Major Reforms Are Urgently Needed to Protect Human Subjects in Research

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By

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Citizens for Responsible Care and Research (CIRCARE) has for the past six years helped bring to public attention the need for major reforms in

protecting human subjects in research. We have predicted serious harm coming to patients, if responsible and major steps are not taken. Based on scientific evidence and case reports, serious adverse events and deaths have already befallen a large number of persons. Under the freedom of information act, we obtained data from 1990-2000 of all reported deaths and adverse events to the federal Office of Human Research Protections.[i] Over a ten year period and for 70 million human subjects, only eight deaths and 386 adverse events were reported. We estimate, based on a statistical analysis, that thousands of deaths and tens of thousands adverse events should have been reported to the authorities. This level of underreporting raises serious questions about research data, since any adverse events should be reported for an honest and scientific outcome.

Especially since the death of an 18 years old volunteer Jesse Gelsinger, there have been many ethically questionable experiments that have reached national attention. Just in the past few months, one of the most prestigious institutions has had three major experimental studies come under scrutiny. Due to an asthma-induction experiment with no prospect of benefit to the volunteer, Ellen Roche, a 24-year-old healthy volunteer and employee of the research institution, died. In response to this and other matters, the federal office of the Human Research Protections (OHRP) shut down, for a few days, the entire clinical research operation at Johns Hopkins University for violations of federal rules. The shutdown is still ongoing for studies for beyond minimal risk. In the case of Ellen Roche, informed consent was lacking in the omission of toxicity studies and the plain fact that inducing asthma carries a risk of serious adverse effects. The lack of informed consent, adequate institutional review, and a possible culture of

coercion were confirmed by an external review requested by Johns Hopkins. In a second experiment, the same institution admitted conducting clinical research trials in India without institutional approval of such research in violation of federal rules. Lastly, a lead paint study at Kennedy Krieger Institute, affiliated with Johns Hopkins University, was severely criticized by the Maryland highest court (Court of Appeals) – which went so far as to compare this study to the infamous Tuskegee experiment. The research protocol allowed and at times *encouraged* families with young children to dwell in houses heavily contaminated with lead, in order to measure the various dosages of lead in the children. The court stated, “The researcher intended that the children to be the canaries in the mines.” The legitimacy of informed consent by children was also questioned by the court: “We hold that in Maryland a parent, appropriate relative, or other applicable surrogate, cannot consent to the participation of a child or other person under legal disability in non-therapeutic research or other studies in which there is any risk of injury or damage to the health of the subject.”

Legislation has just passed, which CIRCARE supported, which attempts to address these problems in the state of Maryland. IRB minutes, absent proprietary information, will be made public, in the hope that greater transparency will insure greater accountability. Furthermore, all private research will now be covered by at least a minimum federal standard, as is now the case with animal studies.

We also call attention to the special risk of *challenge studies*, where pathological conditions are purposively induced. In such experiments the issue of informed consent is especially compounded when vulnerable subjects are used. Using a PCP derivative, ketamine, researchers have induced *psychotic* symptoms in patients who are

hospitalized with diagnoses of schizophrenia. The researchers report that Ketamine "significantly exacerbates psychoses," "recreates acute psychosis," and causes hallucinations, delusions, dissociation.[ii] In other studies panic attacks were artificially induced on veterans already hospitalized for post traumatic stress syndrome - causing flashbacks that were "remarkably vivid and palpable." [iii] Such studies not only violate the physician oath to do no harm, but raise serious questions regarding informed consent, as these subjects are clearly vulnerable due to their condition and the fact that they are living on locked psychiatric wards.

Citizens for Responsible Care & Research (CIRCARE) oppose unethical research. We support research that is conducted in accordance with ethical and professional clinical guidelines, that is respectful of the rights and dignity of every human subject. We believe that it is critical to respect the dignity of a person's thoughts, communication and consent - as the molecular and physiological levels of the body are being explored. Practices which violate human rights, and is over aggressive or manipulative in its use of subjects risks distorting the end results of science.

