NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Appraisal of the use of human growth hormone for the treatment of adults with growth hormone deficiency

Decision of the panel

1. Introduction

1.1 An appeal panel was convened on 3rd July 2003 to consider appeals against the Institute's guidance to the NHS on the use of human growth hormone (HGH) for the treatment of growth hormone (GH) deficiency in adults.

1.2 The appeal panel comprised Professor Sir Michael Rawlins (chair of the appeal panel and chair of the Institute), Mr Roy Luff (non-executive director), Professor Leon Fine (non-executive director), Gill Donovan (patient representative) and Dr Angus Sim (industry representative).

1.3 Appeals were lodged by the following appellants:-

- Eli Lilly
- Novo Nordisk
- Pfizer
- The Society for Endocrinology in association with the Royal College of Physicians ("SoE")
- The British Society for Paediatric Endocrinology and Diabetes and the Royal College for Paediatrics and Child Health ("BSPE")
- The Pituitary Foundation

1.4 All the appellants were represented at the appeal.

1.5 In addition the following individuals involved in the appraisal were present and available to answer questions from the appeal panel: Professor David Barnett (chair of the Appraisal Committee), Anne-Toni Rodgers (corporate affairs director and executive lead for this appraisal), James Partridge (member of the Appraisal Committee), Dr Carol Longson (Appraisals Programme Director), Dr

Karl Claxton (member of the Appraisal Committee) and Dogan Fidan (technical lead).

1.6 Kathleen Dalby (appraisal project manager) and the Institute's legal advisor (Stephen Hocking, Beachcroft Wansbroughs) were also present.

1.7 The three grounds on which the appeal panel can hear an appeal are:

1) The Institute has failed to act fairly and in accordance with its procedures

2) The Institute has prepared guidance which is perverse in the light of the evidence submitted.

3) The Institute has exceeded its legal powers.

2 Appeal Ground One: The Institute has failed to act fairly and in accordance with the Appraisal Procedure set out in the Institute's Interim Guidance to Manufacturer and Sponsors.

2.1 The Pituitary Foundation alleged that the Final Appraisal Determination (FAD) gave no indication as to the rationale behind the key conclusions; and that this lack of transparency restricted the Foundation's capacity to respond to the proposed guidance.

The appeal panel considered that Section 4.3 of the FAD laid out, adequately, the Appraisal Committee's reasons for its advice. The Appeal Panel felt that the appellant had been able to understand the Committee's conclusions, and was sufficiently informed by the guidance and supporting material to make effective submissions on them. The appeal panel did not therefore accept that the Institute had failed to act fairly or in accordance with its procedures.

The appeal panel dismissed the appeal on this point.

3 Appeal Ground Two: The Institute has prepared guidance which is perverse in the light of the evidence submitted.

3.1 The BSPED claimed that the guidance appeared to have been prepared principally for middle aged and elderly patients with GH deficiency. The Society considered that the proposed threshold for clinical and cost effective improvement of 7 points on the AGDHA scale meant that the majority of young adults would be ineligible to continue treatment after the age of 25 years. The BSPED also alleged that the AGHDA quality of life instrument was inappropriate for use in younger patients. Indeed, it had embarked on a research programme to develop a quality of life instrument that would be more appropriate for this patient population. The proposed guidance would discriminate against access to treatment on grounds of age and was therefore perverse.

Prof Barnett explained that the Appraisal Committee had been aware of the limitations of the AGHDA scale but had been advised by endocrinologists that it was the most appropriate instrument for use in deciding on the treatment of GH deficiency in adults. In the absence of any other instrument, the committee had considered that it should also form the basis for determining HGH treatment in younger adults who had attained their maximum linear height and bone mass. Since the proposed treatment threshold would be the same in this group, as in adult-onset GH deficiency, he rejected the allegation that the committee had discriminated on the basis of age.

It was clear to the appeal panel that the proposed treatment threshold, in younger adults, was based on the same change in the AGHDA score as in older patients. The appeal panel did not therefore consider that the proposed guidance discriminated against younger patients on the grounds of age or that the Appraisal Committee had acted perversely.

