United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

March 20, 2009

Via Electronic Transmission

Dr. Drew Gilpin Faust
President
Harvard University
Massachusetts Hall
Cambridge, MA 02138

Dr. Peter L. Slavin
President
Massachusetts General Hospital (Partners Healthcare)
55 Fruit Street
Boston, MA 02114

Dear Drs. Faust and Slavin:

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs and, accordingly, a responsibility to the more than 80 million Americans who receive health care coverage under these programs. As Ranking Member of the Committee, I have a duty to protect the health of Medicare and Medicaid beneficiaries and safeguard taxpayer dollars appropriated for these programs. The actions taken by thought leaders, like those at Harvard Medical School, often have a profound impact upon taxpayer funded programs like Medicare and Medicaid and the way that patients are treated and funds expended.

I have also taken an interest in the almost $24 billion annually appropriated to the National Institutes of Health (NIH) to fund grants at various institutions such as yours. As you know, institutions are required to manage a grantee's conflicts of interest.[1] But I continue to learn that this task is sometimes made difficult because physicians do not consistently report all the payments received from drug companies. To encourage transparency, Senator Kohl and I introduced the Physician Payments Sunshine Act (Act). This Act will require drug companies to report publicly any payments that they make to doctors, within certain parameters.

Recently, I was provided a number of documents, including slides, that became available during ongoing litigation.[2] A number of the documents reviewed by my staff relate to, among other matters: Dr. Joseph Biederman of Harvard University (Harvard) and Massachusetts General Hospital (MGH/Partners), (collectively, the Institutions); and to the Johnson & Johnson Center for Pediatric Psychopathology Research (Center). As part of the litigation, Dr. Biederman produced several slide sets, and my staff have pulled several slides from these various presentations. I am not certain if these slides sets were

[1] Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding is Sought, 42 C.F.R. 50 (1995).
[2] Alma Avila, as Next Friend of Amber N. Avila, an Individual Case vs. Johnson & Johnson, et al., Docket No.: MID- L-6661-06
(In Re Risperdal/Seroquel/Zyprexa; Superior Court of Middlesex County, New Jersey).

United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

created by Dr. Biederman, and I am not certain if he has ever presented these slides publicly. However I do know that they were produced by Dr. Biederman.

The slides raise potential concerns about, among other matters, Dr. Biederman and the Center. My main concern is whether or not the attached slides suggest a predisposition to specific findings and conclusions prior to the studies being commenced. My other concern is whether or not NIH was aware that Dr. Biederman was performing research sponsored by J&J on psychiatric disorders when it awarded him a grant to collaborate with other doctors to study those same psychiatric disorders. I am also wondering if the physicians Dr. Biederman was collaborating with under the NIH grant were notified of Dr. Biederman's corporate sponsored research.

Accordingly, this letter seeks, among other things, your guidance as to whether or not the materials discussed in this letter are in compliance with all applicable rules followed by the Institutions. In addition, I would like to better understand the role played by the Institutions when proposals are drafted by professors, and whether those policies and procedures were followed with regard to the materials attached to this letter.

I. Attachment A

Slides in Attachment A, highlight several "Key Projects for 2005," and state:

- Concerta for the treatment of ADHD NOS in adolescents
  - Extend to adolescents positive findings with Concerta in ADHD NOS in adults

- Randomized Clinical Trial of Risperidone vs. Placebo in children younger than 10 years of age with bipolar disorder
  - Will complement registration efforts of studies with older youth
  - Will provide Janssen with critical competitive data on safety and efficacy of risperidone in children (80% of referrals)

Please explain:

1) Why do these slides suggest an expectation of positive outcomes for the drugs prior to the commencement of the clinical trials?

II. Attachments B and C

Slides set forth in Attachment B seem to explain what MGH would provide Johnson & Johnson in return for the funding. As part of the "deliverables," the slide reads:

- Research posters at major national and international meetings
- Research publications in peer reviewed journals
- Programs and symposia at major national and international meetings
- Help J&J develop state of the art, data based CME [continuing medical education] programs and educational materials

Several of the deliverables set forth in this slide are typical deliverables when performing scientific research, with the exception of the statement that the Center will in some way be helping J&J to create "state of the art, data based" CME programs. Accordingly please explain the following:

1) According to protocols and policies of Harvard/MGH, is it appropriate that a portion of the deliverables include the development of "state of the art data based CME programs and educational materials" for a particular pharmaceutical sponsor, in this case J&J? Please explain.

The slides in Attachment C describe, among other things the "Benefits" of the J&J Center. One slide reads:

- Supports research on the disorders that J&J products treats:
  - Concerta
  - Risperdal
  - Reminyl
  - Topamax

Another slide in Attachment C says the following:

- Provides rationale to treat chronically and aggressively highly morbid child psychiatric disorders

And yet another slide reads:

- Provides ongoing consultation for protocol development of new J&J products or new uses for existing compounds
  - Concerta for adult ADHD NOS
  - Reminyl for ADHD

1) Please explain why the slides set forth above suggest that the study being proposed could find new uses for J&J products?

III. Attachments D and E

The slides in Attachment D highlight several additional issues. The first is entitled "Key Projects for 2004" and says:

- Comparative effectiveness and tolerability of Risperidone vs. competitors in the management of pediatric bipolar disorder: acutely and chronically

  - Will clarify the competitive advantages of risperidone vs. other atypical neuroleptics

Another slide in Attachment D reads, in pertinent part:

- Effectiveness and safety of Risperdone in pre-schoolers

- Will support the safety and effectiveness of risperidone in this age group

The slides in Attachment E titled "Planned Investigator Initiated Studies" seem to complement those in Attachment D and say:

- Randomized Clinical Trial of Risperidone vs. Placebo in children younger than 10 years of age with bipolar disorder
  - Will complement registration efforts of studies with older youth
  - Will provide Janssen with critical competitive data on safety and efficacy of risperidone in children (80% of referrals)

Accordingly, please respond to the questions below regarding Attachments D and E.

