
Monograph:
Payne, J.N. and Richards, R.G. (1997) The use of growth hormones in adults. Other. Guidance Notes for Purchasers (97/08). Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield , Sheffield. ISSN 1900733188

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise, and includes non-clinically qualified scientists and lay members. It is chaired by Professor Sir David Hull.

The committee recommends, on the basis of appropriate evidence, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 20 January 1998 at which this Guidance Note for Purchasers (in a draft form) was considered.

THE USE OF GROWTH HORMONE IN ADULTS

AUTHORS: Payne JN and Richards RG, Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1997. Guidance Note for Purchasers: 97/08.

EXPERT ADVISORS TO TRENT DEC: Dr S Page, Consultant Endocrinologist, Queen's Medical Centre, Nottingham, Dr JN Payne, Consultant Senior Lecturer in Public Health Medicine, ScHARR, the University of Sheffield.

DECISION: The Committee recommended that clear guidelines are produced to aid selection of adult patients who would stand to benefit from growth hormone treatment. The Committee considered that further research is required to identify those patients who would benefit most, and funding should be made available for patients included in appropriate studies which included assessment of long term costs and benefits and general outcome measures.

TRENT DEVELOPMENT & EVALUATION COMMITTEE
c/o Nottingham Health Authority • 1 Standard Court • Park Row • Nottingham • NG1 6GN
Tel: 0115 912 33 44 Fax: 0115 912 33 51

December 1997

THE USE OF GROWTH HORMONE IN ADULTS

JN Payne
RG Richards

Series Editor: Nick Payne

Trent Institute for Health Services Research
Universities of Leicester, Nottingham and Sheffield

GUIDANCE NOTE FOR PURCHASERS 97/08

Published by the Trent Institute for Health Services Research

ISBN 1 900733 18 8

Referencing information:

Payne JN and Richards RG. *The Use of Growth Hormone in Adults.* Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield, 1997. Guidance Note for Purchasers : 97/08.

Further copies of this document are available (price £5.00) from:-

Suzy Paisley
Senior Information Officer
Trent Institute for Health Services Research
Regent Court
30 Regent Street
SHEFFIELD S1 4DA

Tel 0114 222 5420
Fax 0114 272 4095
E-mail scharrlib@sheffield.ac.uk

Please make cheques payable to "The University of Sheffield"

Conflict of Interest None of the authors of this document has any financial interests in the drug or product being evaluated here.

ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Institute:

- provides advice and support to NHS staff on undertaking Health Services Research (HSR);
- provides a consultancy service to NHS bodies on service problems;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor C E D Chilvers (Nottingham); and
Professor M Clarke (Leicester).

Professor Akehurst currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within the University of Sheffield in conjunction with the School of Health and Related Research (ScHARR).

AUTHORS

Dr J N Payne is Consultant Senior Lecturer in Public Health Medicine at the School of Health and Related Research (ScHARR), the University of Sheffield.

Dr R G Richards is a Consultant in Public Health Medicine at North Nottinghamshire Health Authority.

ACKNOWLEDGEMENT

The authors would like to acknowledge the help and advice from Dr Richard Ross, Senior Lecturer in Endocrinology, Northern General Hospital, in the preparation of this report.

FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Purchasing Authorities Chief Executives (PACE) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterDEC, with units in other regions. These are: The Wessex Institute for Health Research and Development, The Scottish Health Purchasing Information Centre (SHPIC) and The University of Birmingham Institute for Public and Environmental Health.

Professor R L Akehurst,

Chairman, Trent Working Group on Acute Purchasing.

CONTENTS

EXECUTIVE SUMMARY

This Guidance Note for Purchasers is based on, and reviews, the work carried out by the Wessex Institute for Health Research and Development examining the use of growth hormone in adults.

Growth hormone deficiency in adults may affect about 1 in 10,000 of the adult population suggesting a prevalence of about 40 in an average health authority (all age) population of 500,000.

Replacement therapy in growth hormone deficient adults has been evaluated in over 26 randomised controlled trials. Evidence from these trials shows benefits in improved exercise performance; improvement in body composition in terms of the ratio of lean to fat mass; increases in bone mineral density; and improvements in cardiac structure and function. Quality of life, as assessed by questionnaire, is reduced in growth hormone deficient adults. However, studies to date have only shown minor changes in quality of life on growth hormone replacement therapy and most studies have not been appropriately evaluated.