The appeal panel therefore dismissed the appeal on this point.

3.2 The BSPED claimed that it was perverse that young adults had to meet the strict criteria for obtaining HGH treatment twice. The BSPED claimed that the requirement for HGH treatment to be withdrawn, in young adults with childhood-onset GH deficiency, once they had completed linear growth and achieved adult bone mass, was unacceptable. It would require their quality of life to drop to an unacceptable level before treatment could be resumed. Instead, the BSPED's representative suggested that decisions about continuation of HGH treatment should be left to the judgement of the physician in consultation with the patient.

The appeal panel noted that the Appraisal Committee had considered there were two separate benefits for young adults from receiving HGH treatment. The first was attainment of adult bone density, a benefit unique to young adults. The second was the quality of life benefit experienced by at least some of the adult patient population generally. The appeal panel did not consider it perverse that one criterion should apply to treatment to secure adult bone density, and that additional criteria should apply once adult bone density had been achieved to benefits experienced by at least some of the adult patient population generally. The appeal panel also reminded the BSPED's representative that the Institute had a duty, imposed by parliament, to take account of both clinical *and* cost effectiveness in providing guidance to the NHS on the use of particular health technologies. The BSPED's proposed approach would fail to ensure that the use of HGH in the proposed manner would be cost effective, or the degree to which it was clinically effective. The panel considered that the Appraisal Committee's approach was not perverse.

The appeal panel dismissed the appeal on this point.

3.3 The SoE claimed it was perverse for the Appraisal Committee to recommend that patients on HGH therapy should be required to show an improvement, after 9

months treatment, of 7 points on the AGHDA scale. The SoE added that there was a lack of a reasoned explanation as to how this figure had been arrived at. Moreover, the guidance failed to consider patients whose initial (ie pre-treatment) AGHDA scores were less than 11 points but who nevertheless improved by 7 points.

Professor Barnett reminded the appeal panel that, after the last appeal, the panel had made specific recommendations (paragraph 3.2):

> "The Institute should undertake further discussions with consultees aimed at defining, with greater precision, appropriate selection criteria for patients with adult GH deficiency in whom treatment with HGH might be clinically and cost effective……. These discussions should also entertain the possibility of identifying patients who, after a defined period of treatment, respond inadequately and in whom therapy with HGH should be withdrawn".

He explained that the Appraisal Committee had explored, in considerable detail, the magnitude of the benefits of treating adult GH deficiency that could reasonably be considered both clinically and cost effective. The committee gave particular consideration to the incremental cost effectiveness ratios (ICERs), for various degrees of improvement in quality of life following treatment with HGH, as reported by ScHARR in its response to stakeholders' comments (dated 20 January 2003). In the committee's judgement only an improvement of at least 7 points on the AGHDA scale, following treatment with HGH, could be considered cost effective. This was based on the most optimistic interpretation of the available data and was independent of patients' pre-treatment scores. He added that the Committee had expressly judged that the evidence and analysis showed that it was improvements of 7 or more points in individual patients that could demonstrate acceptable cost effectiveness: the committee had not reached the conclusion that an average (mean) improvement of 7 points in a patient population was cost effective.

In the light of the appeal panel's previous decision the Appraisal Committee had also considered the minimum pre-treatment AGHDA score that would warrant a trial of HGH therapy. Professor Barnett explained that this was not another cost effectiveness criterion, as some appellants had alleged. The Committee considered that (other than for young adults achieving adult bone density) there was only one cost effectiveness criterion: an individual improvement of 7 points. The Committee's concern was to identify that group of patients where that degree of improvement could reasonably be hoped for.

