How would you revise the human subject research regulations?

4th Annual Medical Research Summit

Baltimore, April 22, 2004

Steven Peckman; *University of California, Los Angeles*

With thanks to **Dale Hammerschmidt, M.D.;** *University of Minnesota*

Flexibility in Informed Consent Requirements at Home and Abroad

- Who are the subjects?
- Basic demographic assumptions
- Majority v Minority

California in the 1940s

89.9% European-American

Who are the subjects? Challenge assumptions….

- California in the 1990s
- Rapid and unprecedented demographic changes challenge our assumptions
  - Population changes reversed the traditional demographic structure and CA now has a minority Euro-American population
  - Similar trends in Texas, New York, Arizona, New Mexico, Florida, and the Chicago area
  - Changing demographic trends challenge our assumptions of minority v majority as well as homogenous Euro-American value systems that may not be applicable to communities of color

David Hayes-Bautista, "Formulating Health Policy in a Multicultural Society," Health Policy and the Hispanic, ed. Antonio Furino, (Boulder, Westview Press, 1992.

Flexibility in Informed Consent at Home and Abroad

- California: Case Study
  - 224 languages spoken in California
  - 40% of LA County residents born in another country

- Those on the front lines of patient care do not doubt a communication gap exists
- Medical access for foreign speakers doesn't simply involve hiring people who speak other languages; it means having interpreters who can deftly convey the doctors' and patients' points of view while protecting confidentiality

Jane E. Allen, LA Times, November 6, 2000

L.A. Workers Held Back By Low Education Rate

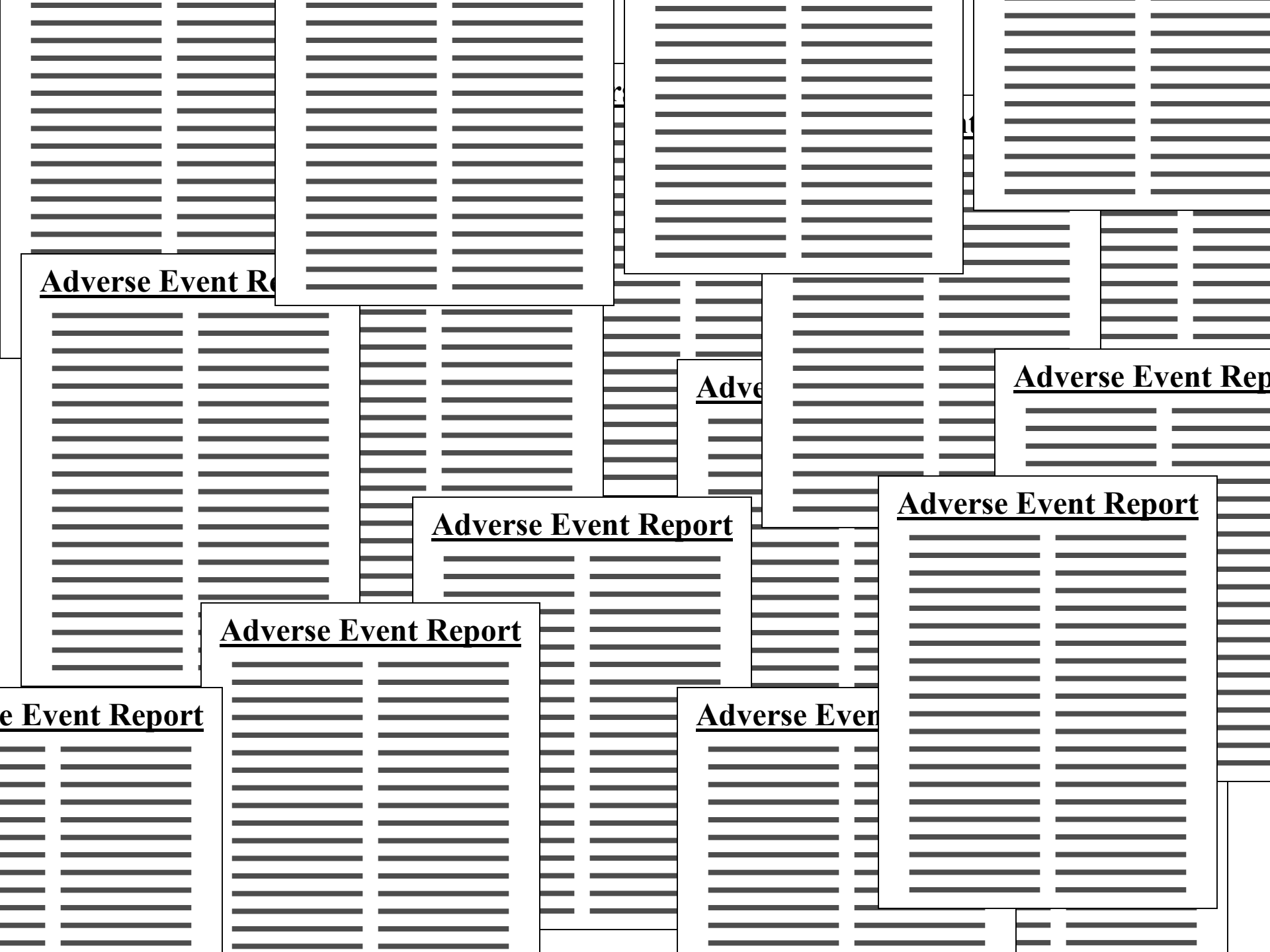
One in 10 adults in the Los Angeles region as six years of education or less. The rate is the worst of all U.S. metropolitan areas, including the immigrant magnets of New York, Chicago, and Miami, and is more than double that of San Francisco and Sacramento….

