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Improving Informed Consent

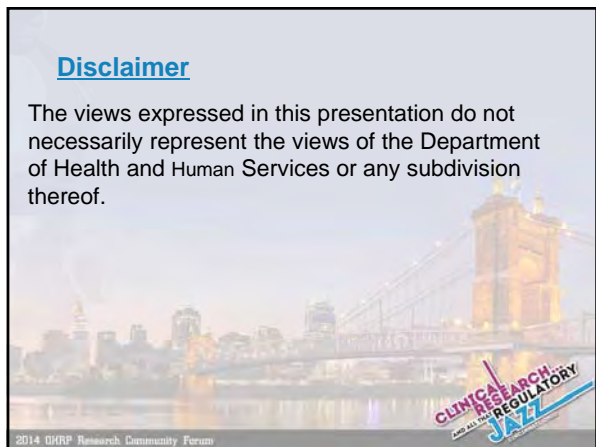


2014 OHRP Research Community Forum

CLINICAL RESEARCH
AND ALL THE REGULATORY
JAZZ

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OIG Report

As we conducted our inquiry, we became increasingly aware of a striking reality: IRBs have little basis for knowing how well they are accomplishing their mission of protecting human subjects.



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OIG Report

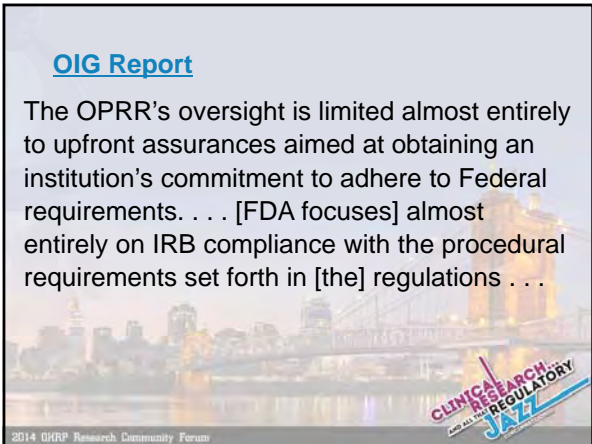
Seldom, we found, do the IRBs seek out feedback from human subjects or their families, examine the few complaints that they do receive to determine if they reflect broader, systemic problems, or initiate probing inquiries



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OIG Report

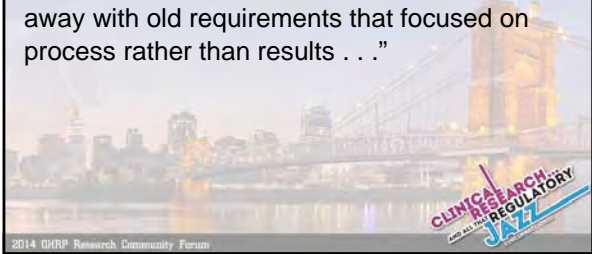
The OPRR's oversight is limited almost entirely to upfront assurances aimed at obtaining an institution's commitment to adhere to Federal requirements. . . . [FDA focuses] almost entirely on IRB compliance with the procedural requirements set forth in [the] regulations . . .



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OIG Report—Recommendations

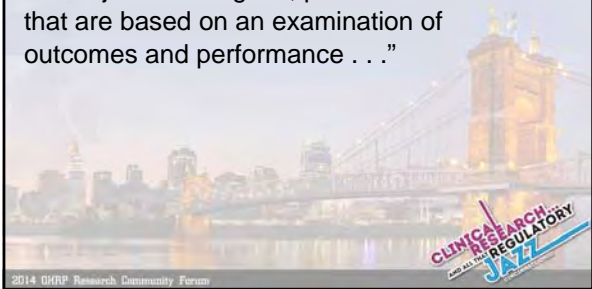
What we call for here is in accordance with what is occurring generally in the field of health care quality assurance. . . . “We are doing away with old requirements that focused on process rather than results . . .”



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OIG Report—Recommendations

An adequate system . . . would require “that [it] be subjected to regular, periodic evaluations that are based on an examination of outcomes and performance . . .”



