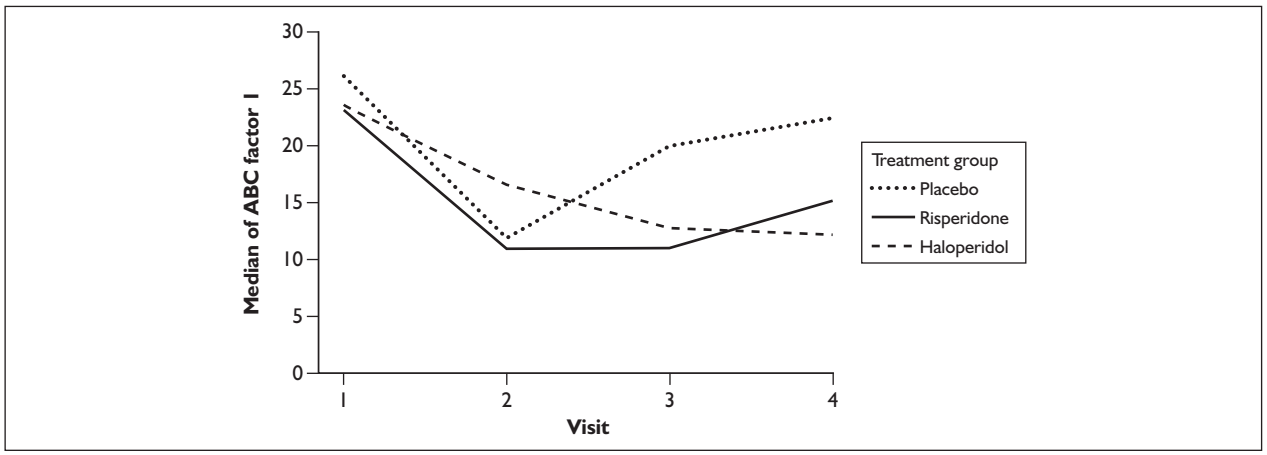

FIGURE 5 *Change in scores on ABC factor 1 (irritability) from baseline to 26 weeks by treatment group. No significant differences at any time point (all* p*-values > 0.3).*

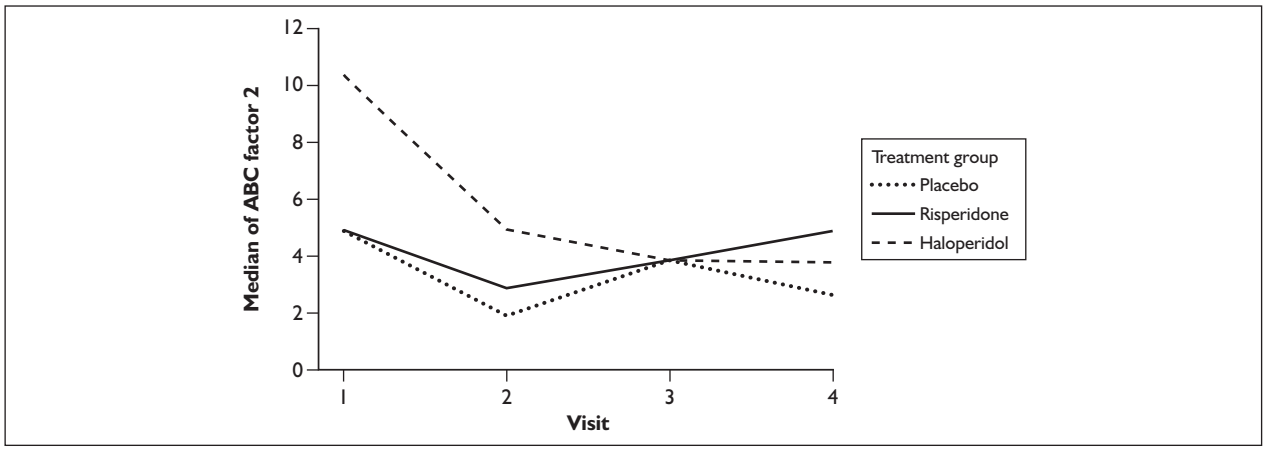

FIGURE 6 *Change in scores on ABC factor 2 (lethargy and social withdrawal) from baseline to 26 weeks by treatment group. No significant differences at any time point (all* p*-values > 0.5). Irritability has been the factor most noted to be influenced by neuroleptic drugs in previous studies.*

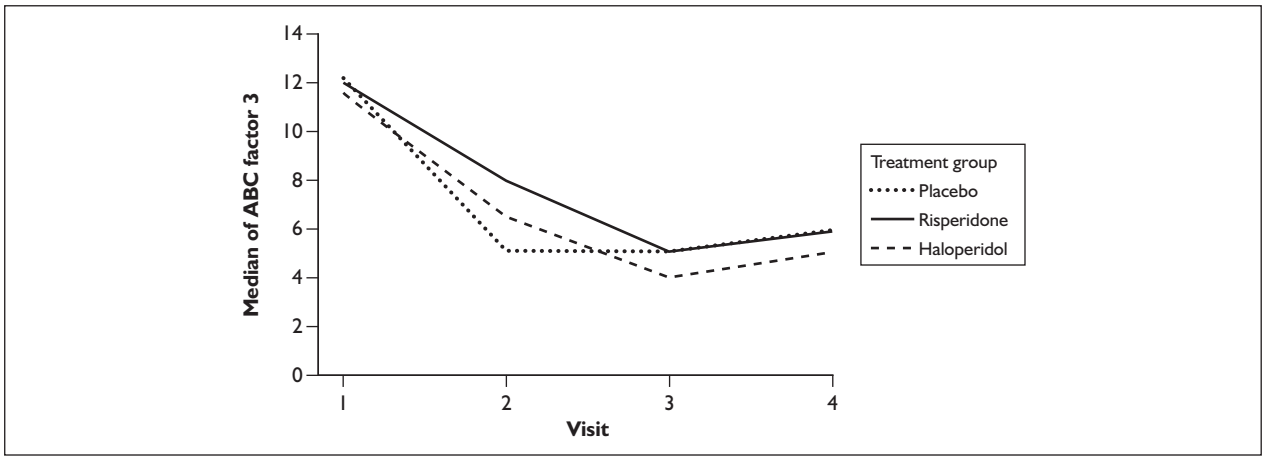

FIGURE 7 *Change in scores on ABC factor 3 (stereotypical behaviour) from baseline to 26 weeks by treatment group. No significant differences at any time point (all* p*-values > 0.3).*

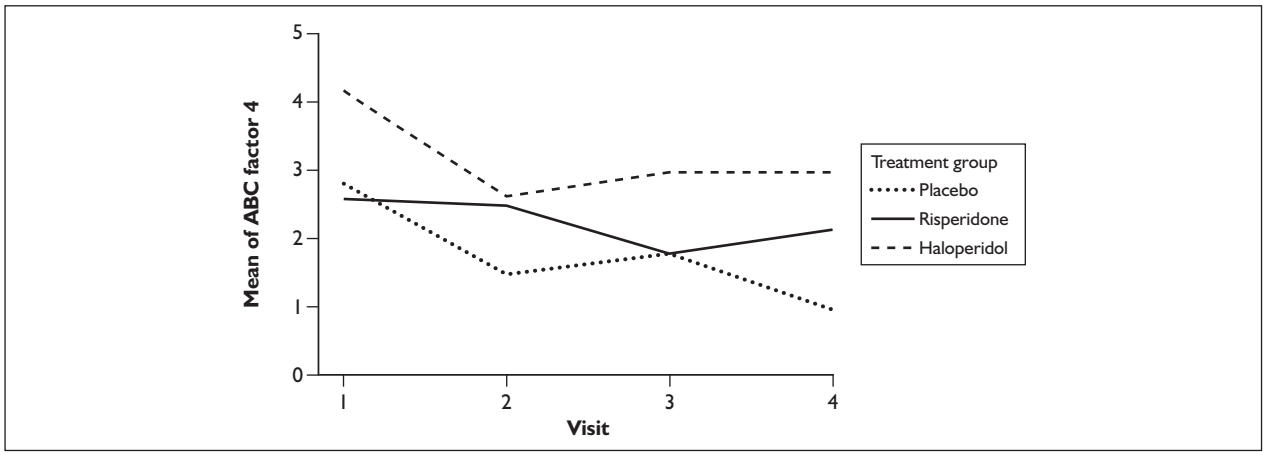

FIGURE 8 *Change in scores on ABC factor 4 (hyperactivity) from baseline to 26 weeks by treatment group. No significant differences at any time point (all* p*-values > 0.25).*

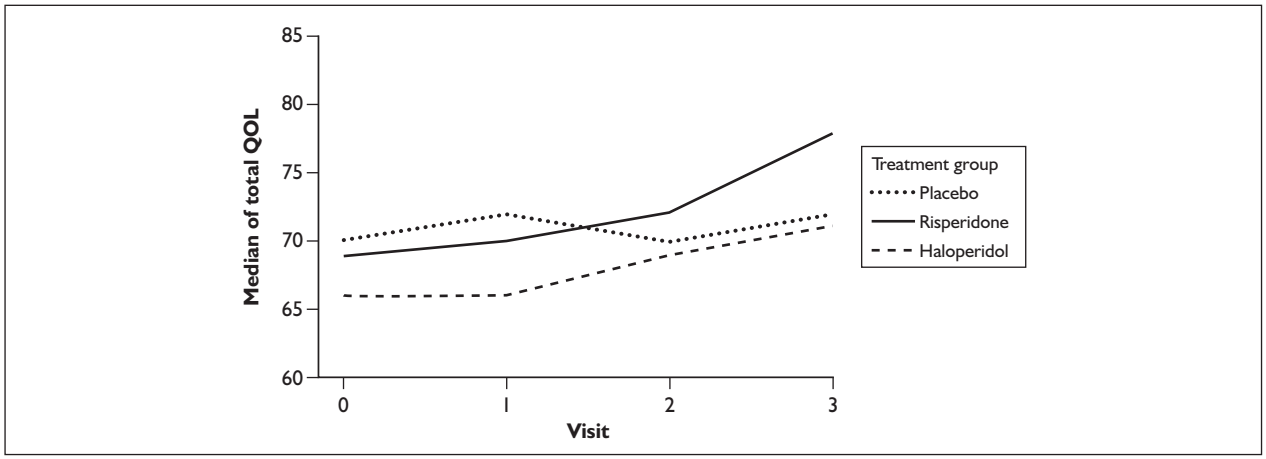

FIGURE 9 *Change in scores on QOL-Q from baseline to 26 weeks by treatment group. No significant differences at any time point (all* p*-values >0.6). Plot based on patients with complete data and compromised by some missing data, particularly for the last two visits.*