There are potential benefits from growth hormone in terms of reduced cardiovascular mortality and reduced fractures. These have not yet been demonstrated by trial evidence because of the difficulty in designing a study for a small population of patients of mixed age and gender.

The Wessex review stated that the total cost of treatment ranged from £3,500 to £7,200 per patient treated per annum. The overall cost-utility of growth hormone treatment for adults is, however, unknown and dependent on whether additional benefit can be demonstrated in terms of reduced cardiovascular mortality and fracture risk.

A European database of over 1,500 patients suggests, however, that dosage, and hence costs of treatment, are lower and that the latter range from £2,178 to £4,356 per patient treated per annum. The present evidence in terms of quality of life improvement suggests

that treatment of those most severely affected is likely to have a cost utility ratio of, or below, £20,000 per Quality Adjusted Life Year (QALY). Indeed, using the first Wessex review's calculation for the cost per QALY in severe growth hormone deficiency, this lower dosage would equate to a cost per QALY of £8,500 (although the Wessex group now has reservations about its earlier attempts to translate quality of life benefit directly into QALYs).

1. INTRODUCTION

Growth hormone (GH) deficiency in children has been treated by hormone replacement since the 1960s, and GH replacement therapy in adults with GH deficiency has been investigated in clinical trials since 1988.

This summary Guidance Note for Purchasers has been produced drawing heavily on the two reports done by the Wessex Institute for Health Research and Development and the South and West Regional Development and Evaluation Committee.[1,2] An agreement has been reached by which South and West reports may be submitted to the Trent Development and Evaluation Committee where a request has been received for Guidance Notes within the Trent Region.

1.1 Incidence and Pathology

The prevalence of GH deficiency in adults has been estimated as about 1 in 10,000 of the adult population (based on the number of known cases of pituitary tumours). Indirect estimates from the Wessex report[1] are that the incidence is around 10 per million per annum, but, unless survival with the condition averages only about 10 years, either the incidence is somewhat lower or prevalence somewhat higher than the above estimates.

GH deficiency in adulthood can arise from a pituitary adenoma; a hypothalamic tumour; or treatment of these conditions with surgery or radiation. Childhood GH deficiency may also result in adult GH deficiency, although at least 30% of children treated for isolated GH deficiency are not growth hormone deficient (GHD) as adults.

1.2 Prognosis and Mortality

Adults with GH deficiency suffer from a variety of symptoms including impaired psychological well-being, increased fat mass (especially abdominal), reduced muscle strength and exercise capacity, and cold intolerance. There are also studies indicating that these patients have an increased mortality risk due to cardiovascular disease. This may, at least in part, be mediated by changes in lipid metabolism as cholesterol levels are higher in these patients. GHD patients have reduced bone mineral density and there is evidence of

an increased risk of fractures. GH deficiency is also associated with decreased sweating, heat intolerance and thin skin.

1.3 Scale of Problem in a 'Typical District'

From the Wessex reports' estimates of prevalence, around 40 adult patients with GH deficiency would be anticipated in an 'average' health authority (all ages) population of 500,000. However, as discussed above, there are considerable uncertainties about this figure and, in any case, there is likely to be considerable variation at any one time about this figure due simply to chance. Thus, for example, one health authority in twenty is likely to have a number at least 30% larger or smaller than this.

2. USE OF GROWTH HORMONE IN ADULTS: SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Summary of Evidence for the Effectiveness of Growth Hormone

There have been two reports to the South and West Development and Evaluation Committee on the use of GH in adults. The first of these reports reviewed the evidence from 11 randomised controlled trials (RCTs) which were available at the time the report was produced (1995).[1] The second report considered a larger number of RCTs which were subdivided in terms of the outcome measures considered:[2]

- Five RCTs evaluated exercise performance;
- Four short-term RCTs evaluated cardiovascular function;
- Twelve RCTs evaluated body composition;
- One RCT, and three case series, examined bone mineral density;
- Four RCTs evaluated quality of life in GHD adults.