1) Please explain how these slides could suggest that a study, which had not yet commenced "will support the safety and effectiveness of…." any particular drug and "complement" other efforts?

2) Is it possible that the study proposed in Attachment D would not support the safety and effectiveness of risperidone in pre-schoolers and if this is the case, why would the slide not so state?

Again, Dr. Faust and Dr. Slavin, I am having difficulty putting the Attachments to this letter in proper context. Indeed, I reached out to a physician researcher for an independent review of the slides attached to this letter. In response to my inquiry, the physician researcher said that it appeared that the slides discussed in this letter were nothing more than marketing tools, as opposed to discussions of independent scientific research.

IV. The Janssen Study

We also learned that these slides did result in funds being paid to Dr. Biederman and that he eventually published a Janssen supported study that found a 30% reduction in ADHD symptoms in 29% of study subjects when taking risperidone. This study was published in 2008 and its finding seem to correlate with the slides that were apparently produced years earlier and attached to this letter.[3] More specifically, Dr. Biederman's study concluded, "treatment with risperidone is associated with tangible but generally modest improvement of symptoms of ADHD in children with bipolar disorder." Even more troubling, the published study lists support from Janssen, the Stanley Medical Research Institute, and the NIH. In fact, the NIH funding for this study raises still more concerns in that federal dollars may have been used to support research when the results may have been "predicted" before the study began.

[3] Biederman, Joseph et al "Risperidone treatment for ADHD in children and adolescents with bipolar disorder" *Neuropsychiatr Dis Treat,* Feb 2008, 4(1): pp 203-207. Published online Feb 2008.

V. Attachment F and Possible Conflict of Interest

There is yet another aspect of documents reviewed in this matter that is concerning me. It is my understanding that Dr. Biederman was seminal in the creation of the Center and that he received almost half a million dollars [Attachment F] from the NIH to run the annual Collaborative Pediatric Bipolar Disorder Conference (2003: $95,015, 2004: $96,631; 2005: $99,209; 2006: $101,865; 2007: $101,567). It appears that running the Center on bipolar disorder, while also running a conference for the NIH on bipolar disorder could be perceived as a conflict. Therefore, I would appreciate your views on this. I also want to advise you that the NIH told me that MGH never informed them of this possible conflict.

VI. Attachments G and H

In addition to materials regarding the Center and Dr. Biederman, I also received materials produced for ongoing litigation by J&J. It seems, based upon a review of J&J internal communications, that the collaboration between the Center and J&J was driven more by business and marketing as opposed to pure science and research. For instance, in Attachment G there are J&J slides titled "2003 Business Plan." In one slide J&J notes that it will "leverage" the MGH Center to raise awareness of bipolar disorder in kids because "use of psychotropic medications in [children and adolescents] remains controversial." Another slide identified as Attachment H was presented by a J&J employee and was titled "A New Initiative! J&J Pediatric Research Center at Mass General Hospital." The relevant slide states that the initial discussions with MGH to create the Center involved participation "with marketing." So I ask, is it typical in your experiences to include the marketing division of a sponsor company during discussions of possible collaboration with your institution?

VII. Attachment J

Another document provided to me is entitled, "PHARMA SALARY SUMMARY" is identified as Attachment J. This document appears to be a summary of payments made to Dr. Biederman over a 3 year period. Accordingly, please respond to the following questions:

1) Explain the payments made and the services provided.

2) Address whether or not these payments were reported to you by Dr. Biederman.

3) Address whether or not if these payments were reported by you to me in previous correspondence.

4) Regarding Attachment J, please explain if Dr. Biederman received compensation from these companies as detailed in the attachment. If yes, provide an annual summary from each company.

VIII. Protocol Violations

Based upon a review of still other documents produced, I see that MGH's Institutional Review Board (IRB) found "a serious breach of the protocol and procedures and provisions" in Dr. Biederman's study of risperidone and olanzapine in preschool children. Based upon the materials in my possession [Attachment I], when this issue was brought to Dr. Biederman's attention in 2004, the human research committee at MGH reported that this was the sixth protocol violation for the study. If a study is supported with federal funds, then such violations should have been reported to the Office for Human Research Protection (OHRP) at the Department of Health and Human Services. Additionally, when the study was apparently published in 2005, the article listed support from the Stanley Medical Research Institute and the National Institute of Mental Health.[4] However, OHRP informed me that it was never notified of any protocol violations for this study.

Accordingly, please respond to the following questions and requests for documents. For each response, first repeat the question followed by the appropriate answer.

1) Why did Harvard/MGH not inform the NIH about Dr. Biederman's collaboration with J&J when it applied for the NIH bipolar disorder grant?

2) Several documents that Dr. Biederman supplied to the court make note of a "JB rent fund." What is the "JB rent fund" and to whom did the money go?

3) Why did MGH not inform OHRP about the IRB protocol violations in Dr. Biederman's study?

4) For that particular study, please explain each IRB protocol violation and how those violations were resolved.

5) Did representatives of MGH discuss collaborating on the Center with marketing people from J&J, as Attachment H states?

6) Were the slides detailed in the attachments to this letter created by Dr. Biederman? If not, who created them?

7) Please explain if these slides were ever presented to an audience. If so, who saw these presentations?

