Endocrinology trial design: Adverse event reporting in randomised controlled trials of recombinant human GH in GH-deficient adults

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Abstract

We have evaluated the reporting of withdrawals due to adverse effects and specific adverse effects in randomised controlled trials of recombinant human GH in adults. A systematic review was carried out of randomised controlled trials of the clinical effectiveness of recombinant human GH in adults with GH deficiency in relation to impact on quality of life. Trials were identified from searching electronic databases, bibliographies of related articles and consulting experts. There was reporting of withdrawals due to adverse effects and specific adverse effects. Rates of oedema and arthralgia were reported in included trials. Seventeen randomised controlled trials, published between 1990 and 1999, met the inclusion criteria for the review. Nine trials reported data on the effectiveness of GH on quality of life in adults. Only five trials (29%) reported both withdrawals from the study because of adverse events and specific adverse events with numbers per study arm and per type. Six further trials (35%) reported either withdrawal details or specific adverse event details or partial data on specific adverse events. Six trials (35%), however, did not report information on either withdrawals or specific adverse events. Ten of the 17 studies (59%) reported the number of patients who withdrew from the study due to adverse events per study arm and type of adverse event per study arm. Seven of the 17 trials (41%) reported the number of specific adverse events per study arm and six (35%) reported the type per study arm. The reporting of adverse events in randomised controlled trials of GH is variable and not consistent across trials. It is not possible to assess the impact that adverse events may have had on unblinding patients, and therefore the extent to which the effects of GH may have been overestimated. Therefore those conducting endocrinology trials in the future need to pay attention to the reporting of withdrawals due to adverse events and specific adverse events.

Introduction

Randomised controlled trials (RCTs) offer the opportunity to assess the frequency and severity of adverse events in an objective setting. However, compared with the development of standardised reporting of trial design, conduct and efficacy outcomes in RCTs as a result of the CONSORT statement (Begg et al. 1996, Moher et al. 2001), the reporting of adverse events has only recently been considered. It has been found that adverse events are often presented erratically or may be missing altogether (Ioannidis & Contopoulos-Ioannidis 1998). Ioannidis & Lau (2001) reported that the quality and quantity of adverse event data were largely inadequate, although they did vary across medical areas, study designs and settings. They proposed an addendum to the CONSORT statement, so that authors would (i) specify the number of patients withdrawn from the study because of adverse effects, per study arm and per type of adverse effect; and (ii) provide the number of specific adverse effects per study arm and per type of adverse effect.

The issue of adverse events is of particular interest in trials of recombinant human growth hormone (GH) because there are some fairly specific adverse effects that may occur in the short term and that are obvious to patients, particularly with the higher doses of GH used in the past. These have the potential to unblind patients, even if the trials are placebo controlled and patients are not told which treatment they are receiving. Such unblinding could be important in assessing effectiveness especially where outcomes are self-assessed as is the case in most of the quality of life scales that are used when monitoring adults receiving GH. Another aspect of uncertainty about the accuracy of outcome measures as a result of unblinding relates to the reporting of withdrawals due to side-effects. Complete follow-up of patients in treated and untreated groups is necessary in order to determine if those who withdrew due to adverse events are different from those who remain untreated.
in the study. This may have an impact on the generalis-
ability of results.

We were commissioned by the NHS Research and
Development Health Technology Assessment Programme
to undertake a rapid systematic review of the clinical and
cost-effectiveness of GH in adults in relation to impact on
quality of life (Bryant et al. 2002). This paper develops our
findings relating to the reporting of adverse events in the
trials included in the systematic review, using some of the
parameters suggested by Ioannidis & Lau (2001) as an
addendum to the CONSORT statement.

Materials and Methods

Electronic databases (Cochrane systematic reviews data-
base, Cochrane controlled trials register, Medline, Health-
star, Embase) were searched from 1985 to 2001. Additional
studies were identified through searching bibliographies of
related publications, through contact with experts and
industry, and hand searching the Clinical Endocrinology
journal from 1993 to August 2000.

We sought published English language RCTs that
compared any dose of recombinant human GH treatment
with placebo; included adults aged 18 years or over
diagnosed with GH deficiency and adults who were
continuing treatment from childhood; and used quality of
life outcome measures.