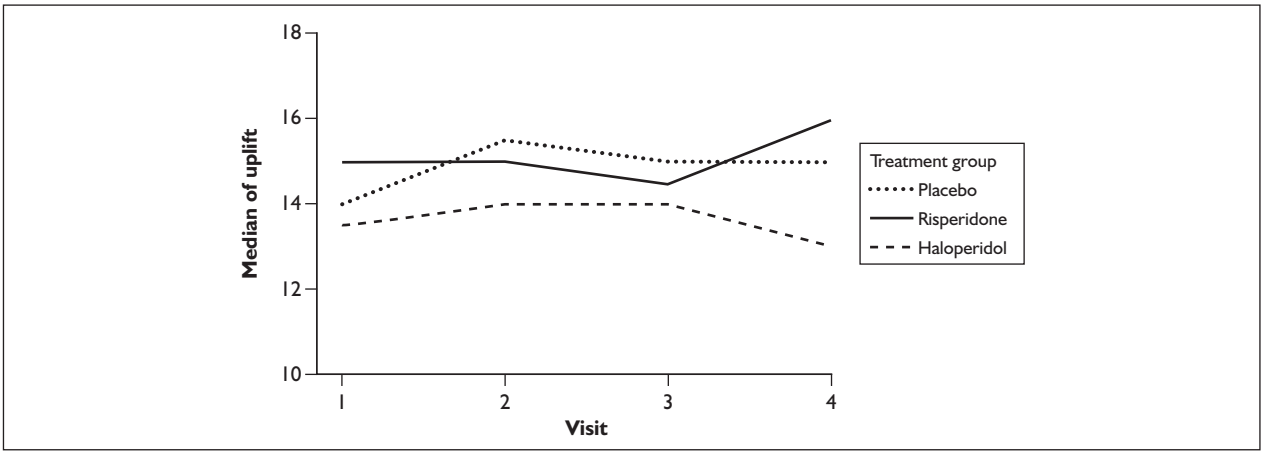

FIGURE 10 *Change in scores on uplift section of Uplift/Burden Scale from baseline to 26 weeks by treatment group. An increase in scores signifies greater uplift. No significant differences at any time point (all* p*-values > 0.6).*

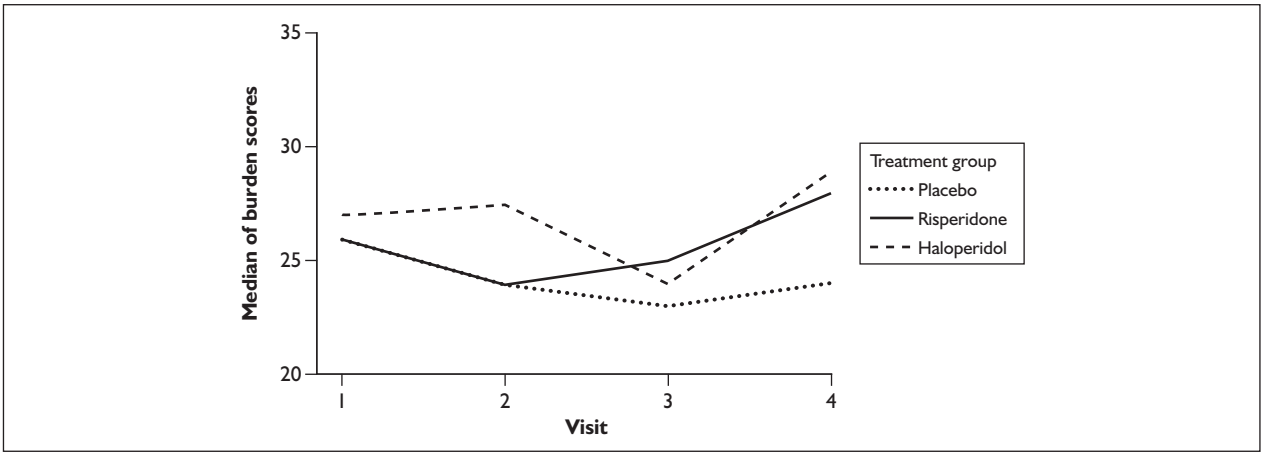

FIGURE 11 *Change in scores on burden section of Uplift/Burden Scale from baseline to 26 weeks by treatment group. A reduction in scores indicates reduced burden. No significant differences at any time point (all* p*-values > 0.4). Plots based on patients with complete data and compromised by some missing data, particularly for the last two visits.*

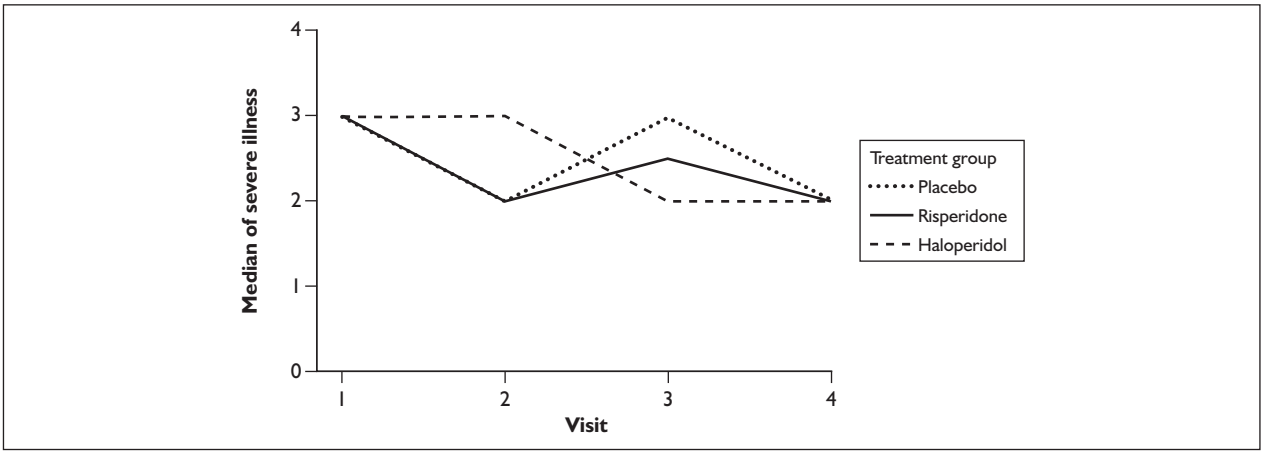

FIGURE 12 *Change in severity of illness scores from baseline to 26 weeks by treatment group. No significant differences at any time point (all* p*-values > 0.5). Note that median scores are the same for all treatments at beginning and end of trial and that a 1-point improvement is found.*

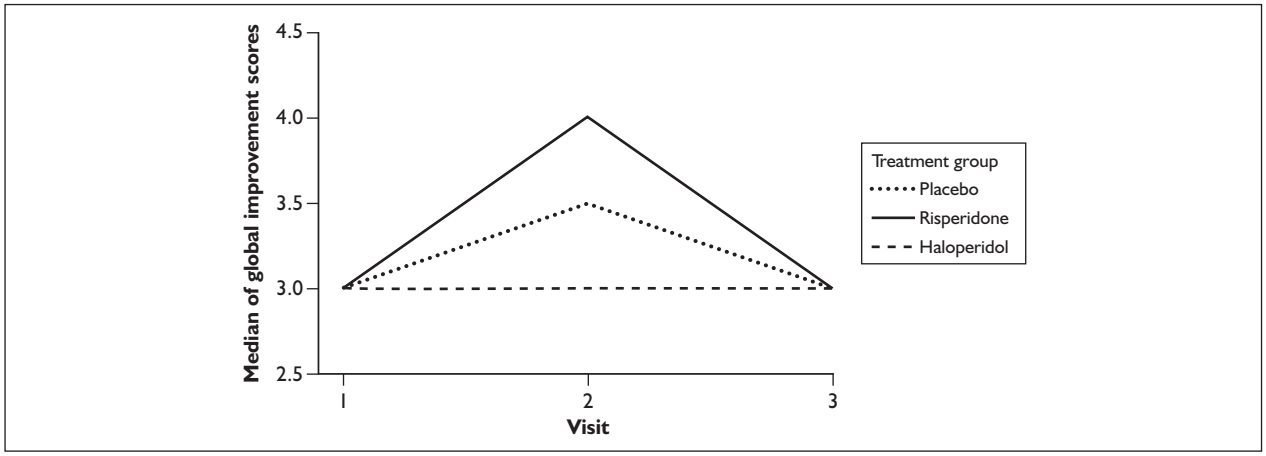

FIGURE 13 *Change in global improvement at 4, 12 and 26 weeks by treatment group. No significant differences at any time point (all* p*-values > 0.4).*

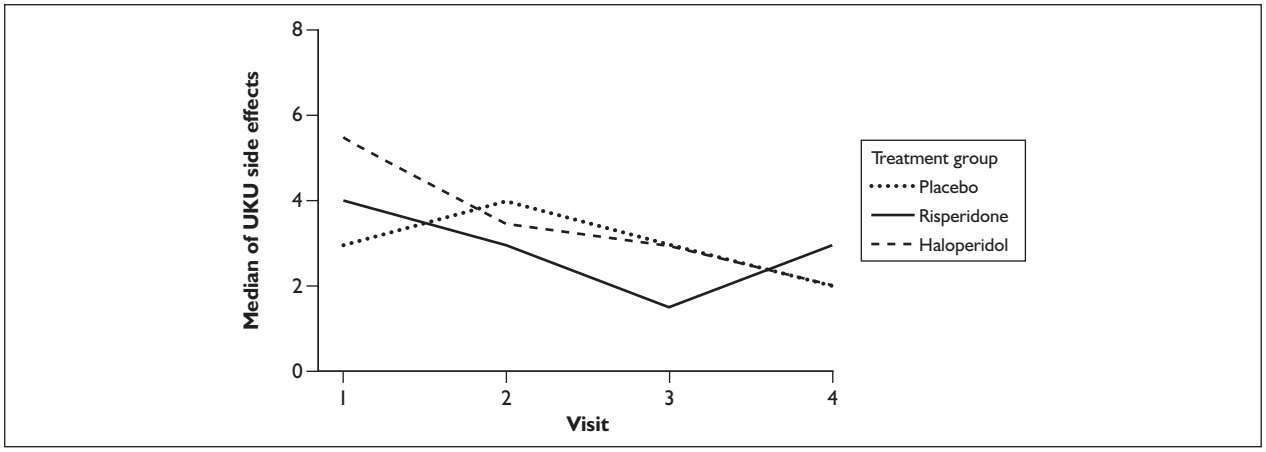

FIGURE 14 *Change in UKU scores from baseline to 26 weeks by treatment group. No significant differences at any time point (all* p*-values > 0.4). Note steady reduction in incidence of adverse effects over time.*

sometimes the case with direct patient interviews. Most of the costs identified were accommodation costs that can also be measured more precisely than many others. The CSRI has been validated for use in two studies in mental health services research. In the first study by Byford *et al.*,[50] the authors found good agreement for overall costs, but GP records provided less reliable information on contacts with other health services. The authors cautioned against reliance on GP records for data collection of hospital services and other community health services. Patel and colleagues[51] found good agreement between the use of GP case records and the CSRI for reporting GP visits.

Although the primary outcome was the change in MOAS score at 4 weeks for the purpose of a full cost-effectiveness analysis, we needed a longer period, and so the assessment at 6 months was compared with the equivalent period at baseline. However, the costs at this time could only be calculated for 58 of these patients (18 allocated to risperidone, 20 to haloperidol and 20 to placebo). There were no significant differences in baseline characteristics for those who were included in the economic analysis compared with those who were excluded. (The 95% confidence intervals were: –4 to 8 for age; –0.2 to 0 for gender; –6 to 16 for total ABC score; –4 to 9 for total MOAS; and –3 to 8 for QOL-Q score.)