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Consent Forms

Let’s try to do that by looking at what happened in some real clinical trials



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TACT

- Trial to Assess Chelation Therapy (TACT)
- To test chelation with EDTA for treating coronary artery disease
- In 2006, ~111,000 received this treatment
- Funded by NHLBI and NCCAM
- 2003 to present, \$30 million funding

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TACT

- 1,600 subjects age 50+
- History of heart attack
- Randomized to EDTA or placebo
- Randomized to low/high vitamins
- 40 weekly/monthly IV infusions

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Complaint about TACT

- Complaint to OHRP in 2008
- Atwood, KC et al, Why the NIH Trial to Assess Chelation Therapy (TACT) Should Be Abandoned. Medscape J Med 2008;10(5):115

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TACT

- Trial conducted at 100+ sites
- Reviewed by ~34 IRBs (one reviewed for ~137 sites)
- Included IRBs at Emory, Hopkins, Mayo Clinic, NYU, Scripps
- IRBs at Duke, U Miami and Mount Sinai (FL) largely accepted the template—unknown what (most) other IRBs did with consent form

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TACT

Let's look at that consent form

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TACT - Consent Form

- FDA has approved chelation for lead poisoning, but not as a treatment for heart disease.
- Chelation therapy has been practiced in the community for many years
- However, like with chelation therapy, there is no evidence that [high-dose vitamin and other supplements] are beneficial for patients like you.

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TACT - Consent Form

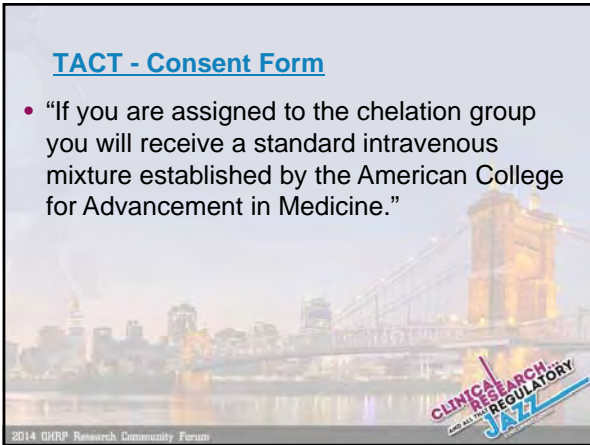
- That's about all the consent form – 12 page long – said about the issue of whether or not chelation might be effective.



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TACT - Consent Form

- “If you are assigned to the chelation group you will receive a standard intravenous mixture established by the American College for Advancement in Medicine.”



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TACT

- What was actually known about chelation treatment for heart disease?



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Some Background About Chelation

- 1998 – Federal Trade Commission settles false advertising charge against ACAM over promotion of chelation therapy



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Some Background About Chelation

FTC Press release:

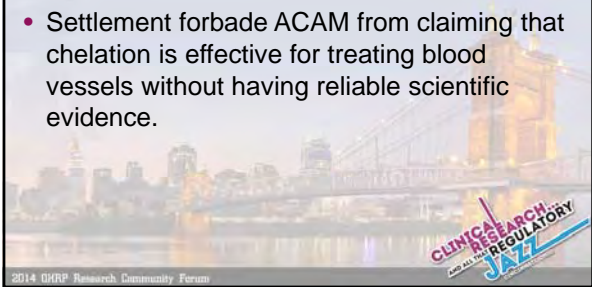
- ACAM promotes chelation in promotional materials
- ACAM's ads said chelation is "safe, effective, and relatively inexpensive"



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Some Background About Chelation

- FTC concluded ACAM's claims were "false and misleading"
- Settlement forbade ACAM from claiming that chelation is effective for treating blood vessels without having reliable scientific evidence.



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Some Background About Chelation

- Physicians disproportionately more likely to have “disciplinary actions, malpractice lawsuits or even criminal conduct.”
- E.g., 59 of the 146 chelation doctors in Florida lack malpractice insurance or hospital privileges (5x above normal rate)

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Some Background About Chelation

- “Organized” medicine has strongly opposed chelation therapy
- E.g., American Heart Association: “No scientific evidence to demonstrate any benefit.”

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AHA FAQs

- For more than 30 years, people may have heard about a "miracle cure" called chelation therapy.
- But you may not know that the American Heart Association and other medical and scientific groups have spoken out against this treatment.