We assessed the quality of RCTs using criteria de-
veloped by Jadad et al. (1996), which considers three
dimensions of reporting of internal validity of trials:
randomisation, blinding and withdrawals. A maximum
score of 5 indicates a high quality study on the Jadad scale,
with points being scored for the study being described as
randomised; using appropriate methods of randomisation;
being described as double blind; using a control indistin-
guishable from the intervention; with attrition described
for each group. Decisions about inclusion criteria and
quality criteria were made independently by two review-
ers, and data extraction was performed by one reviewer
and checked by a second. Any disagreements were
resolved through discussion.

Studies were combined through narrative synthesis with
full tabulation of included studies, and meta-analysis where
possible. Numbers needed to harm (NNHs) with 95%
confidence intervals (95% CIs) were calculated where
figures were presented in an appropriate form.

We summarised adverse event data, following sugges-
tions of Ioannidis & Lau (2001) in terms of trials which
reported (i) the number of patients withdrawn from the
study because of adverse effects, per study arm and per
type of adverse effect; and (ii) the number of specific
adverse effects per study arm and per type of adverse
effect. Rates of the most common adverse events reported
in the included trials were tabulated. Adverse event data
were extracted independently by two researchers.

Results

Results of the systematic review

Seventeen RCTs, published between 1990 and 1999, met
the inclusion criteria for the review. Nine of the 17 trials
reported data on the effects of GH on quality of life in
adults.

Characteristics of included trials

The included trials differed in study design and details
(Table 1). Five studies used a crossover design (Degerblad
et al. 1990, Whitehead et al. 1992, Bengtsson et al. 1993,
Burman et al. 1995, Florkowski et al. 1998) with wash-out
periods ranging from zero to 3 months. Typical trial
duration was 6 months, with one study duration being
only 3 months (Florkowski et al. 1998) and two studies
having trial duration greater or equal to 1 year (Burman
et al. 1995, Baum et al. 1998). Most studies had between
21 and 40 participants, although sample size ranged
from six (Degerblad et al. 1990) to 173 (Attanasio et al.
1997), with three having less than ten (Degerblad et al.
1990, Bengtsson et al. 1993, de Novaes Soares et al.
1999).

Three trials included participants with adult onset GH
deficiency only (Bengtsson et al. 1993, Baum et al. 1998,
Giusti et al. 1998), one had participants with child onset
GH deficiency only (Deijen et al. 1996) while the remain-
der included both child and adult onset participants. In all
trials that reported data, participants with multiple and
isolated deficiencies were included.

A range of GH doses was used in the included RCTs
and differences in the unit of measurement and quality of
reporting makes overall description difficult. However, the
typical range of GH used in the majority of trials fell
between 0·125 and 0·25 IU/kg per week.

The quality of life outcome measures used in the trials
also varied but were typically self-report measures, al-
though in some trials clinical or semi-structured interviews
took place. Twenty-three different quality of life scales
were utilised to evaluate quality of life, the four most
common being the General Health Questionnaire, the
Hamilton Depression Scale, the Nottingham Health Pro-
file and its subscales, and the Psychological Well-Being
Schedule. Details can be found elsewhere (Bryant et al.
2002).

Based on the Jadad quality scale to measure the likeli-
hood of trial bias, one of the included trials received a score
of 5 (Baum et al. 1998), two trials scored 4 (Bengtsson et al.
1993, Cuneo et al. 1998) and one trial scored only 1
(Florkowski et al. 1998). The majority of the included
trials scored 2 or 3, with most failing to give details of
randomisation methods. Two trials were only published as
abstracts and therefore it was impracticable to assess Jadad
quality scores (McKenna et al. 1997a,b).
Assessment of clinical effectiveness of GH in adults as measured by quality of life

Evidence suggests that GH may improve quality of life, although most change scores demonstrated on the quality of life instruments used are modest and only a few are statistically significant. The analysis of the individual dimensions of the Nottingham Health Profile from individual trials demonstrated statistically significant improvements in the GH replacement group compared with the placebo group for pain, emotional reactions and sleep. Meta-analysis showed in favour of GH on the Nottingham Health Profile social isolation dimension, which was statistically significant (Bryant et al. 2002).

Adverse event reporting

The RCTs included in the systematic review were assessed for their reporting of adverse events as recommended by Ioannidis & Lau (2001). Eleven of the 17 studies reported details of either withdrawals due to adverse events reporting in RCTs of GH in adults · J BRYANT and others

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withdrawal events or specific adverse events (see Table 2). Only five trials (29.5%) reported both withdrawals from the study because of adverse events and specific adverse events with numbers per study arm and per type (Whitehead et al. 1992, Beshyah et al. 1995, Verhelst et al. 1997, Baum et al. 1998, Cuneo et al. 1998). Six further trials (35%) reported either withdrawal details (Bengtsson et al. 1993, Florkowski et al. 1998, Giusti et al. 1998, de Novaes Soares et al. 1999) or specific adverse event details (Attanasio et al. 1997) or partial data on specific adverse events (Wallymahmed et al. 1997). Six trials (35%), however, did not report information on either withdrawals or specific adverse events (McGauley 1989, Degerblad et al. 1990, Burman et al. 1995, McKenna et al. 1997a,b, Deijen et al. 1996).