Service use and costs

When the three treatment groups are compared, there are no significant differences in total cost, whether comparisons are made after 4 weeks or for the full 26 weeks, and whether service costs only are included, or service and informal care costs are summed (*Tables 16* and *17*).

For the aggregate service and informal care cost per patient, mean differences over the first 4 weeks were: £218 between risperidone and haloperidol, £433 between risperidone and placebo, and £215 between haloperidol and placebo. In each case, the first-named treatment is the more costly. Over the full 26 weeks, mean differences in aggregate service and informal care cost per patient were: £1328 between risperidone and haloperidol, £2618 between risperidone and placebo, and £1290 between haloperidol and placebo. Again, in each case, the first-named treatment is the more costly.

When informal care costs are excluded, so that only treatment and service costs are included, the ranking of costs changes, with haloperidol being less expensive than placebo. However, our cost-effectiveness analyses focus on the aggregate costs, as set out in the original project analysis plan.

TABLE 16 *Costs of treatment, accommodation, services and informal care at 4 weeks and 26 weeks in 58 patients with full economic data*

	Risperidone (*n* = 18)		Haloperidol (*n* = 20)		Placebo (*n* = 20)	
	Mean[a]	(SD)	Mean[a]	(SD)	Mean[a]	(SD)
4-week period						
Treatment [a]	17	–	1	–	0	–
Specialised accommodation	1798	(2028)	1666	(2157)	1901	(1494)
Inpatient care	41	(77)	67	(284)	27	(58)
Day activities	671	(636)	515	(496)	548	(530)
Community-based activities	60	(146)	46	(127)	30	(42)
Total cost of treatment, accommodation and services	2587	(2184)	2295	(2224)	2506	(1521)
Informal care	573	(962)	647	(1216)	221	(693)
Total cost of treatment, accommodation, services and informal care	3160	(2254)	2942	(2151)	2727	(1489)
26-week follow-up period						
Treatment [a]	127	–	8	–	0	–
Specialised accommodation	10,770	(12,147)	9978	(12,923)	11,386	(8950)
Inpatient care	244	(462)	398	(1703)	159	(347)
Day activities	4019	(3808)	3086	(2973)	3286	(3175)
Community-based activities	358	(874)	278	(761)	179	(254)
Total cost of treatment, accommodation and services	15,518	(13,084)	13,748	(13,316)	15,010	(9115)
Informal care	3436	(5762)	3873	(7286)	1326	(4,153)
Total cost of treatment, accommodation, services and informal care	18,954	(13,502)	17,621	(12,883)	16,336	(8918)

[a] Based on a top-down approach used previously in published analyses of cost-effectiveness of medication.[52] Per patient costs were derived using total cost of treatment medication for each treatment group and averaged across medication users. Sample sizes were: 29 risperidone and 28 haloperidol patients for the first 4-week period; 27 risperidone and 27 haloperidol patients during weeks 5–12; 18 risperidone and 20 haloperidol patients during weeks 13–26.
Note that the last of these periods includes the former, so that 4-week costs are included in 26-week figures.

TABLE 17 *Use of health, day and community-based services over 26 weeks*

	Risperidone (*n* = 18)		Haloperidol (*n* = 20)		Placebo (*n* = 20)	
	n **(% using)**	**Mean[a]**	***n*** **(% using)**	**Mean[a]**	***n*** **(% using)**	**Mean[a]**
Hospital care						
Psychiatric admissions (days)	–	–	1 (5)	36	–	–
General medicine (days)	2 (11)	3	–	–	–	–
Psychiatric outpatient appointments	4 (22)	2	1 (5)	1	3 (15)	5
Other outpatient appointments	6 (33)	2	1 (5)	1	4 (20)	2
A&E visits	3 (17)	1	1 (5)	1	2 (10)	1
Day hospital appointments	–	–	1 (5)	1	–	–
Day activities						
Day centre (hours per week)	10 (56)	25	10 (50)	17	10 (50)	25
Social club (hours per week)	12 (67)	5	9 (45)	4	9 (45)	2
Adult education (hours per week)	5 (28)	14	6 (30)	13	7 (35)	12
Voluntary work (hours per week)	1 (6)	2	–	–	–	–
One-to-one activities (hours per week)	6 (33)	4	6 (30)	9	5 (25)	3
Community-based care						
GP contacts	13 (72)	2	8 (40)	2	14 (70)	2
Community psychiatrist contacts	5 (27)	2	3 (15)	1	3 (15)	2
Community psychiatric nurse contacts	–	–	–	–	–	–
District nurse contacts	–	–	–	–	–	–
LD nurse contacts	4 (22)	12	5 (25)	3	4 (20)	3
Other community nurse contacts	–	–	1 (5)	1	1 (5)	1
Social worker contacts	6 (33)	5	9 (45)	3	4 (20)	2
Chiropodist contacts	6 (33)	2	6 (30)	2	6 (30)	2
Counselling contacts	2 (11)	7	2 (10)	32	–	–
Psychologist contacts	4 (22)	9	2 (10)	2	3 (15)	42
Speech and language therapist contacts	1 (6)	1	2 (10)	3	–	–
Home help contacts	1 (6)	4	2 (10)	51	2 (10)	13
Dentist contacts	7 (39)	1	10 (50)	1	10 (50)	1
Optician contacts	1 (6)	1	10 (50)	1	10 (50)	1
Physiotherapists contacts	–	–	1 (5)	1	–	–
Occupational therapist contacts	–	–	1 (5)	3	–	–
Art therapist contacts	–	–	1 (5)	13	1 (5)	10
Alternative therapist contacts	1 (6)	1	1 (5)	9	–	–

A&E, accident and emergency; GP, general practitioner; LD, learning disability.
a Mean units of use (e.g. appointments or sessions) for users only.

The largest single contribution to the total cost of care and support was specialised accommodation (57% for patients treated with risperidone, 57% for patients treated with haloperidol and 70% for placebo patients). High day service utilisation rates were found (see *Table 15*) and this finding is common for people with intellectual disabilities, particularly when the individual also exhibits challenging behaviour. Consequently, these day activity services contributed quite high proportions

to total cost (21% for risperidone patients, 18% for haloperidol patients and 20% for placebo patients). There were low utilisation rates for inpatient and community-based services (see *Table 2*) and small contributions to total cost (3% for risperidone patients, 4% for haloperidol patients and 2% for placebo patients).

To examine the responsiveness of costs to changes in informal support unit costs, sensitivity analyses were performed. The effects of two scenarios on the total cost of care and support per patient were examined.

The two scenarios for the first sensitivity analysis involved changing the estimate of the minimum wage for care provided by formal and informal carers to: (1) unit cost of independently provided personal home care based on the average of weekend and weekday hour prices in the North (£10.50); (2) unit cost of independently provided home care based on the average weekend and weekday hour prices in the South (£12.75).

In both scenarios there were very few changes in the total mean cost of care and support to patients in the treatment groups. If support was contracted out to independent providers or patients purchased informal support for an independent provider in the North of England, the mean difference in total cost increased across all patient groups by £3707 for risperidone patients, £4181 for haloperidol patients and £1431 for placebo patients. In the second scenario, total costs rose for all patients by £5243 for patients on risperidone, £5907 for patients on haloperidol and £5617 for patients on placebo.

Cost-effectiveness analyses

As noted earlier, the primary outcome for the cost-effectiveness analysis was aggression as measured by the MOAS at the 26-week follow-up point, and the secondary outcome was quality of life as measured by the QOL-Q at the same point. Costs were measured so as to range over all services and informal care.

When costs over the 26-week period are ranked, placebo has a lower cost than the other treatments. In terms of the MOAS measure at this point, the mean score was highest (indicating worst aggressive behaviour) for risperidone patients and lowest for haloperidol patients. In terms of the QOL-Q measure at 26 weeks, the mean score was highest (indicating better quality of life) for risperidone patients and lowest for haloperidol patients. An extended dominance approach was used. This meant eliminating risperidone from the primary cost-effectiveness analysis based on MOAS, and eliminating haloperidol from the secondary cost-effectiveness analysis based on QOL-Q. An ICER was calculated for each analysis, comparing haloperidol and placebo in the primary analysis, and risperidone and placebo in the secondary analysis.

The estimated ICERs are as follows:

- Haloperidol costs £645 more than placebo for each additional point difference on the MOAS.
- Risperidone costs £1245 more than placebo for each additional point difference on the QOL-Q.

We are not aware of any previous research that has computed cost-effectiveness ratios using MOAS or QOL-Q for this population of people, and so cannot comment on whether these incremental ratios are high or low.

Given the uncertainty surrounding the estimation of the ICERs, we plotted the CEACs to examine the probability that, first, haloperidol would be seen as more cost-effective than placebo for different implicit monetary values attached to improvements in aggressive behaviour and, second, risperidone would be seen as more cost-effective than placebo for different implicit monetary values attached to improvements in quality of life. We are not aware of any previous studies that have attached (implicit) monetary values to incremental changes in MOAS or QOL-Q. We explored values ranging from £0 to £3000 per unit improvement. The CEACs are shown in *Figures 15* and *16*.

The likelihood of haloperidol being more cost-effective than placebo is just over 50% if society is not willing to pay anything for an improvement in aggression score (a decline in aggression), but the probability only climbs noticeably above 50% when quite implicit values are attached. If society were willing to pay £3000 for each point improvement in MOAS score – which is a very substantial amount – then haloperidol would have a probability of around 89% of being cost-effective.

