AHRP has been closely monitoring pediatric research trends since passage of the FDA Modernization Act of 1997. We believe that medications used in children should be thoroughly tested for safety, effectiveness and appropriate dose. But unlike adults who can exercise their autonomous right to informed consent, children who are enrolled in clinical trials are non-consensual human subjects. They should not, therefore, be made to assume the burden of testing possibly toxic drugs whose safety is unknown.

These comments are submitted by the Alliance for Human Research Protection (AHRP), a grassroots organization of professional and lay citizens dedicated to advancing responsible and ethical medical research practices, to ensure that the human rights, dignity and welfare of human subjects are protected, and ensure that the risks associated with such endeavors are minimized. AHRP has been closely monitoring pediatric research trends since passage of the FDA Modernization Act of 1997. We believe that medications used in children should be thoroughly tested for safety, effectiveness and appropriate dose. But unlike adults who can exercise their autonomous right to informed consent, children who are enrolled in clinical trials are non-consensual human subjects. They should not, therefore, be made to assume the burden of testing possibly toxic drugs whose safety is unknown. AHRP endeavors to protect children from harmful medical experiments by reminding public officials and the research community of their duty to protect children from experiments that are contrary to their best interest. Parental permission does not always substitute for informed consent. AHRP is guided in its position by the U.S. Supreme Court ruling: “Parents may be free to become martyrs themselves. But it does not follow that they are free, in identical circumstances, to make martyrs of their children.”[1]
It is hoped that IOM Committee members have had an opportunity to read the recently published article in the American Journal of Bioethics, "Children in Clinical Research: A Conflict of Moral Values,"[2] which provides an in-depth analysis of current systemic shortcomings. Child subjects are increasingly put at risk of harm insofar as the current institutional review board (IRB) system that is supposed to review, approve and oversee the scientific integrity and safety of human research is riddled by conflict of interests.[3]

We believe the following are among the most important shortfalls in the conduct of research involving infants, children and adolescents:

- Failure to examine alternative methods of obtaining needed information so that research involving risk for children is minimized. The goal should be to limit the exposure of children to trials that seek vital information that is "unprocurable by other means" - as mandated under the Nuremberg Code and as stipulated in current federal regulations - 45 CFR 46 Subpart D - which restrict the exposure of children to greater than minimal risk. Indeed, until the FDA adopted the "Pediatric Rule"[4] in 1998, high risk, phase I trials in children "had been primarily limited to life threatening diseases and children who had the disease for which the new drug was being proposed." It is difficult to justify a shift in policy that will increase children's exposure to pain and risks of harm.

- Inadequate review: failure to evaluate risks relative to existing empirical evidence of harm.

- Failure to minimize risks, including psychological risks, or to justify them from the perspective of the child.

- Absence of evidence-based guidelines for classifying research protocols "minimal risk," "minor increase over minimal risk," or "greater than minor increase over minimal risk."

- There is a pressing need to examine cases that resulted in harm to children - and to draw policy recommendations on the basis of that evidence - so that we can avoid causing harm in the future. Such an analysis was carried out by the Advisory Commission of Human Radiation Experiments (ACHRE), and for that reason ACHRE stands apart from all subsequent ethics advisory committees whose recommendations were unsupported by evidence.

- Absence of boundaries to limit the level of risk and pain to which a child may legitimately be exposed.

- Pervasive conflict of interests of all involved - including, and especially, institutional review boards that have been shown to rubber stamp approval of harm producing trials.

- Absence of an independent child subject's advocate to monitor his/her well-being.

- Lack of accountability or enforcement of federal safeguards.

- Lack of penalties for those who violate ethical standards.
The absence of adequate safeguards creates incentives for researchers to engage in the kinds of risk-taking that leads to the abuse of children.

Our focus is on recent examples of highly controversial, overreaching experiments that posed greater risks of harm than any evidence-based anticipated benefit:

- Smallpox vaccine trial to test the safety of Dryvax administration to children 2 to 5 years of age. AHRP was instrumental in averting this dangerous, ill-advised vaccine trial.[5]

- Predictive diabetes screening tests in newborns. These tests offer no preventive measures - as none are available.