Thank you again for your continued cooperation and assistance in this matter. As you know, in cooperating with the Committee's review, no documents, records, data or information related to these matters shall be destroyed, modified, removed or otherwise made inaccessible to the Committee.

[4] Biederman, Joseph, et al "Open-Label, 8-week Trial of Olanzapine and Risperidone for the Treatment of Bipolar Disorder in Preschool-Age Children," *Biol Psychiatry*, 2005, 58: pp 589-594.

I look forward to hearing from you by no later than April 17, 2009. All documents responsive to this request should be sent electronically in PDF format to Brian_Downey@finance-rep.senate.gov. If you have any questions, please do not hesitate to contact Paul Thacker at (202) 224-4515.

Sincerely,

Charles E. Grassley
Ranking Member

cc: Raynard Kington, M.D., PhD.
Acting Director
National Institutes of Health

Attachments

Attachment A

Johnson & Johnson Center for Pediatric Psychopathology Research

Director: Joseph Biederman, M.D.

Co- Director: Steve Faraone, Ph.D.

Data Management Director: Eric Mick, Sc.D

Business Administrator: Kate Balcke, MA

Administrative Coordinator: Megan Aleardi

Massachusetts General Hospital
Harvard Medical School

Key Projects for 2005

Planned IITs

- Concerta for the treatment of ADHD NOS in adolescents
  - Extend to adolescents positive findings with Concerta in ADHD NOS in adults

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- Randomized Clinical Trial of Risperidone vs. Placebo in children younger than 10 years of age with bipolar disorder
  - Will complement registration efforts of studies with older youth
  - Will provide Janssen with critical competitive data on safety and efficacy of risperidone in children (80% of referrals)

Attachment B

Deliverables

Johnson & Johnson Center for Pediatric Psychopathology Research

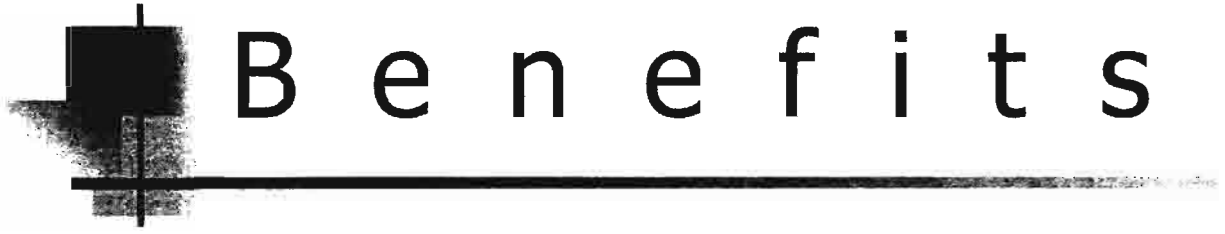
Massachusetts General Hospital

- Research posters at major national and international meetings
- Research publications in peer reviewed journals
- Programs and symposia at major national and international meetings
- Help J&J develop state of the art, data based CME programs and educational material

Deliverables

- Manuscripts
  - ADHD Follow-ups
  - Smoking as Gateway Drug
  - Ris for pediatric bpd
  - Ris for preschoolers
  - Age, gender; anxiety; cohort analyses
  - Driving
  - Lab workplace
  - PET
- Abstracts
  - APA
  - Biol Psych
  - CINP
  - ECNP Stanley
  - Bipolar Conf
  - Special issue

Attachment C


Benefits

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- **Gains access to many millions of dollars in data that have already been collected through NIH and other grants**
- **Gains access to world class experts in a variety of fields**
  - **Pediatric and Adults Psychopathology**
  - **Clinical Trials**
  - **Genetics**
  - **Neuroimaging**
  - **Biostatistics and Epidemiology**
  - **Neuropsychology**
  - **Driving Simulation**

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- **Supports research on the disorders that J&J products treat**
  - Concerta
  - Risperdal
  - Reminyl
  - Topamax

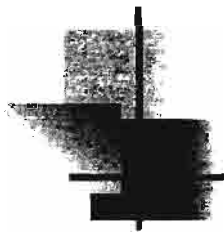
Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- Documents the morbidity and disability associated with ADHD, pediatric bipolar disorder and related psychiatric and cognitive comorbidities
- Provides rationale to treat chronically and aggressively highly morbid child psychiatric disorders

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital



- Puts J&J at the forefront of pediatric psychiatry research
- Provides ongoing consultation for protocol development of new J&J products or new uses for existing compound
  - Concerta for adult ADHD NOS
  - Reminyl for ADHD
- Facilitates pilot and proof of concept studies

Attachment D

Key Projects for 2004

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- Comparative effectiveness and tolerability of Risperidone vs competitors in the management of pediatric bipolar disorder: acutely and chronically
  - Will help clarify the competitive advantages of risperidone vs. other atypical neuroleptics

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- Risperidone in the treatment of pediatric ADHD when comorbid with bipolar disorder
  - Will complement prior work on risperidone for DBD

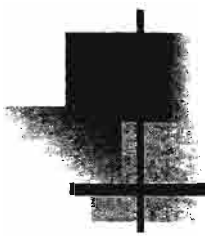
Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- Effectiveness and safety of Risperidone in pre-schoolers
  - Will support the safety and effectiveness of risperidone in this age group
- Pharmacogenetics of Risperidone
  - Will search for markers of response and adverse effects in pediatric bipolar disorder

Attachment E

Planned Investigator Initiated Studies



Planned IITs

- Concerta for the treatment of ADHD NOS in adolescents
  - Extend to adolescents positive findings with Concerta in ADHD NOS in adults

Planned IITs

- PET studies of Concerta in ADHD
  - Further clarification of Concerta's unique pharmacological and therapeutic profile

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- Randomized Clinical Trial of Risperidone vs. Placebo in children younger than 10 years of age with bipolar disorder
  - Will complement registration efforts of studies with older youth
  - Will provide Janssen with critical competitive data on safety and efficacy of risperidone in children (80% of referrals)

Attachment F

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

FEB 13 2009

The Honorable Charles E. Grassley
United States Senate
Washington, D.C. 20510

Dear Senator Grassley:

I am writing in response to your letter of December 19, 2008, regarding Drs. Joseph Biederman and Timothy Wilens of Harvard University (Harvard) and Massachusetts General Hospital (MGH). Specifically, you asked if Harvard and/or MGH notified the National Institutes of Health (NIH) about any potential conflicts of interest regarding NIH grant U13 MH 064077, titled *Collaborative Pediatric Bipolar Disorder Conference*.