Turning to the secondary cost-effectiveness analysis, the probability of risperidone being more cost-effective than placebo is 52% if society is not willing to pay anything for an improvement in quality of life, and remains unchanged even

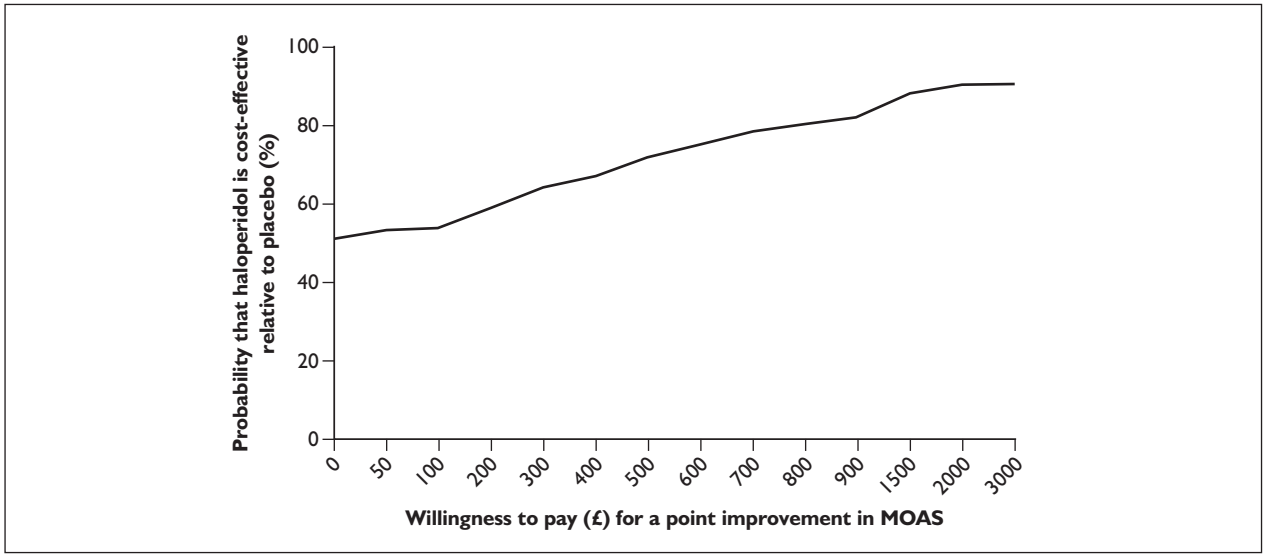

FIGURE 15 *Probability that haloperidol is cost-effective relative to placebo at 26 weeks using MOAS as outcome measure.*

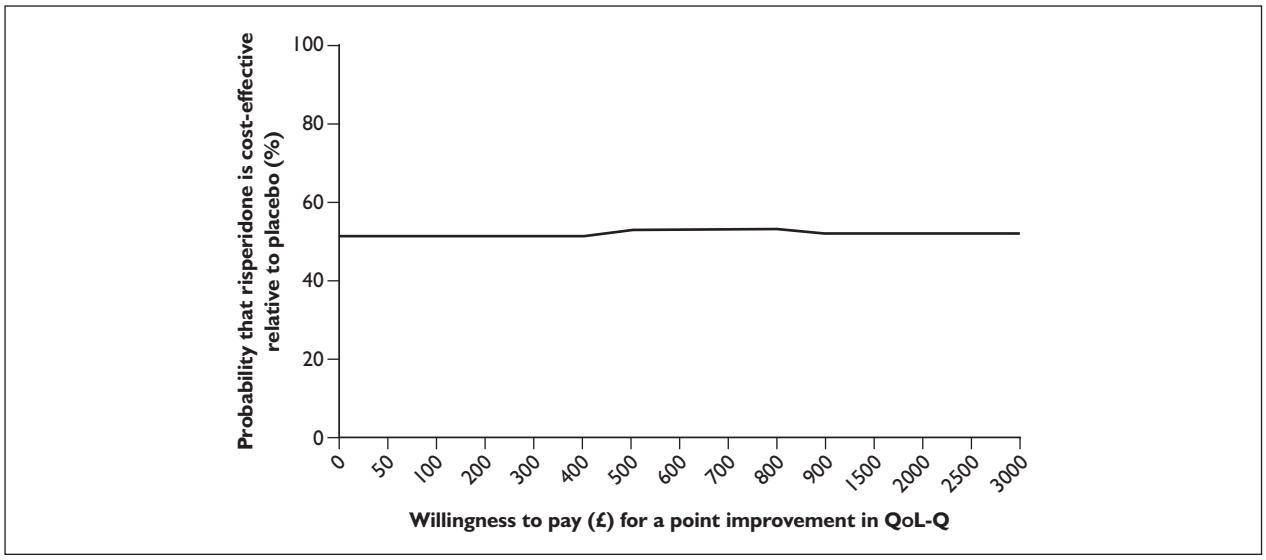

FIGURE 16 *Probability that risperidone is cost-effective relative to placebo at 26 weeks using QOL-Q as outcome measure.*

when higher values for the willingness-to-pay are explored.

From these analyses, we conclude that placebo is more cost-effective than either risperidone or haloperidol.

The economic analyses suggest that risperidone and haloperidol are not dominant treatment choices over placebo over 26 weeks when service implications, costs and effects on aggression and quality of life associated with treatment are considered. Acquisition costs of the newer neuroleptic drugs such as risperidone tend to be considerably higher than those of conventional neuroleptics. In the UK, the costs for 1 month of treatment with risperidone 4 mg/day and haloperidol 10 mg/day are £101 and £4.57 respectively.[14] The costs are inevitably lower as the dosages decrease for services users with learning disabilities. In this study, service users were administered initially with 1 mg risperidone daily or 2.5 mg haloperidol daily (or even smaller dosages as required), with an increase if necessary up to 2 mg risperidone; the average monthly cost per service user is £17 for risperidone and £1 for haloperidol. Medication costs per person are low and constitute a small proportion of the total costs,

but, when assessed alongside the lack of an impact on aggression and quality, may signal the need for spending on more cost-effective interventions.

Furthermore, unlike treatment of service users with schizophrenia, where treatment by risperidone can result in decreased need for hospitalisation and administration of drugs to reduce extrapyramidal symptoms, our findings suggest that there is no such impact on hospital service use as there were no significant differences in the cost of inpatient services.

An investigation into the problems of recruitment with NACHBID

Introduction

It is a common experience that randomised trials of treatments in intellectual disability are difficult to mount, and the NACHBID study was no exception, with less than half of the expected patients being recruited in the initial 2 years of the trial. The results proved to be of great interest because the findings were clear cut;[53] this was fortunate as less definite results would inevitably have led to criticism that the study was underpowered. Because the problem of under-recruitment was a constant theme throughout the trial, we felt it was wise to investigate the reasons for this after the NACHBID study had been completed and the results were known. It must not be assumed, however, that the problems of recruitment are exclusive to trials in intellectual disability. An epidemiological study carried out by Campbell *et al*.,[54] on behalf of the MRC and NHS Health Technology Assessment programme of the trials, showed that only 31% of multicentre trials out of 114 trials that had been funded between 1993 and 2000 actually recruited to 100% or above of the target sample.

We nonetheless decided that the special problems of recruiting into trials in those with intellectual disability was justified using both qualitative and
[9] quantitative methodology.

Design

All 34 clinicians who had registered an interest in recruiting patients for the NACHBID trial were invited to participate in the research. A structured questionnaire, adapted from one originally used to evaluate the recruitment for a previous large, pragmatic randomised trial of maintenance treatment in bipolar disorder (BALANCE),[55] was used. This had the advantage that our results could be compared with those from BALANCE to see if there were consistent differences. The 63 statements from the BALANCE structured questionnaire were reduced to 44, 19 being removed because of their specific relation to BALANCE. The remaining statements were categorised under the following headings:

- general attitudes towards RCTs
- RCTs in psychiatry
- trial participants
- deterrents to recruitment
- the effects of anticipated outcomes for clinicians and patients
- the practical aspects of RCTs
- clinician's previous participation in RCTs
- other factors and additional comments.

Responses were given on a five-point Likert scale, as 'Strongly agree', 'Agree', 'Uncertain', 'Disagree' or 'Strongly disagree' except for the deterrents to recruitment section, which was changed to 'A major deterrent', 'A deterrent', 'Uncertain' or 'Not a deterrent'.

The 34 clinicians were approached initially by email and this was then followed up by telephone calls. Nevertheless, a large number of the clinicians did not respond to the questionnaire or the telephone calls, despite expressing a strong interest in the trial when it was first set up. Our results are therefore incomplete in some respects. Those who were interviewed were asked to elaborate on any points they felt were relevant, and were asked to give further comments at the end of the interview; all their comments were noted.

Most (14/15) of the interviews completed were carried out by Sarah Dickens, who had not previously been involved in the NACHBID study, and who was blind to the individuals' levels of recruitment.

Data analysis

Nine of the questionnaires were completed over the telephone. The questionnaire was emailed to the remaining 25 clinicians linked to the NACHBID study, six of whom responded. Only one of the non-responding clinicians had recruited a patient.

Analysis of quantitative data (Likert scale)

Information on clinicians

Of those who responded, nine were male and six were female, the first completing their psychiatric training in 1978 and the last in 2007 (*Table 18*).

TABLE 18 *Time qualified by recruitment status*

Length of time qualified	Recruited participants to NACHBID	
	Yes	No
0–5 years	1	4
6–10 years	1	2
11–15 years	2	3
15–19 years	0	0
20 years and over	2	0

Is there a difference between the responses of recruiters and non-recruiters?

A chi-squared test was used to compare the responses given on the Likert scale. Very few significant differences were seen, with only three items showing significant or near-significant differences (*Table 19*).

When the responses between BALANCE and NACHBID clinicians were compared, only the statements identified in *Tables 20* and *21* showed any marked differences.

Those questioned about NACHBID were more sceptical about RCTs, with only 20% believing that patients in trials have better outcomes, compared with 47% of respondents in the BALANCE study. Perhaps unsurprisingly, 80% of the consultants in intellectual disability felt that patients would not be able to understand a trial well enough to give informed consent compared with only 64%

TABLE 19 *Comparisons of responses of recruiting and non-recruiting psychiatrists in NACHBID*

Statement	Results	χ^2	df	*p*-value
Patients are more likely to take a treatment provided in a clinical trial (Agree/Uncertain/Disagree)	More recruiting than non-recruiting psychiatrists agreed with this statement	6.67	2	$p = 0.04$
Obtaining written informed consent is a deterrent (Agree/Uncertain/Disagree)	More non-recruiting than recruiting psychiatrists agreed with this statement	5.00	2	$p = 0.082$
Have you ever recruited a patient to an RCT before? (Yes/No)	Positive responders more likely to be recruiters	3.64	1	$p = 0.06$

df, degrees of freedom.

TABLE 20 *Comparisons of 'Agree'/'Strongly agree' between BALANCE and NACHBID*

Statement	'Agree'/'Strongly agree' [% (*n*)]		Fisher's exact test
	BALANCE	NACHBID	
Patients taking part in trials have better outcomes than those in routine care	47 (125/265)	20 (3/15)	$p = 0.05$
RCTs usually involve a lot of extra work for clinicians	80 (213/265)	54 (8/15)	$p = 0.02$
Some patients cannot understand trials well enough to give informed consent	64 (170/264)	87 (13/15)	$p = 0.09$

TABLE 21 *Comparisons of major deterrents to recruitment between BALANCE and NACHBID investigators*

Statement	'A major deterrent'/'A deterrent' [% (*n*)]		Fisher's exact test
	BALANCE	NACHBID	
Suggesting that a patient takes part in a clinical trial	27 (71/265)	60 (9/15)	$p = 0.01$

in the BALANCE group. It was also apparent that expressing doubt regarding the value of a treatment (i.e. admitting to clinical equipoise) deterred clinicians in intellectual disability from recruiting patients to a greater extent than it did psychiatrists from other fields.

One further interesting, and counterintuitive, difference seems to be the perception of 80% of the interviewed clinicians in intellectual disability who felt that RCTs do not involve more work for themselves, compared with only 60% of BALANCE recruiters. This, perhaps, indicates a higher level of ignorance of controlled trials among clinicians in intellectual disability.

Analysis of qualitative data

As well as capturing data by means of the Likert scale questions, those taking part were encouraged to provide any further comments, either over the telephone or in a separately designated part of the questionnaire. Twelve of the 15 respondents provided further comments from either the interviewer's notes or the clinician's written comments, and these were grouped according to topic. The key themes identified are discussed below.