In the absence of any benefit such experiments are unjustifiable as they increase risks to the subjects. For example, parents may be misled to believe that the nontherapeutic nature of diabetes screening tests are akin to therapeutic screening for metabolic and endocrine disorders that require immediate treatment. Parents may overreact if the results of the test are "positive" and may interpret normal behavior as "symptoms" of disease. Infants declared "at risk" for diabetes - though that risk may never materialize - may be subject discrimination by health insurance carriers.[6]

- "Precursors to diabetes" trials that subject children to invasive procedures before there is evidence of disease:

One such experiment conducted at the National Institute of Child and Adolescent Human Development, was suspended by the Office of Human Research Protection following an investigation which found no justification for exposing healthy children to painful glucose tolerance tests.[7] The journal SCIENCE reports that increasingly riskier diabetes "prevention" experiments are being conducted on children - even though all previous studies have failed.[8] Whereas Europeans are retreating from diabetes prevention experiments, some American clinicians are forging ahead with ever more aggressive experimental strategies that expose children to increased risks without any certainty that these children will even develop diabetes. For example, Dr. Kevin Herold of...
Columbia University is experimenting on children with immunosuppressant therapy—an extremely risky exploratory intervention that can only be justified for those whose autoimmune system is so over-active as to cause an immune disorder. But the children to be exposed to such a radical intervention may as a result suffer the consequences of a compromised immune system, which would make them vulnerable to acute infection and to debilitating chronic illness their entire lives.

These risky ventures validate AHRP’s call for improved federal safeguards that set limits on the level of risk that children may be exposed to. Indeed, they are generating furious debate and even acrimony among immunologists, endocrinologists, and pediatricians. "How much risk," they ask, "should we tolerate in trying to prevent or stall a disease that may not threaten life for many decades?" "How well must we understand autoimmunity, or a drug's potential hazards, before treating an 8-year-old?" Dr. Carla Greenbaum, who directs diabetes clinical research at the Benaroya Research Institute in Seattle, warns: "We can't be cowboys on this." AHRP recommends that such radical human experimentation on children - who are non-consensual human beings - be banned. At this stage, diabetes-screening tests involve high risk, and no foreseeable benefit. Corroborating evidence shows, interference with hormonal function for "preventive" purposes precipitates risks of heart attacks, strokes, blood clots and breast cancer.

Similarly, the promotion of statins as a preventive measure against possible heart attacks is unsupportable. Proponents of radical interventions in children who are oblivious to the sobering lessons to be learned from the hormone replacement therapy debacle are irresponsible. These are archetypal examples of medicine in collusion with drug manufacturers: doctors prescribing (often) worthless high priced treatments that increase risks of harm. Who will bear responsibility for the children who may suffer unintended, but predictable health hazards as a result of "diabetes prevention" therapies?

- Psychotropic drug trials are another cluster of pediatric experiments that are of special concern as the increasing number of children are enrolled in clinical trials to test psychostimulants, antidepressants and anti-psychotic drugs.

It is a national concern that millions of children in the U.S. are being diagnosed with loosely defined psychiatric "disorders," for which they are irresponsibly prescribed a variety of psychoactive drugs. For example, Dr. Lawrence Diller, a pediatrician, described one such medical travesty in The Washington Post: Simon, a 29 month toddler was subjected to an uncontrolled drug experiment. Dr. Diller wrote: "I was flabbergasted when I later learned from his mother that Simon saw a highly respected child psychiatrist and was now taking Lithium, Zoloft, and Risperdal, three psychiatric drugs at once." Dr. Diller concluded, "I didn't know who felt crazier, Simon or I."
These powerful psychoactive drugs pose significant hazards even during short-term exposure, and even their promoters acknowledge the absence of data about long-term exposure. Reports that had been submitted during the licensure process to regulatory agencies - including the FDA - have recently been analyzed independent of industry influence, and these reports show that suicide is a significant issue in psychotropic drug trials.[13] The solution to overprescribing psychotropic drugs for children is NOT to expose additional children to the risks these drugs pose - especially as a scientifically valid diagnostic justification does not exist. We offer four illustrative cases of psychotropic drug trials that we believe fail to meet the minimal criteria for ethical research involving human beings who are not volunteers. All four cases were not in the best interest of the children, and all four failed to satisfy attainment of a favorable risk / benefit ratio for the child subjects.

Experts do not agree about the criteria for diagnosing children's behavioral disorders insofar as objective diagnostic tools do not exist. Experts do not agree about the best method for treating children's behavior disorders. In 1998, the National Institute of Health convened a panel of experts to evaluate the evidence about ADHD. The experts failed to reach a consensus about either the diagnosis or treatment of ADHD.[14] Even the Director of Child and Adolescent Treatment and Preventive Interventions Research Branch of the National Institute of Mental Health (NIMH), Dr. Benedetto Vitiello, repeatedly acknowledged "diagnostic uncertainty surrounding most manifestations of psychopathology in early childhood." [15] And he acknowledged "uncertainty about the diagnosis of mental disorder in preschoolers has precluded FDA from requesting studies of psychoactives in younger children." [p.987]

Nevertheless, despite those acknowledgements, NIMH initiated the preschool ADHD treatment study (PATS).

