ADMINISTRATIVE-CONFIDENTIAL

REPORT OF THE NIH HUMAN GROWTH HORMONE PROTOCOL REVIEW COMMITTEE

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Bernadine Healy, M.D.
Director
National Institutes of Health
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Dear Dr. Healy:

Please find enclosed the final report of the National Institutes of Health (NIH) Human Growth Hormone Protocol Review Committee. In accordance with your charge, the Committee reviewed two intramural research protocols involving the administration of biosynthetic human growth hormone in children with extreme short stature and in girls with Turner syndrome. The Committee discussed the study design and protocols, the human subjects review process and issues, and the social and ethical implications of the studies. A summary of the Committee's findings appears on pages 38 and 39 of the report.

On behalf of the entire Committee, we were pleased to have an opportunity to assist in the review of these studies and trust that our report will prove helpful to the NIH.

Sincerely,

William Friedewald, M.D.
Senior Vice President and
Chief Medical Director
Metropolitan Life Insurance Company

Loretta Kopelman, Ph.D.
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August 17-19, 1992

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The use of human growth hormone (hGH) to promote growth in children of extreme short stature has been a topic of research and debate for some time. Although it has been 25 years since growth hormone was demonstrated to stimulate linear growth, limited availability of natural hGH restricted its use to those with unequivocal growth hormone deficiency, for which the diagnosis is straightforward. Prior to the early to mid 1980s, in the United States virtually all patients were treated under research protocols approved by the National Pituitary Agency (later renamed the National Hormone and Pituitary Program), which was responsible for the collection, processing, and distribution of hGH. In 1985 distribution of natural hGH was halted because of the occurrence of Jacob-Creutzfeldt disease in some recipients.

For many years dosage and duration of hGH therapy were strictly limited; for example, therapy would be discontinued when patients achieved "acceptable" heights of 62 inches, or 64 inches in later years. Under these circumstances, there was little incentive to assess hGH as a treatment for extremely short children whose hGH production, though apparently sufficient in quantity, might involve more subtle abnormalities. However, it has long been hypothesized that hGH might increase growth in some extremely short children who appear to have normal or near normal levels of the endogenous hormone as assessed by present techniques.

In 1985, the U.S. Food and Drug Administration (FDA) approved a recombinant human growth hormone, identical to the native human growth hormone other than a methionyl fragment, for "the long term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion." Soon thereafter, a hormone identical to the natural sequence was also approved by the FDA with similar

indications. Both drugs were approved under provisions of the Orphan Drug Act, which provides marketing exclusivity to Genentech for its methionyl version of hGH until October 17, 1992 and to Eli Lilly, pharmaceutical manufacturer of the natural sequence version (Humatrope) used in the study, until March 1994. While expensive--a year's treatment can cost $20,000 or more--there are ample supplies of hGH, thus making it possible to consider as a treatment of extremely short children, who in many respects are comparable to children with classically defined growth hormone deficiency but who produce "normal" amounts of growth hormone in response to the standard provocative challenges.

At present, an estimated 15,000 or more children in the United States are being treated with hGH. Of these, up to half, including girls with Turner syndrome, are children who do not have classical hGH deficiency. Whether such children should be receiving growth hormone is controversial. Short-term, uncontrolled clinical trials in the United States and in Europe have suggested that some of this latter group exhibit increased growth velocity when administered growth hormone, but there is no conclusive information on whether this appreciably alters ultimate adult height. At the same time, the difficulty in establishing a definitive diagnosis of growth hormone deficiency in addition to the ambiguous language of the current FDA approved indications make it quite likely that additional children will nonetheless be placed on hGH treatment. This is particularly likely if, as many observers suggest, prices drop considerably with the expiration of orphan drug status.

At current prices, if most children below the first percentile were treated it would cost a total of $2 to $4 billion annually, a figure which has led many critics to question the cost/benefit of such therapy in an already strained health care system. However, while estimates of cost can be calculated either for specific patients or for the group of

extremely short children as a whole, the ultimate benefits have yet to be defined either in terms of the actual increments in stature achieved or with respect to the perceived psychosocial benefits of these increments to the individuals and to society in general.

Thus, one critical clinical issue in the use of hGH in children without demonstrable growth hormone deficiency is whether it will actually increase ultimate adult height (and, if so, by what degree), versus whether it causes more rapid attainment of the same adult height that would have been reached without treatment. If hGH actually increases ultimate adult height, then the benefit must be weighed by potential users against costs, discomfort, and possible risks of physical and psychosocial harms of such treatment. If final adult height is not increased then use of hGH in such children will not be indicated. Better information is needed in order to improve these decisions. The scientific community agrees that the best information comes from carefully designed, double-blind, randomized, placebo-controlled studies.

Recent concerns have been raised by the Foundation on Economic Trends and the Physicians Committee for Responsible Medicine, as well as by a ruling of an Institutional Review Board (IRB) of the University of Nebraska, that the use of placebo controls are not appropriate in such studies because placebo controls unnecessarily expose children to discomfort and psychosocial risks.

In response to these concerns, the National Institutes of Health (NIH) conducted an internal review of two research protocols currently underway at the National Institute for Child Health and Human Development (NICHD). One protocol is investigating the effects of hGH on girls with Turner syndrome. The other protocol is examining the effects of hGH on children of extreme short stature who do not have classical growth hormone deficiency (hereafter referred to as the short stature protocol). Both protocols have placebo and

tr... ...jects c... be followed until attai..ment of their adult stature.

Based on issues of study design, including statistical power, feasibility, and the use of children in trials such as these, it was determined that review by an independent Data Safety and Monitoring Board (DSMB) was warranted. An ad hoc committee was convened August 17-19, 1992, and again on September 11, 1992, to serve as an interim DSMB to review the study protocols and designs, the human subjects review processes, methods of data collection and analysis, and the social and ethical implications of the studies.

The committee was given the mandate to review a series of questions and report to the Director of NIH within a month. The committee was comprised of pediatric endocrinologists, ethicists, an attorney, biostatisticians, and a physician with extensive clinical trial experience.

In the course of the three and a half days of meetings, the committee heard from the principal investigators for the two studies, NIH officials in the Office of the Director, the Director and scientific officer of NICHD, staff of the NIH Office for Protection from Research Risks (OPRR), staff responsible for Data Safety and Monitoring requirements at NIH, and the assent auditor for the short stature protocol. Much of the discussion the first evening and following day took place without the review of data from the studies. Blinded data on the short stature study were presented to the committee late in the afternoon of the first full day of the meeting and at the second meeting in September. Data from the Turner syndrome study were not available at the time of these meetings and will be reviewed in the near future (see following discussions).

This document briefly describes the protocols under review and reports on the discussions and findings of the committee. Because the committee deferred extensive

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focuses on the short stature protocol. The results of the discussion pertaining to Turner syndrome are presented last.