Value of randomised controlled trials in general

Randomised controlled trials were seen by all the clinicians as 'essential', with 100% of those who carried out the questionnaire agreeing that RCTs are needed.

In general discussions regarding the participants recruited into RCTs, it was noted that, as with all other research which used 'volunteers', the group itself may be atypical in their attitudes and behaviours towards research practices and interaction with the clinicians.

> Patients who are willing to participate are different for more than just the reason that they are taking part in the trial. Their selection potentially indicates they are amenable, less paranoid and less antagonistic. You are therefore automatically selecting a more acquiescent group, and so may be overestimating the true effects.
>
> The evidence gap between psychiatry and other specialities is several generations wide and concerted effort should be made to ensure that standards of care and practice within psychiatry are at least as robust as is found in other medical specialities.

The standard use of placebo treatment in RCTs was discussed further by two of the individuals interviewed; one indicating that it is difficult to convince carers as well as the patients themselves, who are often 'unhappy about the perceived risk of receiving placebo'.

Informed consent

A highly prominent, and probably inevitable, topic raised was that of informed consent (raised by four clinicians in discussion). One said, 'In intellectual disability most do lack the capacity to give informed consent', while another explained that 'The reality of intellectual disability is that patients have a reduced capacity and therefore will always struggle to understand'. It was suggested that you just need to be 'more thoughtful in how you deal with inclusion and consent'.

Complexity of treatment needed with learning disability

There was a general feeling among most investigators that the population recruited to the NACHBID study constituted a more difficult group than is usually involved in trials: 'RCTs are flawed in so many ways with complex groups'. This is not an easy subject to interpret, but the comments made suggested that the general view was that those with intellectual disability need a 'complicated balance of treatments and isolating pharmacology is not looking at the whole picture….' This, of course, is not necessarily

a handicap in undertaking trials; it is their interpretation that is more difficult.[56] However, one clinician was more hopeful, suggesting that 'Complex interventions can be evaluated in RCTs if you supplement them with qualitatively based research' and that this complexity of treatment 'doesn't preclude investigation, but some judgement is needed'.

In addition, the 'inability to change medication at short notice' was a handicap that made some clinicians less comfortable with enrolling patients for RCTs. This, however, should not have been a specific problem for NACHBID investigators, as they were given freedom to change the dosage of the randomised medication throughout the duration of the trial.

An interesting point was raised by one clinician, who explained that those put forward for the trials would already be more difficult to treat, and 'only submitting patients where pharmacology is in doubt, and not those where pharmacology is balanced' therefore biased the sample recruited. (As the evidence base is limited here, it is not clear how situations where 'pharmacology is balanced' are identified.) As, in the NACHBID study, all treatments other than neuroleptics were allowed, the restriction of drug treatment should not have hampered these particular clinicians. Interestingly, one non-recruiting clinician interviewed went on to say that 'my answers would be different from the perspective of a psychiatrist in intellectual disability and that of a general psychiatrist'.

Recruitment process

Some of the more general comments concerning the processes involved in NACHBID were:

> Recruiting patients into NACHBID was difficult. Support by local and national resources was superb. It was a pity more patients could not be found.

> Obtaining local ethics approval took an awfully long time. It went to both Norwich and Cambridge and by the time approval was given, there was only a short time before the trial finished and I was unable to recruit in this period.

One clinician even confessed that he 'often forgot about the trial'.

Implications

Owing to the small sample size, it would be inappropriate to make too many assertions based on this information; however, perhaps the response to the questionnaires was itself indicative of the nature of working in the intellectual disability field. Although conclusions drawn were limited, with few significant differences seen between recruiters and non-recruiters, it is worth noting that, similar to the results of the BALANCE review, clinicians were more likely to recruit if they had recruited to trials previously, a useful point when planning the outcome of future trial recruitment.

It would be interesting to know whether it was assumed by the clinicians who recruited poorly or not at all that the NACHBID trial was not going to provide any useful results. Certainly some who were most sceptical at the beginning of the trial said that it was 'answering the wrong question'. The results of the study clearly called into question the use of neuroleptics as a routine treatment in those with aggressive behaviour who have intellectual disability,[53] but at the time many thought that the value of these drugs had already been proven. Thus, comparing the value of these commonly used drugs with placebo may be seen, at best, to be a waste of time and, at worst, to be unethical and dangerous. We believe that the results of the study show that it was, indeed, addressing an important clinical question, but if the non-participating clinicians did not, it could at least partly explain their poor performance. This is highlighted in Ross *et al.*'s[57] study of barriers to participation in RCTs, which found that one of the key aspects of recruitment was for your study to be seen to be addressing an important question.

It should be remembered that to have such low levels of recruitment is not specific to the NACHBID study, and the fact that the focus was on such a complex population could be expected to further hamper recruitment. As one interviewed clinician summarised, 'Studying learning disability is like playing Jenga. It's an especially complex balance of treatments and therapies and doctors would be reluctant to remove one of these "bricks" in case the whole tower falls down'.

Some comment should be made about the 19 clinicians who were involved in the trial but did not take part in this analysis of reasons. Only one of these had recruited a patient. This leaves 18 clinicians who had expressed an interest in the study and had often attended training days,

and who not only did not recruit during the 4 years of the trial but also did not take part in the recruitment exercise. It is difficult to draw any conclusions in the absence of data, but it is a significant waste of resources to train such a large number of 'sleeping' clinicians who play absolutely no part in the research exercise. Greater expectation might be built into similar trials in the future, with possible sanctions for those who remain totally inactive at all stages of the project.

Chapter 5
Discussion

Introduction

Before describing the implication of the results, it would be useful to summarise some of the difficulties in mounting and completing this trial. The original intention was to recruit all the eligible patients within 2 years, but, despite the trial being extended by 20 months, the total recruited was still less than that planned. This reflects the particular difficulties of the population being studied and is a matter of concern for those mounting similar trials in the future. Ross *et al.*[57] have described the most common problems in failure to recruit: lack of time (10%), inadequate staff and training (14%), impact on doctor/patient relationship (14%) and concern for patient welfare (12%). This study covered all medical interventions, and relatively few were in mental health. In the NACHBID study we found the difficulties over consent and concern over patient welfare to be the dominant issues in reducing failure to recruit. The fact that 57% of all patients were recruited by only four consultants, and that over 50 consultants in active practice expressed a willingness to take part but did not recruit a single patient, shows that it is not the absence of suitable patients that was the barrier to the trial, but the commitment to take part and the determination to overcome the many barriers to randomisation.

The investigation of recruitment problems showed that several specific factors inhibited the involvement of clinicians: (1) inexperience in recruitment; (2) lack of equipoise in a therapeutic area where, until now, dogmatic assertion has been king; (3) a preoccupation with concern over the philosophy of randomisation that leads to paralysing timidity; and (4) great nervousness about withdrawing neuroleptic medication from patients who appeared to be stable. While it is understandable that some clinicians felt that the research question was inappropriate as the value of neuroleptic drugs had already been demonstrated, and others refused to take part as the trial included a 'dangerous drug', haloperidol, which 'should have been banned long ago', it is sad when such views seem to constitute the majority. However, by far the greatest concern was over the process of randomising patients who were vulnerable and in many instances lacked the ability to consent, thus transferring all the responsibility for consent to the carer or health professionals who were often ill-prepared for such a difficult decision. Thus, a care home manager felt unable to make a decision over the randomisation of one patient and referred it to the Department of Health, and the mother of another patient, despite having to give up her job to look after her disabled daughter after she had been excluded from a day centre, could not tolerate the responsibility of making a decision about medication in any form as she felt that this was unfair on her daughter.

In this context it is fair to add that official guidance is so worded that taking part in such trials is almost impossible to justify if all aspects of the guidance are followed strictly. Thus, the European Parliament's recommendation on good clinical practice in the conduct of clinical trials[58] recommends that those incapable of giving consent have to be given special protection and 'may not be included in clinical trials if the same results can be obtained using patients capable of giving consent' (paragraph 3). An additional requirement is that 'normally these persons should be included in clinical trials only when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient, thereby outweighing the risks' (paragraph 3). For psychiatric patients these restrictions become even greater, so that 'normally' is omitted and the wording becomes 'medicinal products for trial may be administered to all such individuals only when there are grounds for assuming that the direct benefit to the patient outweighs the risks' (paragraph 4). The encouragement to obtain similar data from people able to give consent rather than testing this vulnerable group is reinforced by the statement that 'inclusion in clinical trials of incapacitated adults who have not given or not refused informed consent before the onset of their incapacity, shall be allowed only if such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods and relates directly to a life-threatening or debilitating clinical condition from which the incapacitated adult suffers' (Article 5). If these requirements had been

followed to the letter we would not have had ethical approval for this trial of a problem that (1) was not life-threatening; (2) could not be regarded as debilitating in most instances; (3) involved a placebo control that would allow the conclusion that 'the direct benefit would outweigh the risks'; and (4) could in theory be tested on those with greater capacity to consent, such as those with borderline intellectual disability only.

Ethical considerations

The NACHBID team had to undergo serious criticism from several quarters at different times in the trial because of ethical objections. An article written by a member of the group People First and published in *Community Care* under the title 'No grounds for testing',[59] described the NACHBID study and stated:

> The biggest surprise about all this, whatever the study's outcomes, is that no one seems outraged about the tests except for some of our group. We are so good at 'caring for' people but there is an element of control in caring for. What about 'caring about'? In this case it seems to be lacking. Do we really care enough about these issues to make sure that people are not being used by others? This drugs test situation may be a long-term issue that needs looking at. It will need people to address it who truly care about their fellow humans. If this were about lesbian and gay rights or a physical disability or race issue, many people would be actively demonstrating against the injustice. Are people with a intellectual disability the only minority group left where injustice and inequality are accepted on a daily basis? Are they still excluded enough from mainstream life that they are not thought about by those outside of the intellectual disability world? The only thing that bad practice needs to grow is for good people to do nothing.

In responding to this the NACHBID group were able to publish an endorsement from the main charity for the intellectually disabled, MENCAP, for the study and also replied to this criticism in the same journal:[60]

> There are serious implications should the trial not be completed. Those who think that such trials are an abuse of those with intellectual disabilities may see a failure to complete the trial as a triumph of good sense. But the likelihood is that it would also mean that no other large-scale trials would take place in the treatment of intellectual disabilities in the UK for many years. This would mean that people with intellectual disabilities who take neuroleptic drugs for aggressive challenging behaviour would be using them without sufficient knowledge. It would not be known whether the drugs were effective, at what dose they should be given and for how long. As it is, many of those taking the drugs continue to do so because those involved with their care are reluctant to stop them, even though it is suspected that very few conditions which present as challenging behaviour need long-term drug therapy.

It is ironic that those who have been most vociferous in attacking the trial, by criticising the use of drugs for aggressive challenging behaviour, will be those most pleased by the results. While nobody disputes the good intentions of those who are concerned that the abuses of the past in clinical trials are not repeated,[30] it does appear that, if those with intellectual disability are not to become disenfranchised from the conclusions of evidence-based medicine, a redrawing of the ethics of trials in this vulnerable population needs to be undertaken by those who are responsible for the main treatments,[61] and this is likely to need contributions from psychiatrists, psychologists, carers and patients as well as ethicists.