Case 1: Preschool ADHD Treatment Study (PATS)[16]

The NIH sponsored preschool ADHD treatment study (PATS) was designed to test preschool children's tolerance of increased doses of the stimulant, Ritalin. The test subjects are 312 children 2 to 5 year old who are exposed to increasingly higher doses of the drug until they experience adverse effects. The study's principal investigator, Dr. Lawrence Greenhill, acknowledged in Science that ADHD is "not a well-defined psychiatric disorder in this age group." [17] Without a well-defined diagnostic basis the experiment fails to meet ethical standards and the intervention is unsupportable. Scientists have concluded that the mechanism of action of cocaine and Ritalin is almost identical.[18] [19] Ritalin sharpens short-term attention span in whoever takes the drug, whether or not they have been diagnosed with ADHD. But there are adverse side-effects, the most common of which are insomnia, loss of appetite, weight loss, and growth retardation.[20] Dr. Nora Volkow, Director of the National Institute of Drug Abuse, found that Ritalin is more potent than and stays in the brain much longer than cocaine.[21] One of the few long-term follow up studies by Dr. Nadine Lambert found strong evidence linking Ritalin to tobacco and cocaine dependence. Of those who had been exposed to Ritalin as children 40% became heavy smokers compared to 19% for age-mate controls, and 21% of the Ritalin exposed group became addicted to cocaine compared to 10% of the age-mate controls.[22] Were these findings cited in the grant proposal and the informed consent documents? Parents are paid $645 if their child completes the full duration of the PATS study and teachers are paid to fill out forms. These financial incentives to the children's caretakers are most troubling insofar as
the children's best interest is not being served.

Antidepressants - selective serotonin reuptake inhibitors (SSRI)

Contrary to the claims made by drug manufacturers and their promotional campaigns, contrary to the claims made by psychopharmacologists who have financial ties to these companies, SSRIs are not the breakthrough "magic bullets" as their promoters declared.[23]

Recent analyses of clinical trial data submitted to the FDA more than a decade ago reveals the drugs are no more effective than placebo.13 [24] However, they pose far greater risks of harm than the placebo. After its approval for marketing, FDA received the greatest number of severe adverse drug reports about Prozac, [25] the first of the SSRI antidepressants. But the agency didn't investigate those reports, or warn prescribing physicians or the public. Among the severe adverse drug reactions reported (at least 500 times): convulsions, agitation, abnormal thinking, hypertension, cerebro-vascular accidents, sleep disturbances, nightmares, mania, psychosis, severe anxiety, tremors, liver dysfunction, depression. But the promoters of these drugs trivialized the complaints, calling them anecdotal. For years, drug manufacturers and the psychiatrists they fund have vigorously denied that these drugs induced severe adverse reactions in some patients, and they denied the drugs are addictive, which is expressed in severe withdrawal symptoms.[26] Recent independent analyses of secret, unpublished data submitted to the FDA by the manufacturers of these drugs, contradict claims of their effectiveness and validate the case reports about the prevalence of severe adverse drug reactions that continue to pour into the FDA's MedWatch.[29]

Drug manufacturers, the FDA, and the investigators who tested antidepressants in children all knew about the lack of any credible evidence for the effectiveness of these drugs when compared to placebo.13 Indeed, in 2000, Dr. Robert Temple, director, Office of Drug Evaluation at the FDA, acknowledged "the preponderance of negative studies of antidepressants in pediatric populations."[30] All but a single pediatric study that tested antidepressants in children resulted in negative findings. In that study, children tested Prozac, the first antidepressant in the selective serotonin reuptake inhibitors (SSRI) class - the differential between Prozac and placebo was only 8%.2 There is considerable concern about whether, with long-term use, antidepressant drugs produce permanent neurological damage - especially in children whose brains are still developing. [31]

Since the introduction of Prozac, the most contentious allegation by patients and a handful of senior clinical investigators at Harvard,[32] Wales,[33] and UCLA,[34] is that SSRIs trigger violent and suicidal behavior2 in a minority of patients. But just as the adverse reaction reports about these drugs were ignored by the FDA,29 these findings of suicidal behavior were dismissed as anecdotal and not credible by those with vested interests in increasing sales of the drugs. However, independent critics were alarmed. Dr. Joseph Glenmullen[35] of Harvard University compared the neurological damage of SSRIs to the damage caused by antipsychotics. He speculated that future generations may look back on use of the antidepressants and other damaging psychiatric drugs as "a frightening human experiment."[36]
Health care analyst, Thomas J. Moore, who analyzed the FDA data in 1997, noted the very large placebo effect in the treatment of depression, concluding:

"The fact is that antidepressant drugs are overrated by many consumers and doctors, overprescribed because of aggressive marketing, and [are] among the most toxic drugs in widespread use as measured by the number, variety, and severity of adverse effects."  

It is astonishing that these drugs are being widely prescribed for children despite the absence of any scientific basis for even diagnosing depression in children - especially as a credible body of evidence exists showing the drugs pose serious, even life-threatening risks of harm.  