Although a "normal" AGHDA did not appear to have been formally defined, expert advice indicated that a score of up to 4 was commensurate with a normal quality of life. The committee rejected the possibility that all patients undergoing HGH therapy should be expected (or required) to achieve an AGHDA score of 4 or less after 9 months treatment. The committee had concluded, therefore, that patients appropriate for a trial of HGH treatment, and who would have an opportunity to achieve an improvement of at least 7 points, should have a pre-treatment AGHDA score of at least 11 (ie 4 + 7). This also accorded with data from the KIMS database. Whilst the committee could have recommended a pre-treatment AGHDA score of less than 11 points, it would be increasingly difficult for patients to demonstrate the required degree of improvement at any scores lower than 11 points. The Committee observed that there was a significant "opportunity cost" to even a trial of HGH treatment, and that it had to have regard to that cost. It concluded that, although it was mathematically possible that some few patients with a pre-treatment AGHDA score of, say, 10, could achieve a 7 point improvement (3 being an attainable score on the AGHDA scale), evidence showed that too few would do so to justify the resources which would be consumed in conducting a trial in such patients. Hence overall treatment of patients with a score of, say, 10 points, would not be cost effective.

The appeal panel considered that the Appraisal Committee had acted reasonably in basing its advice on

the individual patient's "capacity to benefit" and that the judgement that this was shown by improving their AGHDA score, after 9 months HGH treatment, by 7 points was within the reasonable range. This clearly took account of the need to demonstrate both clinical and cost effectiveness. The panel accepted that the committee's advice was determined on a generous interpretation of the available data and the assumptions used in estimating ICERs. Moreover, the appeal panel did not consider that the Appraisal Committee had acted perversely in advising that continuation of treatment, in an individual patient, should depend on the magnitude of the therapeutic response in that patient: the same principle had been adopted in respect of the Institute's advice on the continuing use of products used for other conditions (eg Technology Appraisal Guidance 31 and 42).

The appeal panel also considered that the Appraisal Committee had acted reasonably in advising on the minimum AGHDA score required before a trial of HGH treatment could be initiated. The panel accepted that this was based on an appropriate interpretation of the available data. The panel also accepted the argument that if the Appraisal Committee had recommended a lower pre-treatment AGHDA score there would have been a significant opportunity cost. The panel therefore did not agree that the FAD did not include guidance for patients with an initial AGHDA score of less than 11.

The appeal panel therefore concluded that the Appraisal Committee's advice on the pre-treatment AGHDA score, and the degree of improvement in the AGHDA scale after 9 months HGH treatment, was not perverse.

The appeal panel therefore dismissed the appeal on this point.

3.4 The SoE alleged that adult patients receiving HGH treatment were required to show a completely different level of cost-benefit to paediatric patients. The SoE further claimed that "the paediatric use of GH has absolutely no cost-benefit data to support its use".

The appeal panel pointed out that this latter statement was incorrect. The Technology Appraisal Guidance (No 42) on the use of HGH in children did, indeed, consider both its clinical *and* cost effectiveness (Section 4.2). The appeal panel recognised that the basis for appraising the clinical and cost effectiveness of HGH in children was different from that in adults, but considered that this was inevitable: the benefits of HGH treatment in children and adults were different. Consequently, the appeal panel did not consider that the Appraisal Committee's advice was either inconsistent or perverse.

The appeal panel therefore dismissed the appeal on this point.

3.5 The SoE claimed that the degree of improvement (7 points on the AGHDA scale) required in the proposed guidance was unachievable for 50% of those patients currently deemed to require treatment.

Professor Barnett emphasised that the 7-point improvement recommended in the FAD was based on a cost effective "capacity to benefit". The acceptance of lesser degrees of benefit would not, in the Appraisal Committee's judgement, be cost effective. The definition of the recommended pre-treatment AGHDA score was therefore based on the committee's judgement about identifying those patients with a cost effective "capacity to benefit".

The appeal panel accepted that the committee had sought to identify those patients in whom HGH treatment would be cost effective; and that this was based on considerations of "capacity to benefit". This was not perverse.

The appeal panel therefore dismissed the appeal on this point.

3.6 The SoE alleged that the proposed guidance perversely set two cost effective hurdles. One hurdle was a pre-treatment AGHDA score of 11 or more; the other was a

response to treatment of 7 points or more on the AGHDA scale.