Recruitment levels

Other ways of improving recruitment to randomised trials will need to be considered if the evidence base for interventions is to be improved. NACHBID cost £11,000 per recruited patient and covered an unnecessarily large geographical area for a condition that is recognised as common. Currently, only the pharmaceutical industry is able frequently to mount trials of this expense, and the results of such studies are much more likely to be positive than those of independent trials.[62] However, once recruited, most of the patients were very happy to stay in the NACHBID trial. Other approaches, such as cluster randomisation of accommodation units for those with intellectual disability, may also be ethically justified and appropriate for this population, and, although requiring a larger number of participants than equivalent trials of individual randomisation,[63] may lead to much greater recruitment levels.

Findings versus current practice

The results show that in the NACHBID trial there were no significant important benefits conferred by treatment with either risperidone or haloperidol in the treatment of aggressive challenging behaviour compared with placebo, and treatment with these drugs was not a cost-effective option. This finding conflicts with current practice, and several arguments could be put forward by those who claim that these drugs are effective. These include: (1) inadequate numbers in the trial to demonstrate efficacy (Type II error); (2) inadequate dosage of active drugs; (3) the trial population was unrepresentative; (4) masking of the effects of the active drugs by rescue medication with lorazepam; and (5) the measures were not sensitive enough to detect change in aggressive behaviour. Each of these will be examined but, first, exactly what was achieved by placebo medication in the trial should be emphasised. All three drug preparations reduced aggression by a around 72% in the first week – equivalent to reducing aggression from persistent abuse, slamming of doors and threatening behaviour to a degree of verbal abuse only – but only placebo maintained this benefit over the 4-week period. In other words, the placebo effect (or other interventions linked to it) was maintained instead of being lost after around 2 weeks, as is commonly seen in those of normal intelligence.

Inadequate numbers

Although the trial did not recruit as many patients as planned, the findings did not show any trends towards superiority of the active drugs. The opposite was the case; such trends that were found favoured placebo, except later in the trial (after 7 weeks), when there was some very slight evidence of greater benefit with haloperidol. If the same effect sizes had been found in a sample of 172 patients – twice the sample size of the study – placebo would have been significantly superior to both neuroleptic drugs on many variables for many of the variables assessed at 4 weeks, and this would at the outer limit of the acceptability time scale for treatment efficacy of a behaviour that is causing acute problems.

Inadequate dosage

The mean dosages of the drugs used in the trial were relatively low and, probably as a consequence of this, there were no differences between them and placebo in the incidence of extrapyramidal adverse effects as measured on the UKU scale (which showed a steady reduction throughout the 26 weeks). It is reasonable to conclude that the findings would have been similar if higher dosage had been used throughout (although the presence of adverse effects might have increased the chances of placebo superiority). Certainly the prescription of higher doses of haloperidol, in particular, would not have been tolerated by most of the clinicians involved in the trial.

Representativeness of trial population

The trial took nearly 4 years to recruit 86 patients, and clearly there were many times more than this number being treated for aggressive challenging behaviour in the services concerned. Could there have been selective referral of less severe cases of aggressive challenging behaviour or some other bias that caused the population being treated to be different? This appears to be unlikely. Of the 180 patients registered for the trial, the 94 who did not take part did not fail to do so because of the severity of their disorder, and the range of disability level (see *Table 3*) and general demographic characteristics were typical of this population. The level of aggression demonstrated at baseline was also quite marked, and, as it took up to 3 weeks to progress from consideration of recruitment to actual randomisation, the aggressive challenging behaviour noted was clearly not a temporary 'adjustment problem'.

The mean MOAS score of nearly 20 for those in the trial also suggests that NACHBID did not have a selected population with little or no aggressive behaviour and that, whatever reservations clinicians had about the trial, when patients were recruited they were exhibiting aggressive challenging behaviour by current definitional descriptions.

Influence of rescue medication

The option of giving rescue medication in the form of lorazepam was felt to be necessary to prevent premature dropout of patients in the trial. Only 11 patients took this drug in the first 4 weeks of the trial, with a similar distribution across the three groups [most to those allocated to risperidone (21%)], so it was unlikely to have influenced the results in any meaningful way.

Insensitive measures

The MOAS was the primary measure used to record aggression, and is a well-validated scale

that has been shown to have good psychometric properties in those with intellectual disability.[46] It also showed significant changes over time (see *Figure 3*) and so cannot rightly be described as insensitive. The ABC has also been found to be sensitive to change in several recent studies of aggressive challenging behaviour, and this too showed considerable variation over time in the NACHBID study. Bearing in mind that all measures failed to show any drug/placebo differences, it is highly unlikely that such differences were there but undetected. The very dramatic fall of 75–80% in aggression scores in the first week of the study (see *Figure 3*) shows that the combination of the intervention of a doctor, medication administration, and extra monitoring and concern constituted a potent therapeutic brew that was quite independent of the pharmacological nature of the prescribed drug. In one sense, the MOAS might therefore be considered too sensitive, as aggression fell most dramatically over the first 4 weeks. The fact that these gains were not maintained subsequently suggests that there were other factors – possibly all related to the so-called Hawthorne effect – where the extra attention given in a randomised trial leads to a somewhat greater response in those with intellectual disability than in those of normal intelligence.

The findings of NACHBID also conflict with recent studies suggesting superiority of neuroleptic drugs over placebo in the treatment of aggressive challenging and autistic behaviours.[64–66] However, there are important differences between the results of these published studies and those of NACHBID. The studies of the Research Units on Paediatric Psychopharmacology Autism Networks in the US,[40,64] a study similar to NACHBID and equally difficulty to mount, showed superiority of risperidone over placebo, but this was with autistic children only and used a somewhat higher dosage of risperidone (2–4 mg/day). The study by Gagiano *et al*.[65] was a pharmaceutical company-sponsored study that used data from four different trials and, despite a positive gloss on the results, demonstrated only a 15% difference between placebo and risperidone on one outcome item that did not appear to be identified in advance as a primary outcome. Haessler *et al.*[66] studied the discontinuation, not the therapeutic, effects of zuclopenthixol after patients with intellectual disability and aggressive challenging behaviour had already been treated with this drug, and so cannot be regarded as an equivalent study.

Chapter 6

Conclusions and implications

The results come at a time in which there is a great deal of activity and concern in the general management of aggressive challenging behaviour in intellectual disability.[67] There is considerable interest in the use of different drug treatments, such as topiramate,[68] and also in psychological treatments in challenging behaviour, with some indications that anger management and cognitive behavioural approaches are effective,[69–72] and developments in these management strategies are likely to be accelerated as a result of our findings.

The results also emphasise the need for research to develop a better evidence base for interventions in intellectual disability. It is unsatisfactory that neuroleptic drugs have been available for over 50 years and been widely used for the treatment of challenging behaviour without good evidence of their value in the adult population. Paradoxically, the use of these drugs in children and adolescents, for whom there are even greater ethical concerns, now has a better evidence base than in adult patients. The question of excessive sensitivity to adverse effects of drugs also needs much more research. It is curious that the common practice of giving low dosage of these drugs, which was by no means universal in the trial, as some practitioners started on a full dose immediately (see *Table 10*), needs urgent review, probably across all areas of drug treatment. While, in the presence of conditions such as epilepsy it is reasonable to be very cautious about initial dosage of other drug treatments, it is not necessarily true for others, and the clear message from the NACHBID trial – that adverse effects of neuroleptic drugs did not rise above baseline over the 26 weeks of increasing dosage in the study – needs to lead to a re-evaluation. We should also emphasise that the results need replication; one swallow of a randomised trial does not lead to an evidence-based summer, and in recommending this are clearly concerned at the likely recruitment problems. We also need similar studies for non-pharmacological interventions, and those which pay particular attention to the environment in the setting of aggressive challenging behaviour, such as nidotherapy,[73,74] are now being tested in controlled studies.

Finally, the general habit of extrapolating from experience in adult psychiatry to intellectual disability in the case of aggressive challenging behaviour is a major matter of concern. The simple fact is that such behaviour does not have an equivalent in adult psychiatry and extrapolation is quite inappropriate. There are many similar areas within the field of intellectual disability where interventions need direct clinical research, preferably using RCTs, and dissemination of these would be valuable in improving clinical practice.

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Contribution of authors

Peter Tyrer was the principal investigator of the NACHBID trial and was involved in planning and supervising the conduct of the study and writing up the report. Patricia Oliver-Africano was the trial co-ordinator from its initiation until September 2005 and was involved in the recruitment of most of the additional centres in the study. Renee Romeo carried out the cost-effectiveness analysis. Martin Knapp supervised the economic arm of the study. Sarah Dickens carried out the recruitment survey after the trial was completed. Nick Bouras was the South London co-ordinator and also advised on the planning and organisation of the trial. Zed Ahmed was the principal investigator at the Wales centre and co-ordinated all referrals there. Sherva Cooray was involved in the initial planning of the trial, organised the referral of many patients in the Brent area of London and helped to recruit other centres. Shoumitro Deb was the co-ordinator at the Birmingham site. Declan Murphy was involved in the planning and design of the trial and in its subsequent organisation. Monika Hare was the research assistant at the Welsh sites. Michael Meade was the main trial co-ordinator from September 2005 onwards and helped in the preparation of the report and analysis. Ben Reece was a research assistant at the North London site. Kofi Kramo was a research assistant at the North London site. Sabyasachi Bhaumik was the Leicestershire site co-ordinator. David Harley was the Queensland site co-ordinator and consultant. Adrienne Regan was responsible for recruiting patients in Harrow and organising the service user contribution from the Harrow forum. David Thomas was responsible for recruiting patients in the Redbridge area of North East London. Bharti Rao was the statistical assistant involved in data entry and data fidelity. Shamshad Karatela was the research assistant at the Queensland site. Laura Lenôtre was the research assistant at the Birmingham site. Joanna Watson was the research assistant at the Leicester site. Theresa Dzendrowskyj was the research assistant at the South London site. Anju Soni was involved in the analysis of data and preparation of the final report. Mike Crawford was involved in the planning and co-ordination of the study from the beginning and an adviser on the analysis of data. Joseph Eliahoo was involved in the statistical analysis of the data. Bernard North was also involved in the statistical analysis of data.