Exercise Performance

All but one of the five trials examined in the second report showed a statistically significant improvement in exercise capacity with GH treatment compared with placebo. Only one trial, however, showed an improvement in muscle strength.

Cardiovascular Function

Epidemiological studies of hypopituitary patients show a statistically significant increased rate of cardiovascular mortality. Four short-term RCTs identified in the Wessex report have evaluated cardiac structure and function in GHD patients and, overall, the results suggest an improvement. However, none was large enough or had sufficient follow-up to examine changes in mortality. Finally, a non-systematic review is reported showing that GH treatment is associated with a decrease in LDL-cholesterol and increase in HDL-cholesterol levels.

Body Composition

Almost all of the 12 RCTs which examined changes in body composition showed a statistically significant increase in lean body mass of 2-5.5 kg and a reduction in fat mass of about 4-6 kg.

Bone Mineral Density

Those trials in which follow-up was only for 12 months mostly showed no increase in bone mineral density. Those followed up for longer, and indeed longer-term case series, found a significant increase at 18 months which is probably sustained. A 10% change in age- and sex- related bone mineral density was shown after a 50 month follow-up.[3] Studies have not evaluated whether an increase in bone mineral density leads to a decrease in fracture rate for GHD adults. However, if trials were set up to examine this they would need to be impracticably large in terms of numbers of GHD patients recruited.

Quality of Life

Cohort studies have shown that GHD adults (without GH replacement) have a reduced quality of life compared with age, sex and socio-economic class matched control populations. The first Wessex report attempted to use the IHQL index to assess the state of adults with mild, moderate and severe symptoms of GHD and the degree of benefit they were likely to experience from treatment.[1] These were then translated into Quality Adjusted Life Years (QALYs) gained. This analysis and assessment can be criticised because it extrapolated substantially beyond the evidence and the outcomes actually presented in the trials that were available. The Wessex Institute team themselves now feel that this analysis is unsatisfactory (Milne R, personal communication).

The second Wessex report examined four RCTs which used quality of life as an outcome and was more cautious in its conclusions.[2] The best of these four trials showed a non-significant increase in quality of life on treatment. All these trials were of short duration, contained small numbers of patients, and presented conflicting results. The treatment effects were said to be incorrectly analysed in two of the trials and compliance problems were noted in another.

The use of quality of life measures in assessing the effects of replacement therapy in adult GH deficiency, however, is not without some substantial problems. Not all the dimensions of the Nottingham Health Profile (NHP) are affected to the same extent, with energy level in particular showing improvement.[4,5] It is argued that there is a need for a disease-specific questionnaire instrument to examine quality of life in GHD adults. This would be based on a patient's ability to meet his or her needs and, thus, would be particularly patient-centred and take account of the needs of each patient. Such a tool is being developed and preliminary results suggest that it is more sensitive than the NHP, (McKenna, personal communication).

2.2 Conclusion on Direction of Evidence and its Quality

From the more recent Wessex report[2] and elsewhere, the evidence can be summarised as:

The benefits from GH treatment are:

- Increased exercise capacity;
- Near normalisation of body composition;
- Improved cardiac structure and function;
- Increased bone mineral density; and
- Improvement in lipid profile.

The potential benefits from GH treatment are:

- Reduced cardiovascular mortality and morbidity; and
- Reduced fracture risk.

It is difficult to assess the utility of treatment simply in terms of QALYs because of the widespread action of GH on different systems within the body. In addition, there are problems of quantifying the benefits associated with GH treatment given the methodological limitations associated with the published trials on quality of life, and the use of proxy measures to evaluate other benefits such as in cardiovascular risk.

It would, in theory, be possible to model some of these proxy measures, in particular cardiovascular disease risk, if trial data were available but, using the existing information, it is likely that too many unfounded assumptions would have to be made.

In summary, the potential range of benefits associated with treatment (over and above placebo) could be relatively small in relation to quality and quantity of life gained, equally, they could be quite large (if GH treatment does substantially reduce fracture rates and/or cardiovascular mortality).