Noting Professor Barnett's remarks in paragraphs 3.3 and 3.5 (above) it was clear to the appeal panel that the basis for the Appraisal Committee's advice was on the "capacity to benefit" as represented by an improvement of 7 points, or more, on the AGHDA scale after 9 months treatment with HGH. Moreover, as indicated in paragraph 3.3 (above), the ICER of this degree of improvement was independent of the pre-treatment AGHDA score. The appeal panel did not therefore consider that the Appraisal Committee's advice was based on two cost effectiveness hurdles, nor that its conclusions were perverse.

The appeal panel therefore dismissed the appeal on this point.

3.7 The SoE alleged that the guidance misrepresented the economic evidence and was therefore perverse. The Society claimed that the ScHARR analysis demonstrated that either patient selection via a baseline threshold, or treatment by continuing only those from the entire population who reached a given level of benefit, would result in cost effective therapy. The Society considered that by combining the two approaches the Appraisal Committee had acted perversely.

Professor Barnett explained (see paragraphs 3.3, 3.5 and 3.6 above) that the Appraisal Committee's advice was based on the ICERs derived from patients' responses to 9 months HGH treatment and not on their pre-treatment AGHDA scores, and that the data relied on were at the optimistic end of a spectrum. Inclusion of patients who were unlikely to achieve the cost-effective benefit of 7 or more points would tip the judgement against cost effectiveness and an effective use of NHS resources.

The appeal panel considered that the SoE's interpretation of the economic basis for the Appraisal Committee's advice was incorrect and that the committee had not acted perversely.

The appeal panel therefore dismissed the appeal on this point.

3.8 The SoE claimed that the proposed guidance could not be implemented, within the NHS, on ethical grounds. The SoE alleged that both withholding treatment from patients who have demonstrated benefit, and the different approaches to the treatment of adults and children, were unethical.

The appeal panel reminded the Society (see paragraph 3.2 above) that the Institute has a responsibility to take cost effectiveness, as well as clinical effectiveness, into account when giving advice on the use of technologies within the NHS. In doing so, the Institute considers it has a duty to be fair to all patients who rely on the NHS for their healthcare. Consequently the Appraisal Committee has to take account of the opportunity costs associated with all its guidance.

It was apparent to the appeal panel, in the light of Professor Barnett's comments above (paragraphs 3.3, 3.5 and 3.6 above), that the Appraisal Committee had drawn its conclusions on the cost effectiveness of HGH treatment from the standpoint of individual's "capacity to benefit". The appeal panel did not consider this to be perverse or unethical.

Furthermore, noting its conclusions in paragraph 3.4 (above), the appeal panel considered that in view of the differing objectives of HGH treatment in children and adults it was inevitable that different considerations would pertain. The panel did not, therefore, accept that this was perverse or unethical.

To the extent that any clinician felt that, in the case of any given patient the strict application of the guidance would be unethical, the Appeal Panel reminded itself that the FAD was expressed to take effect as guidance only and not to override the clinical judgement of the medical professional, which would always include ethical considerations.

The appeal panel therefore dismissed the appeal on this point.

3.9 The SoE claimed that the guidance would lead to the unsafe and unsupervised use of HGH. The Society claimed that some patients would seek to obtain HGH from other sources.

Professor Barnett indicated that the Appraisal Committee had appreciated this possibility but considered that its responsibilities were concerned with offering advice, to the NHS, on the clinical and cost effectiveness of HGH in adults.

The appeal panel accepted that, whilst the Appraisal Committee had clearly taken this matter into account, the Appraisal Committee could not (as a general rule) be responsible for the reactions of others to its guidance (especially when those reactions might be of questionable legality). The panel did not, therefore, consider that the Appraisal Committee had acted perversely about this issue.

The appeal panel therefore dismissed the appeal on this point.

3.10 The Pituitary Foundation claimed that the requirement for a 7-point change in the AGHDA scale, after 9 months treatment with HGH, was mathematically dubious and the reasoning perverse. It appeared that all patients undergoing treatment were expected to achieve this "average".

Professor Barnett explained that the requirement for a 7-point improvement on the AGHDA scale did not represent an "average" change, but the minimum degree of improvement necessary for the continuing use of HGH to be cost effective as well as clinically effective.

