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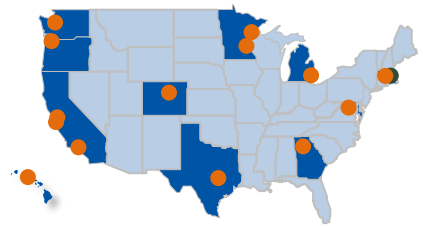

Design Decisions in Pragmatic Trials: Separating Rigor from Idolatry

Greg Simon

Kaiser Permanente Washington Health Research Institute

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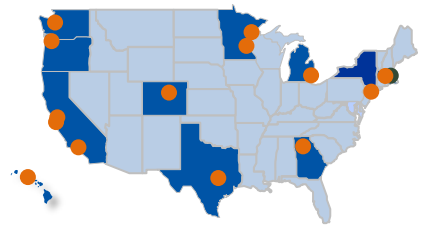

Outline

- Terminology/history
- Clarifying the study question
- Target setting & population
- Level of assignment
- Method of assignment
- Control over intervention delivery
- Control over “usual care”
- Blinding
- Informed consent
- Analytic decisions

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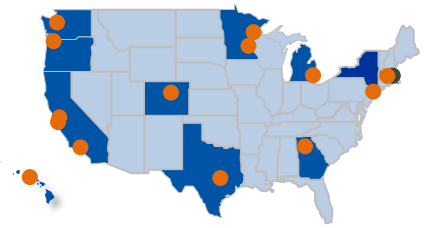

Take home message:

- Every trial answers a question.
- Some trials answer the question they intended.

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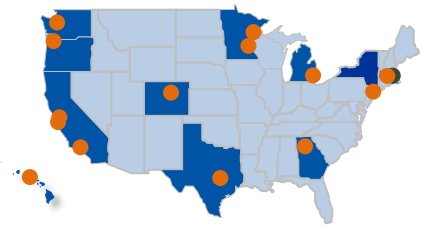

Terminology

- Pragmatic clinical trials
- Hybrid effectiveness/implementation trials
- Real-world evidence

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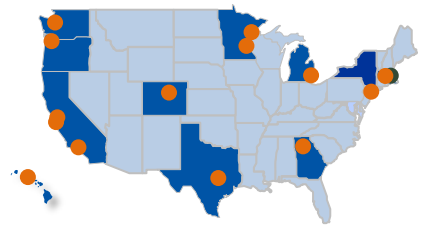

The idea is not new

ELSEVIER

Journal of Clinical Epidemiology
Volume 48, Issue 3, March 1995, Pages 363-373

Original article

Cost-effectiveness comparisons using "real world" randomized trials: The case of new antidepressant drugs

Gregory Simon, Edward Wagner, Michael Vonkorff

STATISTICS IN MEDICINE, VOL. 3, 409–420 (1984)

WHY DO WE NEED SOME LARGE, SIMPLE RANDOMIZED TRIALS?

SALIM YUSUF* RORY COLLINS AND RICHARD PETO
Clinical Trial Service Unit, Radcliffe Infirmary, Oxford, UK

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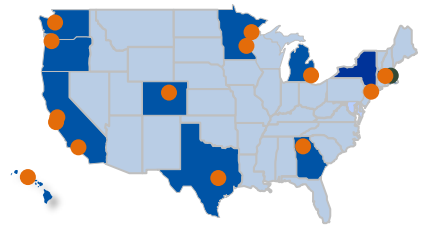

History: Two motivations

- Generalizability to real-world clinical or policy decisions
- Improved efficiency (in cost and time)

These two are not always aligned!

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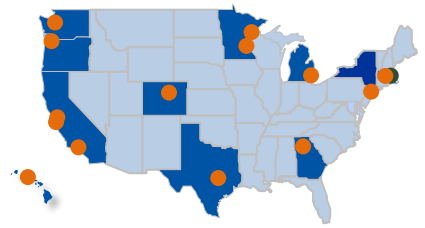

Orthodoxy (Idolatry) of Traditional Trials

- Strict eligibility (and onerous assessment)
- High level of motivation/commitment
- Tight control of interventions (“experimental” and “control”
- “Double-blind”

