Presentation given to

Secretary's Advisory Committee on Human Research Protections

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By

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Good morning ladies and gentlemen. I am Paul Gelsinger, vice president of Citizens for Responsible Care and Research. CIRCARE is a 501 C3 nonprofit corporation, and the oldest citizen advocacy group dedicated to effective protection of humans in research. For nearly a decade CIRCARE has worked to bring the need for major reforms in the protection of humans in research to the attention of federal agencies, legislators, and the public. CIRCARE has an interest in the continuance and improvement of protection of human subjects in research, along the lines described in the legislated purpose of this committee.

I would like to thank you for responding to our request by giving us this opportunity to share our views with SACHRP. Let me say at the outset that my presentation today is limited in scope because we were asked for our opinion about the current system of human subject protection under the jurisdiction of the Office for Human Research Protections, rather than to discuss any particular strategies to extend or strengthen the protection of research subjects. It seemed more sensible, however, to describe the conditions in which potential or actual research subjects find themselves rather than our opinion of these conditions. Matters of opinion are open to endless debate, while matters of fact are tolerated or remediated.

Society has a moral obligation not to exploit altruistic individuals who willingly serve the public good by acting as research subjects. The current human subject protection system does not effectively protect the rights and welfare of humans in research because it works *post hoc*: such compliance efforts as exist are not engaged until a subject is harmed or an allegation of non-compliance is made. Acting in response to harm in preference to proactively preventing it is unjust, and a poor recompense for subjects' altruistic impulse. The current system does not effectively protect the rights and welfare of research subjects because it relies on the goodwill of institutions and investigators, yet the prestige and ranking of institutions are largely determined by the value of research grants awarded, and investigators depend upon research grants for career advancement, prestige, and often their salaries. These powerful motivators can conflict with the protection of research subjects, and when they do, they often prevail to the detriment of research subjects.

The current system does not effectively protect the rights and welfare of research subjects because it doesn't create rights for research subjects, rather the system gives remedies to the regulator to make the non-compliance stop. Practically speaking, this is accomplished through determination letters issued by OHRP. On rare occasions, the agency has suspended an institution's Federal Wide Assurance, and on equally rare occasions, the Department of Justice will prosecute institutions for failure to comply with the terms of NIH awards. The pace is glacial, and the public must wonder that the Department of Justice swiftly prosecuted an NIH supplier of defective mice under the False Claims Act, yet prosecution of a case involving human research dragged on for five years. (1)

The current system does not effectively protect the rights and welfare of research subjects because it holds the institution rather than the investigator responsible for compliance, and as a result, no consequences befall an investigator who fails to protect research subjects. So far as we can determine, institutions rarely if ever impose penalties for failing to protect research subjects, and their refusal to condemn such failures, or their silence in the face of demonstrable non-compliance, is taken as approbation by the public at large. The current system does not effectively protect the rights and welfare of research subjects because even if there was the will to aggressively deter non-compliance and provide proactive oversight, OHRP staff appears to be inadequate given the volume of research. As of February 2005, more than 8,000 Federal Wide Assurances were on file with OHRP, yet the Division of Compliance Oversight has six employees. This works out to each employee being responsible for the oversight of more than 1333 institutions and IRBs. (2) This is perverse.

Finally, we know the current system does not effectively protect the rights and welfare of research subjects because the same things keep happening over and over again, much like the movie Groundhog Day. Although IRB review and approval under the Common Rule has been required for federally funded research since 1981, OHRP determination letters even today, 25 years later, find that

IRBs cannot reliably distinguish between research and medical care, approve consent forms without the required elements, approve proposed research on condition of revision without ensuring revisions are made, approve proposed research without adequate information, fail to maintain quorum at meetings, fail to review research at appropriate internals, fail to make required determinations for review of research with children and prisoners, and don't have appropriate Standard Operating Procedures. For their part, investigators fail to obtain IRB approval, fail to supply material information to the IRB, fail to report unexpected serious adverse events or report expected serious adverse events, fail to obtain informed consent, fail to maintain records, engage in questionable subject recruitment schemes, and fail to follow research protocols. Serious non-compliance is memorialized in a letter from OHRP, the institutions and investigators excuse themselves, and they're back at it the next day. Many people would agree that after a quarter century, institutions and investigators that are unable or unwilling to comply with the Common Rule should not be conducting research.