MGH, the grantee institution responsible for reporting financial conflicts of interest to NIH under the regulation at 42 CFR Part 50, Subpart F, *Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought*, has not notified the NIH of any potential conflicts of interest concerning the above-referenced grant for which Dr. Biederman served as Principal Investigator.

Subsequent to your letter, MGH informed the NIH of the results of its financial conflict of interest review for those NIH grants under which Drs. Biederman, Wilens, and/or Spencer had a role in the design, conduct, or reporting of the research. The NIH is in the process of following up with MGH regarding its review, including, specifically, its review of U13 MH 064077.

I hope this information is helpful. If you need any additional information, please contact Marc Smolonsky, NIH Associate Director for Legislative Policy and Analysis, at (301) 496-3471.

Sincerely yours,

Raynard S. Kington, M.D., Ph.D.
Acting Director

			assess how gene variants will predict adult outcome. In our preliminary work, we have begun to address each of the Specific Aims that are the focus of the proposed work. We view the proposed extension of our work as an essential step for several reasons. First, although there have been seven follow-up studies of ADHD children and only two (our included) used DSM-III-R criteria. Moreover, unlike most prior follow-up studies, the proposed work can comprehensively address psychiatric comobidity in ADHD because we did not use comorbid conditions to exclude cases at baseline and we assessed for a wide range of comorbid conditions at each assessment. Only a few prior studies assessed intelligence, achievement and school functioning, none have thoroughly examined attentional-executive neuropsychological functions and only one examined psychosocial and family functioning. In contrast, our study has taken a multidimensional approach to measurement; we have assessed these domains of functioning at baseline and each follow-up assessment. Because the treatment interventions used in our sample are not being controlled, we will be able to document to naturalistic course of treatment use. Also, we are the only long-term study to collect clinical and molecular genetic data on all first degree relatives and to follow the siblings of ADHD and control subjects into adulthood. For these reasons, we expect the proposed work to clarify the course and outcome of ADHD.	
2003	1U13MH064077-01A1	Collaborative Pediatric Bipolar Disorder Conference	DESCRIPTION (provided by applicant): We are proposing a multi-year conference grant which seeks to establish a forum for researchers to pursue collaborative studies of pediatric bipolar disorder. This application was conceived in response to a recent roundtable discussion convened by the NIMH's Director, Dr. Steve Hyman, in collaboration with the Developmental Psychopathology and Prevention Research Branch and the Child and Adolescent Treatment and Preventive Intervention Research Branch. Despite controversy, the notion that pediatric bipolar disorder is exceedingly rare has been challenged by case reports and emerging research findings that suggest that this disorder may not be rare but, rather, that it is difficult to diagnose. It is also quite clear that, despite debate over nosological issues, many clinicians recognize that a sizable number of children suffer from a severe form of psychopathology associated with extreme irritability, violence, and incapacitation that is highly suggestive of bipolar disorder. Since a sizable clinical population currently exists for which relatively little systematic information is available, efforts that increase the pace and utility of research are desperately needed. Thus, an appropriate mechanism designed to facilitate regular communication among investigators and clinicians is needed as a first step to build collaborative research and guide clinical efforts that will foster a more efficient and streamlined approach to the understanding and treatment of this perplexing disorder. The main aim of the proposed conference grant is to overcome the hurdles to collaboration by establishing yearly conferences among investigators studying pediatric bipolar disorder. Subgoals of these conferences are: (1) to define the boundaries of the bipolar spectrum phenotype and determine if children who technically meet criteria for bipolar disorder actually have this disorder or are affected with another condition.; (2) to standardize data collection methods across different centers to facilitate pooling of diagnostic data and validation of the disorder; (3) to facilitate joint submissions of large collaborative projects that will enable the study of a broad spectrum of scientific questions including genetic, imaging and therapeutic protocols; and (4) to create a mechanism for pooling samples so that potential findings from one group may be cross-validated on	$95,015