3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

The most important element of the cost of GH treatment in adults is the annual cost of the drug itself. The Wessex report[2] quotes the (British National Formulary) recommended dose range as 0.125 to 0.25 units/kg per week, which translates to an annual cost range (for a 70kg person) of around £3,500 to £7,000. That report also estimates diagnostic and monitoring costs, but together these add no more than about £200 per annum. This dose range, however, probably considerably overestimates the actual average (median) dose used in clinical practice which is 0.12 units/kg per week (range 0.8 to 2.4). At this dose the average cost per annum would be only around £3,300. (These dosage data are from a physician-led European database of over 1,500 patients - personal communication, Monson J).

For an average sized health authority with a population of 500,000 this could, therefore, translate into an additional cost of about £130,000 per annum.

Two additional considerations, however, are highlighted in the Wessex report[2] which might further mitigate these costs. The first is that some patients (nearly half in the study reported) did not continue with GH replacement. Those who did choose to continue, however, tended to have a greater severity of GH deficiency. The second is that GH manufacturers have given an assurance that they will provide funding for the first three months of treatment if the NHS continues funding if the patient is deemed to have benefited. The duration of this arrangement is unknown.

Without trial evidence that additional benefits might accrue to treated patients, no estimate is possible of the cost reduction by events possibly averted, such as, those in association with cardiovascular disease (for example, fewer heart attacks), or improved bone mineral density (fewer fractures). However, if they do indeed occur, then the true net costs of treatment might be substantially lower.

What can be considered at this stage, however, is how much benefit might have to be produced by treatment to put the use of GH in GHD adults in the same range of cost-

effectiveness as other interventions provided by the National Health Service (NHS). Two ends of a cost-effectiveness spectrum can be considered:

a. Quality of Life Improvement with no Cost Savings by Events Averted

In order to produce a cost utility of £20,000 per Quality Adjusted Life Year (QALY), treatment of GHD adults would need to produce an average of 0.16 QALYs per person treated per annum. Using the largely unfounded assumptions from the first Wessex report,[1] this would only be obtained if treatment were confined to those with severe symptoms. In these patients the cost per QALY would be £8,500 for the median dose of GH currently used in the group of patients analysed on the European database described above.

b. Improvement in Mortality and Cost Savings by Events Averted

The evidence is deficient to allow more than speculation in this area, but some indication may be gained by comparison of the possible cardiovascular effects with statin therapy for cholesterol lowering. Those in the 4S trial[6] had an all cause mortality around 1.7 times the overall population of the same average age. This is about the same excess for cardiovascular mortality as has been described for patients with GH deficiency.

Whilst the use of statins reduced total cholesterol by 25% at one year (and LDL-cholesterol by 35%), GH treatment lowers cholesterol by a smaller amount (8% is cited in the first Wessex report[1]). The cost-effectiveness of secondary prevention with statins has recently been estimated at a gross cost of £5,000 per life-year gained, or £4,000 if a net cost (i.e. considering savings from events averted such as myocardial infarctions or revascularisations) is estimated.[7] However, even if GH reduced cardiovascular mortality by as much as statins in the 4S (secondary prevention) population, the net cost-effectiveness of GH in this respect would still be at least £24,000 per life year gained, as the annual costs of GH treatment are probably around six times those of statins.

The above analysis is only an approximation, but it does give some measure of comparison with other treatments in respect of the assessment of cost utility. In this case, however, only one effect of GH is being assessed and, if there were other beneficial cardiovascular effects,

and reductions of fractures, it may well be that the cost per life year gained would be considerably less.

In summary, therefore, if GH replacement in adults is within what is normally regarded as cost-effective within the NHS, it is most likely to be so in respect of treatment of the most severely affected.

As an example of criteria for determining severe GH deficiency and use of replacement therapy, the following have been used in Sheffield:[8]

- Presence of known pituitary disease including other pituitary hormone deficiency;
- Peak GH less than 9mU/l during a glucagon or insulin tolerance test;
- Severely impaired quality of life based on a validated GH specific quality of life measure;
- Bone mineral density standard deviation score of <-1; and
- Continued treatment is based on a review of the results of a six month trial of therapy at the end of which baseline and post-treatment measurements of body composition measures and quality of life will be assessed.

4. OPTIONS FOR PURCHASERS AND PROVIDERS

Option 1 Do not fund from mainstream NHS funds unless there are exceptional circumstances. Press for further trial evidence on long-term benefits.