The appeal panel, noting its comments and conclusions in paragraphs 3.3, 3.5 and 3.6 (above), did not consider that the Appraisal Committee's approach was either mathematically dubious or perverse.

The appeal panel therefore dismissed the appeal on this point.

3.11 The Pituitary Foundation claimed that the requirement for a patient's quality of life to be restored to normal, by treatment with HGH, was perverse.

Noting Professor Barnett's comments in paragraph 3.3 (above), it was apparent to the appeal panel that the Appraisal Committee had not based its guidance on "normalising" patients' AGHDA scores. The panel therefore rejected the Pituitary Foundation's claim and considered that the committee had not been perverse.

The appeal panel dismissed the appeal on this point.

3.12 The Pituitary Foundation claimed that, on basis of the experience of patients and experts, continuing treatment with HGH should be offered to those who achieved a 20% improvement in their AGHDA score.

Professor Barnett explained that the basis for the Appraisal Committee's recommendation was on patients' "capacity to benefit" (see paragraphs 3.3, 3.5 and 3.6 above). The committee had, indeed, considered the possibility that (as implicit in the Pituitary Foundation's proposal) treatment should be offered to patients depending on their pre-treatment AGHDA score. The ScHARR report (Table 6) suggested, however, that in these circumstances the ICERs were strongly associated with age as well as with the pre-treatment AGHDA score. Moreover, the use of a percentage change to determine continuation of HGH treatment would disadvantage patients with the more severe symptoms because, in this subgroup, patients would have to achieve a greater absolute reduction on the AGHDA scale to achieve the same percentage reduction. Further, the AGHDA scale had only ordinal properties, making the concept of a percentage improvement meaningless.

The appeal panel concluded that the Appraisal Committee had, appropriately, rejected a percentage change in

AGHDA score as the criterion for offering continued HGH treatment and had not acted perversely.

The appeal panel therefore dismissed the appeal on this point.

3.13 The Pituitary Foundation claimed that some patients with GH deficiency had other medical problems. Whilst they could benefit from HGH treatment they might fail to achieve a 7-point improvement because of their co-existing problems.

Ms Rodgers explained that this possibility was inherent in many of the Institute's Technology Appraisal Guidance. It was one of the reasons why the preamble to all appraisals invariably included the following statement:

> "This guidance does not override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer."

The appeal panel considered that it would be impossible for the Appraisal Committee to include the potential impact of co-morbidity in its guidance. The statement to which Ms Rodgers referred provided a framework through which individual health professionals could exercise their clinical judgement in the face of co-morbidity. The panel did not consider that the Appraisal Committee had acted perversely.

The appeal panel therefore dismissed the appeal on this point.

3.14 The Pituitary Foundation claimed that 50% of patients, on HGH for 9 months, would be denied further treatment because they fail to achieve a 7-point improvement on the AGHDA scale. The Pituitary Foundation that this was perverse.

Professor Barnett explained that, as described previously (paragraph 3.3, 3.5 and 3.6 above), the requirement for a

7-point improvement was derived from the committee's consideration of the ICERs of treatment and not from an average response rate.

The Appeal Panel considered that the Committee's task was to provide guidance in accordance with the Institute's directions. Whether any given percentage of patients would or would not receive treatment could not, on its own, indicate perversity. Noting its previous conclusions (paragraphs 3.3, 3.5, 3.6 and 3.8), the appeal panel did not consider that the Appraisal Committee had acted perversely.

The appeal panel therefore dismissed the appeal on this point.

3.15 The Pituitary Foundation claimed that it was perverse for the Appraisal Committee to have used the EQ-5D data for the point improvement but not for the cost per QALY calculation.

Professor Barnett explained that the EQ-5D data had, indeed, been used to estimate the costs per QALY (see ScHHAR report dated 20th January 2003).

The appeal panel accepted this and did not consider that the Appraisal Committee had been perverse.

The appeal panel therefore dismissed the appeal on this point.