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Appendix 1

TABLE 22 *NACHBID trial client characteristics*

	Randomisation group [*n* (%)]			
	Risperidone	**Haloperidol**	**Placebo**	**Total**
Total sample	29 (34)	28 (32)	29 (34)	86
Level of intellectual disability				
Borderline	0 (0)	0 (0)	1 (4)	1
Mild	11 (38)	8 (29)	11 (38)	30
Moderate	15 (52)	14 (50)	12 (41)	41
Severe	3 (10)	6 (21)	5 (17)	14
Gender				
Male	19 (66)	17 (61)	17 (59)	53
Female	10 (34)	11 (39)	12 (41)	33
Ethnicity				
White (English, Scottish or Welsh)	23 (81)	20 (72)	20 (69)	63
White Irish	0 (0)	1 (3)	2 (7)	3
Other White	1 (3)	2 (8)	0 (0)	3
Black African	0 (0)	1 (3)	0 (0)	1
Black Caribbean	1 (3)	1 (3)	4 (14)	6
Indian	2 (7)	0	3 (10)	5
Pakistani	1 (3)	1 (3)	0 (0)	2
Bangladeshi	1 (3)	0 (0)	0 (0)	1
Other	0 (0)	2 (8)	0 (0)	2
Marital status				
Single/never married	27 (94)	28 (100)	28 (97)	83
Married/living with partner	1 (3)	0 (0)	1 (3)	2
Separated/divorced	1 (3)	0 (0)	0 (0)	1
Level of education				
No education	4 (14)	6 (21)	6 (21)	16
Primary	1 (4)	1 (4)	2 (7)	4
Secondary	3 (10)	0 (0)	0 (0)	3
Special education	21 (72)	17 (61)	21 (72)	59
Community college	0 (0)	4 (14)	0 (0)	4

TABLE 23

Study period (weeks)	Behavioural interventions [*n* (% of those in study at this time)]	Therapeutic sessions [*n* (%)]	OT and SALT [*n* (%)]	Additional medication [*n* (%)]	Intervention 5 [*n* (%)]	Intervention 6 [*n* (%)]
Placebo						
0–4	7 (8.14)	2 (2.32)	0 (0)	16 (18.60)		
4–12	5 (6.33)	13 (16.45)	3 (3.80)	11 (13.92)		
12–26	6 (9.52)	1 (1.59)	0 (0)	14 (22.22)		
Risperidone						
0–4	6 (6.98)	2 (2.32)	1 (1.16)	16 (18.60)		
4–12	9 (11.39)	18 (22.78)	2 (2.53)	12 (15.19)		
12–26	6 (9.52)	1 (1.59)	2 (3.17)	7 (11.11)		
Haloperidol						
0–4	11 (12.79)	5 (5.81)	6 (6.98)	13 (15.12)		
4–12	7 (8.86)	22 (27.85)	1 (1.26)	14 (17.72)		
12–26	5 (7.94)	3 (4.76)	2 (3.17)	10 (15.87)		

OT, occupational therapist; SALT, speech and language therapy.

The percentages will have to be carried out on those in the trial at that time; this is clear from the data in the results table from the main paper.

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Quality-of-life measures in chronic diseases of childhood.
By Eiser C, Morse R.

No. 5
Eliciting public preferences for healthcare: a systematic review of techniques.
By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, *et al*.

No. 6
General health status measures for people with cognitive impairment: learning disability and acquired brain injury.
By Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

No. 7
An assessment of screening strategies for fragile X syndrome in the UK.
By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

No. 8
Issues in methodological research: perspectives from researchers and commissioners.
By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, *et al*.

No. 9
Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.
By Cullum N, Nelson EA, Flemming K, Sheldon T.

No. 10
Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.
By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, *et al*.

No. 11
Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.
By Jobanputra P, Parry D, Fry-Smith A, Burls A.

No. 12
Statistical assessment of the learning curves of health technologies.
By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

No. 13
The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.
By Dinnes J, Cave C, Huang S, Major K, Milne R.

No. 14
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.
By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

No. 15
Home treatment for mental health problems: a systematic review.
By Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, *et al*.

No. 16
How to develop cost-conscious guidelines.
By Eccles M, Mason J.

No. 17
The role of specialist nurses in multiple sclerosis: a rapid and systematic review.
By De Broe S, Christopher F, Waugh N.

No. 18
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 19
The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.
By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 20
Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in preoperative assessment in elective general surgery.
By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, *et al*.

No. 21
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.
By Marshall M, Crowther R, Almaraz- Serrano A, Creed F, Sledge W, Kluiter H, *et al*.

No. 22
The measurement and monitoring of surgical adverse events.
By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23
Action research: a systematic review and guidance for assessment.
By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.
By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al*.

No. 25
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.
By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al*.

No. 27
The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.
By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, *et al*.

No. 28
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29
Superseded by a report published in a later volume.

No. 30
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

No. 31
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.
By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, *et al*.

No. 32
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
By David AS, Adams C.

No. 35
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.
By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al*.

No. 36
Cost analysis of child health surveillance.
By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002

No. 1
A study of the methods used to select review criteria for clinical audit.
By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.
By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al*.

No. 3
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.
By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al*.

No. 4
A systematic review of discharge arrangements for older people.
By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al*.

No. 5
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.
By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al*.

No. 8
Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.
By Carroll B, Ali N, Azam N.

No. 9
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.
By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al*.

No. 10
A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11
Screening for gestational diabetes: a systematic review and economic evaluation.
By Scott DA, Loveman E, McIntyre L, Waugh N.

No. 12
The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.
By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

No. 13
The clinical effectiveness of trastuzumab for breast cancer: a systematic review.
By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al*.

No. 14
The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
By Lewis R, Bagnall A-M, King S, Woolacott N, Forbes C, Shirran L, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

No. 16
The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al*.

No. 17
A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18
Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.
By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al*.

No. 19
Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.
By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al*.

No. 20
Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

No. 21
The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22
A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23
A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

No. 24
A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.
By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al*.

No. 25
A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.
By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, *et al*.

No. 26
A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.
By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al*.

No. 27
A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.
By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, *et al*.

No. 28
Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29
Treatment of established osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30
Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.
By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, *et al*.

No. 31
Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.
By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al*.

No. 32
The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, *et al*.

No. 33
The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34
A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.
By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, *et al*.

No. 35
A systematic review of the costs and effectiveness of different models of paediatric home care.
By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, *et al*.

Volume 7, 2003

No. 1
How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
By Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J.

No. 2
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.
By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al*.

No. 3
Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.
By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4
A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.
By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al*.

No. 5
Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.
By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al*.

No. 6
The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.
By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al*.

No. 8
A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.
By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al*.

No. 9
Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.
By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10
Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.
By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al*.

No. 11
First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).
By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12
The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.
By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13
A systematic review of atypical antipsychotics in schizophrenia.
By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al*.

No. 14
Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.
By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al*.

No. 15
Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.
By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al*.

No. 16
Screening for fragile X syndrome: a literature review and modelling.
By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17
Systematic review of endoscopic sinus surgery for nasal polyps.
By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18
Towards efficient guidelines: how to monitor guideline use in primary care.
By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19
Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.
By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20
Prioritisation of health technology assessment. The PATHS model: methods and case studies.
By Townsend J, Buxton M, Harper G.

No. 21
Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.
By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al*.

No. 22
The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.
By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23
The role of modelling in prioritising and planning clinical trials.
By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24
Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.
By Allsup S, Gosney M, Haycox A, Regan M.

No. 25
The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.
By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26
Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.
By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27
Evaluating non-randomised intervention studies.
By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al*.

No. 28
A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.
By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, *et al*.

No. 29
The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.
By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30
The value of digital imaging in diabetic retinopathy.
By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, *et al*.

No. 31
Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.
By Law M, Wald N, Morris J.

No. 32
Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.
By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33
Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.
By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34
Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.
By Royle P, Waugh N.

No. 35
Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.
By Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K.

No. 36
A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.
By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37
Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.
By MacArthur C, Winter HR, Bick DE, Lilford RJ, Lancashire RJ, Knowles H, *et al*.

No. 38
Estimating implied rates of discount in healthcare decision-making.
By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

No. 39
Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling.
By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, *et al*.

No. 40
Treatments for spasticity and pain in multiple sclerosis: a systematic review.
By Beard S, Hunn A, Wight J.

No. 41
The inclusion of reports of randomised trials published in languages other than English in systematic reviews.
By Moher D, Pham B, Lawson ML, Klassen TP.

No. 42
The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.
By Bankhead CR, Brett J, Bukach C, Webster P, Stewart-Brown S, Munafo M, *et al*.

Volume 8, 2004

No. 1
What is the best imaging strategy for acute stroke?
By Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, *et al*.

No. 2
Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.
By Mant J, McManus RJ, Oakes RAL, Delaney BC, Barton PM, Deeks JJ, *et al*.

No. 3
The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
By Garside R, Stein K, Wyatt K, Round A, Price A.

No. 4
A systematic review of the role of bisphosphonates in metastatic disease.
By Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, *et al*.

No. 5
Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.
By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

No. 6
Effectiveness and efficiency of guideline dissemination and implementation strategies.
By Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, *et al*.

No. 7
Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.
By Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P.

No. 8
Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.
By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9
Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.
By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10
A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.
By Kaltenthaler E, Bravo Vergel Y, Chilcott J, Thomas S, Blakeborough T, Walters SJ, *et al*.

No. 11
The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.
By Barton P, Jobanputra P, Wilson J, Bryan S, Burls A.

No. 12
Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review.
By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

No. 13
Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation.
By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J.

No. 14
Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.
By Townsend J, Wolke D, Hayes J, Davé S, Rogers C, Bloomfield L, *et al*.

No. 15
Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.
By Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, *et al*.

No. 16
A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.
By Reeves BC, Angelini GD, Bryan AJ, Taylor FC, Cripps T, Spyt TJ, *et al*.

No. 17
Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.
By Gilbert FJ, Grant AM, Gillan MGC, Vale L, Scott NW, Campbell MK, *et al*.

No. 18
The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.
By Clark W, Jobanputra P, Barton P, Burls A.

No. 19
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.
By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al*.

No. 20
Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.
By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

No. 21
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.
By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, *et al*.

No. 22
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.
By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.
By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, *et al*.

No. 25
Development and validation of methods for assessing the quality of diagnostic accuracy studies.
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.
By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, *et al*.

No. 27
Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-β and glatiramer acetate for multiple sclerosis.
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28
Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29
VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, on behalf of the VenUS Team.

No. 30
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.
By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, *et al*.

No. 31
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.
By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, *et al*.

No. 33
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.
By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

No. 35
Coronary artery stents: a rapid systematic review and economic evaluation.
By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, *et al*.

No. 36
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.
By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*.

No. 37
Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.
By Knight C, Hind D, Brewer N, Abbott V.

No. 38
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al.*

No. 39
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al.*

No. 41
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.
By Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, *et al.*

No. 42
Involving South Asian patients in clinical trials.
By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44
Identification and assessment of ongoing trials in health technology assessment reviews.
By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al*.

No. 45
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

No. 46
Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.
By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al*.

No. 47
Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48
Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.
By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al*.

No. 49
Generalisability in economic evaluation studies in healthcare: a review and case studies.
By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al*.

No. 50
Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.
By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al*.

Volume 9, 2005

No. 1
Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.
By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al*.

No. 2
Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

No. 3
Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.
By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, *et al*.

No. 4
Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5
A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6
Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7
Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al*.

No. 8
Lay public's understanding of equipoise and randomisation in randomised controlled trials.
By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, *et al*.

No. 9
Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10
Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.
By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, *et al*.

No. 11
Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.
By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, *et al*.

No. 12
A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.
By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13
Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

No. 14
Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.
By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, *et al*.

No. 15
Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.
By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, *et al*.

No. 16
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.
By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, *et al*.

No. 17
Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.
By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, *et al*.

No. 18
A randomised controlled comparison of alternative strategies in stroke care.
By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

No. 19
The investigation and analysis of critical incidents and adverse events in healthcare.
By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20
Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

No. 21
Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.
By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al*.