Option 2 Produce clear guidelines to aid the selection of adult patients who stand to benefit the most from GH treatment. Press for further research to inform these guidelines, and provide funding to allow this group of patients to be treated.

Option 3 Provide additional funds to allow all adult patients with GH deficiency to receive treatment.

5. DISCUSSION AND CONCLUSIONS

After consideration of the first report from the Wessex Institute for Health Services Research,[1] the South and West Regional Development and Evaluation Committee concluded that this treatment fell into its "borderline" category.

The second report[2] from the Wessex Institute on GH replacement was more cautious, particularly about interpretation of the evidence for benefit in terms of quality of life. It was felt that there was high quality evidence demonstrating the effectiveness of GH in improving exercise performance, body composition, bone mineral density and cardiovascular status. However, the extent of its impact upon quality of life and future mortality and morbidity was deemed to remain unclear on a re-examination of the relevant evidence. In addition, information was lacking on potential long-term side effects of GH treatment. The South and West DEC again felt this treatment to be in its "borderline" category and expressed the need for guidelines to aid the selection of patients who stand to benefit most from treatment, and that further research is needed to inform these guidelines.

The main conclusions are:

- That there is good evidence in the published literature that GH has important actions on exercise capacity, body composition, bone density, and lipid profiles. Body composition and exercise capacity are important patient outcome measures

- The quality of life data in the literature is weak and better information should be collected using better and more specific quality of life questionnaire measures.

- Dosage levels, and hence costs, are now substantially less than projected by the Wessex report.[2]

6. USE OF GROWTH HORMONE IN ADULTS: SUMMARY MATRIX

PATIENT GROUP	PATIENT CRITERIA (GUIDELINES NOT PROTOCOLS)	ESTIMATED FUTURE ACTIVITY	OPPORTUNITY FOR COST SAVING	AUDIT POINTS	EFFECTS THAT COULD BE EXPECTED IN RELATION TO STARTING POINT	COST-EFFECTIVENESS
Adult patients with GH deficiency.	Adult patients with severe GH deficiency. Guidelines could be further improved on the basis of further research evidence when available.	Up to 40 adult patients on treatment in an average health authority of 500,000 population. Potential additional costs could be £130,000 per annum assuming average dose used is 0.12 units/kg/week.	Possible but undetermined.	Numbers of patients treated. Patient compliance with treatment. Physician compliance with guidelines for treatment.	Improvement in exercise tolerance, body composition, bone density, and lipid profile Uncertain degree of benefit in terms of quality of life improvement.	Largely unproven, but the limited available evidence suggests that for adult patients with severe GH deficiency the average cost per QALY may be as low as £8,500.

REFERENCES

(1) Wessex Institute of Public Health Medicine. *Growth hormone (somatropin) for growth hormone deficient adults. Development and Evaluation Committee Report No. 47.* R&D Directorate, South and West Regional Health Authority; Bristol; 1995.

(2) Wessex Institute for Health Research and Development. *Growth hormone for growth hormone deficient adults. Development and Evaluation Committee Report No. 75 (second edition).* Research and Development Directorate, NHS South and West; Bristol; 1997.

(3) Kann P, Piepkorn, Schehler B, et al. Effects of long term treatment with growth hormone on bone metabolism, bone mineral density, and bone elasticity in growth hormone deficient adults. *Clinical Endocrinology* 1998; (in press).

(4) McGauley G. *Acta Paedr Scand* 1989; 356:55-9.

(5) Carroll PV et al., *Journal of Clinical Endocrinology and Metabolism* 1998; (in press).

(6) Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heat disease; the Scandinavian Simvastatin Survival study (4S). *Lancet*; 344: 1383-9.

(7) Pickin DM, Payne, JN, Haq IU et al. *Statin therapy/HMG Co-A Reductase Inhibitor Treatment in the Prevention of Coronary Heart Disease.* Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield; Sheffield 1996. Guidance Note for Purchasers; 96/04.

(8) Ross R, Sutcliffe R. *Sheffield protocol for shared care of growth hormone replacement in growth hormone deficient adults.* Sheffield Health Authority, Sheffield; 1996.