3.16 The Pituitary Foundation claimed that the Appraisal Committee had been perverse in requiring the reassessment of those patients, already on treatment at the time the guidance was issued to the NHS, to be reassessed taking account of the guidance in Section 1.1 of the FAD. The Pituitary Foundation's interpretation of this was that HGH treatment would have to be withdrawn from such patients until their AGHDA score reached 11. Only if their score reached this level would they be eligible for a trial of 9 months HGH treatment.

Professor Barnett explained that it was not the intention of the Appraisal Committee to require that, in such patients, HGH therapy should be withdrawn. He accepted, however, that Section 1.3 of the FAD could be misinterpreted in this manner. He suggested that this Section be reworded by the Guidance Executive to eliminate any misunderstanding. He added, however, that the Committee had indeed intended that child and young adult patients receiving HGH should be reassessed in the light of the guidance when they reached the transition thresholds identified within it.

The appeal panel agreed that the Institute's policy was to recommend that patients, already on a particular treatment at the time of the publication of appraisal guidance, should not have their therapy withdrawn as a result of the publication of the Institute's guidance.

Although the appeal panel did not consider, in the light of Professor Barnett's explanation, that the Appraisal Committee's intentions had been perverse the wording of Section 1.3 required modification.

The appeal panel therefore dismissed the appeal on this point but, in order that there should be no misunderstanding of the Institute's position, the Guidance Executive should replace Section 1.3 of the FAD with clearer advice. This could be similar to the wording of Section 1.3 of the June 2002 FAD. The Guidance Executive should ensure that it remains clear that the reworded section 1.3 does not refer to children or young adults currently receiving HGH, who achieve one of the transition thresholds referred to in the FAD: it should consider whether a re-ordering of paragraphs 1.3-1.5 would be helpful in that regard.

3.17 The Pituitary Foundation alleged that it was perverse, in Sections 4.3.17, 4.3.18 and 4.3.19 of the FAD, for young adults who had been treated for childhood-onset GH deficiency to have HGH withdrawn until such time as they achieved an AGHDA score of 11.

Professor Barnett explained that the indications for treating young adults, once they had completed linear growth and achieved adult bone mass, were similar to those with adult-onset GH deficiency. Unless they underwent a trial of withdrawal, it would be impossible to assess their need for continuing HGH treatment.

The appeal panel, noting their conclusions in paragraphs 3.1 and 3.2 (above), did not consider that the Appraisal Committee had acted perversely in reaching this conclusion.

The appeal panel therefore dismissed the appeal on this point.

3.18 The Pituitary Foundation claimed that the Appraisal Committee's conclusions perversely contradicted the expert advice of the Royal College of Physicians and the Society of Endocrinology.

Professor Barnett explained that the Appraisal Committee had devoted many hours to discussing the use of HGH with clinical experts. Nevertheless, the committee had reached its conclusions on both clinical and cost effectiveness grounds.

The appeal panel was satisfied that the Appraisal Committee had had the benefit of appropriate expert advice. The committee's failure to adopt the recommendations did not necessarily amount to perversity: the committee was obliged to take a broader view of the relevant issues and to take into account the interests of all NHS patients (see paragraph 3.8 above). The committee had not therefore acted perversely.

The appeal panel therefore dismissed the appeal on this point.

3.19 Pfizer claimed that the guidance contradicted the evidence provided to the Appraisal Committee. In particular, the advice requires patients to satisfy two cost effectiveness hurdles before being eligible for long-term treatment with HGH.

The appeal panel, noting the explanations given by Professor Barnett in paragraphs 3.3, 3.5, 3.6 and 3.8, together with its own conclusions in these paragraphs, did not consider that the Appraisal Committee had acted perversely.

The appeal panel therefore dismissed the appeal on this point.

3.20 Pfizer claimed that the Appraisal Committee had over-simplified the clinical benefits of HGH by excluding the impact of treatment on patients' Standard Mortality Ratios (SMRs).

Professor Barnett indicated that the Appraisal Committee had, indeed, given full consideration to the effect of HGH on SMRs and its conclusions were summarised in Sections 4.3.7 and 4.3.8 of the FAD.