			pooled data from other groups. Although scientific projects studying pediatric bipolar disorder are likely to be funded in the coming years, these efforts will likely take many years to unfold. This scientific void and ongoing diagnostic and therapeutic uncertainties calls for immediate action to foster contact and dialogue among interested parties in the clinical and scientific community. While the field faces a dearth of information, more and more children and families are being referred to clinics for evaluation and treatment. Thus, steps that increase the identification of children with bipolar spectrum disorder and the development of initial therapeutic approaches to help them is of high clinical, scientific and public health importance. While the proposed conference does not intend to solve all outstanding problems associated with pediatric bipolar disorder, it will provide a forum to begin formulating a solution.	
2004	5R01HD036317-07	Adult Outcome of Attention Deficit Hyperactivity Disorder	same as 2R01HD036317-06	$541,514
2004	5U13MH064077-02	Collaborative Pediatric Bipolar Disorder Conference	same as 1U13MH064077-01A1	$96,631
2005	5R01HD036317-08	Adult Outcome of Attention Deficit Hyperactivity Disorde	same as 2R01HD036317-06	$559,193
2005	5U13MH064077-03	Collaborative Pediatric Bipolar Disorder Conference	same as 1U13MH064077-01A1	$99,209
2006	5R01HD036317-09	Adult Outcome of Attention Deficit Hyperactivity Disorde	same as 2R01HD036317-06	$566,125
2006	5U13MH064077-04	Collaborative Pediatric Bipolar Disorder Conference	same as 1U13MH064077-01A1	$101,865.
2007	1R03MH079954-01	Course of psychopathology in female youth: Analysis with extant longitudinal data	DESCRIPTION (provided by applicant): Although attention-deficit/hyperactivity disorder (ADHD) is more prevalent in boys than girls, little doubt exists that ADHD is also an important cause of psychiatric disability in girls. Despite this, the scientific literature on females with ADHD is scarce, and mostly cross-sectional. Thus, large-scale studies examining the course and outcome of psychopathology in ADHD in girls are sorely needed. Such information can inform patients, families, teachers and clinicians and facilitate prevention and intervention efforts for females with ADHD, an understudied population. We propose a data analysis project that utilizes an existing longitudinal database to address these questions. The overall goal of this application is to use longitudinal measurements, a multigenerational perspective and an extensive assessment of multiple domains of functioning to investigate the developmental course and outcome of psychopathology in female youth with and without ADHD. Our specific aims are to: 1) examine the risk for psychopathology associated with ADHD across development; 2) describe the clinical characteristics of psychopathology in a sample of ADHD girls; 3) estimate the effect of antecedent risk factors on psychopathology in a sample of ADHD girls; and 4) to estimate the effect of psychopathology on subsequent functional outcomes in a sample of ADHD girls. The psychopathological conditions to be examined	$87,500

Attachment G

Child and Adolescent & Other New Business

2003 Business Plan

July 29, 2002

Strategic Initiatives

Use of psychotropic medications in C&A remains controversial	*Limited education and awareness of appropriate use of APSs*	*Physician misperception of RIS safety profile*	*Lack of indication*
Raise awareness regarding prevalence, economic and emotional burden	***Develop educational platform***	***Establish Risperdal as having a favorable risk-benefit ratio***	***Partner with JJPRD to facilitate development plans***
• Partner with advocacy to drive caregiver education • Generate and disseminate data supporting clinical rationale and utility of APS in C&A • Leverage CAPRI initiative with NIMH • Leverage J&J-MGH Pediatric Psychopathology Center to drive awareness	• Partner with McNeil to drive and leverage educational program • Targeted medical education to pediatricians and neurologists • Leverage J&J-MGH Pediatric Psychopathology Center to drive educational needs	• Neutralize safety and tolerability concerns • Leverage current datasets • Develop EMRP plan addressing datagaps: ADHD, bipolar disorder, autism, acute agitation, Tourette's • Maximize RUPP autism publication	• Work to expedite enrollment in ongoing Schizophrenia trial • Assist in development of adolescent bipolar trial • Expedite transfer and analysis of RUPP database • Work with JJPRD and Pediatric Development Group to expedite receipt of written request

Use of psychotropic medications in children is controversial

- Raise awareness regarding prevalence, economic, and emotional burden of untreated C&A mental illnesses and the long-term implications

Key Tactic: C&A Mental Health Summit

Description

One day national summit which addresses current issues in mental illnesses in children and adolescents

Audience

Advocacy, KOLs, AACAP, NIMH

Limited education and awareness of appropriate use of APS

- Develop educational platform to establish the role of APSs in the treatment of C&A mental illness

Key Tactic#1: "Branded" educational initiative

Description

Multi- medium, comprehensive branded educational campaign on the role of APS in the treatment of C&A mental health: Centers of excellence, Regional CME symposia, monographs

Audience

National and regional key opinion leaders, community based physicians

Key Tactic#2: Academic collaboration (MGH and CAPRI)

Lack of indication

- Partner with JJPRD and J&J Pediatric Institute to facilitate current development plans
  - RUPP (autism)
  - Schizophrenia
  - Bipolar Disorder
  - Exclusivity

Risperdal C&A 2003 PME's

Description	2002 PME ($K)	Proposed 2003 PME ($K)	2003 PME (%)
Medical Marketing/Education	**3,890**	**3,300**	**51.6%**
CME Branded Initiative		1,800	
PsychLink/Teletopics		450	
Symposia (2)		350	
Publications		500	
National Ad Board		200	
Advisory Boards (RAB/HOV)	**1,800**	**1,900**	**29.7%**
Public Relations	**325**	**500**	**7.8%**
C&A Summit		400	
Other		100	
Grants	**160**	**300**	**4.6%**
Other	**225**	**400**	**6.3%**
Total PME	**$6,400**	**$6,400**	**100%**

Subject to legal and regulatory review

Attachment H

J&J Pediatric Research Ctr. at MGH Background *(continued)*

- With marketing, held initial discussions with MGH to discuss collaboration re: specific extramural research with risperidone
- Discussed the concept of a J&J center at MGH, reviewing specific scientific questions related to key business areas
- Discussed partnerships with J&J sister companies (OMP, McNeil) to coordinate support of MGH collaboration
- Designed a model methodology for collaboration, with specific scientific deliverables and timelines for delivery

Attachment I

INVESTIGATOR REPORT OF MAJOR PROTOCOL VIOLATION

This form is to be used to report **major** protocol violations. Protocol violations are deviations from the IRB-approved protocol that are not approved by the IRB prior to initiation or implementation. A **major protocol violation** is a violation that may impact subject safety, affect the integrity of the study data, and/or affect the willingness of the subject to participate in the study. Refer to PHRC guidance document Protocol Violations, Deviations, and Exceptions for more information and for examples of major and minor violations, see http://healthcare.partners.org/phsirb/prodevex.htm.

