

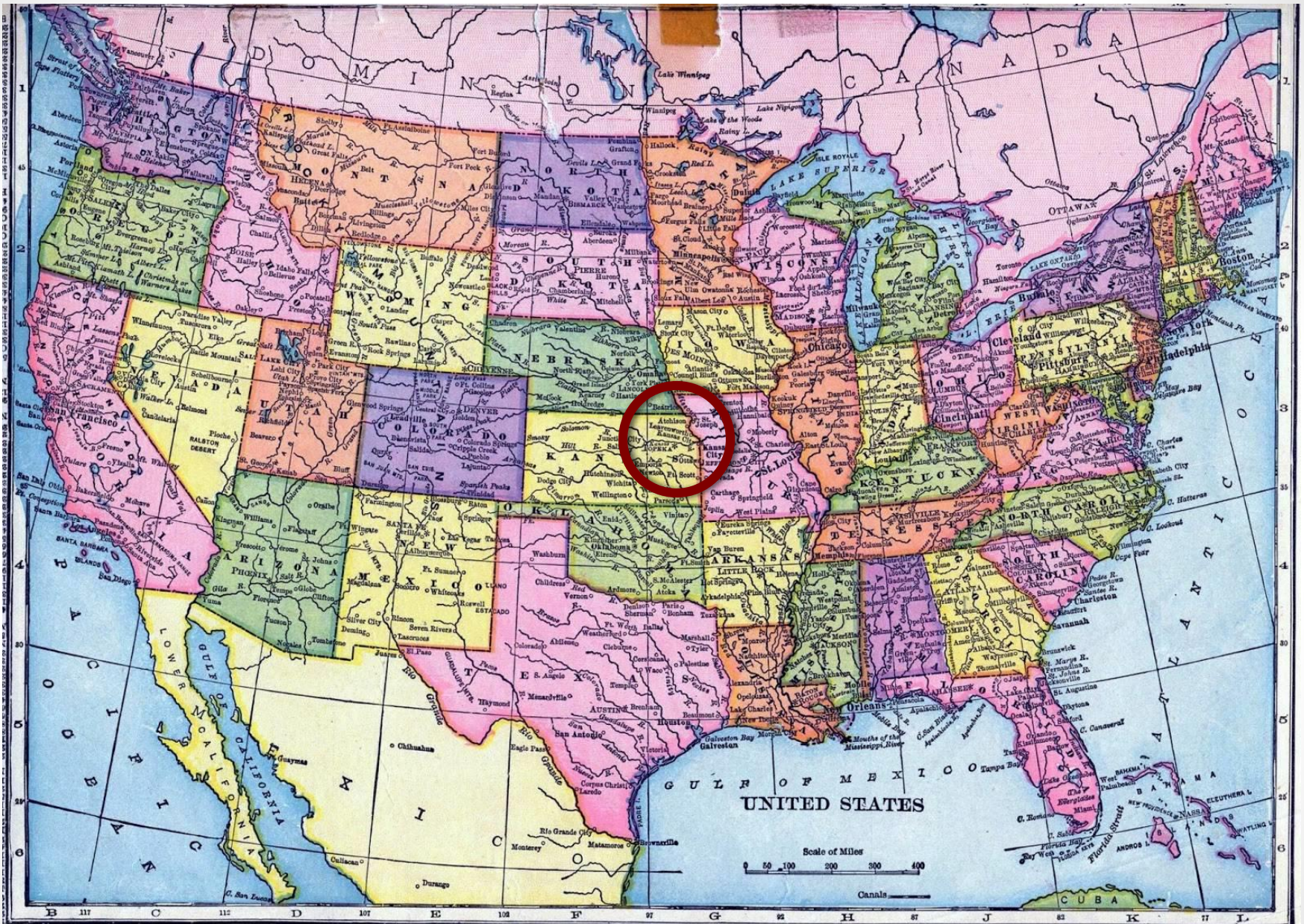


# **Considerations in the evaluation and determination of minimal risk in research studies.**

John D. Lantos MD.