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AHA FAQs

AHA then quotes views of others, including:

- FDA: No party has ever provided us with an organized submission attempting to show [chelation is effective]; instead, we have been handed unorganized data without any attempt to describe a formal study. Under the circumstances, we have had no choice but to attempt to prevent improper promotion of the drug and to point out its unproven status. [And once was in FDA list of "Top 10 Health Frauds".]

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AHA FAQs

National Heart, Lung and Blood Institute (NIH):

- There is no reason to expect benefit from chelation in the management of arteriosclerosis. More importantly, there has been no scientific evidence of such benefit — and there *is* scientific evidence of *no* benefit.

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State Regulations on Chelation

2001 -- Missouri added regulations saying:

- "Chelation of no medical value."
- Physicians would be subject to discipline unless special consent form signed (in clinical setting)

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Missouri Consent Form

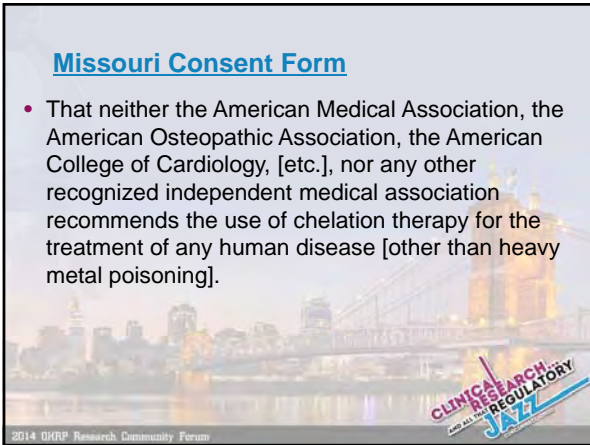
- “The Missouri Board . . . for the Healing Arts has monitored [the scientific literature] and has concluded that [chelation] has been **authoritatively demonstrated to be ineffective** in the treatment of vascular diseases.”



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Missouri Consent Form

- That neither the American Medical Association, the American Osteopathic Association, the American College of Cardiology, [etc.], nor any other recognized independent medical association recommends the use of chelation therapy for the treatment of any human disease [other than heavy metal poisoning].



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Missouri Consent Form

- That the Missouri State Board of Registration for the Healing Arts **strongly recommends** that Missouri citizens not undergo chelation therapy for the treatment of any disease other than heavy metal poisoning.



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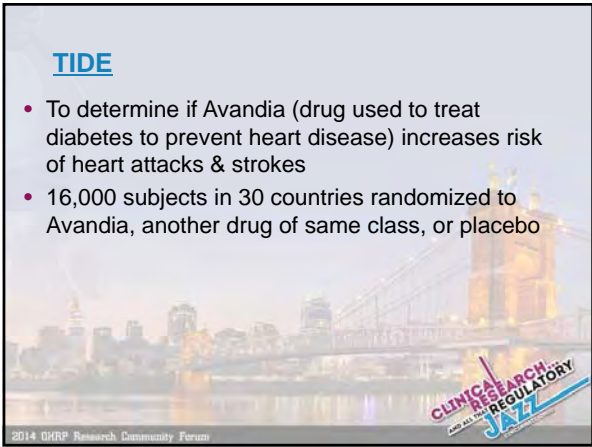
State Regulations on Chelation

- Worth noting: It is well accepted that consent to research should be more meticulous than consent to clinical care.



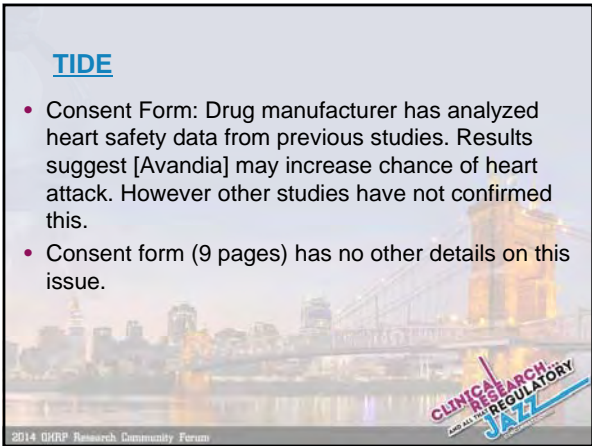
TIDE

- To determine if Avandia (drug used to treat diabetes to prevent heart disease) increases risk of heart attacks & strokes
- 16,000 subjects in 30 countries randomized to Avandia, another drug of same class, or placebo



TIDE

- Consent Form: Drug manufacturer has analyzed heart safety data from previous studies. Results suggest [Avandia] may increase chance of heart attack. However other studies have not confirmed this.
- Consent form (9 pages) has no other details on this issue.