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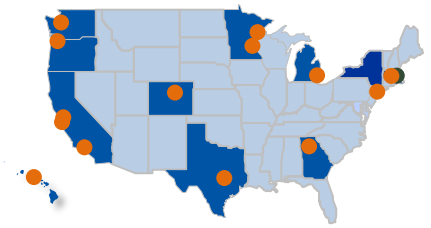
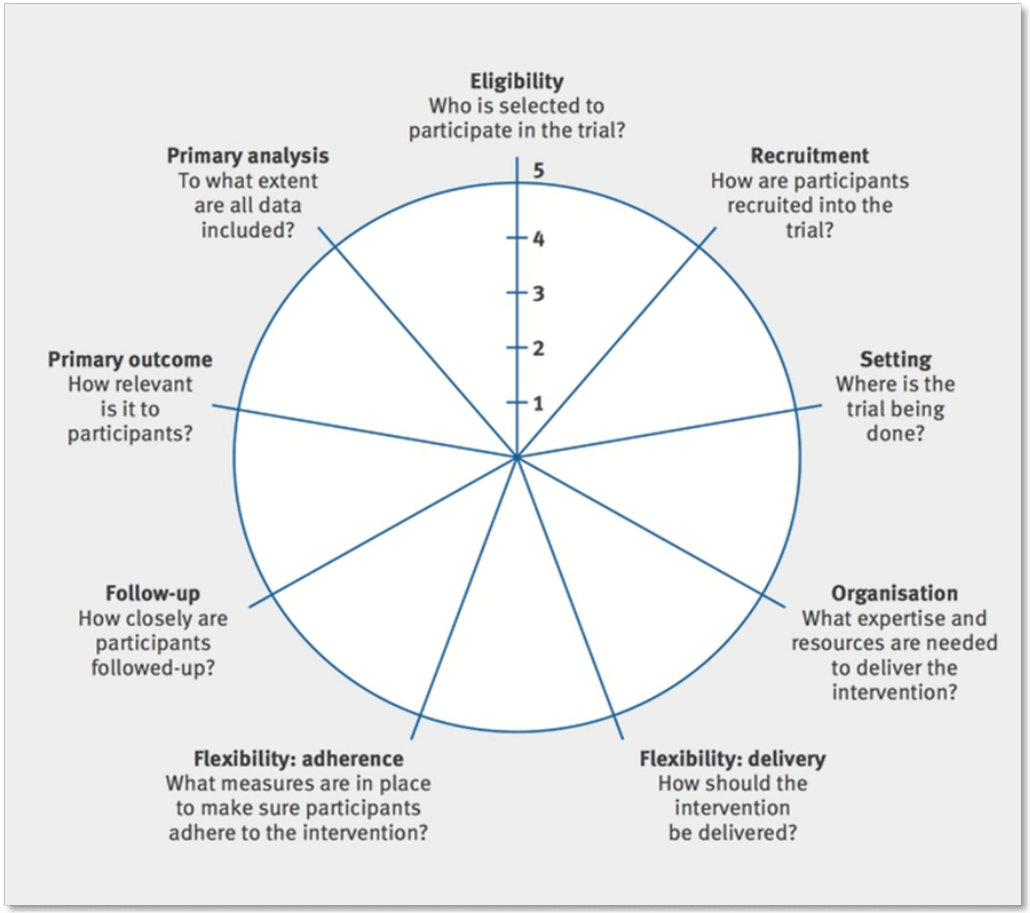


New Orthodoxy (Idolatry) of Pragmatic Trials



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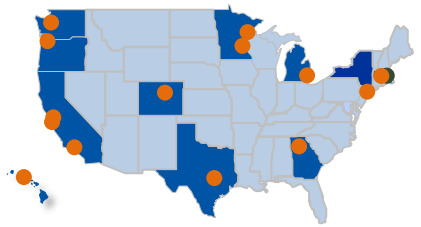
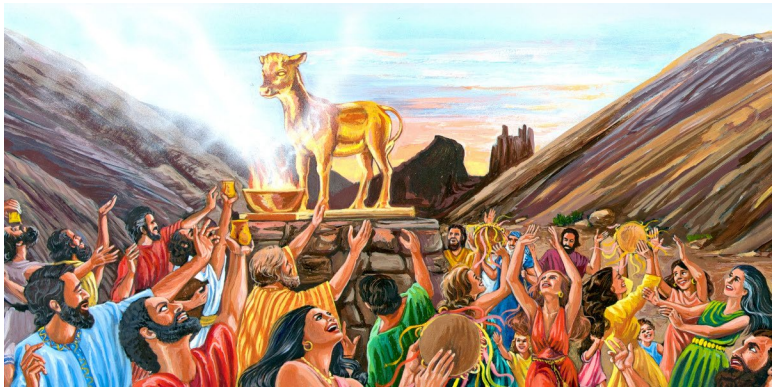


What is the Gold Standard…

and what is just the Golden Calf?



It depends.

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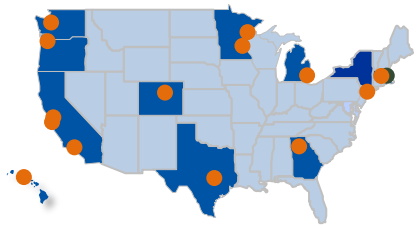

Clarifying the question: Who is your customer?