Withdrawals

Ten of the 17 studies (59%) reported the number of patients who withdrew from the study due to adverse events per study arm and per type of adverse event (Whitehead et al. 1992, Bengtsson et al. 1993, Beshyah et al. 1995, Verhelst et al. 1997, Wallymahmed et al. 1997, Baum et al. 1998, Cuneo et al. 1998). Six further trials (35%) reported either withdrawal details (Bengtsson et al. 1993, Florkowski et al. 1998, Giusti et al. 1998, de Novaes Soares et al. 1999) or specific adverse event details (Attanasio et al. 1997) or partial data on specific adverse events (Wallymahmed et al. 1997). Six trials (35%), however, did not report information on either withdrawals or specific adverse events (McGauley 1989, Degerblad et al. 1990, Burman et al. 1995, McKenna et al. 1997a,b, Deijen et al. 1996).

Specific adverse events

Seven of the 17 trials (41%) (Whitehead et al. 1992, Beshyah et al. 1995, Attanasio et al. 1997, Verhelst et al. 1997, Wallymahmed et al. 1997, Baum et al. 1998, Cuneo et al. 1998) reported the number of specific adverse events details, all reporting per study arm and all reporting per type except one (Wallymahmed et al. 1997). This study reported specific adverse events grouped together for mild transient side-effects and GH-specific side-effects by number per arm. Only one of the five crossover trials reported specific adverse event data per study arm or per type (Whitehead et al. 1992), although two (Degerblad et al. 1990, Bengtsson et al. 1993) did report overall specific adverse event data.

Reported rates of adverse events

The most common adverse events in studies of GH in adults are oedema (see Table 4) and arthralgia (see Table 5).

Oedema

Rates of oedema in the trials that report data were consistently higher (10–17%) in the GH replacement participants than those in the placebo groups. In one study (Baum et al. 1998) no reports of oedema were noted in the placebo group while 10% of patients in the intervention group reported oedema. The number of reports of oedema were greater in the GH replacement group compared with control by 15% (Beshyah et al. 1995), 17% (Verhelst et al. 1997) and 18% (Cuneo et al. 1998). One trial (Attanasio et al. 1997) described rates of oedema separately for patients with adult onset GH deficiency and patients with child onset GH deficiency. Rates of oedema in the adult onset GH deficiency patients were shown to be greater in the GH replacement group than in the placebo by 24.5%; in those with child onset GH deficiency the rate of oedema was 18.5% in the GH replacement group compared with 5.4% in the placebo group.
Oedema was 6.3% in the GH replacement group and nil in the placebo group.

Arthralgia Rates of arthralgia in the trials that report data were also found to be higher (10–17%) in the GH replacement participants than in the placebo groups, except in the one trial where no reports of arthralgia were noted (Baum et al. 1998). Reported rates of arthralgia were nil in the placebo group and 10% in the GH replacement group (Beshyah et al. 1995), and increased rates of 13% (Verhelst et al. 1997) and 17% (Cuneo et al. 1998) in the GH groups compared with the placebo groups. Rates of arthralgia in the adult onset GH replacement participants was 16.6% more than those in the placebo group, and in the child onset GH replacement participants 6.3% reported arthralgia compared with none in the placebo group (Attanasio et al. 1997).

Table 3 Numbers (%) of patients who withdrew due to adverse events in studies that reported data