Case 2: Children in "forced titration experiments" testing sertraline (Zoloft)

"Forced titration" experiments push children's endurance until they suffer dose-related severe adverse effects. One such example tested the antidepressant Sertraline (Zoloft) in children as young as 6. The trials are described in Pfizer's Expert Report submitted to the FDA in October 1997. Serious adverse events (SAE) are described in the report as: "events which were fatal; life-threatening or potentially life-threatening; resulted in permanent disability; required hospitalization or prolongation of hospitalization; a drug overdose or suggested significant hazard to the patient." [p 27] The Pfizer report provides data from trials in children aged 6-12 and adolescents aged 13-17 years who were diagnosed with either depression or obsessive compulsive disorder (OCD). In the 51-day open label "forced titration" study, there were 61 children recruited to test the pharmacokinetics of and tolerance to sertraline (Zoloft) after single and multiple doses. Of these 61 children 44 were depressed, and 17 were diagnosed with OCD. During the first four weeks of the trial the children's dose was increased to 200mg - a dose higher than was tested in adult trials. According to the Pfizer report: "the mean maximum daily dose of sertraline was considerably higher in the paediatric studies (185mg) than in the adult OCD studies (148mg). This higher mean maximum daily dose is due to the design of the paediatric studies." [p. 31] The rationale for testing a higher dose in children remains unclear. It is also unclear why the FDA approved a "forced titration" study design, which at the very least increased risk and discomfort for children who were put under increased stress. Within the group of 44 depressed children, 4 who tested Zoloft attempted suicide - a rate of 9%. [38]

Suicide attempts in the main occurred within a few days of dose escalation. One of the children who became suicidal was an eight-year-old boy who had been in the sertraline dose tolerance study for 36 days. A Pfizer 1996 suicides report submitted to the FDA states: "Patient was hospitalized for a suicide gesture, and dropped from the study. The patient #4 mutilated himself by cutting his feet with a razor blade and tying a tie around his neck." [38] There was no previous history of self-mutilation or suicidality. Pfizer's Report acknowledges: "The event was attributed to study drug by the investigator." Another boy in the same Pfizer study was a 14 year old who had been receiving 200mg/day of Zoloft until he was hospitalized...
on the 35th day of the study for "a moderate suicide gesture."

Indisputable evidence - such as internal company documents - were uncovered during U.S. court proceedings. Only recently has that evidence been made public. These internal documents reveal that the companies knew, but concealed the fact that SSRIs, the most widely prescribed antidepressants, pose serious risks of self-harm for adults and children. Company documents show that the suicide risk exists whether the test subjects are depressed or not - even healthy volunteers became suicidal after taking an SSRI. The UK Guardian reported that when the risk was discovered in early pre-marketing tests, Eli Lilly took the precaution of adding benzodiazepines "to control the agitation" in subsequent trials. No doubt, the addition of benzodiazepines produced results favorable for FDA approval, but was this addition ever disclosed in published reports to alert physicians of the need to take such a precaution? Most compelling for the IOM Committee is evidence from company documents that suicide is a significant issue in psychotropic drug trials, and in pediatric trials the problem is even greater. These concealed documents reveal that a high percentage of adult and child subjects in controlled clinical trials suffered severe adverse effects - including withdrawal/dependency symptoms and high rates of suicide attempts - even during short clinical trials.

As early as 1990 psychiatrists observed a tendency toward agitation and self-harm in children treated with Prozac. But those observations were not further examined. Most recently, the UK government medicines board examined GlaxoSmithKline documents pertaining to nine pediatric trials of Paxil (Seroxat), confirming that children testing Paxil were found to have a two to three-fold suicide risk compared to those on placebo. These revelations led the British Government to issue a ban on June 10, 2003, instructing UK physicians not to prescribe Paxil (Seroxat) to children under 18. Clinical trials of SSRIs also revealed that these drugs cause severe withdrawal symptoms - a sign of their addictive effect. GlaxoSmithKline changed the label for Seroxat in the UK, deleting its previous claim that the drug was not addictive, and issued a letter to UK healthcare professionals, acknowledging a suicide risk in children taking Seroxat this is double the risk for those given placebo. The company issued no such warning to US physicians.

However, a front page article in the New York Times on August 7, 2003, reported that the safety of the SSRI antidepressants was now being questioned by 7 of the 10 experts who had served on FDA's expert advisory panel in 1991. These experts had cleared SSRIs from a suicide link. And on August 12, 2003, the director of the psychopharmacology clinic at Cornell University conceded that clinical trial finding reports were biased and "government approval [on the basis of those trials] is not a guarantee of safety." For these compelling reasons AHRP believes that it is unconscionable to test these drugs in young insofar as the risks far outweigh any foreseeable benefit for the children. The following two disturbing cases epitomize a culture of "generally accepted research abuses" in nontherapeutic pediatric research. The cases reveal that the research community thinks nothing of subjecting children to pain and foreseeable risks of harm - including producing drug-induced chronic debilitating disease without any foreseeable, evidence-based, benefit.
We believe the cases make a powerful case for legislated protections that focus on strong enforcement and oversight activities on academic institutions.