Other papers published by the Trent Institute for Health Services Research are listed below:-

Guidance Notes for Purchasers

96/01	Working Group on Acute Purchasing: The use of DNase in Cystic Fibrosis (1996) by JN Payne, S Dixon, NJ Cooper and CJ McCabe.	£6.00
96/02	Working Group on Acute Purchasing: Tertiary Cardiology (1996) by J Tomlinson, J Sutton and CJ McCabe.	£6.00
96/03	Working Group on Acute Purchasing: The use of Cochlear Implantation (1996) by Q Summerfield and J Tomlinson.	£6.00
96/04	Working Group on Acute Purchasing: Statin Therapy / HMG Co-A Reductase Inhibitor Treatment in the Prevention of Coronary Heart Disease (1996) by MD Pickin, JN Payne, IU Haq, CJ McCabe, SE Ward, PR Jackson and WW Yeo.	£6.00
97/01	Working Group on Acute Purchasing: The Clinical and Cost-effectiveness of Computed Tomography in the Management of Transient Ischaemic Attack and Stroke (1997) by A Ferguson and CJ McCabe.	£10.00
97/02	Working Group on Acute Purchasing: Prostacyclin in the Treatment of Primary Pulmonary Hypertension (1997) by TW Higenbottam, SE Ward, A Brennan, CJ McCabe, RG Richards and MD Stevenson.	£10.00
97/03	Working Group on Acute Purchasing: The Use of Riluzole in the Treatment of Amyotrophic Lateral Sclerosis (Motor Neurone Disease) (1997) by J Chilcott, P Golightly, D Jefferson, CJ McCabe and S Walters.	£10.00
97/04	Working Group on Acute Purchasing: Recombinant Factor VIII Versus Plasma Derived Factor VIII in the Management of Haemophilia A: An Examination of the Costs and Consequences (1997) by C Green and RL Akehurst.	£10.00
97/05	Working Group on Acute Purchasing: The Use of Cisplatin and Paclitaxel as a First Line Treatment in Ovarian Cancer (1997) by SM Beard, R Coleman, J Radford and J Tidy.	£10.00
97/06	Working Group on Acute Purchasing: The Use of Alpha Interferon in the Management of Chronic Myeloid Leukaemia (1997) by RG Richards and CJ McCabe.	£10.00
97/07	Working Group on Acute Purchasing: Spinal Cord Stimulation in the Management of Chronic Pain (1997) by J Tomlinson, CJ McCabe and B Collett.	£10.00

Discussion Papers

No. 1.	Patients with Minor Injuries: A Literature Review of Options for their Treatment Outside Major Accident and Emergency Departments or Occupational Health Settings (1994) by S Read.	£7.00

96/01	Working Group on Acute Purchasing: The role of Beta Interferon in the Treatment of Multiple Sclerosis (1996) by RG Richards, CJ McCabe, NJ Cooper, SF Paisley, A Brennan and RL Akehurst.	£7.50
96/02	The Mid-level Practitioner: A Review of the Literature on Nurse Practitioner and Physician Assistant Programmes (1996) by P Watson, N Hendey, R Dingwall, E Spencer and P Wilson.	£10.00
96/03	Evaluation of two Pharmaceutical Care Programmes for People with Mental Health Problems Living in the Community (1996) by A Aldridge, R Dingwall and P Watson.	£10.00
97/01	Working Group on Primary and Community Care Purchasing : Report of the Sub-Group on the promotion of Quality in Primary Care - Effective Purchasing of Primary and Community Health Care: Promotion of Quality in the Provision of Primary Care (1997) by S Jennings and M Pringle.	£10.00
97/02	Working Group on Primary and Community Care Purchasing : Report of the Sub-Group on Information Needs for Health Needs Assessment and Resource Allocation (1997) by T Baxter, A Howe, C Kenny, D Meechan, M Pringle, P Redgrave, J Robinson and A Sims.	£10.00

Copies of these documents are available from:-

Suzy Paisley
Senior Information Officer
Trent Institute for Health Services Research
Regent Court
30 Regent Street
SHEFFIELD S1 4DA

Tel 0114 222 5420
Fax 0114 272 4095
E-mail scharrlib@sheffield.ac.uk

Please make cheques payable to "The University of Sheffield".