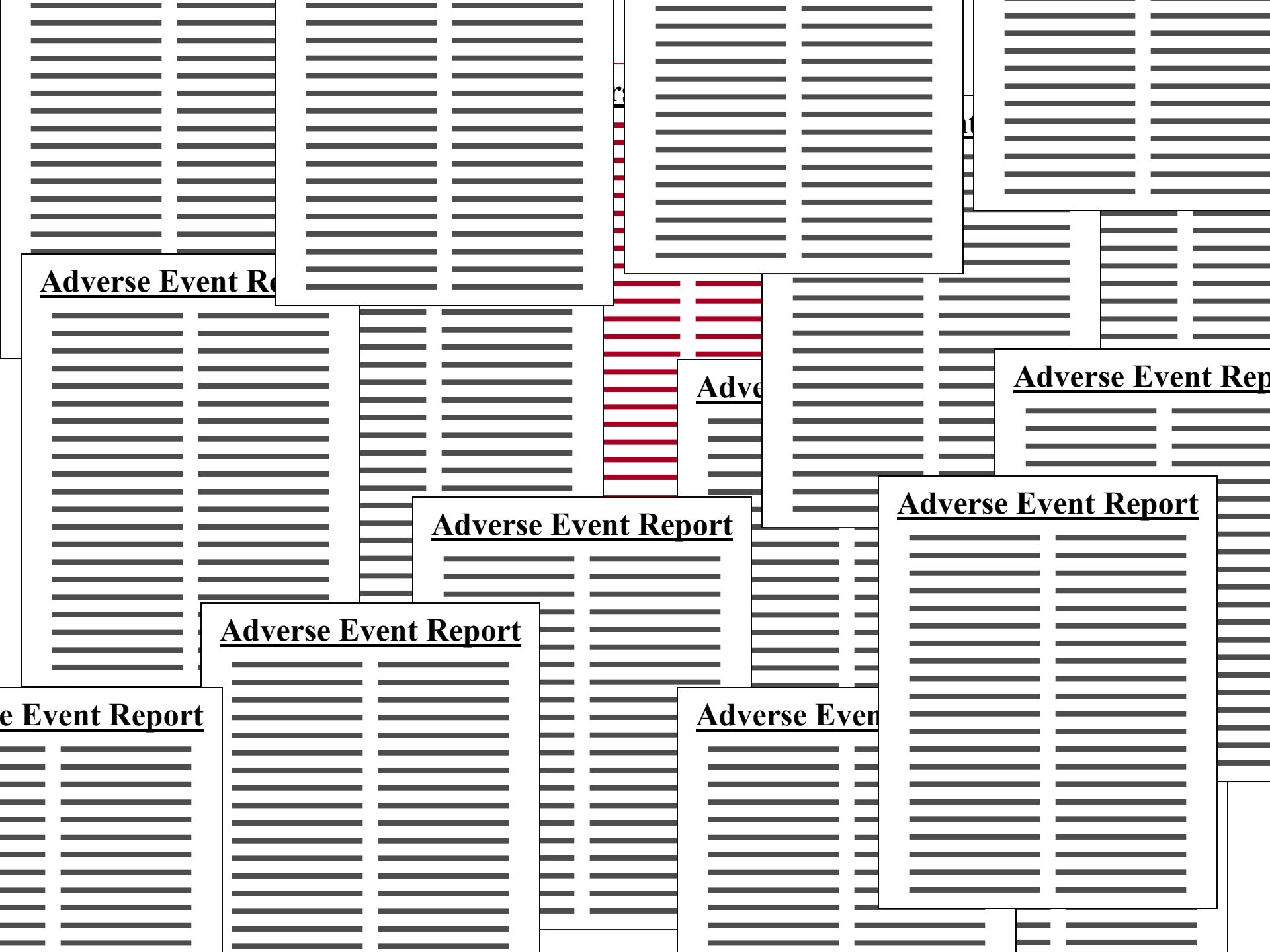
- Nancy Cleeland, L.A. Times, February 5, 2002.