THE SHORT STATURE PROTOCOL

To answer the questions of the benefits and risks of hGH treatment for extreme short stature not due to classical growth hormone deficiency, an investigative protocol was submitted in 1984 to NICHD. Prepubertal children of extreme short stature and normal responses to growth hormone provocative tests are administered hGH until adult height is reached. The study is double-blind, randomized, and placebo-controlled, and is designed to determine if long-term treatment with hGH actually increases adult height. The children are to be followed over time to monitor not only growth but also general health and psychosocial status. To qualify for the original study, children had to meet the following conditions:

- a height at least 3.00[1] standard deviations below the mean at the time of evaluation, or a Bayley Pinneau prediction of adult height that is at least 3.00 standard deviations below the mean;
- proportionate short stature;
- prepubertal or in Tanner stage 2 puberty at the start of the 6-month pretreatment period;
- girls age 9 to 14, boys age 10 to 15;
- unfused carpal and phalangeal epiphyses by bone age x-ray; and
- growth hormone responses to arginine-insulin and levodopa provocative tests

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[1]The protocol was amended with inclusion criteria of 2.5 standard deviations below the mean in 1987, and was amended back to 2.25 standard deviations below the mean in 1990. The most recent protocol was reviewed by the committee.

The original protocol, which was to use pituitary-derived growth hormone, was reviewed and approved with amendments by an NICHD Clinical Research Subpanel, an ethicist, and officials of the NIH Clinical Center. The trial was then delayed because of reports of Jacob-Creutzfeld disease risks associated with natural hGH and the possibility that a synthetic version of the hormone would soon be available that would not carry similar risks. In 1985, an FDA-approved biosynthetic growth hormone became available for treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion. The study was subsequently amended to incorporate new research findings and the first patients were enrolled in 1989. There have been 36 subjects enrolled of the planned 80; 2 have dropped out.

In reviewing the protocol, the committee addressed a number of questions: 1) is the study in compliance with the regulations pertaining to research with human subjects? 2) what is the importance--both socially and scientifically--of the study? 3) is the placebo arm necessary? 4) will the study have sufficient statistical power? 5) is recruitment a problem? 6) are there intermediate endpoints that can shorten the length of the study? 7) is compliance adequately monitored? 8) should a Data Safety and Monitoring Board be established to oversee the protocol? and 9) was assent/consent obtained free from coercion?

<u>Has the short stature protocol complied with all applicable Human Subjects Guidelines of the Department of Health and Human Services?</u>

In the view of almost all the members of the committee, the regulatory guidelines for the protection of human subjects (45 CFR 46, including Subpart D, specifically regarding children) were satisfied by the short stature protocol. At the same time, there

was a recognition by all that the scientific, theoretic and social policy issues raised by this protocol are difficult and important. Given that as many as 15,000 children in the United States are currently being treated with hGH, a determination of the efficacy and safety of these drugs was felt to be imperative. Studies like the one under consideration were deemed to offer the best hope for doing so. At the same time they pose regulatory and ethical issues about which informed and intelligent people of good will can disagree.

The committee evaluated the protocol in terms of 45 CFR 46 of the regulations pertaining to the protection of human subjects in research. The findings of the committee were of necessity based on interpretations of general, occasionally ambiguous language in the regulatory guidelines. These interpretations were informed by references to the history of the regulations, published discussion of their application, and by two general principles:

> I. Interpretations should be reasonable. Language should be given its plain, ordinary, or common meaning whenever possible. Ambiguities should be resolved in ways that seems most reasonable.
>
> II. Respect should be paid to the intent of the authors of the regulations both in general and with regard to the meaning of particular terms. In this regard, three goals of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research guided the committee's interpretations:
>
> > 1) the protection of human subjects, with special concern for the rights and welfare of vulnerable populations like children.
> >
> > 2) the recognition that research is essential for medical progress; the regulations are meant to guide, not stifle, research.
> >
> > 3) latitude in interpretation should be left to individual institutional review boards.

Section 46.404, the first substantive requirement for approving research involving children, states that research can be approved as long as it is "research not involving greater than minimal risk," and that adequate provisions are made for soliciting the assent

(The assent/permission requirements of Subpart D, section 46.408 are discussed below.) The National Commission gave some guidance by further defining "minimal risk." Risk is minimal when "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations." No one on the committee believed that this protocol could be approved under this category.

All children enrolled in the study receive injections three times a week, some for up to seven years. The committee determined that it is reasonable to consider this a greater than minimal risk. Risks of other harms are more speculative. Some tests and measurements--physical, radiological, and psychological--that are administered when the children visit NIH are beyond those "ordinarily encountered." Merely being enrolled in the research may encourage unreasonable expectations so that some children may be disappointed if they fail to gain in stature up to their subjective expectations. Being involved in research or a study designed for children with short stature may increase self-consciousness about height or reinforce a harmful and misguided view that they are "abnormal" on medical rather than statistical criteria, and may accentuate parental anxiety regarding the child's height. It is difficult to weigh or to calculate the probability of these risks, but they were considered worthy of attention.

For the treatment arm of the study, there are no currently recognized, negative side effects, though the consent form mentions some potential ones, e.g., the possibility of leukemia, which appears to be small, if present at all, in this group of children, or the possible development of antibodies to human growth hormone, which is an eventuality with little or no known clinical significance. There is a further possibility, observed in

are [illegible] hormone would enter puberty earlier or that their puberty would be accelerated, with consequent earlier closure of the epiphyseal growth centers, resulting in a final height attainment that is less than would have occurred without treatment. There may, of course, be unforeseen short or long term risks, but their likelihood and significance cannot be currently calculated.

Only one member of the committee argued that the risks and burdens from the short stature protocol exceeded more than a minor increase over minimal risks because it exposed children in the placebo arm to unwarranted discomfort, inconvenience, and psychological risk. Yet since the group, in general, found the threshold or benchmark of 46.404 to be very low, it was unanimously concluded that the subjects were exposed to risks that were greater than minimal.

Given this determination, the group then turned to 46.405 which addresses "research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects." This provision has two steps. First, and akin to the question about risks in 46.404, IRBs are asked to determine whether or not the research "presents the prospect of direct benefit to the individual subject."[2] If any reasonable prospect of

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[2]An institutional review board in Nebraska published a summary of their analyses of the language of Subpart D in Prentise, E.D., et al., "Can Children Be Enrolled in a Placebo-controlled Randomized Clinical Trial of Synthetic Growth Hormone?" IRB 11(1):6-10 (1989). That board reviewed and rejected a protocol similar to the NIH Turner syndrome study under consideration. Two important differences exist between the Nebraska protocol and that under consideration here. First, the former was about Turner syndrome girls; not children with extreme short stature of unknown etiology. Second, the former was designed to test the short-term effects of hGH and estrogen; both NIH protocols are designed to gauge the impact of hGH on the final height of subjects. In spite of these differences, the reasoning of the Nebraska IRB is relevant and will be addressed when appropriate. Finally, it should be noted that protocols like that rejected by the Nebraska IRB were reviewed and approved

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risks using the following standards: a) is the risk justified by the anticipated benefit to the subject; and b) is the relation of the anticipated benefits to the risks at least as favorable to the subjects as that presented by alternative approaches.