1. PROTOCOL INFORMATION

Protocol #:	**2001-P-000422**
Principal Investigator:	**Joseph Biederman, MD**
Title of Study:	**Open-Label Comparative Study of Risperidone Versus Olanzapine for Mania in Preschool Children 4 to 6 Years of Age with Bipolar Spectrum Disorder**

2. SUBJECT INFORMATION

Subject(s) ID #	Subject Initials	Date of Violation	Date of Discovery
3601102	**MATMCD**	**03/07/02**	**03/12/04**

3. DESCRIPTION OF THE VIOLATION

Briefly describe the protocol violation.

Subject MATMCD missed visits 4 through 6 during the acute phase of the study and subsequently all the necessary tasks (ie questionnaires, vitals) were not completed. Additionally, six weeks instead of the usual four lapsed between the week 3 and week 7 visits. At week 8, the subjects olanazpine dose was increased beyond the protocol specifications. For the purpose of stabilizing the subject, the dose was increased to 10 mg/QD when the maximum dose per protocol is 7.5 mg/QD. At month 1 of extension, the dose was again increased to 12.5 mg/QD. Each increase was well tolerated and was initiated for the purpose of stabilizing the subject.

4. CORRECTIVE ACTION

For guidance on appropriate corrective action, see http://www.partners.org/phsqi/ Contact the Quality Improvement/Human Subject Protection Program if additional guidance is needed.

☐	None to date
☒	Note-to-file was prepared
☐	Subject was consented/re-consented
☐	Other, describe below

NOTE: Major violations should be reported to the sponsor in accordance with the reporting requirements in the sponsor's protocol.

5. PREVENTIVE MEASURES

Describe below preventive measures developed/implemented to prevent similar violations from occurring in the future.

In no way was the subject's safety jeopardized as the treating clinician was in constant contact with the family and made adjustments to the dosing regimen based on reports from the subject's primary reporter. Study coordinators have been asked to stress the

importance of subjects' coming into the office for each weekly appointment. Furthermore, study coordinators will contact subjects before each visit in order to remind them of their appointments. The treating clinician and study staff will be instructed to follow the protocol strictly.

6. CHANGES TO THE PROTOCOL DOCUMENTS AND/OR CONSENT FORM

☒ No	☐ Yes	If Yes, submit amendment form and revised documents, as applicable

7. SIGNATURE OF PRINCIPAL INVESTIGATOR (required)

Signature of Principal Investigator	Date

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

15 Parkman Street, WACC 725
Mail Zone WAC 725
Boston, Massachusetts 02114-3139
Tel: 617 726-1731, Fax: 617 724-1540
E-mail: jbiederman@partners.org

Joseph Biederman, M.D.
Chief, Clinical and Research
Program in Pediatric Psychopharmacology
and Adult ADHD
Massachusetts General Hospital
Professor of Psychiatry
Harvard Medical School

DATE: April 9, 2004
TO: Human Research Committee

RE: Response to IRB review of Violation: "Open-Label Study of Risperidone Versus Olanzapine for Mania in Preschool Children 4 to 6 years of age with Bipolar Spectrum Disorder"

Dear Committee Members:

Enclosed please find a response to your review of a violation that will be brought to a full committee.

Sincerely,

Joseph Biederman, MD

INVESTIGATOR RESPONSE TO IRB QUESTIONS/CONCERNS

PROTOCOL#: 2001-P-000422

1. PRINCIPAL/OVERALL INVESTIGATOR:

(cannot be resident or research fellow-except for hem/onc studies)

Name: **Joseph Biederman, MD**
First Name, Middle Initial, Last Name, Degree(s)

Institution: ☐ BWH ☐ DFCI ☒ MGH Employee ID#: 231-03-91

Dept/Service: **Psychiatry** Div/Unit: **Pediatric Psychopharmacology Unit**

Address: **185 Alewife Brook Parkway, Suite 2000, Cambridge MA 02138**

Telephone: **617-503-1063** Beeper: **35417** FAX: **617-503-1092**

E-Mail/Internet Address: **jbiederman@partners.org**

2. STUDY TITLE

Open-Label Comparative Study of Risperidone Versus Olanzapine for Mania in Preschool Children 4 to 6 Years of Age with Bipolar Spectrum Disorder

3. IRB Review Date: Please indicate date of IRB Review

4/1/04

4. Submission Reviewed: Indicate what was reviewed; e.g., 8/8/96 Amendment

Major Violation

5. RESPOND POINT BY POINT TO IRB QUESTIONS/CONCERNS:

I am fully aware that this breach will be brought to the attention of the full Partners Healthcare Human Research Committee as it represents a major violation. While this serious violation should never have occurred and is not justified, the HRC should be aware of the circumstances in which the violation occurred.

The main points are:
1) The clinician raised the dose above the protocol limit in an attempt to stabilize a very sick child who was experiencing severe psychopathology.
2) The dose used was above that approved in the protocol but within the range of what is used clinically. The correct procedure would have been to terminate the child and continue treatment at the higher clinically indicated dose.
3) The child experienced no adverse outcome.