Children's Mercy Hospital, KCMO

Based on a paper by John D. Lantos, David Wendler,  
Edward Septimus, Sarita Wahba, Rosemary Madigan,  
Geraldine Bliss, Clin Trials, 2015.



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# Goals for today

- Definitions of “research,” “QI” and “CER”
- Present a few hypothetical studies, all of which seem to entail similar levels of risk, but would trigger different IRB responses
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# What is research?

- “A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”
  - The Common Rule, 45 CFR 46.102(d)



# What is QI?

- Systematic, data-guided activities designed to bring about immediate improvements in health care delivery in particular settings.
  - Lynn J, Baily MA, et al. The Ethics of Using Quality Improvement Methods in Health Care. *Ann Int Med*, 2007



# Research v. QI

- They sound very similar
- They involve the same sorts of interventions
- They both seek generalizable knowledge



# An Odd Distinction

- “particular settings” vs. “generalizable knowledge.”
  - “Usually the knowledge that results from QI is most applicable to the local situation. But insights about one setting ordinarily have some applicability to other settings.”
    - Lynn, Baily, Ann Int Med, 2007



# What is “comparative effectiveness research?”

- Comparative effectiveness research is designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options, all of which are within current standards of care.”
  - AHRQ, <http://effectivehealthcare.ahrq.gov/index.cfm/what-is-comparative-effectiveness-research1/>

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# Risks of Oxygen study #1

- Doctors want to determine the optimum level of oxygen to give premature babies.
- They analyze de-identified data from EHRs at ten NICUs that use different target O<sub>2</sub> saturations.
  - Five target a higher saturation, five a lower one.
- Outcomes are rates of
  - mortality,
  - retinopathy of prematurity (ROP)
  - neurodevelopmental impairment. (NDI)



## Of note...

- 50% of the babies are treated in NICUs that target higher saturation. 50% in NICUs that target lower saturation.
- Parents are unaware of the different approaches.
- Parents don't choose their NICU




# By current standards

- It is research
- It doesn't involve human subjects and therefore has no risk to human subjects.
- It may be carried out without parental consent or knowledge.

# Risks of Oxygen study #2

- Doctors want to determine the optimum level of oxygen for preemies.
- They find five NICUs that target sats of 85-90%, five that target sats of 90-95%,
- They prospectively enroll babies in an observational study in which they monitor
  - Mortality
  - ROP
  - NDI

- 
- Needs IRB approval
  - No need for consent
  - Minimal risk

# Risks of Oxygen study #3

- Doctors in a single NICU become convinced, based on retrospective studies, that lower oxygen saturation targets are safer.
- They change their clinical practice so that, instead of targeting an O<sub>2</sub> sat of 90-95%, they now target 85-90%.
- They then retrospectively analyze data from the two time periods and compare rates of survival, ROP, and NDI.



# By current standards

- This is observational research
- It requires IRB approval and parental consent
- It is minimal risk

# At that same hospital...

- Doctors notice that only 50% of babies are kept within the targeted range of O2 saturations. They implement a QI program that includes education about the relationship between O2 sats and outcomes. The program leads to higher compliance with the protocol. Now 75% of babies are within the target O2 sat range.





# By current regulations

- Quality improvement, not research
- No need for consent or IRB approval



# Risks of Oxygen study #4

- Doctors want to determine the optimum level of oxygen to give premature babies.
- They prospectively randomize babies to target oxygen saturations of 85-90% or 90-95%.
- They analyze the relationship between these oxygen saturations, mortality, ROP, and NDI.



# By current standards

- Greater than minimal risk
- Parental consent required
- Must warn parents of the risks of death, ROP and NDI.



# Of note

- Doctors don't know which level of oxygen is best
- In all these “studies,” half of the babies would get more oxygen, half less.
- Actual risk to the babies seems pretty similar
- How does it compare to what they would get outside of the study?