There are two major difficulties in evaluating the short stature protocol according to section 46.405. First, the section is unclear about how to determine the "prospect of direct benefits for the individual subject." Second, there are questions about balancing the benefits, if any, against the risks.

Though the committee felt the section required an evaluation of the reasonable prospects for each individual subject[3], the regulations do not indicate how that evaluation should be done. Should the prospect of benefit be calculated before randomization or after the subjects have been separated into the treatment and placebo arms? On the (yet unproven) assumption that treatment with hGH is beneficial, and that the benefit exceeds the risks, the former approach would allow approval because each subject in this protocol

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by a number of IRBs at other institutions. This committee did not have access to the analyses of these other boards.

[3]The committee added "reasonable" and "each," as did the Nebraska IRB to reflect a desire to err, if at all, toward protection of children. The Nebraska IRB interpreted "direct" to include immediacy, i.e."a reasonable prospect of direct, relatively immediate benefit." This committee did not find sufficient reason for doing so. Nothing in the work of the National Commission suggests or requires that restriction. Moreover, though temporally distant consequences are often more difficult to trace causally than immediate ones, such is sometimes not the case. The relation between directness and temporal distance is contingent. The committee decided the requirement that benefit be a direct result of the research be evaluated should be just that--direct, no matter how delayed its manifestation.

att[illegible] Some children in either arm may enjoy and be proud of the knowledge that they are participating in an important study. Even if the information gathered by the study were of no immediate benefit to the children, it might well help them later as parents. If, for example, their biological children are more likely than others to have extreme short stature, their concerns and options as parents may be better informed as a result of this study.[7]

Like its regulatory predecessor, this first part of 46.405 sets only a minimal condition: that there be some reasonable expectation of a benefit accruing to each research subject and directly attributable to participation in the research. Given some genuine prospect of benefit for all the subjects in the short stature protocol, it is irrelevant whether one adopts the strategy of looking at aggregate benefit before randomization and discounting the probability of each individual getting that benefit, or looking for benefits likely for subjects in each arm. A majority of the committee concluded that some benefit was a reasonable prospect for each individual in the protocol, thus satisfying the threshold requirement of 46.405.

Once the prospect of benefit is determined, an IRB must compare those benefits against the burdens. Two standards must be met:

a) Are the risks justified by the anticipated benefit?

b) Is the risk/benefit ratio at least as favorable as alternative approaches?

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[7]It was suggested that there was potential for subjects in both arms to benefit from greater final height--the treatment group because of hGH injections (assuming efficacy of the treatment) and both groups because of a placebo effect. However, the data available was deemed insufficient to support the claim of a placebo effect and this (the claim) played no part in committee determinations. The data on the efficacy of the hGH injections with regard to final height were also deemed insufficient, supporting the view that the arms are in equipoise.

of good data about the probability of risks, and by the absence of common measures of their significance. While there are studies reporting short-term growth enhancement with growth hormone therapy of children with short stature who do not have classical growth hormone deficiency, none of these has been rigorously controlled, in contrast to the rigorous controls in the NIH study under review. Furthermore, there are few, and no reported, data on long-term effects and on final adult height. The preliminary blinded data from the NICHD protocol--reviewed by the committee in strict confidence to protect the blinding essential for its successful conclusion--gave the committee no cause to recommend termination of the study, either because of significant signs of therapeutic benefits or of risks. Hence the committee was left weighing the potential benefits of regular check-ups, the possible gratification of participating in an important study, the perceived benefit from the unknown probability of some increase in height, and information that may later be useful to one as a parent against the expected discomfort of 600 to 1,100 self-administered shots, the potential psychosocial risks to the children, the likely inconveniences of traveling to NIH and being tested periodically, and the possible disappointment if less than expected height is not achieved.

For each member of the committee the judgments called for were difficult and the comparisons troublesome. No one believed there was a clear case to be made either way. A minority of the panel believed that the study could be justified under 46.405(a), i.e. that when the nature and probability of the possible harms and benefits were compared, the balance favored benefits to each subject (even those in the placebo group). Another minority found the probable benefits were outweighed (even for those in the treatment group) by the certainty of discomfort and inconvenience from the many injections. Others

felt the calculation too speculative or too close to call.

It was suggested that 46.405(a) could be understood as requiring, in a study like this one, equipoise. When attention turned to the question of clinical equipoise, unanimity returned. Randomization of patients is only justifiable if the treatments are in clinical equipoise. Clinical equipoise exists if, after considering the evidence regarding the trade-off of risks and benefits for each treatment strategy, there remains sufficient collective uncertainty regarding which strategy is superior so that opinion would be divided among reasonable medical experts. These are the circumstances in which a randomized trial provides essential scientific information.

Another way of describing equipoise is to say that it requires the risk/benefit ratio within each arm to be the same. Thus a study with two arms could be in equipoise if it were symmetrical: if for one arm there was great probability of both benefit and harm while for the other arm there was a small probability of benefit and a proportionately small probability of harm.[8] To use the case at hand, equipoise would exist were the treatment group to have a pronounced potential for benefits (e.g., increased height) but also a genuine risk of harm (e.g., leukemia) and the placebo group had a small chance of benefit balanced by a proportionately small risk of injury.

In the short stature protocol the committee concluded that there was clinical

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[8]In fact, equipoise is indifferent (though 46.405 is not) to the balance between risk and benefit within an arm, and could countenance a study with two arms each carrying great burden and little potential benefit, as long as they carried proportionately greater harm over benefit. Hence the two minorities discussed above--one finding a net balance of benefit over burden in each arm and another finding a net balance of burden over benefit in each arm--could both agree that the short stature protocol is in equipoise. They did, of course, disagree with its compatibility with 46.405(a) which *prima facie* requires that potential benefits <u>outweigh</u> risks.

eq[illegible] made it impossible to favor clearly one arm over another, and because the ratios of potential benefits to risks in each arm seemed comparable.

Section 46.405(b) asks that the risk/benefit ratio for the individuals in the study be at least as favorable as alternative approaches. Comparison is made somewhat easier by the virtual absence of universally accepted alternatives to hGH therapy for children with extreme short stature.[9]

Since administration of hGH is the prevailing therapeutic option for extreme short stature of unknown etiology the committee concluded that the requirements of 46.405(b) were satisfied.

As noted above, only a minority of the committee believed the short stature protocol satisfied 46.405(a). Since approving a protocol under 46.405 requires compliance with subsections (a) and (b), approval by the committee as a whole necessitated turning to the strictures of 46.406: "Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition." The committee concluded, almost unanimously, that the short stature protocol satisfied this provision.