To avoid the recurrence of this unfortunate and unacceptable event, the following steps were taken:
1) A stern notification was sent to all research clinicians in my program via email alerting them of this violation and stating the utmost seriousness of the event and the absolute need to fully comply with all aspects of an IRB approved research protocol and its dosing

requirements.
2) A formal meeting was held on 4-6-04, with the clinical staff of our research program to review this critical issue and formalize procedural changes moving forward.
3) Research staff was informed that in the case that an urgent or otherwise compelling clinical situation were to arise that appeared to warrant an exception to the approved protocol, the clinician will contact the PI immediately to review the situation and if the clinical circumstances are judged to warrant a potential protocol deviation, the PI will contact Harry Demonaco, Dr. Jonathan Alpert, or Dr. Elizabeth Hohmann at the IRB to review the situation and seek appropriate authorization to move forward with a protocol exception per PHRC guidelines . Without such authorization, no changes will occur.
4) If changes are still deemed necessary and the proposed exception is not authorized, the subject will be dropped from the protocol and treated clinically.

I hope that these procedures will avoid future inappropriate violation as the one that occurred. Please feel free to contact me with additional suggestions and recommendations if you feel that these procedures are inadequate and I will be happy to implement them immediately.

Principal/Overall Investigator Signature (required)

4/8/04
Date

Human Research Committee
Massachusetts General Hospital
Lawrence House
10 North Grove Street
Boston, MA 02114
(617) 726-3494

Violation/Deviation: Notification of IRB REVIEW
Protocol #: 2001-P-000422/40; MGH

Date: 04/05/2004

To: Joseph Biederman, MD
Psychiatry
Warren 705

From: Ronda Cox Goldman
MGH Research Management
LRH 3

Title of Protocol:	Open-Label Comparative Study of Risperidone Versus Olanzapine for Mania in Preschool Children 4 to 6 Years of Age with Bipolar Spectrum Disorder
IRB V/D #:	6
IRB Review Type:	Expedited
IRB Review Date:	04/01/2004
IRB Review Action:	Requires Modification

This Violation/Deviation has been reviewed by the MGH IRB, Assurance # FWA00003136. During the review of this Violation/Deviation, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for securing and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Please read this memo carefully and respond in a point-by-point manner to the issues raised below within 60 days of the review date.

This is a serious breach of the Protocol procedures and provisions. The maximum dose of olanzepine allowed during the study participation is 7.5mg. The dose escalation to 12.5mg in the context of non-compliance on the part of the parents to study procedures seems inappropriate based on study requirements. Although the distinction between clinical care and clinical research is blurred in this subject population, the absolute requirements of the Protocol should have required subject discontinuation from the study and clinical management. Continued participation in this subject is a serious violation of study procedures.

Human Research Committee
Massachusetts General Hospital
Lawrence House
10 North Grove Street
Boston, MA 02114
(617) 726-3494

This breach will be brought to the attentionof the full Partners Healthcare Research Committee as it represents a major violation. Any additional information concerning this subjects' participation should be forwarded as soon as possible. This is the sixth violation of Protocol procedures noted in the study file. One other violation involved the addition of prohibited concomitant medications. The investigator is asked to provide additional details concerning procedural changes that will ensure that clinicians follow mandated study procedures. This subject should be considered discontinued from further study participation and managed clinically as deemed appropriate by caregivers.

Direct any questions, correspondence and forms to Ronda Cox Goldman, (617) 724-2130.

c: Stephanie Dunkel, BA

FAX COVER SHEET

To: Joseph Bleckman MD / Stephanie Bonkel From: Ronda Cox Goldman

Fax #: 617 583-1060 Tele #: 617-724-2130

Fax #: 617-724-1919

Date: 4-5-04

Message:

Number of Pages: 3

Human Research Committee
Massachusetts General Hospital
Lawrence House
10 North Grove Street
Boston, MA 02114
(617) 726-3494

Violation/Deviation: Notification of IRB Approval/Activation

Protocol #: 2001-P-000422/41; MGH

Date: 05/10/2004

To: Joseph Biederman, MD
Psychiatry
Warren 705

From: Ronda Cox Goldman
MGH Research Management
LRH 3

Title of Protocol:	Open-Label Comparative Study of Risperidone Versus Olanzapine for Mania in Preschool Children 4 to 6 Years of Age with Bipolar Spectrum Disorder
Sponsor:	Private Grant
IRB Review Type:	Full
IRB Approval Date:	04/27/2004
Approval Effective Date:	05/10/2004
IRB Expiration Date:	01/06/2005

This Violation/Deviation has been reviewed and approved by the MGH IRB, Assurance # FWA00003136. During the review of this Violation/Deviation, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for securing and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Please note that if an IRB member had a conflict of interest with regard to the review of this project, that member left the room during the discussion and the vote on this project.

NOTES: Subject MATMCD missed visits 4 through 6 during the acute phase of the study and none of the study procedures were completed. In addition, the time between weeks 3 and 7 visits was six weeks rather than four weeks. At week 8 the subject's dose was increased to 10 mg/QD and the protocol states the maximum is 7.5 mg/QD. At month one of the extension phase of the study the dose was increased to 12.5 mg/QD. Each increase was well tolerated.

The investigator responded to HRC concerns and the full HRC reviewed the violation.

As Principal Investigator you are responsible for the following:

1. Submission in writing of any and all changes to this project (e.g., protocol, recruitment materials, consent form, etc.) to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB within 24 hours.

Human Research Committee
Massachusetts General Hospital
Lawrence House
10 North Grove Street
Boston, MA 02114
(617) 726-3494

2. Submission in writing of any and all adverse event(s) that occur during the course of this project that are both serious and unexpected within 10 working/14 calendar days of notification of event.
3. Submission in writing of any and all unanticipated problems involving risks to subjects or others.
4. Use of only IRB approved copies of the consent form(s), questionnaire(s), letter(s), advertisement(s), etc. in your research. Do not use expired consent forms.
5. Informing all physicians listed on the project of changes, adverse events, and unanticipated problems.