The appeal panel considered that the FAD explained the Appraisal Committee's conclusions on this matter, and it did not consider that the committee had been perverse.

The appeal panel therefore dismissed the appeal on this point.

3.21 Eli Lilly alleged that it was perverse of the Appraisal Committee to recommend the use of a scale, as part of its guidance, that is not freely available.

In response to questioning by the chairman of the appeal panel, the representatives of Pfizer stated that their company claimed the copyright and intellectual property rights associated with the AGHDA scale. Nevertheless, the company were prepared to permit the use of the scale for the purposes of routine treatment of patients irrespective of the manufacturer of the product. The chairman of the appeal panel then asked Pfizer if their company had any objection to the Institute publishing the AGHDA scale, as an appendix to its guidance, for prescribers to use in the routine management of patients under their care. The company's representatives

indicated that they were seeking permission for this from their senior executives in the USA. They expected to be able to respond positively within a few days.

Some days after the appeal hearing, a letter was duly received from Pfizer in the terms attached.

Eli Lilly also indicated that they also wished to have unfettered access to the AGHDA scale for research purposes. They claimed that this was necessary if they were to meet the Appraisal Committee's research recommendations as well as for auditing treatment. They asserted that it would be anticompetitive for the Institute to issue guidance referring to a scale not freely available to all manufacturers.

The appeal panel noted the extensive use, and importance, of the AGHDA scale in the appraisal of HGH for the management of GH deficiency in adults. The appeal panel considered that it to be in the best interests of patients for the AGHDA scale to be incorporated into the Institute's guidance, for use by those responsible for the care of adult patients with GH deficiency. The appeal panel did not, however, consider that the Institute had any powers in respect of the use of the AGHDA scale for research purposes. The panel noted that recommendations for future research were not part of the Institute's guidance to the NHS. Further, the panel observed that the Institute's duty was to produce guidance in accordance with its Directions. That guidance might affect the commercial position of one manufacturer or another, was neither the purpose of the guidance nor of itself a reason to hold that the guidance was perverse. The relative positions of manufacturers might well be affected by their respective intellectual property rights, and those rights were not incompatible with competition obligations. The assertion of intellectual property rights could not be permitted to prevent the Institute from producing the best possible guidance within its directions. The Panel did not consider that there was a distinction in kind to be drawn between an intellectual property right attaching to a product itself (eg a patent), and one attaching to a tool applied in the use of the product (eg

copyright in the QoL-AGHDA questionnaire and scale). The panel was mindful that the aggressive assertion of such a right with a view to gaining commercial advantage might indeed have to be reflected in the content of guidance, but concluded that provided the QoL-AGHDA questionnaire and scale was made available with the guidance for use in clinical practice that was not the case here.

The appeal panel did not consider that the Appraisal Committee had been perverse in its recommendation of the use of the AGHDA scale for routine clinical purposes. The panel felt that Pfizer's offer of the use of the scale and questionnaire, in the terms of the attached letter, was satisfactory, and that the guidance did not give Pfizer an unacceptable (or indeed any) advantage over other manufacturers.

The appeal panel therefore dismissed the appeal on this point.

3.22 Eli Lilly claimed that there was insufficient evidence to substantiate the proposal that HGH treatment should be confined to patients achieving a score of 7, or more, on the AGHDA scale after 9 months treatment.

The appeal panel, noting the explanations given by Professor Barnett in paragraphs 3.3, 3.5 and 3.8, together with its own conclusions in these paragraphs, did not consider that the Appraisal Committee had acted perversely.

The appeal panel therefore dismissed the appeal on this point.

3.23 Eli Lilly claimed that it was perverse of the Appraisal Committee to recommend that the criteria for continuing therapy with HGH until peak bone density has been achieved, in confirmed GH deficient patients who have reached their final height, includes the need to meet a quality of life threshold.