Case 3: Olanzapine (Zyprexa) trial masquerades as “schizophrenia prevention”:

Eli Lilly’s powerful antipsychotic drug, olanzapine (Zyprexa) is being tested in healthy adolescents - some as young as twelve - on the basis of the investigators’ speculative hypothesis that the adolescents, though undiagnosed with any illness, are “at risk” of schizophrenia because a sibling has been diagnosed with the disorder. But the risk for siblings of schizophrenia patients is no more than 9%—therefore 91% of the subjects are not at risk of schizophrenia, but by taking Zyprexa they are at considerable risk of severe, drug-induced adverse reactions and drug-induced chronic debilitating illness.

Among the reported severe adverse side effects experienced by the subjects during clinical trials of olanzapine: cardiovascular complications (10% to 15%); acute weight gain (50%), an effect that signaled an increased risk for diabetes. Parkinson-like motor impairment (11.7%); and akathisia (mental and physical restless and agitation) (7.3%).

It has been strongly suggested by senior psychiatrists at premier research institutions and in internal Eli Lilly documents that akathisia is the likely catalyst for suicidal and homicidal thoughts and acts. During pre-marketing clinical trials, olanzapine was linked to serious, in some cases life-threatening side effects requiring hospitalization in 22% of the adults in whom it was tested.

According to FDA data, there were 22 deaths - 12 of which were suicides. The drop-out rate during 6-week clinical trials was 65%. In an extended (one year) trial, the drop out rate had been 83%.48

Until the introduction of the atypical antipsychotic drugs, such as clozapine (Clozaril) and olanzapine (Zyprexa), diabetes was rare in children and adolescents. Since its approval, a review by officials of the Center for Drug Evaluation of FDA’s MedWatch database reveals a causal association between Zyprexa and new onset diabetes that is ten times higher than in the general population.

How can anyone justify exposing healthy youngsters to a drug that has a ten-fold probability of causing diabetes?

Case 4: Spinal Taps for Science:

In 1996, F. Xavier Castellanos,[50] and a team of child psychiatrists from NIMH and three other institutions[51] reported about a nine-week, cross-over, multiple drug experiment they had conducted on 45 boys, aged six to eleven. The investigators indicated they were replicating their own previous research.[52]

The children in the replication study had been diagnosed with ADHD and other equally controversial behavioral disorders, including "conduct disorder", "oppositional disorder", and "mild overanxious disorder". The purpose of the experiment was to test the effect of stimulant drugs (methylphenidate, dextroamphetamine, compared to placebo) on the cerebrospinal fluid (CSF) levels of dopamine (HVA), norepinephrine (MHPG), and serotonin (5-H1AA) and to find a correlation between HVA levels and hyperactive behavior.
enormous financial incentives to pharmaceutical companies who reap a
six month extension of patent exclusivity if they test patented drugs
in children. For Eli Lilly, for example, a six-month patent extension
for Zyprexa can mean a billion dollars, and for the psychopharmacologists
and their institutions, this windfall means increased income and expanded
pediatric trials. Indeed, the number of child research subjects has
grown from about 16,000 in 1997 to about 45,000 in 2001.[53]
Unfortunately, the law failed to balance financial incentives with new
(or improved) safeguards to protect an increased number of young children
who are being exposed to the hazards of research. As a result, children
who are legally precluded from exercising the right to refuse are being
aggressively recruited to bear the burden of testing drugs that may
(or may not) be safe or in their best interest.

Children are especially vulnerable in the research setting. Their
inability to exercise the adult right to informed consent or to protect
themselves from unwanted experiments relegates children to the category
of involuntary human subjects. Their dependency on others to decide
what serves their best interest places them at particular disadvantage.
Children’s “assent” is not equal to legally valid informed consent.
Case 3 is an example of a speculative, high risk experiment that subjects
children to the adverse effects of Eli Lilly’s most lucrative patented
antipsychotic drug, Zyprexa on the basis of a speculative presumed genetic
predisposition. However, as the risk for siblings is between 3% and
9% more than 90% are unlikely to develop schizophrenia. Those conducting
the experiment and those who approved it, ignore the evidence from FDA’s
MedWatch that demonstrates youngsters taking Zyprexa are ten times more
likely to get diabetes than the general population. What is the justification
for exposing children to the risk of diabetes? Do the Yale consent documents
disclose the ten-fold risk of diabetes to parents of the adolescents
in the Zyprexa trial?