More Flexible Informed Consent Documentation Requirements

- Ensure equity and justice
- Recognize the changing demographic and non-western non-legalistic approach
- Acknowledge international nature of research
- Acknowledge and address the historical basis for the negative connotations many people bring to signing documents

Adverse Event Reporting….


Adverse Event Report
Adverse Event Report
Adverse Event Report
Adverse Event Report
Adverse Event Report


Adverse Event Report
Adverse Event Report
Adverse Event Report
Adverse Event Report
Adverse Event Report

DSMBs & Reforming the National System*:

What is the route of an AER?

- PI notes an AE and reports it to her/his sponsor and IRB.
- The sponsor reports the AE to the FDA and participating PIs at each site.
- The PI at each site provides the AER to the local IRB.
- The IRB reviews the AER.
- What does the FDA do with the AER?

*Steve's points not cleared with Dale

Possible Solutions: DSMB

- The current AER system does not include a mandatory independent centralized monitoring system
- Only two entities have complete information about each protocol testing a given product and only two entities have all information regarding adverse event reports related to a given product:
  - The sponsor
  - The FDA
- Sponsor = conflict of interest
  - competing interests:
    - protecting their economic investment in the product
    - the success of the trial.

Possible Solutions: DSMB

- Data Safety Monitoring Board (DSMBs)
  - DSMBs rarely meet in real time relationship with receipt of AERs and therefore may take months to uncover and understand a trend that may pose immediate harm to subjects.
  - DSMBs are unlikely to account for multiple uses of a product across various experiments
  - Commonly report minimal information, such as “things are going well.”
    - Never received a DSMB report that indicates which arm of the study has more AER or
    - the DSMB biostatistician resigned because the sponsor was uncooperative as described by Dr. Janet Wittes during a national meeting last year.

IRBs, DSMBs, SAEs

- IRBs may need complete information regarding subjects' assignment to study arms in order to maximize the protection of the subjects,
- Regardless of the scientific impact of unblinding the data.
- The investigator or the research team need not have such information but certainly the IRB should have the information necessary to effectively deliberate and determine appropriate mechanisms for minimizing risks.

IRBs, DSMBs, SAEs

"…receipt of data that are neither aggregated nor interpreted does not provide useful information to the IRB to allow it to make an informed judgment on the appropriate action to be taken, if any."

Department of Health and Human Services. "NIH Initiative to Reduce Regulatory Burden," www.grants.nih.gov/policy/regulatoryburden/index.htm (1999) in W.J. Burman, et.al., Breaking the Camel's Back: Multicenter Clinical Trials and Local Institutional Review Boards, Annals of Internal Medicine, v134, n2:154.

Assessing Significance

"If an IRB receives a report about an unexpected adverse outcome experienced by a local subject, it will be hard pressed to assess the significance of that information unless it knows how many such outcomes have occurred for the overall trial."

DHHS, Office of Inspector General, IRBs: A Time for Reform, 1998

IRBs, DSMBs, SAEs

"Meaningful evaluation of AERs from multicenter clinical trials requires a group of experts with the resources to monitor the data continuously and to compare adverse event data to predetermined stopping or modification rules."

Elizabeth Bankert, Robert Amdur. The IRB is Not a Data and Safety Monitoring Committee, IRB: A Review of Human Subjects Research, v22, n6: November – December 2000.

Possible Solutions

- Need a central clearing house with the requisite knowledge and expertise to analyze adverse event reports and provide real-time and complete guidance to IRBs.
- FDA receives all adverse events for drugs, devices, and biologics long before the local site receives a Medwatch report.
- FDA employs experts in the disease area and biostatisticians to analyze IND and IDE applications.
- FDA has an electronic AER system that includes a pharmacovigilence component.

Possible Solutions

- Propose FDA as the regulatory body with the most information about the protocol and all uses of the product help IRBs address AE reporting
- FDA should continue to collect all the raw material as they currently do and then provide local IRBs with meaningful reports and recommendations that help us accomplish our task….
- Protection of the rights and welfare of human research subjects

"Regardless of whether one believes that the ultimate justification for government policies is the goal of promoting welfare and minimizing harms or respect for self-determination, one can agree that policies represent commitments to action and hence generate obligations."

Advisory Committee on Human Radiation Experiments. Final Report, Washington D.C: (1995)