Moreover, learned advisory bodies make recommendations for improvements in research protection only to have them gather dust; the Office of Inspector General identifies problems and proposes solutions, and while everyone accepts the proposals for the most part, nobody implements them. (3) Indeed some of the troubling issues that drew OIG's attention several years ago appear to be more pronounced today. For example, in 2000 OIG described a number of troubling recruiting practices in industry-sponsored research, of which one was an inducement whereby the order in which co-investigators would be listed as authors in the study publication depended upon the number of subjects recruited. This practice was recently replicated in an NIH-sponsored trial published in the *New England Journal of Medicine* in 2005. (4)

The take-away message from all this is clear enough: the current system for protecting humans in research is ineffective, and since no meaningful improvements have been instituted, investigators, sponsors, and research institutions must prefer that the system remain the way it is.

Now I’m going to shift gears a bit and talk about the ways in which our current system of research protection affected my life.

CIRCARE has long been concerned with the adequacy of reporting of unanticipated serious adverse events to OHRP as required under the Common Rule. This issue is important because failure to report unanticipated SAEs means subjects are needlessly exposed to risk. Failure to report unanticipated SAEs affects IRB review and approval of proposed studies because it prevents the IRB from minimizing risks to the subjects, and may cause informed consent to fail if not disclosed in the consent form. Without doubt, subjects cannot consent to undertake risks which are not disclosed to them. OHRP and FDA administrative actions attest to widespread failure to report unanticipated SAEs. (5)

If this were not enough, when gene therapy research came under increased scrutiny in 2000, in response to an NIH reminder to institutions regarding mandatory reporting of unanticipated SAEs, OHRP was overwhelmed by more than 900 SAE reports. (6) Compare this to a total of 383 reports made to OHRP during the ten year period between 1990 and 2000. (7) We appreciate the committee’s interest in SAE reporting to IRBs, and we realize that multiple reports of the same unanticipated SAE and reports of expected SAEs can take up valuable time better spent on review and oversight of research. At the same time, however, it’s difficult to see how streamlining the reporting of SAEs would affect the pressing problem of investigators who are unwilling to report SAEs, unanticipated or not. If investigators are unaware of reporting obligations or unable to distinguish between anticipated and unanticipated SAEs, it begs the question of why an IRB approved them as investigators in the first place. Investigators who refuse to report unanticipated SAEs touches on the largest problem with our current research protection system: because no consequences follow upon their non-compliance, investigators may be encouraged to do the same thing over and over again.

My personal involvement in the protection of humans in research began in 1999 following the death of my son, Jesse Gelsinger, in a non-therapuetic gene therapy study. Many of you may recall that this phase I clinical trial was being conducted at the University of Pennsylvania, by the then-president of the American Society of Gene Therapists (ASGT), and overseen by the FDA and the NIH's Recombinant DNA Advisory Committee (RAC). Jesse's decision to participate in this safety study was based on his entirely altruistic desire to help infants and others born with the homozygous variant of ornithine transcarbamylase deficiency (OTC), which is invariably fatal. He was aware there would be no direct medical benefit for him. The experiment was designed to test whether this technology was safe to use in newborns with the worst form of OTC, of which Jesse had the mild heterozygous variant. My son died of a massive immune response four days after receiving an infusion of a modified cold virus that carried copies of the gene designed to correct his disorder. An unanticipated SAE in a previous dose cohort was not reported, and this information, along with deaths of animals receiving the test article, were not incorporated into the consent form. I cannot tell you if this information would have changed Jesse's decision, but widely shared ethical principles and the Common Rule demand that this information be disclosed to him in the consent form.