Federal regulations require sufficient evidence to expect that the
research "is likely" to provide essential knowledge, which is of "vital
importance" for "the subjects' disorder or condition." Those who have
a financial stake in the research enterprise have suggested that research
involving more than minimal risk without a prospect of direct benefit
is approvable based on the unproven claim of "long-term benefit of children."
They also claim that a prohibition on such research involvement would
result in long-term detriment to children. However, as Dr. Lainie Friedman
Ross[54] points out, those who
raise such arguments have not explained why non participation in nontherapeutic
research would be harmful to a particular child.

As the sample cases demonstrate, children are being recruited to assume
risks of harm and pain with no personal benefit.[55]
Children are being recruited for speculative experiments whose value
is questionable.[56] AHRP is deeply
concerned that the ethical principles underlying federal safeguards
for children are being distorted to facilitate nontherapeutic experiments
involving greater than minimal risk on otherwise healthy children. There
are research stakeholders who have declared "prematurity, infancy, adolescence,
poverty, living in a compromised physical environment, and institutionalization"
as "disorders or conditions" that warrant permissible research in children
even if the risks posed are greater than minimal risk and without a
prospect of direct benefit to the child. Their pronouncements are a
radical departure from commonly held views about what constitutes the
normal developmental stages of childhood and cannot muster support from
evidence-based medicine. Children need protection from speculative experiments
that later prove harmful.
To be credible, the IOM Committee's report and recommendations to Congress should follow the example of the Advisory Committee on Human Radiation Experiments (ACHRE) whose report and recommendations are based on an examination of the evidence. A most telling observation in the 1994 ACHRE report is the following observation:[57]

"Many experiments that prove to be of little value in the advance of medical knowledge are, at the time they are implemented, well designed and appropriate attempts to address important research questions."

Indeed, long-held assumptions about the value of early detection and intervention are being overturned. Those assumptions are being widely challenged by independent scientists who have not only raised serious doubts about evidence of benefit, but have raised concern about the harm that followed from overdiagnosis[58] and unnecessary medical interventions. These developments underscore the need for adopting a precautionary principle in order to avoid unjustifiable risks of harm - particularly when children are involved, as they are non-consenting subjects. The IOM committee needs to examine evidence about the experience of children in pediatric trials since the enactment of FDAMA. Such evidence is available from the NICHD, NIMH, and the FDA.

A series of articles published by the Boston Globe in 2001 revealed that the number of children enrolled in clinical trials in 1997 was 16,000: by 2001, the number reached 45,000. The Globe found that children enrolled in clinical trials had suffered and died, and that ethical standards had been violated.[59] Financial incentives for parents, physicians, and researchers had undermined children's welfare. Children are currently being recruited with Toys 'R Us gift certificates. Parents in need of money are offered as much as $1,000 to "volunteer" their children for drug experiments that involve risks of harm.[60] The physicians who are engaged in such coercion receive as much as $5,000 in kickbacks (euphemistically called, "referral fees") for the recruitment of children.[61] None of these disturbing facts were brought to the attention of the U.S. Congress when it passed the Best Pharmaceuticals for Children Act in 2002. The evidence, however, shows that children are being deprived of existing, more protective federal regulations under 45 CFR 46, Subpart D, and are being subjected to foreseeable risks of harm and discomfort, often on the basis of a presumed potential risk for which there is no empirical evidence.[62] The FDA acknowledged that before FDAMA the use of children as subjects in phase I safety drug studies "had been primarily limited to life threatening diseases and children who had the disease" in question.[63] The policy prior to FDAMA protected children from harmful experiments in accord with the 1983 federal regulations (45 CFR 46.404-409). Following passage of FDAMA, however, federal policy broadened the criteria for inclusion of children in research generally and for participation of children entered in high-risk experiments. In 1999 the FDA acknowledged that the post-FDAMA policy change "led to an increasing number of proposals for studies of safety and pharmacokinetics, including those in children who do not have the condition for which the drug is intended."[64]

One can only speculate about the negative impact this policy change had on the healthy children who had been subjected to drug trials before
the FDA rescinded the policy. FDA Associate Director of Pediatrics, Dr. Dianne Murphy, was reported to have stated at a conference (April 3, 2001): "FDA will no longer accept information submitted to the agency for pediatric exclusivity if the data is derived from children who are not patients and for whom there is no foreseeable benefit."[65] Yet, young children who have not been diagnosed with any psychiatric disorder are being exposed to potent psychiatric drugs with foreseeable risks of harm - including the risk of addiction. Small children are being subjected to psychotropic drugs on the basis of a presumed potential risk for which there is no empirical evidence. Dr. Vitiello of NIMH provided confirmatory evidence that FDAMA has been a catalyst for recruitment of children for psychotropic drug trials when stating "pediatric psychopharmacology has recently seen an unprecedented expansion . . . NIMH-funded research for clinical trials in youths has more than doubled in the last few years."[66] Considering that a six-month patent extension for Prozac, for example, can mean an additional $831 million for Eli Lilly,[67] what chance does a disadvantaged poor child have against marketplace incentives of such magnitude? Economists would characterize them as extreme "moral hazard" and the kind of market failure that cries out for legislated reform. Unsuspecting children and their parents are bearing the spill-over costs of the production of highly-profitable drugs by pharmaceutical companies. Society and taxpayers are burdened with paying the clean-up costs.