In addition to assent and permission provisions, Section 46.406 requires three things:

a) that the risks to the subjects represent only a minor increase over minimal

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[9]Androgens can be used in certain children with constitutional delay in growth and pubertal development. There is some research being conducted with other anabolic agents and with clonidine, but none of the approaches were considered appropriate or possible for all children in the study. Reassurance and lack of therapeutic intervention is also an approach.

risk;

b) that the intervention presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or emotional situations; and

c) that the expected knowledge is of vital importance for the understanding or amelioration of the subject's disorder or condition.

The committee had little difficulty with 46.406(a), although there was disagreement regarding whether or not its strictures were satisfied. The National Commission recommends that four perspectives be adopted in evaluating the degree of risk: "a common-sense estimation of the risk; an estimation based on investigators' experience with similar interventions or procedures; any statistical information that is available regarding such interventions or procedures; and the situation of the proposed subjects." There are no known major risks from administration of hGH in the patterns and dosages of the two studies. The risks listed pursuant to 46.404, in particular the discomfort and inconvenience of the injections, however, seemed to only one member of the group as more than a minor increase over minimal risk.

Differing judgments about risk of harm--reasonable, given the uncertainties in this study--reflected different perspectives on the problem raised by research on children. Foremost was disagreement on how heavily to weigh the pain, discomfort, and inconvenience of the many shots each child would receive.

To a substantial degree, the committee's concerns regarding the risk/benefit ratio in the control group rested on the assumption that the requirement for multiple injections represented, if not a substantial risk, nonetheless one significantly greater than minimal, especially with respect to potential benefits. For some members of the committee, this alone was sufficient to preclude consideration under 46.405 and, at least for one member of the committee, under 46.406. This estimate, however, is based on the subjective

judgment of the adults reviewing the protocol [illegible] giving multiple injections, especially in the protocol under question. There were no good data available to the committee to resolve this uncertainty,[10] and the committee felt strongly that the children already enrolled in the study should be asked about their experiences in receiving injections. A survey instrument should be developed to assess the reaction of the subjects to the protocol, especially to the thrice weekly injections. The committee expects these data would enable a more informed decision regarding the protocol's conformance with 46.405 and 46.406 and would assist a Data Safety and Monitoring Board in its ongoing review (see discussion below).

The next section, 46.406(b), was somewhat more contentious because part of the regulation itself is unclear. What is meant by "Experiences. . . commensurate with those inherent in their actual or expected medical. . . situation"? The National Commission comments were crucial in this discussion. "Ordinary experience" refers to the experiences of the child "when being treated for that condition," i.e., extreme short stature. The major difference is that children in the NIH protocol are likely to have a more comprehensive and rigorous follow-up evaluation as a consequence of the research protocol. Given the relatively benign nature of these tests and their potential for detecting risks, most of the committee considered the protocols consonant with the requirements of 46.406(b).

Most discussion of this provision focused on the meaning of 46.406(c), whether or not "the expected knowledge is of vital importance for the amelioration of the subject's

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[10]The committee believed the experience of children who must regularly receive injections because of allergies or diabetes to be of some, but only marginal, use in resolving the conflict. Information regarding the behavior and attitudes of those children is ambiguous, diverse, and of questionable relevance to a placebo study.

[illegible] such a carefully designed and administered study; but is that information "of vital importance for the understanding or amelioration of the subjects. . . condition"?

Given the care with which this protocol was designed, the unique capacity and preeminence of NIH, and the absence of other systematic studies, the committee agreed that the study had a reasonable prospect of yielding knowledge which itself is vital to understanding or ameliorating the disorder or condition. One member of the committee was not convinced that it was necessary to have double-blinded placebo controls to gain this knowledge and recommended other forms of control or control groups. However, in the end, most of the committee agreed that 46.406(c) was satisfied in this study.

All agreed that because there are thousands of children without classical growth hormone deficiency being treated for extreme short stature, learning about the effects of hGH in this population is an important public health issue. Concern was expressed, however, that the importance of the research was based, in part, by the possibility of indiscriminate demand for and prescription of hGH.

The majority of the group agreed that the short stature protocol met the standards for balancing risks and benefits in either 46.405 or 46.406,[11] contingent upon the suggested modification to the assent/consent forms, as discussed below. A minority felt the protocol satisfied both requirements of 46.405 as well.

Having completed an analysis of the risk/benefit provisions in light of the

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[11]Because most of the committee agreed that the protocol satisfied the requirements of 46.406, it was unnecessary to settle the question of approval of a protocol when no single regulatory provision satisfies a majority. A majority of an IRB might unanimously approve a protocol, even when no single provision--46.404 or 405 or 406--has a majority approval.

regulations, the committee turned its attention to the provisions addressing consent, Sections 46.408 and 46.416. A discussion of the adequacy of the current procedures and recommendations for modifications are found below.

Are the consent and assent forms and procedures adequate?

The panel found that, as currently written, the consent and assent forms of the short stature protocol fail to inform guardians and subjects that some pediatric endocrinologists would prescribe hGH therapy to children who fulfil the criteria for inclusion in the study, even though the efficacy of such treatment is not known. Changes were suggested to imrpove the assent/consent processes.

There is substantial literature demonstrating the presence of high and often unrealistic expectations in children receiving hGH. Many fail to appreciate increases in height velocity--especially short term--that are regarded by supervising endocrinologists as representing satisfactory responses to therapy. Though it was expected that parents would be verbally informed of this recognized phenomenon as a matter of course, the committee believed this should be explicitly described as a potential "risk and discomfort," in the consent form. Suggested text is as follows:

> Children receiving growth hormone therapy frequently have unreal expectations of how much and how rapidly their growth will increase. Such children frequently imagine that they will achieve a height comparable to that of their friends and classmates after a short series of injections. They may experience disappointment, or may even become depressed, when this fails to occur. This may be even more likely should your child be assigned to the control group receiving a placebo that does not contain any medicine.

The consent form should also reflect changes in clinical practice. The following text is suggested for insertion at the end of the second paragraph on page one of the consent form:

treat certain short children who do not have growth hormone deficiency with growth hormone in an attempt to increase their height. However, other physicians would not treat these children with growth hormone. It is not known whether growth hormone increases the eventual adult height of extreme short children who do not have growth hormone deficiency, and the long term effects of growth hormone in these children are not fully understood. For these reasons, we have undertaken the current research study.

Because the committee recommended that the children in the study be routinely interviewed regarding their experiences as a participant, the consent form should be amended to include this aspect of the study (preferably as a modification to point #7 on page three of the consent form).

As it reads now, the consent form overemphasizes the dangers of stopping hGH treatment before adult height has been reached (see point #8 on page five of the consent form). Because the effects of stopping hGH are not known, the consent language as currently stated could be construed as manipulative or coercive. Parents trying to decide whether to withdraw their child from the protocol could be deterred because they fear these claimed, but unproved, deleterious consequences. The following language should be added to the consent form:

> The effects of stopping growth hormone therapy before a child has reached adult height are unknown. There is a possibility that taking extra growth hormone can stop the body from making its own growth hormone for a time after the extra growth hormone is stopped. Therefore, if therapy is halted, a child might temporarily grow more slowly than if he or she had never taken growth hormone. We do not know how often this actually occurs. If you decide to withdraw your child from this trial, we recommend that you consult with the investigators and your own pediatric endocrinologist about future care.