Where I once completely trusted the system of clinical research before Jesse's death, I now find myself unable to trust that system. In my attempt to understand the circumstances that led to Jesse's death, and as a result of my affiliation with CIRCARE, I have come to understand that in addition to our troubled research protection system, the integrity of the research enterprise itself has been undermined by several forces. And an enterprise it is. Human experimentation is big business, with billions paid out each year to investigators and institutions. The increased volume of research over the last decade or more has exacerbated the tension between institution and investigators on one hand, and the need to protect human subjects on the other, as financial rewards increase and growing numbers of trials strain IRBs.

Financial conflict of interest contributed to Jesse's death. The principal investigator at Penn owned a 30% interest in a biotechnology company that stood to profit should his research show favorable results. This same company owned the patents on the investigator's gene transfer products and procedures, and through the standard material transfer agreement, the University of Pennsylvania owned stock in this company. As a result, the person charged with ensuring the safety of research subjects stood to profit from conducting the research, and the entity charged with reviewing and approving the proposed research – to say nothing of ensuring that risks to subjects were minimized to the extent possible – also stood to profit from the research. In fact, just about the only person who didn't stand to profit was my son. By allowing the investigator to own a larger percentage of the company than normally permitted, instead of remediation or removal of financial conflict of interest, the institution increased it.

This actual financial conflict of interest is only a part of the story. The experiment that killed Jesse was a dose-escalation study. At one-tenth the dose that Jesse received, four consecutive subjects in previous dose cohorts developed liver toxicities that should have stopped the study. The FDA was well aware of the first two reactions but never did anything to stop this study. My questions as to why the researchers were allowed to continue with dose-escalation have never been adequately answered. There were additional serious protocol violations that were not detected and addressed by the FDA or the Penn IRB. Some of those violations were deliberately concealed from the oversight authorities.

In February of this year, after nearly four years of investigation conducted with the assistance of FDA's Office of Criminal Investigation, the Department of Justice decided not to file criminal charges against the people responsible for Jesse's death. The civil settlement that the Department of Justice offered these investigators and their institutions essentially allowed research on human beings to resume pending retraining and supervision of the investigators. The institutions paid a fine. (8) When I insisted that the institutions would have to publicly acknowledge wrongdoing and release pertinent documents , I was told that this was impossible.

Our current system of research protection did not protect my son. Unexpected SAEs went unreported, and because nobody detected this, they were not disclosed in the consent form. As a result, my son did not give legally effective voluntary informed consent, yet the "system" obligates both the investigator and the IRB to ensure that he did so. The institution and investigators were subjected to the severest penalties the system can muster, yet this is inadequate because the investigators will conduct research on humans again, and will do so within a system that lacks the capacity for pro-active oversight or the will and the means to enforce compliance. I now question the integrity of the entire system, and I distrust it.

In order to restore trust, we believe that it is critical to respect the dignity of a person as a human being and to preserve her autonomy. Practices which constrain autonomy and cause human subjects to become merely the means to investigators' ends are reprehensible and unacceptable, and the burden imposed on individuals outstrips the benefit of research to society.

To finish up, as you might expect, CIRCARE has a number of proposals for the effective protection of research subjects, and I'm going to briefly run through them now. This is what's in your handout.

CIRCARE believes that certain core principles should be adopted:

1. Independent oversight of research.
2. Special protections for vulnerable subjects, especially in non-therapeutic research which is greater than minimal risk.
3. Meaningful informed consent.
4. Accountability and reporting of serious adverse events.
5. Reduce or eliminate institutional conflict of interest. Non-profit, tax-payer supported research institutions should not profit from clinical trials.

Specifically, we call for the following national reforms:

<u>General measures</u>

Passage of A National Human Subject Protection Act to provide legal and ethical safeguards for all human subjects in experimental research, ensuring that in all clinical research, all patients are provided the best diagnostic and therapeutic methods available. (9) Safeguards for human subjects should be at least equal to those currently provided to laboratory animals under the National Animal Welfare Act of 1966. What does it say of us that we have a law that protects the rights of animals in research but have no comparable law to protect human beings?