TIDE

- Study was being conducted because of 2007 New England Journal of Medicine article, meta-analysis of Avandia data by leading U.S. cardiologist
- Study claimed 7-year risk of heart attack, if drug used, increased by about 50%
- Front page headlines in New York Times
- Stock price of drug company dropped by 8%

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TIDE

- FDA asked panel of experts whether to remove drug from market
- Drug was kept on market, with new risk warnings; FDA expert panel divided 8-7 on whether to stop sale of drug
- Many front page newspaper stories about the continuing controversy
- How much detail should subjects be told?

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RECESS

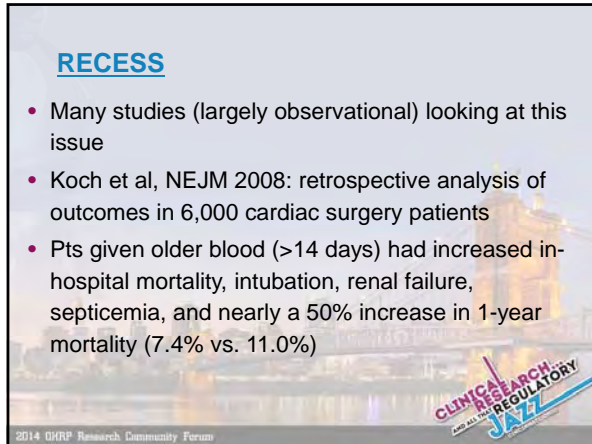
- Red Cell Storage Duration Study in cardiac surgery patients (RECESS)
- To determine if there is a difference in organ failure or mortality between getting transfused with red blood cells stored for 10 days or less vs. 21 days or more

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RECESS

- Many studies (largely observational) looking at this issue
- Koch et al, NEJM 2008: retrospective analysis of outcomes in 6,000 cardiac surgery patients
- Pts given older blood (>14 days) had increased in-hospital mortality, intubation, renal failure, septicemia, and nearly a 50% increase in 1-year mortality (7.4% vs. 11.0%)

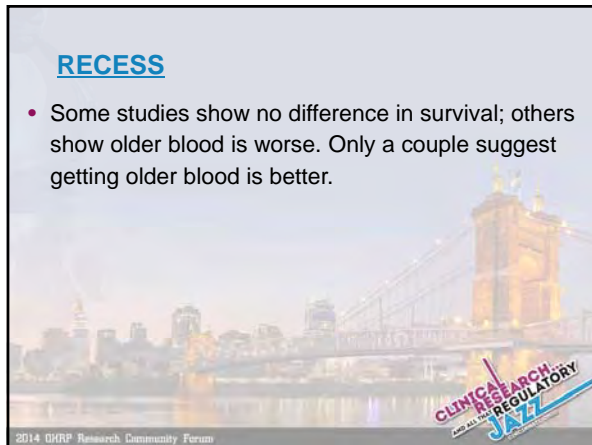


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RECESS

- Some studies show no difference in survival; others show older blood is worse. Only a couple suggest getting older blood is better.

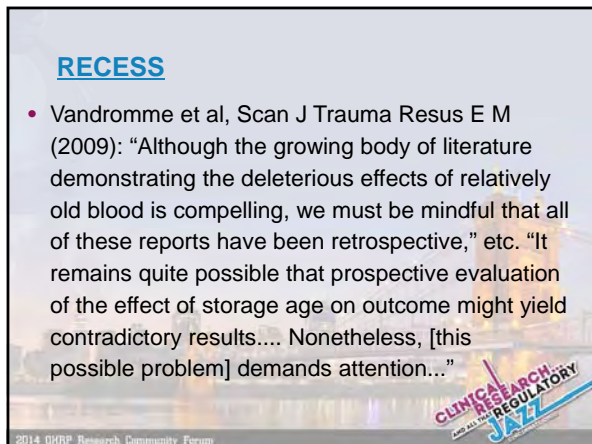


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RECESS

- Vandromme et al, Scan J Trauma Resus E M (2009): "Although the growing body of literature demonstrating the deleterious effects of relatively old blood is compelling, we must be mindful that all of these reports have been retrospective," etc. "It remains quite possible that prospective evaluation of the effect of storage age on outcome might yield contradictory results.... Nonetheless, [this possible problem] demands attention..."