Under "Other pertinent information" on page five of the consent form, point #1 should be explicit in stating that "your child might be able to get hGH through other sources, such as a pediatric endocrinologist, even though the efficacy of such treatment is

not [illegible] approaches other than hGH that should be considered before enlisting your child in the study.

In the assent form, there is undue emphasis on the placebo effect. The first paragraph on page two of the form should be rewritten to read:

> Half of the children in this study will receive shots, called a placebo that do not contain any medicine. Neither you, your parents, nor your doctor will be told whether or not your shots contain the medicine Humatrope.

The committee concluded that the assent of the children should be renewed annually, at least verbally, during periodic follow-up visits to NIH by someone skilled in interviewing children. In this fashion, the child's accumulated experience will permit an increasingly more informed assent decision.

With these changes in the assent and consent forms, and with procedures in place for regular monitoring and updating of assent and consent, the committee agreed that the study would be in compliance with 46.116 of the regulations.

<u>Review and evaluate the scientific merit and relative importance of the non-growth hormone deficient short stature protocol (short stature protocol) to the field of pediatric endocrinology, taking into consideration the current state of the art and prior scientific evaluations.</u>

It has been argued that the use of growth hormone purely for height enhancement rather than to replace a specific hormonal deficiency is a somewhat frivolous use of scarce resources. Nonetheless, there is substantial evidence that extreme short stature carries distinct disadvantages, including functional impairment and psychosocial stigmatization, and that it could be considered unjust to deny access to treatment for children who are otherwise indistinguishable from those with classical growth hormone deficiency, simply on the basis of an acknowledged, currently imprecise definition of "deficiency," <u>if</u> the ultimate stature achieved is similar. Furthermore, extreme short stature is one of the most

co... ...endocrinologists.

The NIH study is the only rigorously designed placebo-controlled trial in extremely short children without classical growth hormone deficiency that is intended to continue until adult height is reached. Thus, it offers the opportunity, through the use of a generally accepted clinical trials methodology, to test the long term efficacy of hGH. The data may warrant the cost--both financial and psychological--and the exposure to potential (although currently unknown or mainly theoretical) risks. If the study can be concluded in a timely fashion, the availability of the data should help guide physicians in selecting appropriate patients for therapy. With the study already ongoing and with the resources and preeminence of the NIH, it is probable that this study represents the only opportunity to address these questions in a reasonable time frame.

<u>Review and evaluate the merit and relative importance of the short stature protocol to the individuals in the study as well as to the public health at large and to public policy.</u>

The public health aspects of the short stature protocol relate primarily to issues of cost/benefit and resource allocation. Before devoting the majority of its attention to the specifics of the protocol design and adherence to federal regulations governing research in children, the committee agreed that data derived from this study held the promise of providing factual information that could illuminate the growing public debate on the use of growth hormone in significantly short children. Determining the efficacy of hGH therapy is an important issue in pediatric endocrinology. In addition the knowledge of the efficacy, or lack thereof, of hGH in this circumstance could be of value to the participant children in their role as possible future parents with potentially similar height children.

treat certain short children who do not have growth hormone deficiency with growth hormone in an attempt to increase their height. However, other physicians would not treat these children with growth hormone. It is not known whether growth hormone increases the eventual adult height of extreme short children who do not have growth hormone deficiency, and the long term effects of growth hormone in these children are not fully understood. For these reasons, we have undertaken the current research study.

Because the committee recommended that the children in the study be routinely interviewed regarding their experiences as a participant, the consent form should be amended to include this aspect of the study (preferably as a modification to point #7 on page three of the consent form).

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Under "Other pertinent information" on page five of the consent form, point #1 should be explicit in stating that "your child might be able to get hGH through other sources, such as a pediatric endocrinologist, even though the efficacy of such treatment is

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Are the participants in the short stature protocol [illegible] condition exist which the administration of hGH is meant to improve?

Some short children in the study group may be biologically normal and represent the extreme lower end of the height spectrum of healthy children. Others, however, may have subtle disorders that interfere with growth but are not detectable by current methods. The proportion of the study population represented by each of these groups cannot be determined with current diagnostic methods. Predicted final adult height of some candidates for the short stature protocol is similar to that of untreated children with classical growth hormone deficiency who are generally considered to be appropriate candidates for growth hormone therapy. Like those with untreated classical growth hormone deficiency, children and adults with extreme short stature may experience difficulty with physical aspects of the culture generally designed for individuals taller than themselves (e.g., driving a car). They may also be harmed by deeply ingrained prejudices resulting in stigmatization and impaired self-esteem.

Is it necessary to use a placebo arm for the short stature study and is the placebo arm properly constituted?

The committee found that the arms of this protocol appear to be in equipoise. That is, there seems to be no clear advantage in being assigned to the experimental group receiving the hGH or to the control group that does not receive it.

This acknowledged, the committee then addressed the appropriate type of control group. In selecting a control group a number of issues challenge the validity of the conclusions of the study. These are that:

a) the treatment groups may have inherently different prognoses due to selection biases;

b) the mere act of administering a therapy may lead to a psychologically-induced response (e.g., the placebo effect);

c) the investigators may allow their opinions to subconsciously affect their evaluations of the study endpoints; and

d) non-compliance with the prescribed treatments may seriously confound the treatment comparison.

Four prominent approaches to selecting controls were considered, as follows.

1) An historical control group was discussed. For example, this would involve using existing growth charts for children and from these, projecting adult height for the children entered in the study, all of whom would receive hGH. Thus, each child's attained adult height would be compared with his or her projected height. This would markedly reduce the cost and length of the study as fewer children would be necessary. However, it is well known that this approach does not address satisfactorily any of the four issues above. In particular, self-selection of the study cases may render the treatment group a nonrepresentative sample of potential candidates for the study, leading to bias. Because of these issues, studies with historical controls enjoy low credibility in the scientific community.

2) Another possible control group is that of a randomized, concurrent control group, but with treatment assignment known to the children, their parents, and the clinical research team (an "unblinded" study). The advantage to the children assigned to such a control group is that they are spared the multiple placebo injections. The disadvantage is the concern that the placebo group will gradually become less of a true control group as they differentially receive other ancillary therapies, and also as a significant number of them probably receive hGH outside the study. There are multiple examples from other clinical trials demonstrating that this is a real concern, not just a theoretical concern.