The IRB can and will terminate projects that are not in compliance with these requirements. Direct questions, correspondence and forms (e.g., continuing reviews, amendments, adverse events, safety reports) to Ronda Cox Goldman, (617) 724-2130.

c: Stephanie Dunkel, BA, Psychiatry, 185 Alewife

Attachment J

PHARMA SALARY SUMMARY

	2005	2006	2007
JB concerta (MCNEIL)	$ 14,888	$ 16,411	$ -
Lillt Ctr (ELI LILLY)	$ 30,034	$ 27,697	$ 13,143
J&J Ctr	$ 7,919	$ 7,266	$ 3,976

DETAILS

	Biederman, Joseph Oct-06	$	1,490.49
	Biederman, Joseph Sep-06	$	1,490.43
	Biederman, Joseph Aug-06	$	1,473.11
	Biederman, Joseph Jul-06	$	1,490.58
	Biederman, Joseph Jun-06	$	1,490.58
	Biederman, Joseph May-06	$	1,490.58
	Biederman, Joseph Apr-06	$	1,490.58
	Biederman, Joseph Mar-06	$	1,490.58
	Biederman, Joseph Feb-06	$	1,490.58
	Biederman, Joseph Jan-06	$	1,490.58
JB CONCERTA 2006		$	14,888.09
	Biederman, Joseph Dec-05	$	1,490.58
	Biederman, Joseph Nov-05	$	1,490.58
	Biederman, Joseph Sep-05	$	1,490.58

	[redacted]	$	1,490.58
	Biederman, Joseph Jul-05	$	1,490.58
	[redacted]	$	1,490.58
	Biederman, Joseph May-05	$	1,490.58
	[redacted]	$	1,490.58
	Biederman, Joseph Mar-05	$	1,490.58
	[redacted]	$	1,490.55
	Biederman, Joseph Jan-05	$	1,505.34
JB CONCERTA 2005		$	16,411.11
	Biederman, Joseph Jun-07	$	2,070.77
	[redacted]	$	2,070.77
	Biederman, Joseph Apr-07	$	2,070.77
	[redacted]	$	2,310.40
	Biederman, Joseph Feb-07	$	2,310.40
	[redacted]	$	2,310.40
Lilly crtr 2007		$	13,143.51
	[redacted]		

	2005	2006
JB concerta (MCNEIL)	$ 14,888	$ 16,411
Lillt Ctr (ELI LILLY)	$ 30,034	$ 27,697
J&J Ctr	$ 7,919	$ 7,266

	Biederman, Joseph Dec-06	$	2,310.40
	Biederman, Joseph Nov-06	$	2,310.40
	Biederman, Joseph Oct-06	$	2,310.40
	Biederman, Joseph Sep-06	$	2,310.23
	Biederman, Joseph Aug-06	$	2,283.49
	Biederman, Joseph Jul-06	$	2,310.36
	Biederman, Joseph Jun-06	$	2,310.36
	Biederman, Joseph May-06	$	2,310.36
	Biederman, Joseph Apr-06	$	2,310.36
	Biederman, Joseph Mar-06	$	2,310.36
	Biederman, Joseph Feb-06	$	2,310.36
	Biederman, Joseph Jan-06	$	2,310.36
Lilly crtr 2006		$	27,697.44
	Biederman, Joseph Dec-05	$	2,310.36
	Biederman, Joseph Nov-05	$	2,310.36
	Biederman, Joseph Oct-05	$	2,310.36

	Biederman, Joseph Sep-05	$	2,310.36
	Biederman, Joseph Aug-05	$	2,310.36
	Biederman, Joseph Jul-05	$	2,310.36
	Biederman, Joseph Jun-05	$	2,310.36
	Biederman, Joseph May-05	$	2,310.36
	Biederman, Joseph Apr-05	$	2,310.36
	Biederman, Joseph Mar-05	$	2,310.36
	Biederman, Joseph Feb-05	$	4,620.71
	Biederman, Joseph Jan-05	$	2,310.36
Lilly crtr 2005		$	30,034.67
J&J			
	Biederman, Joseph Jun-07	$	661.18
	Biederman, Joseph May-07	$	661.18
	Biederman, Joseph Apr-07	$	661.18
	Biederman, Joseph Mar-07	$	661.18
	Biederman, Joseph Feb-07	$	661.18
	Biederman, Joseph Jan-07	$	661.18

J&J crtr 2007		$	3,967.08
	[redacted]		
	Biederman, Joseph Dec-06	$	661.18
	[redacted]	$	661.18
	Biederman, Joseph Oct-06	$	661.18
	[redacted]	$	661.29
	Biederman, Joseph Aug-06	$	653.57
	[redacted]	$	661.39
	Biederman, Joseph Jun-06	$	661.39
	[redacted]	$	-
	Biederman, Joseph Apr-06	$	661.39
	[redacted]	$	661.39
	Biederman, Joseph Feb-06	$	661.39
	[redacted]	$	661.39
J&J crtr 2006		$	7,266.74
	[redacted]		
	Biederman, Joseph Dec-05	$	661.39
	[redacted]	$	661.39

	Biederman, Joseph Oct-05	$	661.39
	[redacted]	$	661.39
	Biederman, Joseph Aug-05	$	661.39
	[redacted]	$	661.39
	Biederman, Joseph Jun-05	$	661.39
	[redacted]	$	661.39
	Biederman, Joseph Apr-05	$	661.39
	[redacted]	$	661.39
	Biederman, Joseph Feb-05	$	661.14
	[redacted]	$	644.92
J&J crtr 2005		$	7,919.96