<table>
<thead>
<tr>
<th>Study</th>
<th>GH treatment</th>
<th>Placebo/no treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baum et al. (1998)</td>
<td>5/20 (25%)</td>
<td>1/20 (5%)</td>
</tr>
<tr>
<td>Bengtsson et al. (1993)</td>
<td>1/10 (10%)</td>
<td>0/10 (0%)</td>
</tr>
<tr>
<td>Beshyah et al. (1995)</td>
<td>2/20 (10%)</td>
<td>0/20 (0%)</td>
</tr>
<tr>
<td>Cuneo et al. (1998)</td>
<td>19/83 (23%)</td>
<td>11/80 (14%)</td>
</tr>
<tr>
<td>Florkowski et al. (1998)</td>
<td>0/20 (0%)</td>
<td>0/20 (0%)</td>
</tr>
<tr>
<td>Giusti et al. (1998)</td>
<td>1/13 (8%)</td>
<td>0/12 (0%)</td>
</tr>
<tr>
<td>de Novaes Soares et al. (1999)</td>
<td>0/5 (0%)</td>
<td>0/4 (0%)</td>
</tr>
<tr>
<td>Verhelst et al. (1997)</td>
<td>0/71 (0%)</td>
<td>0/77 (0%)</td>
</tr>
<tr>
<td>Wallymahmed et al. (1997)</td>
<td>2/19 (10%)</td>
<td>0/13 (0%)</td>
</tr>
<tr>
<td>Whitehead et al. (1992)</td>
<td>2/7 (29%)</td>
<td>2/7 (29%)</td>
</tr>
</tbody>
</table>

Table 4 Rates of oedema reported in included RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo event rate</th>
<th>GH event rate</th>
<th>Difference</th>
<th>NNH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attanasio et al. (1997) (AO)</td>
<td>4.3%</td>
<td>28.8%</td>
<td>24.5%</td>
<td>5 (10 to 3)</td>
</tr>
<tr>
<td>Attanasio et al. (1997) (CO)</td>
<td>0</td>
<td>6.3%</td>
<td>6.3%</td>
<td>16 (5 to 25 benefit)</td>
</tr>
<tr>
<td>Attanasio et al. (1997) (all)</td>
<td>3%</td>
<td>20%</td>
<td>17%</td>
<td>6 (12 to 4)</td>
</tr>
<tr>
<td>Baum et al. (1998)</td>
<td>0</td>
<td>10%</td>
<td>10%</td>
<td>10 (4, 14)</td>
</tr>
<tr>
<td>Bengtsson et al. (1993)*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Beshyah et al. (1995)</td>
<td>20%</td>
<td>35%</td>
<td>15%</td>
<td>7 (3 to 8 benefit)</td>
</tr>
<tr>
<td>Burman et al. (1995)*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cuneo et al. (1998)</td>
<td>30%</td>
<td>48%</td>
<td>18%</td>
<td>6 (32 to 4)</td>
</tr>
<tr>
<td>Degerblad et al. (1990)*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Deijen et al. (1996)</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Florkowski et al. (1998)*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Giusti et al. (1998)</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>McGauley (1989)</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>McKenna et al. (1997a)</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>McKenna et al. (1997b)</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>de Novaes Soares et al. (1999)</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verhelst et al. (1997)</td>
<td>1.2%</td>
<td>18%</td>
<td>16.8%</td>
<td>9 (26 to 5)</td>
</tr>
<tr>
<td>Wallymahmed et al. (1997)</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Whitehead et al. (1992)</td>
<td>0</td>
<td>14%</td>
<td>14%</td>
<td>7 (2 to 4 benefit)</td>
</tr>
</tbody>
</table>

*Crossover trial, data combined for placebo and control groups.
N/A no data presented, AO adult onset, CO child onset, NNH number needed to harm at end of follow-up period, calculated using Arcus Quickstat (Biomedical) software.

Discussion

This review, which was guided by an expert advisory panel of experts and the principles of undertaking a
systematic review, applied consistent methods of critical appraisal, presentation and transparency. The evidence for the clinical effectiveness of GH on quality of life in GH-deficient adults came from 17 RCTs. An evaluation of adverse event reporting in these RCTs shows that such reporting is variable, not consistent across trials and with few descriptions of how clinical adverse events were defined.

Not only are data on withdrawals from studies due to adverse events or specific adverse events often missing, with nearly one-third of trials neglecting to report anything at all, but what is reported is often poorly and ambiguously presented making interpretation difficult. For example, where results are expressed as percentages it is not always clear whether this is percentage of total participants or per study arm; side-effects are sometimes only reported at a frequency of greater or equal to 5%; numbers in tables and text do not always match; drop-outs are not always reported explicitly, although results may suggest that all participants are accounted for. Crossover trials have the additional problem in that for all but one crossover trial, adverse event data were not separated for GH and placebo groups but presented as combined data. With unclear presentation of data there is a missed opportunity to maximise the usefulness of adverse event data that has been collected.