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# The disturbing phenomenon of practice variation

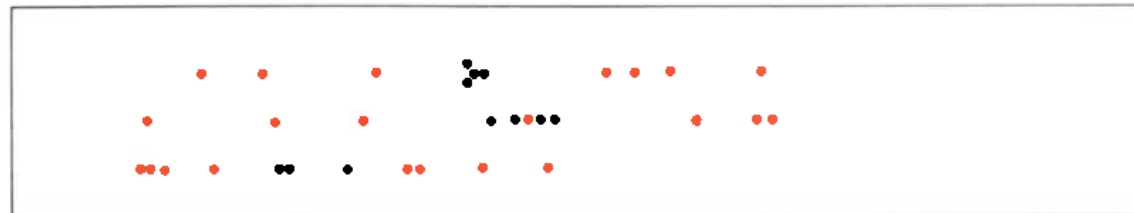
- Clinical choices vary in dramatic, irrational, and unpredictable ways.
- Studies pioneered by Wennberg in 70s and 80s.
- It is seen everywhere

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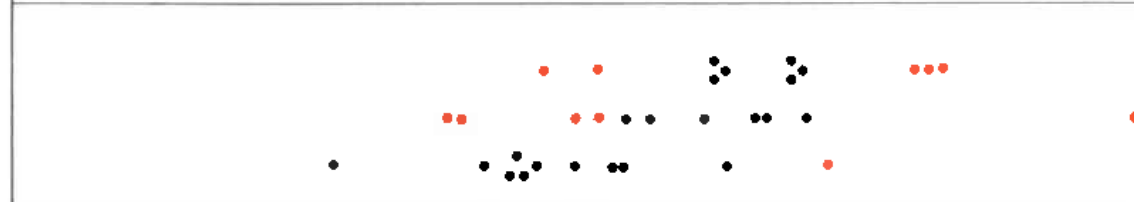


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**CHOLECYSTECTOMY**

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**APPENDECTOMY**

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0 10 20 30 40 50 60 70 80 90

PROCEDURES PER 10,000 PEOPLE PER YEAR

Table 1. Hospital Use by Medicare Beneficiaries in Boston and New Haven, Fiscal Year 1985.

MEASURE	BOSTON	NEW HAVEN	RATIO BOSTON:NEW HAVEN (95% CONFIDENCE INTERVAL)
<b>All hospitalizations</b>			
Discharges (no.)	28,030	5,717	—
Beneficiaries (no.)	85,781	26,558	—
Discharges per 1000 beneficiaries (no.)	324.2	221.0	1.47 (1.43–1.51)
Length of stay (days)	11.8	10.3	1.15 (1.11–1.18)
Days per 1000 beneficiaries	3,813.2	2,268.2	1.68 (1.65–1.71)
Reimbursements per case (dollars)	5,317	4,355	1.22 (1.19–1.25)
Reimbursements per capita (dollars)	1,724	962	1.79 (1.76–1.82)
<b>Hospitalized beneficiaries with one or more discharges</b>			
No.	18,272	4,151	—
Percent of all beneficiaries	21.3	15.6	1.37 (1.32–1.41)