Protection of Vulnerable Subjects

A prohibition on conducting greater than minimal risk experiments on vulnerable persons who are incapable of evaluating the risks or appreciating the consequences themselves unless they can be demonstrated to be in the subject's best interest.

A moratorium on symptom provocation or challenge studies, washout periods, and placebo control groups in the case of persons with life threatening or potentially life-threatening conditions.

Institute of Medicine Recommendations

Adoption of the well thought out recommendations of the IOM report "Responsible Research." (10)

Office of Human Research Protections

Expansion of the authority and personnel of a federal agency (e.g., Office of Human Research Protection (OHRP)) to provide effective real-time oversight, to include: unannounced site inspections and random audits focusing on the safety of subjects; maintenance of medical records of research of human subjects; an 800 hotline for anonymous reporting of potential violations.

Informed Consent

Informed consent process should be witnessed by an independent party and videotaped. Information should include (in addition to currently required elements): accurate description of the purpose of the study; full disclosure of known and potential risks and possible benefits, sponsors, financial interests of investigators and institution, what alternative treatment is available, and what follow-up care is provided. It should state who is legally responsible for monitoring the experiment to ensure the best interests of the patient during his/ her participation in research.

Advance Directives, where permitted by state law, must enable individuals to exercise their right to refuse to be a research subject, and allow every individual to set limits on the degree of risk and discomfort he / she is willing to assume. Blanket consent to unspecified research should be prohibited. The Advance Directive should not be regarded as a contract.

Accountability and Reporting

Require no-fault personal injury insurance for each research subject to cover the duration of the research and one year following completion. We believe such insurance, in the amount of about $250,000 per subject (premiums to be paid by the sponsor/ research team/ institutions) would be an incentive to reduce unnecessary risks and would compensate individuals / family for harm. It would also reduce the taxpayers' burden for uninsured persons who may require costly after-care as a result of injuries sustained in research.

Mandatory certification of all investigators through a comprehensive educational program of 15 to 20 graduate credit hours (or CME equivalent) and to include practicum. It is odd to require training and education for all other personnel involved in research with humans except the most important one, namely the clinical investigator. One cannot perform research with animals without adequate training but no such requirement exists for human research.

Require institutional review boards to be accredited by an independent agency. Accreditation should include requirements for training and education.

51% of IRB membership be local independent community members.

Establish a national database of research protocols, including consent documents, to facilitate the flow of information and progress, and to avoid unnecessary duplication of research.

Mandatory and timely reporting of adverse incidents of all phases of research including post-marketing to a federal oversight board, indicating what remediation has been taken so that such incidents are not repeated. All adverse drug jreactions in clinical trials should be reported to the FDA's existing Physician Hotline. We specifically call for:

a. simplified uniform and comprehensive system
b. single national data system
c. continuous tracking and trend analysis
d. single agency to deal with adverse events, and
e. oversight

In closing, remind yourself once a day that research subjects depend upon you to stay alive. Put teeth in the regulations by supporting a system for protecting research subjects that's codified in law. that we have it mandated by law. The people at CIRCARE and I, as Jesse's dad, optimistically await effective protection of humans in research. Make it so that we don't have another tragedy that damages us all. We owe that much to Jesse and more... Thank you.

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1. Compare mice and men: "NIH Supplier Agrees to Pay U.S. $7.2 Million to Settle Defective Products Claim", (May 2005). Accessed 2005-07-16 at: http://www.usdoj.gov/usao/md/press_releases/press05/HSDSettlePR.pdf ; "U.S. Settles Case of Gene Therapy Study That Ended With Teen's Death" (2005-05-09). Accessed 2005-07-16 at:

http://www.usdoj.gov/usao/pae/News/Pr/2005/feb/UofPSettlement%20release.html.