3) A third design would be to choose controls from the community who are as closely matched as possible to individuals within the study. Such a design might result in a larger consenting cohort of both treated and control subjects. Controls who had not sought hGH treatment may be less likely to seek hGH outside of the trial than would randomized controls who came to NIH for possible therapy. Unlike historical controls, these controls would be concurrent and could be measured with the same rigor as treated subjects. However, the need to identify and recruit subjects who either had not sought therapy for their short stature or had decided against it could pose substantial logistical and ethical problems. Another disadvantage of this design is that these controls could differ in subtle and non-measurable ways--both biologically and psychologically--from the treated group. This could produce an estimate of treatment effect that is biased or less precise than with randomized controls, and given less credence by the medical community. In addition, the degree of crossover to hGH by these controls over the next decade, while probably less than in a randomized, unblinded non-placebo design could still be substantial. Finally, this design cannot

4) The best clinical trial design from a scientific viewpoint is acknowledged to be the randomized, double-blind concurrent control design. This creates groups that are more comparable in measured and unmeasured ways than any other design, and minimizes, albeit not eliminates, crossover. It would allow the control of any placebo effect, and would produce a result that has the highest precision and credibility for this number of subjects. Given that the results of this study may affect treatment decisions for thousands of children in the future, the majority of the panel felt that this degree of precision and credibility was necessary, particularly given the relatively small number of subjects in the trial. Because of concerns about the related problems with the other types of controls, the majority of the committee felt that the placebo arm was indeed necessary to be able to obtain the most scientifically valid and least challengeable answer to the study hypothesis.[12]

The study investigators also responded to the panel's concerns over injections for the placebo group saying such injections were necessary for scientific purposes. They suggested that the use of injections in and of itself might have a placebo effect, so that failure to use the placebo could lead to misleading results from the trial. Although some members of the committee thought this was possible, the panel did not feel that it had received convincing data either supporting or disputing the contention, and so left open the possibility that a placebo effect might exist.

One criticism of the inclusion of the placebo arm is that the children in it are disadvantaged in comparison with those in the treatment arm. The committee concluded that, since the arms are in equipoise, there is no clear disadvantage to being in one arm or another. Most members of the committee agreed that the study should be continued with double-blind, placebo controls. One member of the committee held that another kind of

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[12]One member of the panel felt that the choice of option 4 over option 3 was a very close one that could be affected by better understanding of variables such as probabilities of crossover, variation in current height, height velocity, and familial height patterns of subjects, and the existence, or lack thereof, of a placebo effect.

control group should be accepted that is unblinded and does not receive the placebo injections.

(One panelist objected to the children in the control group receiving saline injections three times a week from the time they entered the study until they reached adult height, arguing that the 600 to 1,100 injections cause discomfort and expose them to psychosocial risks. In addition, the child and family must bear whatever inconvenience there may be in getting a child to take the injections for so many years. This committee member recognized the importance of the study, and recommended continuing it with another kind of control group or groups, such as historical or unblinded controls. If historical controls cannot be used, the chief difficulty with a different type of control group would be that of compliance as those in the unblinded control group may leave the study.)

<u>Are the participants in the short stature protocol too heterogeneous (e.g., some from families with a history of short stature versus short children from families with no such history), so as to diminish the power of the study results?</u>

The fact that the study is randomized ensures that there will be no systematic bias favoring one treatment over the other regardless of the degree of heterogeneity of the subjects. However, as in all randomized trials, it is wise to stratify the design on the basis of important prognostic factors to guarantee good balance between the groups. In this study patients are stratified only on the basis of predicted height. The investigators chose not to stratify on the basis of sex. Although recruitment is open to both sexes there is a preponderant referral of boys (approximately 10 percent of the subjects are female to date), consistent with general referral patterns for this condition. There is a small risk of a maldistribution due to the fact that so few girls will be randomized. The committee recommends that the investigators, in consultation with a statistician, reexamine the issue

of [illegible] by gender.

<u>Does the recruitment period of the short stature protocol (6-9 years or another 2-4 years from this date) added to the follow-up (maximum: 9 years from the final entry) adversely impact on the study?</u>

It is important that the study be completed in an expeditious time- frame, since use of biosynthetic human growth hormone for treatment of conditions other than classical growth hormone deficiency appears to be increasing rapidly. Currently almost half of the target accrual of research subjects is complete (36 of 80). A review of the accrual history shows a steady accrual over the five year accrual period, with a marked increase in the recent past.

The investigators argued that there is a high likelihood that accrual can be completed, probably in the next one to two years. There was some committee concern, however, that the cut-off for recruitment be set at height 2.5 standard deviations or more below the mean value for height for age in order to ensure that participation is limited to children of extreme short stature. The few understandable exceptions made in early recruitment for certain children 2.25 standard deviations below the mean should continue in the trial and be reported in the data with an explanation for their inclusion. No additional children with a height above 2.50 standard deviations should be included in the study. Minus 2.5 standard deviations in height for chronologic age is equivalent to the 0.6 percentile or 6 children per 1,000. The committee was uncomfortable with the notion that hGH could be used for purposes of "cosmetic endocrinology," and believed that limiting the study and its subsequent findings to minus 2.5 standard deviations may discourage such use.

<u>Will the [illegible] short stature study protocol (a total of [illegible] children), allowing for the [illegible] enough statistical power to support the hypothesis?</u>

There are significant concerns regarding how the power of the study was calculated, particularly given the absence of qualified statisticians to do this calculation and to assist in the planning and monitoring processes. The records show that the investigators have been advised to obtain statistical input on more than one occasion. Yet, to give one example, there still exists no satisfactory statistical justification for the target sample size of 80. Concerns on this issue extend also to the analysis of data, especially the absence of a precise definition of the primary and secondary endpoints. Although two new drafts of statistical calculations were presented at the meeting, the committee nonetheless concluded that reevaluation of these issues by a statistical consultant is necessary. This individual should be a co-investigator, and should work actively with the clinical investigators to develop a plan that clearly defines endpoints, covariates, and methods to deal with dropout/crossover, as well as the analytic implications of these choices.

Furthermore, it was the committee's opinion that ideally the data management and statistical analyses should be performed independently of the sponsoring company. At a minimum the primary statistical analysis must be conducted by an independent statistical consultant. This recommendation is intended to protect the credibility of the conclusions in a study with considerable visibility, and is not in any way intended to suggest that these activities are being handled without objectivity.

<u>Will there be enough power in the short stature protocol to support the null hypothesis?</u>

It is never possible to "prove" that treatments are equivalent. However, one can

provide probabilistic support for the hypothesis that the treatments do not d... ... the their outcomes by more than a difference which is too small to be clinically significant. In general such "equivalence" trials require larger sample sizes than trials designed to reject a simple null hypothesis. Scientists at the National Cancer Institute have developed formulas for determining the necessary sample size for such studies and could be consulted regarding the applicability of those methods for this study.

Are there intermediate endpoints that can shorten the length of the short stature protocol?

Because increasing final adult height is the primary endpoint of the protocol, it is unlikely that an intermediate end point can be defined in advance that will permit substantial shortening of the protocol. However, the committee suggests that a Data Safety and Monitoring Board be established to review this possibility. Periodic reviews by the DSMB may indicate a need to shorten the study based on subjects nearing adult height (e.g., growth rate less than 0.75 cm/year with advanced bone age), or by establishing a different outcome as the basis for stopping the study. The DSMB should also evaluate emerging data from the current protocol or other studies that alter assessment of the risk/benefit ratio.