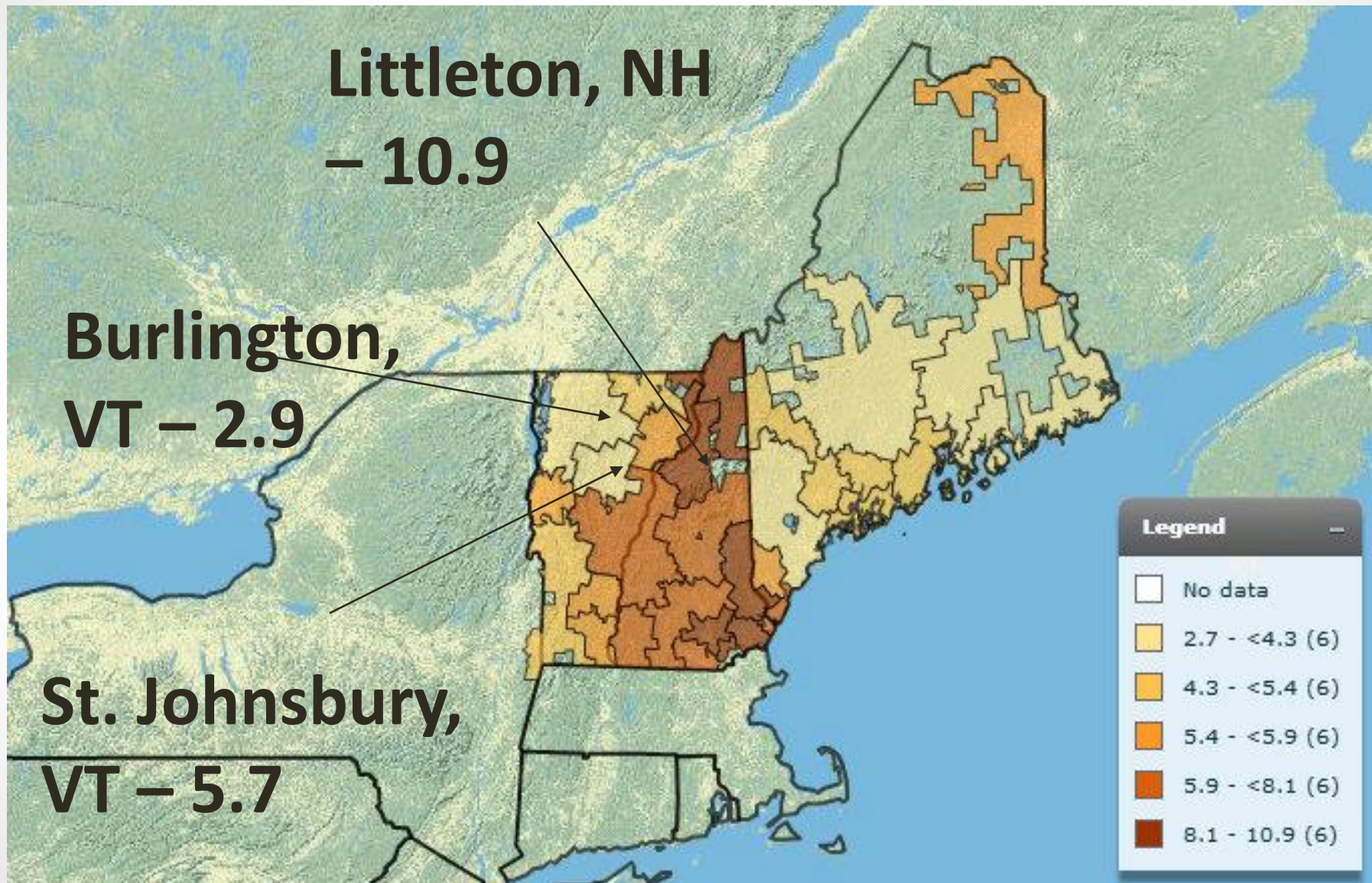
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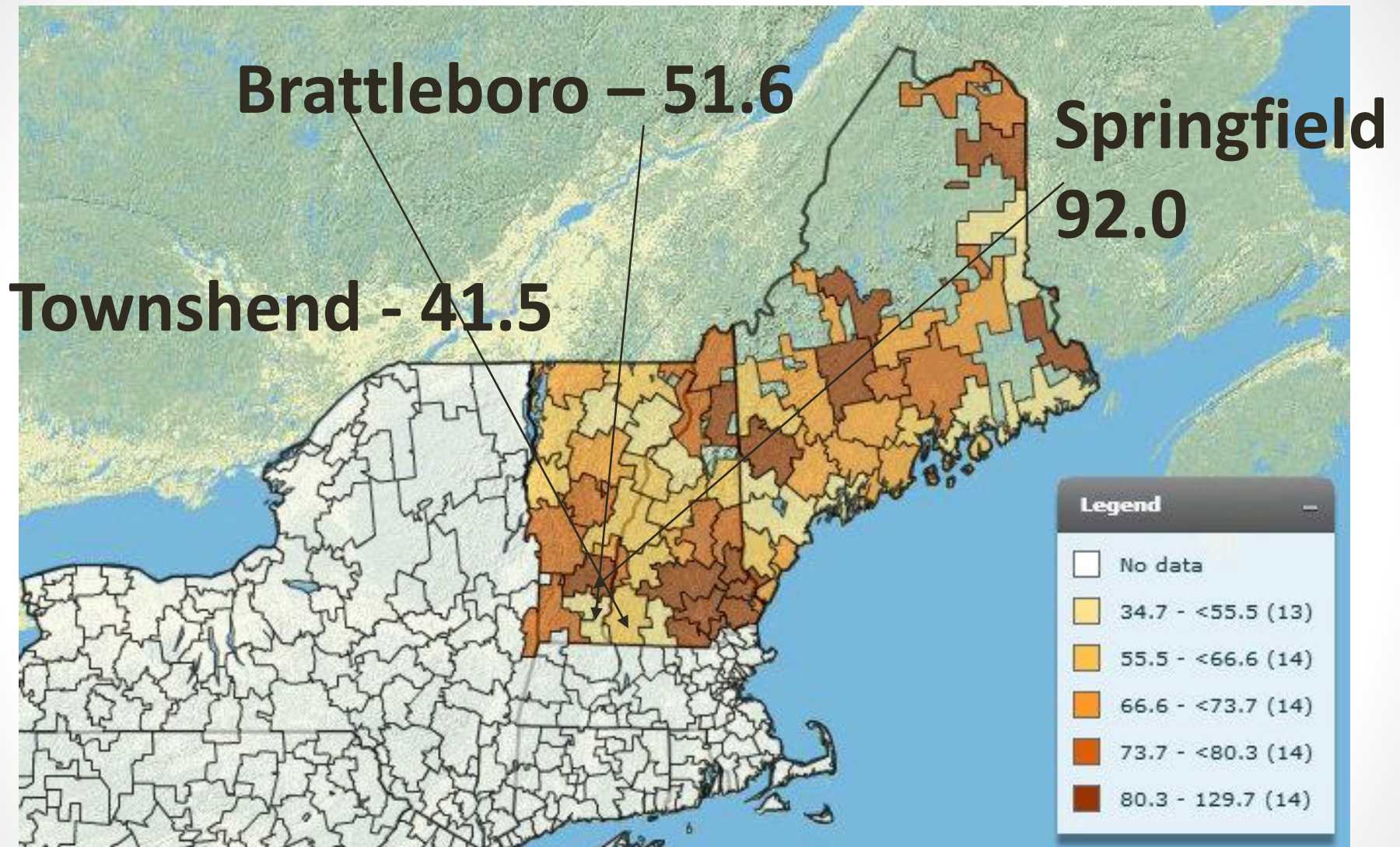
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# Tonsillectomies per 1000 children/year, 2007-10



