



THE LAWSON WILKINS PEDIATRIC ENDOCRINE SOCIETY
2005-2006

0029 5 NOV -1 A10 :09

October 31, 2005

President

Lynne Levitsky M.D.
Boston, Massachusetts

Secretary

Alan D. Rogol M.D., Ph.D.
Charlottesville, Virginia

Treasurer

John Kirkland M.D.
Houston, Texas

President Elect

Kenneth Copeland M.D.
Oklahoma City, Oklahoma

Past President

Ora H. Pescovitz M.D.
Indianapolis, Indiana

Directors

Janet H. Silverstein M.D.
Gainesville, Florida

Frank Diamond, Jr. M.D.
Tampa, Florida

Charles A. Stanley M.D.
Philadelphia, Pennsylvania

Division of Dockets Management (HFA-305)
Docket Number 2005N-0404
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Sir/Madam,

Lawson Wilkins Pediatric Endocrine Society (LWPES) Position letter regarding use of the federal 407 process.

The Office of Human Research Protection (OHRP) and the Food and Drug Administration (FDA) are convening a joint panel, referred to as a "407 panel", on Nov 15, 2005 on 'the risk-benefit ratio' of a protocol involving a study relevant to pediatric endocrinology.

The IRB at the University of Chicago has sent OHRP a research protocol that involves children for 407 panel review. The protocol, authored by Robert L. Rosenfield, M.D., a pediatric endocrinologist and LWPES member, compares sleep-related luteinizing hormone (LH) increase at puberty (which is used as the "gold standard" to determine the onset of puberty) compared to the gonadotropin and sex steroid response to a gonadotropin releasing hormone agonist (leuprolide) test of pituitary-gonadal function. At issue is the recruitment of healthy children as controls. Interestingly, although the University of Chicago IRB approved this protocol previously, they were recently made aware that Federal Regulations prohibit IRB's from approving research judged to represent a "minor increase over minimal risk" in healthy children because they do not stand to benefit from it and, thus, such protocols must go to OHRP for review by a 407 panel. This protocol has been classified in this category due to the length of hospitalization (over 24 hours) and the use of leuprolide, which represent more medical attention than a healthy child would "ordinarily encounter in daily life or during the performance of routine physical or psychological examinations or tests". The regulations are not new but are only recently being scrutinized by OHRP and the FDA.

The 407 panel will make the determination of whether the study could have indeed been approved by the University IRB (i.e., whether they overestimated the degree of risk) or whether it is "research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children". Part of the 407 approval process is that there will be a period (beginning November 1, 2005) during which public comment is solicited by announcement in the Federal Register prior to the meeting of the panel.

SECRETARIAL ADDRESS: Alan D. Rogol, M.D., Ph.D.
685 Explorers Rd
Charlottesville, VA 22911-8441
PHONE (434) 971-6687 • FAX (434) 293-7921
secretary@lwpes.org

2005N-0404

C 2

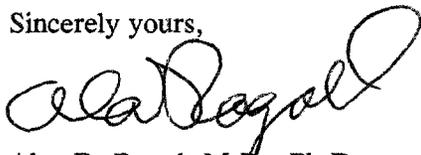
The LWPES does not review clinical research protocols and thus does not and cannot issue statements regarding the risk-benefit ratio of a specific project. However, we will briefly state that leuprolide is used in the routine diagnostic testing of children to determine the initiation of puberty. It is a highly useful test for which normative data are sparse and a necessary prerequisite for the precise diagnosis of pubertal disorders in children.

The LWPES will also comment on the use of the Federal 407 process and the use of healthy children as control subjects. Due to its nature of solicitation of opinion, the 407 approval process may suffer from uninformed or biased lay comments. Furthermore, there is tremendous variation in the interpretation of minimal risk by different IRB panels and, consequently, which protocols a particular IRB considers approvable and appropriate to refer for 407 review. This, although not under the purview of the 407 process, may lead to inconsistency and confusion. However, the summation of these factors may make the process lack a basis for sound scientific and clinical judgment, as well as prove cumbersome to research progress. The LWPES, in contrast, strongly supports the input of two panel members who are pediatric endocrinologists to represent the scientific and clinical viewpoints of their colleagues and the Society.

We believe that although protection of children must be guaranteed, clinical protocols must be allowed to proceed through review in a timely and efficient manner. Additionally, the process must allow for the use of control groups to validate diagnostic and therapeutic interventions. The Society does not support the concept that all pharmaceuticals, even if approved for children and routinely used in diagnostic testing, are considered a minor increase over minimal risk, and hence use in healthy children must go to a Federal (407) panel.

The LWPES supports the participation of normal children as control subjects in clinical research under clearly defined circumstances. Obtaining normative data may in some circumstances be the only basis for determining safety and efficacy of medications and medical tests. The LWPES calls for the rational use of the panel, with a triage system that is based on scientific and ethical expertise and is consistent at a national level.

Sincerely yours,



Alan D. Rogol, M.D., Ph.D.

SECRETARIAL ADDRESS: Alan D. Rogol, M.D., Ph.D.
685 Explorers Rd
Charlottesville, VA 22911-8441
PHONE (434) 971-6687 • FAX (434) 293-7921
secretary@lwpes.org