Is compliance with the hGH injections in the short stature protocol adequately monitored and can compliance be ensured?

The investigators indicated that they have evaluated patient compliance with standard techniques and that it is generally satisfactory, with only two problem cases. In this study patients maintain a written log and return vials at every visit, procedures which are state-of-the-art for this kind of study. The committee suggested that summary data on compliance be presented at future evaluations of a Data Safety and Maintaining Board.

Should there have been an independent data safety and monitoring board established to oversee these protocols? Should such a board be established at this point in the protocol? If so, what should be its composition and role?

The committee concluded that a Data Safety and Maintaining Board should be established for the short stature protocol. As with other DSMB's the role would be to provide an independent review of the accumulating data in the study on a regular basis, and to evaluate the appropriateness of continuing the study in the context of these data and any other relevant data which have been published on this topic. The DSMB should be composed of independent investigators who have no financial interest in the sponsoring or competing company; its member should include experts in such fields as pediatric endocrinology, biostatistics and medical ethics; and should be chaired by an individual with previous experience on a DSMB. The DSMB should review data regarding primary and secondary endpoints, power calculations, compliance issues, toxicity, and on a regular basis evaluate the indications for continuing the study, as well as assess subjects' responses to multiple injections.

In general, the committee found the initial review of the protocol by the Clinical Research Subpanel of the NICHD (referred to as the ICRS) to have been quite satisfactory and for the most part exemplary. A number of modifications in the protocol, such as the provision for an independent assent monitor, resulted directly from the ICRS review. However, the ICRS should have ensured that the assent and consent forms were sufficiently updated to accurately reflect the status of a rapidly changing clinical field. This is a common problem experienced by all IRBs, and requires that procedures be developed to identify protocols requiring more comprehensive review other than the review that occurs as part of the three-year renewal process. More comprehensive review is particularly necessary for longstanding protocols, for protocols that are ethically sensitive,

and for protocols in which clinical options available to potential subjects have changed. Noting that all of these circumstances applied to the short stature protocol, the committee called for a reevaluation of the extent and timeliness of the ICRS review of continuing protocols in general.

What were the role and activities of the assent auditor in the enrollment process for the hGH protocol and what were the circumstances under which the assent of each child was obtained?

Currently, the short stature protocol assent auditor is a clinical nurse specialist on the ward where several clinical protocols are underway. She has no direct tie to the hGH study, and her salary is not dependent on it. The auditor discusses the protocol with the child during the first NIH admission, either before or during the procedural investigations. The discussion generally takes place in the absence of both the parents and the principal investigators. The auditor asks the child to explain his/her understanding of the study, and seeks to ensure that the child understands the need for continuing admissions to hospital, the chance of being assigned to the placebo group, the need for injections, and the expectation that the injections would be required for several years. The child is given an injection as an example before assent is accepted. If the auditor perceives lack of understanding and/or reservations about the study, the assent form is not signed, and the auditor discusses the matter with the investigators.

The committee agreed that the involvement of an assent auditor to act as a child advocate and to ensure that prospective study participants fully understand the study and the therapeutic options is a good approach and should be continued. The committee suggested that the auditor's interview take place before the child begins the study procedures, and that it take place with the auditor and child alone in all cases. It was

further suggested that the assent auditor discuss the protocol with subjects on a yearly basis during the course of the study in order to ensure continuing understanding as the child matures, and to ensure that any possible reservations about participation can be addressed. In addition, the committee recommends that a specific procedure be put into place to ensure that a child who is reluctant to continue in the study can be assisted in withdrawing, perhaps by a child psychiatrist or similarly trained individual.

Were there any elements of coercion or manipulation in enrolling patients into the short stature protocol?

Coercion involves bending another to one's will by force or threat. Manipulation involves altering another's beliefs or behavior by subverting or bypassing his or her rational capacities. Patients are coerced into participating in research if, for example, their physicians threaten to abandon them unless they enroll in a particular protocol. They are manipulated if their participation results from deliberate misinformation. Coercion and manipulation undermine the ability to make free and informed choices. There is no evidence that subjects or guardians were coerced or deliberately manipulated into this protocol.

The average cost for the administration of hGH is $20,000 per year for an average of four years. Might offering such an expensive therapy be considered coercive? If cost alone is adopted as a general reason for regarding studies as coercive, however, we could rarely study expensive procedures. Moreover, a considerable effort has been made to determine if the choice to participate is free and informed and autonomous. The child's decision and self-image as a subject, for example, are continually monitored.

Parents or guardians who bring a child to the NIH may feel overly eager to participate and may be intimidated by the setting. These cannot be general reasons for

regarding studies to be coercive. The salient question is whether parents or guardians can give voluntary and informed permission and children voluntary and informed assent. It was the committee's judgment that both adults and children would be better informed by the recommended improvements in the assent and consent forms. The willingness of children to participate and guardians to consent should be monitored and they should be aware they can withdraw at any time.

THE TURNER SYNDROME PROTOCOL

Girls with Turner syndrome, caused by an absent or abnormal X chromosome, generally are characterized by short stature, infantile sexual development, amenorrhea, and variable other physical anomalies. Although there is variability in phenotypic expression of the syndrome, the vast majority of patients have short stature, considered to be significant and handicapping, with reported mean adult heights ranging from 140 to 146 centimeters (4 ft. 6.5 inches to 4 ft. 9 inches).

Several treatments have been used to increase growth rate in Turner patients including oxandrolone, growth hormone, and low dose estrogen. Findings from previous studies indicate short-term growth stimulating effects of estrogen and growth hormone but the long-term effect on adult height remains uncertain. In 1987 a protocol was submitted to NICHD for a double-blind, randomized, placebo-controlled trial of the effect of biosynthetic growth hormone and/or ethinyl estradiol on adult height in patients with Turner syndrome. The protocol was reviewed by the NICHD Clinical Research Subpanel, the Bioethics Program of NIH, and officials of the Clinical Center, and approved with amendments. The first subjects were enrolled in 1988. The protocol has 4 treatment arms:

1) early low dose estrogen (from entry into the study until age 12);

2) growth hormone (from entry into the study until adult height);

3) early low dose estrogen (from entry into the study until age 12) and growth hormone (from study entry to adult height); and

4) placebo control (from study entry to adult height).

The study design is based on the hypothesis that hGH not only accelerates growth velocity in patients with Turner syndrome but also increases ultimate height. Estrogen therapy is also hypothesized to improve the growth rate and increase height. The effects of combined estrogen-hGH therapy are hypothesized to produce a synergistic effect. One hundred and ten girls of 160 planned have been enrolled in the trial since 1988.

Some members of the committee felt that hGH is now increasingly being used in the treatment of girls with Turner syndrome, due to many encouraging, if not fully conclusive, studies. Other members questioned whether growth hormone therapy could be justifiably regarded as the standard of care. If it should be so regarded, then arguably the different arms of the study are not in equipoise and children allocated to placebo are receiving sub-optimal care.