The appeal panel considered that the guidance in Sections 4.3.17 and 4.3.18 of the FAD clearly advises, for those with childhood-onset GH deficiency who have completed linear growth but who remain severely deficient in GH according to biochemical tests, treatment with HGH should continue until adult bone mass is achieved. The appeal panel noted that there was no requirement, at this stage, for patients to meet a quality of life threshold. The panel concluded that the Appraisal Committee had not been perverse in its consideration of this issue.

The appeal panel therefore dismissed the appeal on this point. Nevertheless, the appeal panel requests that the Guidance Executive reviews this part of the guidance to ensure that there can be no misunderstanding about the Institute's advice.

3.24 Novo Nordisk claimed that the monitoring criteria for patients to continue on HGH therapy was too stringent, and would deny treatment to patients whose improvement was clinically significant.

The appeal panel, noting the explanations given by Professor Barnett in paragraphs 3.3, 3.5, 3.6 and 3.8, together with its own conclusions in these paragraphs, did not consider that the Appraisal Committee had acted perversely.

The appeal panel therefore dismissed the appeal on this point.

3.25 Novo Nordisk was concerned that the FAD failed to provide clarity in terms of the copyright and intellectual property rights associated with the use of the AGHDA scale.

In response to questioning by the chairman of the appeal panel, the representatives of Pfizer stated that their company claimed the copyright and intellectual property rights associated with the AGHDA scale. Nevertheless, the company were prepared to permit the use of the scale for the purposes of routine treatment of patients irrespective of the manufacturer of the product. The

chairman of the appeal panel then asked Pfizer if their company had any objection to the Institute publishing the AGHDA scale, as an appendix to its guidance, for prescribers to use in the routine management of patients under their care. The company's representatives indicated that they were seeking the views of this from their senior executives. They expected to be able to respond positively within a few days.

Some days after the appeal hearing, a letter was duly received from Pfizer in the terms attached.

Novo Nordisk also indicated that they also wished to have unfettered access to the AGHDA scale for research purposes. They claimed that this was necessary if they were to meet the Appraisal Committee's research recommendations.

The appeal panel noted the extensive use, and importance, of the AGHDA scale in the appraisal of HGH for the management of GH deficiency in adults. The appeal panel, again, considered that it was in the best interests of patients for the AGHDA scale to be incorporated into the Institute's guidance, for use by those responsible for the care of adult patients with GH deficiency. The appeal panel did not, however, consider that the Institute had any powers in respect of the use of the AGHDA scale for research purposes. The panel noted that recommendations for future research were not part of the Institute's guidance to the NHS. Further, the panel observed that the Institute's duty was to produce guidance in accordance with its directions. That guidance might affect the commercial position of one manufacturer or another, but that was neither the purpose of the guidance, nor of itself a reason to hold that the guidance was perverse. The relative positions of manufacturers might well be affected by their respective intellectual property rights, and those rights were, clearly, not incompatible with competition obligations. The assertion of intellectual property rights could not be permitted to prevent the Institute from producing the best possible guidance within its directions. The Panel did not consider that there was a distinction in kind to be drawn between an intellectual

property right attaching to a product itself (eg a patent), and one attaching to a tool applied in the use of the product, eg copyright in the QoL-AGHDA questionnaire and scale. The panel was mindful that the aggressive assertion of such a right with a view to gaining commercial advantage might indeed have to be reflected in the content of guidance, but concluded that provided the QoL-AGHDA questionnaire and scale was made available with the guidance for use in clinical practice that was not the case here.

The appeal panel did not consider that the Appraisal Committee had been perverse in its recommendation of the use of the AGHDA scale for routine clinical purposes. The panel felt that Pfizer's offer of the use of the scale and questionnaire, in the terms of the attached letter, was satisfactory, and that the guidance did not give Pfizer an unacceptable (or indeed any) advantage over other manufacturers.

The appeal panel therefore dismissed the appeal on this point.

4. Appeal Ground Three: The Institute has exceeded its legal powers.

4.1 There were no allowable grounds of appeal under this Ground.

5. Conclusions

5.1 The appeal panel dismisses all points in this appeal. The panel, however, draws the attention of the Guidance Executive to its comments in paragraphs 3.16 and 3.23 (above).