No. 22
A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

No. 23
A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.
By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al*.

No. 24
An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.
By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al*.

No. 25
Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.
By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al*.

No. 26
Indirect comparisons of competing interventions.
By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, *et al*.

No. 27
Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.
By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al*.

No. 28
Outcomes of electrically stimulated gracilis neosphincter surgery.
By Tillin T, Chambers M, Feldman R.

No. 29
The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.
By Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, *et al*.

No. 30
Systematic review on urine albumin testing for early detection of diabetic complications.
By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al*.

No. 31
Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.
By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32
Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.
By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al*.

No. 33
Cost-effectiveness and safety of epidural steroids in the management of sciatica.
By Price C, Arden N, Coglan L, Rogers P.

No. 34
The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.
By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35
Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.
By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al*.

No. 36
The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.
By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37
A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.
By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al*.

No. 38
The causes and effects of socio-demographic exclusions from clinical trials.
By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al*.

No. 39
Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.
By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al*.

No. 40
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.
By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al*.

No. 41
Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.
By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42
Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.
By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al*.

No. 43
The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44
Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.
By Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45
The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.
By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al*.

No. 46
The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.
By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.
By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al*.

No. 48
Systematic review of effectiveness of different treatments for childhood retinoblastoma.
By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.
By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al*.

No. 50
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.
By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al*.

Volume 10, 2006

No. 1
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.
By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al*.

No. 2
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.
By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al*.

No. 4
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.
By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al*.

No. 5
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6
Systematic review and evaluation of methods of assessing urinary incontinence.
By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.
By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al*.

No. 8
Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.
By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al*.

No. 10
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11
Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.
By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al*.

No. 12
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.
By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al*.

No. 13
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).
By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al*.

No. 14
The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, *et al*.

No. 15
Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.
By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al*.

No. 16
Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.
By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al*.

No. 17
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.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al*.

No. 18
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.
By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al*.

No. 19
Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.
By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al*.

No. 20
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.
By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al*.

No. 21
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22
Pressure relieving support surfaces: a randomised evaluation.
By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al*.

No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.
By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al.*

No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.
By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al*.

No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.
By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al*.

No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.
By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al*.

No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context.
By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al*.

No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.
By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29
An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.
By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al*.

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.
By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al*.

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.
By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al*.

No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.
By Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al*.

No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.
By Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, *et al*.

No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.
By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al*.

No. 35
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.
By Brazier J, Tumur I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al*.

No. 36
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.
By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al*.

No. 37
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.
By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38
A comparison of the cost-effectiveness of five strategies for the prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.
By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, et al.

No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.
By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).
By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, *et al*.

No. 41
The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.
By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.
By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al*.

No. 43
Telemedicine in dermatology: a randomised controlled trial.
By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

No. 44
Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.
By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

No. 45
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.
By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al*.

No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.
By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al*.

No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.
By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al*.

No. 48
Evaluation of the ventricular assist device programme in the UK.
By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*.

No. 49
A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.
By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al*.

No. 50
Amniocentesis results: investigation of anxiety. The ARIA trial.
By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, *et al*.

Volume 11, 2007

No. 1
Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.
By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, *et al*.

No. 2
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.
By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al*.

No. 3
A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.
By Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al*.

No. 4
The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.
By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5
A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.
By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, *et al*.

No. 6
Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.
By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, *et al*.

No. 7
Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8
Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.
By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al*.

No. 9
Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.
By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al*.

No. 10
Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.
By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, *et al*.

No. 11
Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12
Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.
By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13
A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.
By Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al*.

No. 14
A systematic review and economic evaluation of statins for the prevention of coronary events.
By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.
By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, *et al*.

No. 16
Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.
By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17
Screening for type 2 diabetes: literature review and economic modelling.
By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, *et al*.

No. 18
The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, *et al*.

No. 19
The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.
By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20
A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.
By Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, *et al*.

No. 21
The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.
By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22
A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.
By Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, *et al*.

No. 23
Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.
By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, *et al*.

No. 24
The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.
By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al*.

No. 25
A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.
By Boyle J, McCartney E, Forbes J, O'Hare A.

No. 26
Hormonal therapies for early breast cancer: systematic review and economic evaluation.
By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27
Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.
By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.
By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al*.

No. 29
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.
By Colbourn T, Asseburg C, Bojke L, Philips Z, Claxton K, Ades AE, *et al*.

No. 30
Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.
By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al*.

No. 31
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.
By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al*.

No. 32
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.
By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, *et al*.

No. 33
The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.
By Black C, Cummins E, Royle P, Philip S, Waugh N.

No. 34
Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.
By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al*.

No. 35
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Homebased compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.
By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, *et al*.

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A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.
By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, *et al*.

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A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.
By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al*.

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Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anti-coagulation therapy: a systematic review and economic modelling.
By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, *et al*.

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A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.
By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, *et al*.

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Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.
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No. 41
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.
By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al*.

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Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.
By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

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Contamination in trials of educational interventions.
By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, *et al*.

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Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.
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The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.
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Drug-eluting stents: a systematic review and economic evaluation.
By Hill RA, Boland A, Dickson R, Dündar Y, Haycox A, McLeod C, *et al*.

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The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.
By Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, *et al*.

No. 48
Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.
By Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, *et al*.

No. 49
Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial.
By Sharples L, Hughes V, Crean A, Dyer M, Buxton M, Goldsmith K, *et al*.

No. 50
Evaluation of diagnostic tests when there is no gold standard. A review of methods.
By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

No. 51
Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.
By Leontiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW, *et al*.

No. 52
A review and critique of modelling in prioritising and designing screening programmes.
By Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, *et al*.

No. 53
An assessment of the impact of the NHS Health Technology Assessment Programme.
By Hanney S, Buxton M, Green C, Coulson D, Raftery J.

Volume 12, 2008

No. 1
A systematic review and economic model of switching from nonglycopeptide to glycopeptide antibiotic prophylaxis for surgery.
By Cranny G, Elliott R, Weatherly H, Chambers D, Hawkins N, Myers L, *et al*.

No. 2
'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.
By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

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A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.
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Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial.
By Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F.

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A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.
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Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.
By Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, *et al*.

No. 7
The use of economic evaluations in NHS decision-making: a review and empirical investigation.
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Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.
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The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.
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Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.
By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

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Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.
By Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, *et al*.

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The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation.
By Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y, *et al*.

No. 13
Stepped treatment of older adults on laxatives. The STOOL trial.
By Mihaylov S, Stark C, McColl E, Steen N, Vanoli A, Rubin G, *et al*.

No. 14
A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial.
By Goodyer IM, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, *et al*.

No. 15
The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.
By Hind D, Tappenden P, Tumur I, Eggington E, Sutcliffe P, Ryan A.

No. 16
Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.
By Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A.

No. 17
Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.
By Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, *et al*.

No. 18
Structural neuroimaging in psychosis: a systematic review and economic evaluation.
By Albon E, Tsourapas A, Frew E, Davenport C, Oyebode F, Bayliss S, *et al*.

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Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in adults and children aged 12 years and over.
By Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, *et al*.

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Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years.
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Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.
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Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study.
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No. 23
A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial.
By George S, Pockney P, Primrose J, Smith H, Little P, Kinley H, *et al*.

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A review and critical appraisal of measures of therapist–patient interactions in mental health settings.
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The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation.
By Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J.

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A systematic review of the clinical effectiveness and cost-effectiveness and economic modelling of minimal incision total hip replacement approaches in the management of arthritic disease of the hip.
By de Verteuil R, Imamura M, Zhu S, Glazener C, Fraser C, Munro N, *et al*.

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A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration.
By Karnon J, Czoski-Murray C, Smith K, Brand C, Chakravarthy U, Davis S, *et al*.

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Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation.
By Shepherd J, Jones J, Frampton GK, Tanajewski L, Turner D, Price A.

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Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product categories.
By Fader M, Cottenden A, Getliffe K, Gage H, Clarke-O'Neill S, Jamieson K, *et al*.

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A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness.
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The effectiveness and cost-effectivness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial.
By Grant A, Wileman S, Ramsay C, Bojke L, Epstein D, Sculpher M, *et al*.

No. 32
Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review.
By Takeda A, Loveman E, Harris P, Hartwell D, Welch K.

No. 33
Performance of screening tests for child physical abuse in accident and emergency departments.
By Woodman J, Pitt M, Wentz R, Taylor B, Hodes D, Gilbert RE.

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Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation.
By Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, *et al*.

No. 35
Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.
By Lourenco T, Armstrong N, N'Dow J, Nabi G, Deverill M, Pickard R, *et al*.

No. 36
Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation.
By Wang D, Cummins C, Bayliss S, Sandercock J, Burls A.

Volume 13, 2009

No. 1
Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation.
By McLeod C, Fleeman N, Kirkham J, Bagust A, Boland A, Chu P, *et al*.

No. 2
Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis.
By Simpson EL, Stevenson MD, Rawdin A, Papaioannou D.

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Surgical procedures and non-surgical devices for the management of non-apnoeic snoring: a systematic review of clinical effects and associated treatment costs.
By Main C, Liu Z, Welch K, Weiner G, Quentin Jones S, Stein K.

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Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis.
By McDaid C, Griffin S, Weatherly H, Durée K, van der Burgt M, van Hout S, Akers J, *et al*.

No. 5
Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review.
By Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, *et al*.

No. 6
The harmful health effects of recreational ecstasy: a systematic review of observational evidence.
By Rogers G, Elston J, Garside R, Roome C, Taylor R, Younger P, *et al*.

No. 7
Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients.
By Mowatt G, Houston G, Hernández R, de Verteuil R, Fraser C, Cuthbertson B, *et al*.

No. 8
The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports.
By Taylor RS, Elston J.

No. 9
Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial.
By Potter J, Mistri A, Brodie F, Chernova J, Wilson E, Jagger C, *et al*.

No. 10
Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation.
By Pilgrim H, Lloyd-Jones M, Rees A.

No. 11
Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation.
By Tappenden P, Jackson R, Cooper K, Rees A, Simpson E, Read R, *et al.*

No. 12
Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods.
By Hobart J, Cano S.

No. 13
Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial.
By Cooke MW, Marsh JL, Clark M, Nakash R, Jarvis RM, Hutton JL, *et al.*, on behalf of the CAST trial group.

No. 14
Non-occupational postexposure prophylaxis for HIV: a systematic review.
By Bryant J, Baxter L, Hird S.

No. 15
Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial.
By Farmer AJ, Wade AN, French DP, Simon J, Yudkin P, Gray A, *et al*.

No. 16
How far does screening women for domestic (partner) violence in different health-care settings meet criteria for a screening programme? Systematic reviews of nine UK National Screening Committee criteria.
By Feder G, Ramsay J, Dunne D, Rose M, Arsene C, Norman R, *et al*.

No. 17
Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation.
By Simpson, EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J.

No. 18
The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost-effectiveness and natural history.
By Fortnum H, O'Neill C, Taylor R, Lenthall R, Nikolopoulos T, Lightfoot G, *et al.*

No. 19
Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study.
By Little P, Turner S, Rumsby K, Warner G, Moore M, Lowes JA, *et al.*

No. 20
Systematic review of respite care in the frail elderly.
By Shaw C, McNamara R, Abrams K, Cannings-John R, Hood K, Longo M, *et al.*

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Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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