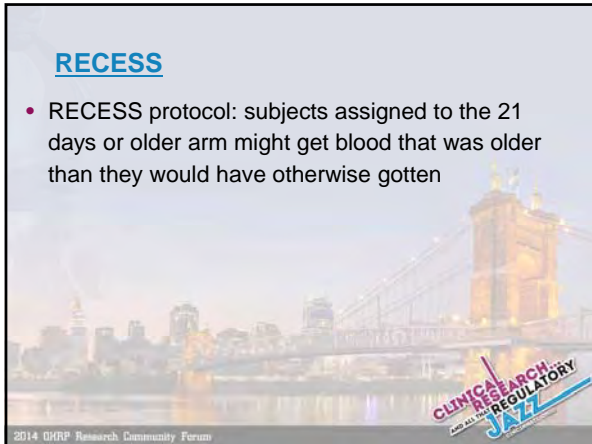


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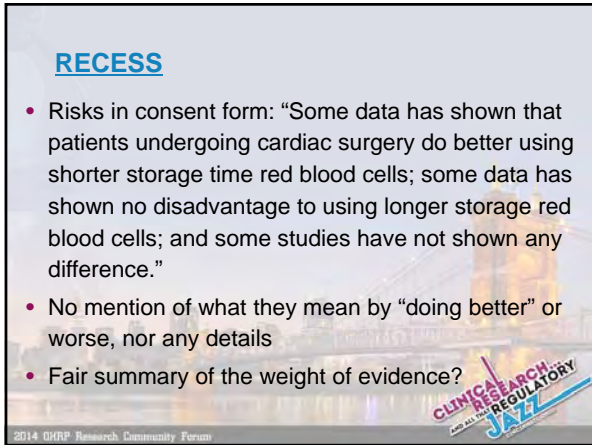
RECESS

- RECESS protocol: subjects assigned to the 21 days or older arm might get blood that was older than they would have otherwise gotten



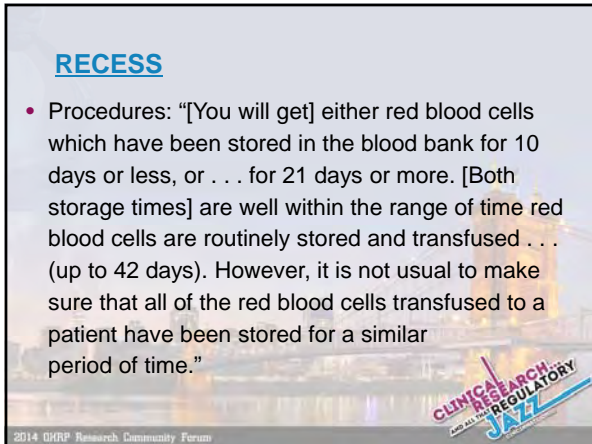
RECESS

- Risks in consent form: “Some data has shown that patients undergoing cardiac surgery do better using shorter storage time red blood cells; some data has shown no disadvantage to using longer storage red blood cells; and some studies have not shown any difference.”
- No mention of what they mean by “doing better” or worse, nor any details
- Fair summary of the weight of evidence?



RECESS

- Procedures: “[You will get] either red blood cells which have been stored in the blood bank for 10 days or less, or . . . for 21 days or more. [Both storage times] are well within the range of time red blood cells are routinely stored and transfused . . . (up to 42 days). However, it is not usual to make sure that all of the red blood cells transfused to a patient have been stored for a similar period of time.”



Off-Label Alternatives

- In many studies, the “new treatment” arm involves off-label use of marketed drugs.
- Should subjects be clearly told that nothing prevents them from obtaining that new treatment directly from a doctor?
- Getting it 100% of time vs. 50%.
- This is frequently not clearly disclosed.

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THE END

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