We believe that such marketplace incentives are unseemly and inherently coercive. Children should not be treated as commodities to increase the profits of big business.[68] Furthermore, the literature underscores the essential truth of the common sense assumption that financial inducements are the main reason that healthy persons volunteer for research.[69] But children are not free agents. Financial incentives ensure that disadvantaged children will be disproportionately used as experimental subjects because those whose parents are more educated and economically advantaged "are likely to refuse to participate and are underrepresented in most research."[70] How does this square with the principle of distributive justice? It is an ethical problem that the IOM committee will hopefully address in depth.

It is clear that children currently do not have independent advocates to protect their best interests in the research oversight system. Beyond representation on IRBs - children need for special advocates throughout the research process. The IOM Committee might well reconsider the wisdom of the original 1973 proposed federal regulations that would appoint a "Protection Committee" to serve as an advocate for child research subjects. The Protection Committee was to monitor the selection of child subjects, assess the reasonableness of the parents' consent, and monitor the child subject's continued willingness to participate in the research.

[71] AHRP makes the following 10 recommendations to improve the protection of children in clinical research:

- Federal regulations--45 CFR 46 Sub-part D - should severely restrict the use of children in medical experiments involving greater than minimal risk, if there is no potential medical benefit for them or their condition.
This is based on the assumption that Federal regulations are predicated on the moral responsibility of society to protect children who are not volunteers from being used in medical or behavioral experiments that are not in their best interest.

- Only children whose narrowly defined currently diagnosed medical conditions can potentially be helped should be recruited to test drugs or other medical devices or procedures insofar as such experimentation is typically accompanied by the risk of harm from adverse side-effects.

- Legislation for the protection of children's health and welfare should place the burden of proof on those seeking to conduct research on minors under the age of eighteen (18) to establish the existence of "compelling circumstances" that justify such research on children. Investigators should be required to provide the criteria for demonstrating that the benefits of the research outweigh severity, duration, frequency and likelihood of the risks. Children should be assured that current "best medical practice" standards of treatment will be compared to any new or experimental treatment, and that those consenting on their behalf can be held accountable for making research decisions that are in the child's best interest.

- Children should not be recruited for experiments involving greater than minimal risk on the basis of vague speculations about them being "at risk" of some unproven condition that may or may not ever materialize. Before research involving children can be considered, a rigorous set of standards should be established so that the phrase "at risk" can be identified by specific demonstrable risk factors as currently existing on a more likely than not basis. Investigators should be required to demonstrate that the nature, severity, duration, and frequency of the risk is greater than the intervention proposed.

- All clinical trials involving the use of children, as previously defined, should provide no-fault insurance coverage for both short-term and long-term adverse effects that may arise from or in the course of participation in the stated clinical trials.[72]

- Selection of child subjects should not place an unfair burden on disadvantaged families who may not have access to current "best practice" standards of treatment in their community. Thus, care should be taken to ensure that the population from which sick children are recruited represents families from diverse socio-economic strata. When children are sought from a specific ethnic or socio-economic population, evidence should be provided to demonstrate approximate proportion to prevalence of the condition under study to that specific population in the United States or elsewhere.[73]

- Recruitment of children via provision of financial enticements to their caregivers should be completely prohibited and sanctioned with heavy fines.
The record demonstrates that the current system of review of both the scientific and ethical components of research protocols involving sick children, have failed to protect children such as nine-month old Gage Stevens or eight year old Jennifer Munger from harmful experiments that killed them.[74]

Therefore,

A. There is a need for oversight by a "Children Protection Committee" in addition to review by an institutional review board (IRB) that would serve as the child subjects' advocates, monitoring their selection, assessing the reasonableness of their parents' consent, the adequacy of disclosure in the informed consent documents, and monitoring their continued willingness to participate in the research.[75]

B. The majority of the Children Protection Committee (51%) should be drawn from the community, among them representatives from the same socio-economic strata as the children in the specific clinical trial.

- All of the members of the ethics review board and the Children Protection Committee should be vetted for complete absence of conflicts of interest.

- The expenses for the process of safeguarding children's best interest in research - including community members who are involved in implementing the research review and monitoring process - should be paid from a government fund established for that purpose. The government should, in turn, be authorized to recapture its costs, including oversight of all pediatric research, by way of reimbursement from the drug or medical device manufacturers who are eventually licensed to market such drugs or medical devices that result from approved pediatric research.