There is also a mismatch between reporting of effectiveness data and adverse event data. Data on effectiveness of GH in terms of quality of life were given in only eight trials, of which only three reported both withdrawals from the study because of adverse events and specific adverse events with numbers per study arm and per type (Beshyha et al. 1995, Baum et al. 1998, Cuneo et al. 1998). Conversely, two studies (Whitehead et al. 1992, Verhelst et al. 1997) reported complete adverse event data even though no effectiveness data were reported. In order to use quantitative evidence for making therapeutic decisions there needs to be adequate reporting of both effectiveness and safety of treatments.

Most of the studies described here are small but had they all reported specific adverse event data in a standardised way, meta-analysis may have been possible, which could have complemented the meta-analysis performed on the effectiveness measures.

Due to the variability in adverse event reporting and the different trial designs (in terms of dose ranges, dose administration, length of follow-up, etc.) in the trials included in the review, it is not possible to rank the studies in terms of the effect of adverse events on unblinding. Therefore the risk of bias and overestimation of treatment effects is also impossible to estimate.

Adverse events due to GH treatment are more frequent at higher doses of GH as used in these studies, and may not be an issue with the doses in practice today, which are carefully titrated from low starting doses. However, response to GH varies considerably between individuals and some adults experience side-effects even with a low dose. Careful monitoring of the individual and recording of side-effects will always be required. Long-term side-effects of GH replacement therapy are not known.

Apart from the importance of reporting adverse events in trials of GH in adults, adverse event and withdrawals

### Table 5 Rates of arthralgia reported in included RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo event rate</th>
<th>GH event rate</th>
<th>Difference</th>
<th>NNH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attansio et al. (1997) (AO)</td>
<td>6·5%</td>
<td>23·1%</td>
<td>16·6%</td>
<td>5 (10 to 3)</td>
</tr>
<tr>
<td>Attansio et al. (1997) (CO)</td>
<td>0</td>
<td>6·3%</td>
<td>6·3%</td>
<td>7 (41 to 4)</td>
</tr>
<tr>
<td>Attansio et al. (1997) (all)</td>
<td>4%</td>
<td>17%</td>
<td>13%</td>
<td>8 (25 to 5)</td>
</tr>
<tr>
<td>Baum et al. (1998)</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bengtsson et al. (1993)*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Beshyah et al. (1995)</td>
<td>0%</td>
<td>10%</td>
<td>10%</td>
<td>10 (4 to 14 benefit)</td>
</tr>
<tr>
<td>Burman et al. (1995)*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cuneo et al. (1998)</td>
<td>13%</td>
<td>30%</td>
<td>17%</td>
<td>6 (20 to 4)</td>
</tr>
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<td>Degerblad et al. (1990)*</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>Deijen et al. (1996)</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Florkowski et al. (1998)*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Giusti et al. (1998)</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>McGauley (1989)</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
</tr>
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<td>McKenna et al. (1997a)</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
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</tr>
<tr>
<td>McKenna et al. (1997b)</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>de Novaes Soares et al. (1999)</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Verhelst et al. (1997)</td>
<td>3%</td>
<td>16%</td>
<td>13%</td>
<td>8 (24 to 5)</td>
</tr>
<tr>
<td>Wallymahmed et al. (1997)</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Whitehead et al. (1992)</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Crossover trial, data combined for placebo and control groups.
N/A no data presented, AO adult onset, CO child onset, NNH number needed to harm at end of follow-up period.
reporting is of general interest within the field of endocrinology and to those performing technology assessment reviews in this area. Without the adequate description of how ‘attrition’ is handled and who has dropped out, it is difficult to assess the quality and internal validity of trials.

In summary, the reporting of adverse events in RCTs considering the impact of GH on quality of life in adults is generally inadequate. Consequently, this placed limitations on our systematic review to investigate safety aspects of GH in adults, because of the dependency of the review on poorly presented data in the primary studies. Although we have only looked at a small subset of endocrinology trials, some of which were published several years ago, and although there is no intention to criticise authors, our work highlights deficiencies which make it hard to assess both the validity of the results and what the results are. Therefore those reporting endocrinology trials in the future need to pay attention to the suggestions of Ioannidis & Lau (2001). This will make it possible to systematically review adverse event data and add to the evidence base for making informed decisions about the value of endocrinological treatment.

Acknowledgements

We thank the advisory group (list published elsewhere, Bryant et al. (2002)) for advice and peer review throughout the project; Dr Pam Royle and Ms Liz Hodson for their support with obtaining information. This review was funded by the NHS R&D Health Technology Assessment Programme. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NHS Executive. Conflicts of interest: none.

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Received 17 April 2002
Accepted 2 July 2002