The committee reviewed the Turner syndrome protocol in light of the human subjects regulations in the same systematic manner used for reviewing the short stature protocol. Like the short stature study, there was a great deal of discussion regarding the use of placebo. Unlike the short stature study, the committee did not have access at this time to the current study data and felt that a critical review of the existing literature on treatment of Turner syndrome girls and of preliminary data from the study was warranted in order to make two essential determinations: 1) whether the protocol continues to be in compliance with the regulations protecting human subjects in research; and 2) whether the placebo arm remains necessary and appropriate.

Has the Turner syndrome protocol complied with all applicable Human Subjects Guidelines of the Department of Health and Human Services?

The committee felt it had insufficient information available to appraise the risks or benefits of the Turner syndrome protocol and delayed final determination of the compatibility of that protocol with 46.405 until those data were reviewed. Regulation 46.405 requires that the "risk is justified by the anticipated benefit to the subjects" and that the "relation of the anticipated benefit to the risk is at least as favorable to the subject as that presented by available alternative approaches." There was sufficient concern that, given recent data generated by several studies, the question of equipoise in this study should be reevaluated.

However, the majority of the committee felt that the protocol was provisionally in compliance with 45 CFR Part 46, pending review by a Data Safety and Monitoring Board that has full access to the unblinded study data (see discussion below).

Is it necessary and appropriate to use a placebo arm for the Turner syndrome study and is the placebo arm properly constituted?

The committee addressed the question of whether a placebo control group is needed for the Turner study. Most members of the panel felt that further systematic analysis of the design and outcomes of other studies regarding the use of hGH in Turner syndrome is needed before the question of a placebo group for the current study can be adequately addressed. Though as far as the committee could determine, there are no studies as carefully designed to measure the impact of estrogen and hGH on final height in Turner syndrome girls, there was uncertainty about the power and scope of existing studies that have been recently reported. The committee suggested that such data be examined as soon as possible, and that the examination involve, at a minimum, biostatisticians, bioethicists, and pediatric endocrinologists. The decision about the use of

a [illegible] their [illegible]ysis.

If the DSMB determines that a) there is already sufficient evidence to establish within reasonable certainty the safety of hGH therapy and its effectiveness in promoting increases in final adult height; or b) hGH treatment of Turner syndrome patients is already warranted standard practice, then the purposes for this experiment are attenuated and maintenance of a placebo group would fail to satisfy Subpart D of the regulations governing the use of human subjects in research. Hence, the committee's views regarding the appropriateness of continuation of the Turner's protocol are provisional, pending a Data Safety and Monitoring Board's findings regarding the absence of both conditions.

If the trial is to be continued, a Data Safety and Monitoring Board, with full access to the study data, should consider whether the evidence on Turner syndrome warrants special efforts to keep participants apprised of developments that might affect their continued consent to participate. Further, an assent auditor should be used for the study. If the arms of the study are in clinical equipoise, one panelist still objected to having the children in the control group receive many hundreds of saline injections, arguing that they cause discomfort, expose them to psychosocial risks, and represent an inconvenience to the child and family for many years.

Are the assent and consent forms and procedures adequate?

As in the short stature protocol, the committee found that the assent and consent forms would be improved by the same changes described in the previous section on assent and consent in the short stature protocol.[13] They include:

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[13]See pages 19-21 of this report for suggested language to amend the short stature protocol assent and consent forms. The same changes are recommended for the assent and consent forms of

- [illegible] pediatric endocrinologists routinely treat Turner syndrome girls with hGH, the hormone may be available through sources other than the study; and

- indication in the consent form that hGH may be most effective when begun early in childhood.

As in the short stature protocol,the committee recommended that following language be added to the consent form:

> "Children receiving growth hormone therapy frequently have unreal expectations of how much and how rapidly their growth will increase. Such children frequently imagine that they will achieve a height comparable to that of their friends and classmates after a short series of injections. They may experience disappointment, or may even become depressed, when this fails to occur. This may be even more likely should your child be assigned to the control group receiving injections of an inactive substance."

As in the short stature study, the consent form overemphasizes the dangers of stopping hGH treatment before adult height has been reached. Because the effects of stopping hGH are not known the consent language, as stated, could be construed as manipulative or coercive (see changes suggested on page 20 of this report).

In the assent form, there is undue emphasis on the placebo effect. The first paragraph on page two of the form should be rewritten to read:

> Some of the children in this study will receive shots, called a placebo, that do not contain any medicine. Neither you, your parents, nor your doctor will be told whether or not your shots contain the medicine Humatrope.

The committee concluded that the assent of the children should be renewed annually, at least verbally, during periodic follow-up visits to NIH by someone skilled in interviewing children. In this fashion, the child's accumulated experience will permit an increasingly more informed assent decision. An assent auditor should be used for this study in a manner similar to that used in an recommended for the short stature study.

With these changes in the assent and consent forms, and with procedures in place

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the Turner syndrome study.

for regular monitoring and updating of assent and consent, the committee agreed that the study would be in compliance with 46.111 of the regulations.

SUMMARY

In the opinion of this committee, determining the safety and efficacy of hGH in the treatment of children with extreme short stature (whether the cause is known or unknown) is an important public health issue and worthy of investigation by the National Institutes of Health, given its scientific importance, the extent of current use, and the prospect of increasing demand. The two protocols under review raise different ethical, regulatory, and methodological issues and, therefore, should be reviewed independently.

The majority of the committee found that the short stature protocol is in general compliance with Title 45 CFR Part 46, pertaining to protection of human subjects in research, and should be allowed to continue in its basic, original design, including the placebo control group, but with prompt efforts to comply with the committee's recommended changes in the assent and consent forms and in the plans for data analysis.

The committee also found that an investigation into the experiences of the children participating in the study could have significant implications for the question of whether to maintain the placebo arm. One member of the committee believed that the 600 to 1,100 placebo injections in both studies constitute unwarranted discomfort, inconvenience, and psychosocial risk. The full committee concluded that having access to data concerning the children's experiences would assist a DSMB in judging whether both arms of the study continue to be in equipoise or whether placebo injections constitute more than a minor increase over minimal risk.

Other modifications to the protocol were suggested to improve its design, including

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a recommendation that a statistician be recruited as a coinvestigator into the study as soon as possible. The committee also recommended that this protocol be subject to periodic review by a Data Safety and Monitoring Board.

The Turner syndrome protocol was found, provisionally, to be in compliance with 45 CFR Part 46 by the majority of the committee. However, there was sufficient concern about the current status of growth hormone treatment of short stature in Turner syndrome patients to warrant an immediate review of existing research in the field as well as a review of the unblinded study data. Since the unblinded data were not available for review by this committee, it was recommended that a Data Safety and Monitoring Board be convened within three months of submission of this report to the Director of NIH. The DSMB should review the protocol and all available data, as well as relevant data from other studies, to determine whether continuation of the study is warranted as currently designed with specific attention to maintenance of the placebo arm.