17. The lure of riches fuels testing. The Boston Globe, front page;
for Doctors.

for sale? New England Journal of Medicine. 342: 1516-1518; Kauffman,
m. and Julien, A. 2000, April 9. Surge in corporate cash taints the
integrity of academic science. Hartford Courant, front page; Birch,

Lemmens, T, Miller, PB. 2003 (in press). The human subjects trade:
ethical and legal issues surrounding recruitment incentives. Journal
of Law, Medicine and Ethics.

[4] FDA. Pediatric Rule, online
at: http://www.fda.gov/cder/pediatric/pedethics-1199.htm

AHRP comments submitted to FDA. http://www.ahrp.org/ahrpspeaks/smallpox1202.php
and public comments at: http://www.fda.gov/ohrms/dockets/dockets/02n0466/02n0466.htm

the ethics of predictive diabetes mellitus screening research in newborns.
Arch Pediatr Adolesc Med, 157:89-95

[7] See Protocol 96-CH0101. OHRP
letter of determination to the National Institutes of Health, Nov. 3,
2000 online at: http://ohrp.osophs.dhhs.gov/detrm_letrs/nov00a.pdf

new world. SCIENCE, vol 300: 1162-1165.

skeptics and the bad news about statin drugs, online at:
http://www.medicalconsumers.org/pages/cholesterol_skeptics.html

New Study Links Hormones to Breast Cancer Risk. The New York Times,

[11] Zito, JM., Safer DJ., dosReis,


[14] Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder. NIH Consensus Statement. 1998 November 16-18. 16(2): 1-37. Accessed January 30, 2003 online at: http://odp.od.nih.gov/consensus/cons/110/110_statement.htm. The panel noted the following risks for children using stimulant drugs in its Statement: "psychostimulants have abuse potential; psychostimulants, particularly of amphetamines, may cause central nervous system damage [in high doses], cardiovascular damage, and hypertension. In addition, high doses have been associated with compulsive behaviors and, in certain vulnerable individuals, movement disorders. There is a rare percentage of children and adults treated at high doses who have hallucinogenic responses. Drugs used for ADHD other than psychostimulants have their own adverse reactions: tricyclic antidepressants may induce cardiac arrhythmias, bupropion at high doses can cause seizures, and pemoline is associated with liver damage."


[16] PATS, a collaborative, six-site, randomized clinical trial (to be conducted September, 2000–August, 2003), was launched as "New Frontiers in Pediatric Psychopharmacology" at the 47th annual meeting of the American Academy of Child and Adolescent Psychiatry, held at the Hilton-New York in New York City, October 24 - 29, 2000. PATS trials will be conducted at Columbia University, Duke University, Johns Hopkins University, New York University, and the University of California campuses at Los Angeles and Irvine.


http://www.washingtonian.com/health/hardtoswallow.html

[30] Dr Robert Temple, director office of drug evaluation at the FDA, indicates that "at least" 12 pediatric trials have demonstrated that tricyclic depressants lack efficacy in children.


5. Declaration submitted to the U.S. District Court, District of Hawaii in Forsyth v. Eli Lilly and Company, CV-95-00185 ACK.


[41] Boseley, S. 1999, October


[45] Harris GA. 2003, August


[51] The three centers were:
Medical College of Pennsylvania; Institute for Juvenile Research, University of Illinois, Chicago; and Virginia Polytechnic Institute


[55] Examples of cases within the last 5 years in which children suffered harm in clinical trials:


Note: The FDA and the IRB at Children's Hospital (Pittsburgh) approved a protocol that required some babies to be given a deadly combination—Propulsid and Tagamet—despite the fact that in Canada the drug label warned physicians that there is a contraindication in the use of Tagamet and Propulsid together.


[56] Silverman, W. 2000. "Bad Science and the Role of Institutional Review Boards," Archives of Pediatric Adolescent Medicine, vol 154, pp. 1183-84; See also, Marcia Angell, former editor of The New England Journal of Medicine, who confirmed: "We have floods of me-too drugs. So much research is trivial duplication." See, Time Magazine .


[58] The debate began with questions about the value of early detection of breast cancer through mammograms, then spilled over to other cancer screening tests - e.g., prostrate cancer and. raise doubts about their value much touted research findings that had led to scientifically invalid assumptions about. Indeed, it is being argued that screening and early intervention have done more harm than good.


See also, Grady, G. 2002, April 18. "Scientists Question Hormone Therapies for Menopause Ills," The New York Times,


This is the identical phrasing of the language of state and federal workers' compensation laws that provide such no-fault insurance coverage to virtually all employees of U.S. businesses.

This requirement reflects the ethical principle articulated in the Belmont Report relating to justice; namely, equal sharing of the burden and benefit of research.


The recommendation for a Children Protection Committee had been proposed by the Department of Health Education and Welfare in 1973 but never adopted. See 28 Fed. Reg. 31, 738 (1973)