Except under unique and compelling circumstances, we oppose experiments that use disadvantaged persons - such as the uninsured, the mentally disabled, the homeless, and children in high risk experiments with no medical benefits to the individual. We oppose research that violates the human rights, welfare or best medical interests of patients in the name of science. In advocating for specific reforms, CIRCARE believes that certain core principles should be followed:

1. Independent oversight of research.
2. Special protections for vulnerable subjects, especially in no-benefit research which is greater than minimal risk.
3. Meaningful Informed Consent as an essential protection.
4. Accountability and reporting of adverse effects.

Specifically, we call for the following national reforms:

General measures:

Enactment of **A National Human Subject Protection Act** (NHSP) 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. Safeguards for human subjects should be at least equal to those currently provided to laboratory animals under the *National Animal Welfare Act* of 1966. To ensure compliance, the Act should provide criminal penalties for violations.

Protection of Vulnerable Subjects

I. A prohibition on conducting above-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 these patients' best interest. Mental capacity should be assessed by an independent physician.

II. A moratorium on symptom provocation experiments – challenge studies and "washout or "placebo" studies on persons with potentially life-threatening conditions. Especially we are concerned about persons diagnosed with schizophrenia, where such experiments would seriously risk exacerbating their vulnerable condition.

Independent review

I. Establish an independent federal review board with at least one-third non-scientists to provide guidance and oversight for research involving patients - regardless of funding source - to ensure that our public policy and community values are upheld. Approved research designs should be open to public scrutiny.

II. Require that at least 51% of Institutional Review Board members be independent scientists, physicians, and community representatives not affiliated with the institution. When considering the inclusion of vulnerable subjects (e.g., children and mentally

disabled persons) advocates representing the best interests of those vulnerable groups should be included.

III. Expand the authority of a federal agency (e.g., Office of Human Research Protection (OHRP)) to provide oversight by making unannounced site inspections; examine medical records to determine if human subjects are protected; to maintain an 800 hotline for reporting potential violations (anonymously).

IV. Require independent monitoring of human subjects by an independent physician not connected with the project-to ensure their well being and continued consent.

Informed Consent

I. Informed consent procedures should be witnessed by an independent person not connected with the research team and videotaped. Information should include: Full disclosure of known and potential risks, 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.

II. Advance Directives, if permitted under state law, must enable individuals to exercise their right to refuse to be a research subject, allow every individual to set limits on the degree of risk and discomfort he / she is willing to assume, and the right to withdraw at any time. Blanket consent to unspecified, potentially harmful experimental research should be prohibited. Advance Directive should not be regarded as a contractual obligation to participate in research, since everyone has an inalienable right to change his/her mind in the future.

Accountability and Reporting

I. Require a no-fault personal injury insurance for every human subject of research 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 undue harm. It would also reduce the taxpayers' burden for uninsured persons who may require costly after-care as a result of experimental adverse consequences.

II. Require certification of all researchers who conduct human subject research to undergo special education in ethics and ethical human research procedures. Require Institutional Review Boards to be accredited by an independent agency.

III. Establish a national data bank, including informed consent documents, for human subject research in order to facilitate the flow of information and progress, and to avoid unnecessary duplication of efforts, thereby minimizing the use of human subjects involved in more than minimal risk experiments.

IV. Mandatory and timely reporting of adverse incidents to a federal oversight board, indicating what remediation has been taken so that such incidents are not repeated. All adverse drug reactions in clinical trials should be reported to the FDA's existing Physician Hotline.

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

[ii] Malhotra, A. et al. (1997). Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. *Neuropsychopharmacology,* 17, (3): 141-150.

[iii] Southwick, S. M. et al. (1997). Noradrenergic and serotonergic function in post-traumatic stress disorder. *Archives of General Psychiatry*, 54: 749-758.