# Chest X-rays per 1000 children/year – 2007-10





# Risks of practice variation v. research

- Would it be riskier for the children of Vermont and NH to be randomized to “more aggressive” or “less aggressive” approaches to tonsillectomy?
- Or the citizens of Boston and New Haven to different algorithms to decide on hospitalization?



# Key question

- Which is riskier?
  - Undisclosed and unstudied idiosyncratic practice variation?
    - OR
  - Deliberate formal randomization with careful monitoring and evaluation?



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# The determination of “minimal risk” matters.

- If an IRB determines that a clinical trial only entails “minimal risk,” it may:
  - Allow a waiver or alteration of the informed consent process;
  - Permit the study to be performed in certain vulnerable populations;
  - Use an expedited review process.





# But...

- Definition of minimal risk is non-specific
- IRBs clearly vary in their determinations of risk levels
- Risk-averseness can restrict valuable research
- Variation may hamper multicenter research

# Federal definition of minimal risk

- “The probability and the magnitude or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”
  - 45 CFR 46.102(i)



# Two problems

- Different people's daily lives involve different sorts of risks. It is unclear whether the proper comparator is the risk of an individual person's daily life or an average person's daily life (whatever that might mean.) (Wendler 2005)
- In the context of clinical research, the “routine physical and psychological examinations or tests” that a potential research participant might ordinarily encounter are quite different from those that a healthy person might encounter (Rid 2010).