2. OHRP News: "Effective February 1, 2005, OHRP stopped mailing copies of approved Federalwide Assurance (FWA) documents to the Signatory Officials of filing institutions. This was necessitated by the volume of FWA documents OHRP is managing. There are currently over 8,000 approved FWAs." Accessed 2005-07-16 at: http://www.hhs.gov/ohrp/news/recentnews.html#20050210 ; OHRP Staff Directory, Division of Compliance Oversight. Accessed 2005-07-16 at: http://www.hhs.gov/ohrp/about/staff.html

3. For example, the final recommendations of the National Bioethics Commission remain unimplemented; “Protecting Human Research Subjects: Status of Recommendations”, HHS-OIG Report OEI-01-97-00197; 4/00, accessed 2005-07-16 at: http://oig.hhs.gov/oei/reports/oei-01-97-00197.pdf; “Low-Volume Institutional Review Boards”, HHS-OIG Report OEI-01-97-00194; 10/98, accessed 2005-07-16 at: http://oig.hhs.gov/oei/reports/oei-01-97-00194.pdf; “Institutional Review Boards: Their Role in Reviewing Approved Research”, HHS-OIG Report OEI-01-97-00190; 6/98, accessed 2005-07-16 at: http://oig.hhs.gov/oei/reports/oei-01-97-00190.pdf; “Institutional Review Boards: Promising Approaches”, HHS-OIG Report OEI-01-97-00191; 6/98, accessed 2005-07-16 at: http://oig.hhs.gov/oei/reports/oei-01-97-00191.pdf; “Institutional Review Boards: The Emergence of Independent Boards”, HHS-OIG Report OEI-01-97-00192; 6/98, accessed 2005-07-16 at: http://oig.hhs.gov/oei/reports/oei-01-97-00192.pdf; “Institutional Review Boards: A Time for Reform”, HHS-OIG Report OEI-01-97-00193; 6/98, accessed 2005-07-16 at: http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf.

4. “Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research”, HHS-OIG Report OEI-01-97-00195; 6/00, p. 17. Accessed 2005-07-16 at: http://oig.hhs.gov/oei/reports/oei-01-97-00195.pdf ; Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. (2005) *N Engl J Med*. Jan 20;352(3):225-37, appendix.

5. A recent survey of FDA warning letters issued to clinical investigators between February 2002 and February 2004 found that in the thirty-six letters issued, nearly half of them described failure to report or late reporting of adverse events. Bramstedt, Katrina A. (2004) A study of warning letters issued to clinical investigators by the United States Food and Drug Administration. Clin Invest Med : 27(3):129-34. A similar survey of FDA warning letters issued to IRBs between January 1997 and July 2004 found that of the fifty-two letters issued, forty-seven letters described failure to prepare and maintain adequate documentation of IRB activities, and thirty-six described failure to provide adequate continuing review of approved studies. Bramstedt, Katrina A. and Katy Kassimatis. (2004). A study of warning letters issued to institutional review boards by the United States Food and Drug Administration. Clin Invest Med; 27(6):316-23.

6. Nelson, D. and Weiss, R. (2000). “Gene Test Deaths Not Reported Promptly.” The Washington Post, Jan. 31, A1.

7. A. Shamoo (2001), Adverse Events Reporting – The Tip of an Iceberg. *Accountability in Research* 8:1-22.

8. Department of Justice settlements with institutions: Institute for Human Gene Therapy , University of Pennsylvania, Settlement Agreement (2005-02-09). Accessed 2005-07-21 at: http://www.circare.org/foia3/IHGT_settlement_5.pdf ; Institute for Human Gene Therapy, Settlement Exhibit "Promoting Safety in Clinical Research at the University of Pennsylvania" (2005-02-09). Accessed 2005-07-21 at: http://www.circare.org/foia3/ihgt_exhibittosettlement.pdf ; Mark Batshaw, M.D., and Children's National Medical Center (CNMC) Settlement Agreement (2005-02-09). Accessed 2005-07-21 at: http://www.circare.org/foia3/batshawsettlement_draft_1.pdf.

9. CIRCARE Testimony before the House Committee on Government Reform, Adil Shamoo Ph.D., CIRCARE Co-Founder (April 1998).

10. *Responsible Research: A Systems Approach to Protecting Research Participants*. (2003) Institute of Medicine, National Academies of Science.