# Two research domains

- Studies with intention of providing benefit to study participants
  - “non-therapeutic” studies
    - Observational studies
    - Phase I/pharmacokinetic studies
- Studies with a goal of providing benefit
  - Most clinical trials, especially prospective randomized trials

# No possibility of benefit

- Absolute assessment of risk
  - Minimal risk
  - Minor increase over minimal risk
  - Greater than a minor increase over minimal risk.

# If possibility of benefit...

- Balance of benefits and harms.
- Areas of controversy
  - Research vs. QI
  - Attributable risk in randomized trials



# Studies often classified as minimal risk

- Use of existing databases
- Retrospective chart reviews
- Survey research
- Prospective collection of observational data

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# Areas of controversy

- Can a randomized, controlled trial ever be classified as “minimal risk?”
  - Emergency research may be allowed without consent even if not minimal risk because it is important and infeasible to do with consent, not because it is minimal risk.
- Are QI studies that have an experimental design “minimal risk?” Are they even research?

# What makes randomization risky?

- Instead of an individualized decision by the patient's doctor, treatment is assigned at random.
- Treatment delivered by standardized protocol.
  - If individualized care choice of treatment, or changes in treatment, would result in a better outcome, then participation increases risk.
  - But how would we know? Participation in the RCT could increase, decrease or have no effect on risk.

# Minimal risk in RCTs?

- Should the risks of the treatments being studied be considered a risks of a study of the relative efficacy of those treatments.
  - Common rule says “No.”
  - OHRP Draft Guidance says “Yes.”



# Common Rule

- “In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).”
  - (CFR 46.111 (a)(2))



# OHRP Draft Guidance

- “If a person in a research study is being asked to undergo procedures that involve reasonably foreseeable risks that they would not have otherwise been exposed to, then that person needs to be told about those risks. Only in this way can people make a truly informed decision about whether they are willing to participate.”
- “The reasonably foreseeable risks of research include already-identified risks of the standards of care being evaluated as a purpose of the research.”



# Imagine two studies

- Antibiotics for otitis media
- Stents for asymptomatic coronary artery disease

# Antibiotics for otitis media

- Two FDA-approved antibiotics - A and B - are in widespread use.
- There is known practice variation among doctors in the use of A and B. Some prefer A, some B.
- Both are associated with GI problems, diaper rashes, and, in very rare cases, anaphylactic reactions.
  - In an RCT of A vs. B, are the GI problems, diaper rashes and possibility of anaphylaxis a risk of the study?
  - Or is the risk of the study simply the risk of being assigned to one or the other at random, rather than based on doctor or patient preferences?



# Stents for coronary artery disease (CAD)

- Some cardiologists recommend a stent for patients with asymptomatic CAD. Other think that stents increase risk, and recommend optimum pharmacological management but no invasive procedures.
  - In a study of stents vs. medical management, are the risks of a stent properly considered as risks of the study?





But here's the thing...



## But here's the thing...

- The current system seems to focus on the measurable risks, but, as the examples show, that isn't the central concern.
- It is about something deeper and more intangible



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# It isn't about measurable risk

- It is about the very nature of this thing that we call research and the people who do it.

# It isn't about measurable risk

- “Ultimately, the issues come down to a fundamental difference between the obligations of clinicians and those of researchers. Doctors are required, even in the face of uncertainty, to do what they view as being best for their individual patients. Researchers do not have that same obligation.”
  - Letter from OHRP to University of Alabama at Birmingham.  
[http://www.hhs.gov/ohrp/detrm\\_lettrs/YR13/jun13a.pdf](http://www.hhs.gov/ohrp/detrm_lettrs/YR13/jun13a.pdf). Accessed 11-19-13.



# Motives and intentions

- “It is the doctors, not the researchers, who have a fiduciary obligation and long-standing ethic to pursue the patient’s best interests above all other considerations.”
  - Macklin R, Shepherd L. Informed Consent and Standard of Care: What Must be Disclosed? Am J Bioeth 2013.

# Motives and Intentions

- “A physician must be guided by a fiduciary obligation to the patient. A researcher has no such obligation.”
  - Annas G. Presentation for HHS Public Meeting on Protection of Human Subjects. <http://www.regulations.gov/#!documentDetail:D=HHS-OPHS-2013-0004-0034>. .



# The real fear



# The real fear

- **The dark and conflicted heart of the medical researcher**





# and conflicted heart medical researcher





nd cor  
dical



**Or  
Devils?**



# This is crucial

- Actual studies can be safer or riskier than conventional therapy
- But if the problem is the loyalty of the researcher, then any activity that is seen as “research” leaves people unprotected.
- No such concern with QI.



# Researchers are thought to ignore patient welfare

- “In the context of medical care...beneficence entails the health care provider to do what is best medically for particular patients. In clinical research, in contrast, **beneficence directs investigators to promote social value** by generating scientific knowledge.”
  - Joffe S, Miller FG. Mapping the moral terrain of clinical research. *Hast Center Rep*, 2008; 38(2): 30-42.



# Researchers have a moral imperative to be unethical

- “Researchers are required to modify their ethical commitments to individual patients.”
  - Hellman S, Hellman DS. Of mice but not men. Problems of the randomized clinical trial. NEJM 1991; 324:1585-9.



# And they can't help it

- “The (researcher-subject relationship) by its very nature, compels or urges to certain priorities and inclinations to perceive and act in certain ways.”
  - Churchill L. Physician-Investigator/Patient-Subject: Exploring the Logic and the Tension. J Med Philos 1980; 5:215-24.



# The researcher is seen as...

- Driven to pursue knowledge.
- Committed to a utilitarian ethic.
- In need of constant oversight.



Researchers = addicts.





# But is it true?

- Many researchers see themselves as exquisitely attentive to patient's interests.
- They see researchers as honest questioners and are suspicious of the value of the clinician's individualized clinical judgment when there is no good evidence.



# Research is for current patients

- “It would not be responsible to give an unstudied treatment to you in an uncontrolled way, because neither you, nor I, nor future patients would ever know whether it helped or hurt.”
  - Fost N. Waived consent for emergency research. *Am J Law Med*, 1998; 24: 163-84.

# Researcher as fiduciary

- “I have a fiduciary obligation to provide optimal treatment. I also have a moral obligation to know what the optimal treatment is. And I have a moral obligation to keep trying to find out what the best treatments may be.”
  - Barrington K. [www.neonatalresearch.org](http://www.neonatalresearch.org), 9/18/2013



# Intertwined obligations

- “The multiple purposes of medical practice, caring for patients, advancing science, improving the health of the community, nations, and future generations cannot be separated clearly.”
- “Research and therapy, pursuit of knowledge and treatment, are not separate but intertwined.”
  - Katz J. The education of the physician-investigator. *Daedalus*, 1969; 98, 480-501.

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- **Where to go from here?**



# A crisis in research regulation

- Issue of AJOB devoted to “minimal risk.”
- Hastings Center Special Report in Jan
- PCORI planning a special journal issue on the ethics and regulation of CER, pragmatic trials, use of “big data” and other issues
- The phenomenon of practice variation
- The clash of principles between ethics and QI



# Need for a new framework

- Current framework based on Belmont
- Belmont looked backwards to Tuskegee and Nazi experiments
- Current problems are different and need a different analysis.





# Ethics of Learning Health Care System

- A just health care requires a constantly updated body of evidence about the effectiveness and value of health care interventions and of alternative ways to deliver and finance health care.

Faden, Kass, et al, Hast Ctr Rep, 2013

# Seven ethical obligations

- 1) respect the rights and dignity of patients;
- 2) respect the clinical judgment of clinicians;
- 3) provide optimal care to each patient;
- 4) avoid imposing nonclinical risks and burdens on patients;
- 5) reduce health inequalities among populations;
- 6) conduct responsible activities that foster learning from clinical care and clinical information;
- 7) contribute to improving the quality and value of clinical care and health care systems.



# Obligations 5-7 depart from traditional research ethics


- 5) Reduce health inequalities among populations;
- 6) Conduct responsible activities that foster learning from clinical care and clinical information
- 7) Contribute to the common purpose of improving the quality and value of clinical care and health care systems.

Faden, Kass, et al, Hast Ctr Rep, 2013



Traditional presumptions need to change. Just as health professionals and organizations have an obligation to learn, patients have an obligation to contribute to, participate in, and otherwise facilitate learning.

Faden, Kass, et al, Hast Ctr Rep, 2013

- 
- A learning health care system will
    - Link the obligation to respect the rights and dignity of patients with the obligation to contribute to improving the quality of health care.
    - Disclose to patients that learning occurs constantly throughout the health care system.
    - Give concrete examples of how care has been improved as a result of learning.

Faden, Kass, et al, Hast Ctr Rep, 2013



# New framework

- The obligation to improve quality
- The justice concerns of opting out.
- The riskiness of idiosyncratic practice variation
- A new research paradigm that doesn't starkly dichotomize research and clinical practice.



# Conclusion

- The central dogma of research regulation today is that clinical investigators cannot be trusted to make moral judgments about their own research.



# The change we need

- Need to acknowledge two things:
  - Research can often benefit current patients, not just future ones, if only by protecting them from the harms of unstudied practices.
  - Clinical researchers are no more conflicted than practicing physicians. Both should be expected to balance their moral obligations to their patients with other conflicting obligations.





What makes an activity “research?”



What makes an activity “research?”

What makes an activity “risky?”



What makes an activity “research?”

What makes an activity “risky?”

Why do we care?

Answers are not so clear



# Ethics of research

- Research is seen as risky and optional.
- No ethical obligation to engage in research.
- Need protection from research
- The risk is a philosophical one:
  - That humans will be treated as a means to an end, rather than an end in themselves.



# Ethics of quality improvement

- Doctors and hospitals have an ethical obligation to provide high quality care.
  - A core competency of residency training
  - A requirement for MOC by ABP
  - The ABIM requires evaluation of quality



# Ethics of quality improvement

- No risk
- No need for consent
- No need for prior approval or oversight
- Perhaps no right to refuse to participate



Is CER more like “research” or more like “QI?”

Is there an obligation to participate or a need to be protected?





# Moving forward

- Is the current system of research regulation and oversight obsolete?
  - Big data
  - Learning health care systems
  - Continuous quality improvement
- What about input from research participants?
  - We need studies to understand how prospective participants think about the acceptable risk levels.
  - Goal: balance of transparency, scientific rigor, and empowerment

THANKS!

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# QI as minimal risk research

- Your hospital is participating in a (research) (quality improvement project) designed to help doctors figure out the best way to prevent central line infections.
- Step-wedge design: Different hospitals will implement a patient safety program at different times.
- Each hospital will be its own control, and results will pool the “before” and “after” measurements from each hospital.

# Intervention

- Doctors and nurses will be taught the importance of five procedures that have been shown to reduce central line infections:
  - Hand washing,
  - Using gowns, masks, and gloves during the insertion of central lines
  - Cleaning the skin with chlorhexidine
  - Inserting these lines anywhere except the groin if possible
  - Quickly removing the central lines when no longer necessary.
- Each of these procedures is currently recommended by the Centers for Disease Control. However, not all doctors and nurses follow these procedures every time they insert a catheter.

# Intervention

- Five interventions to help staff
  - An educational session about central line infections.
  - Creation of a “catheter insertion cart” that has both instructions and equipment;
  - A checklist for the five activities.
  - A nurse associated with the project will ask clinicians, every day, whether a catheter can be removed.
  - Empower nurses to stop a catheter-insertion procedure if they observe a violation of the guidelines.



# Questions

- Is it research?
- Is there equipoise?
- Can it be done without consent?



# Similarities Between QI and Research

- Human participants
- A “study question” and “study design”
- Outcome measures
- Data collection, data analysis, designed to answer a question
- Often, a goal of publication in peer-reviewed journal



# Confusion and disagreement about minimal risk :

- IRBs differ in their classification of minimal risk.
- Federal guidelines are ambiguous about classifying risk as “attributable” to the study.
- Distinction between research and QI is murky.