- What is their role?
- What decision do they face?
- What options are available?
- What are their constraints?
- What is their threshold for action?

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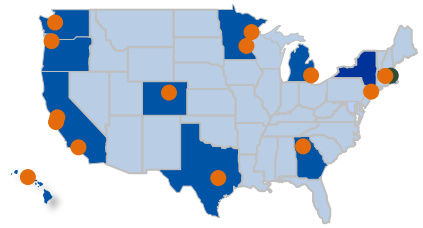

Design decisions:

- Target setting & population
- Level of assignment
- Method of assignment
- Control over intervention delivery
- Control over “usual care”
- Blinding
- Informed consent
- Analytic decisions

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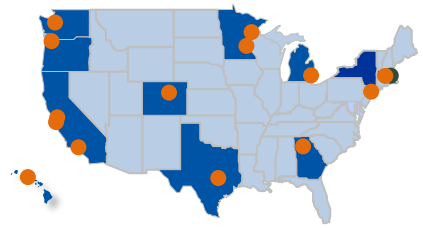

Target population can be defined by:

- Service or catchment area
- Clinical severity/prognosis
- Motivation or engagement
- Demographic characteristics
- Social determinants/environmental conditions

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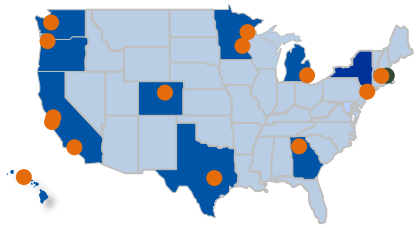

Target population depends on:

- What are the people/place/setting where these results would be applied?
- Who are the people your customer hopes to serve?
- What information or tools can your customer use to identify those people?

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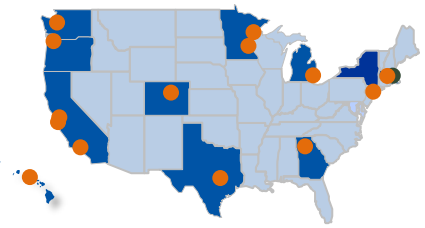

Levels of allocation

- Individuals
- Clinicians
- Facilities
- Systems or communities

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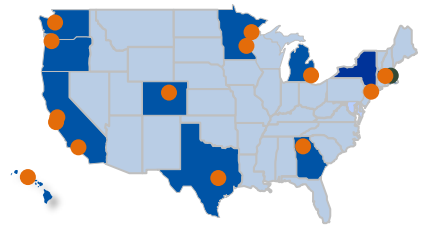

Level of allocation depends on

- Where is the intervention applied?
- Where does the intervention act?
- Can (or should) action of the intervention be contained?
- What resources are needed to implement or deliver it?

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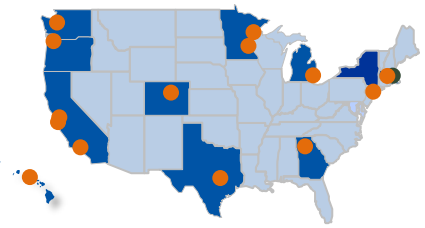

Cluster allocation/analysis: Thou shalt…

- Intervention must be delivered at the cluster level (e.g. clinician training)
- Intervention effects spill over within clusters (e.g. clinician changes their “usual care”)

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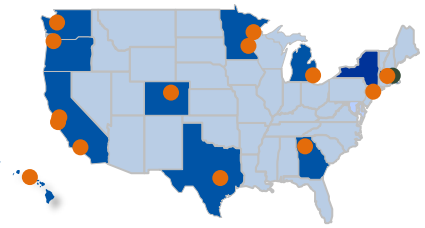

Cluster allocation/analysis: Thou shalt not…

- Patients/participants move between clusters
- Intervention leads to differential eligibility or enrollment

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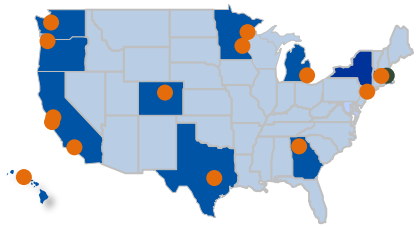

Example:
Safer Use of Antipsychotics in Youth

- Randomized trial of decision support and care navigation to reduce unnecessary use of antipsychotics
- Intervention directly focused on clinician behavior
- SO, prescribing clinicians randomized to intervention condition or usual care

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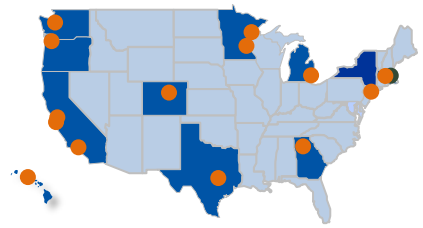

Example:
Suicide Prevention Outreach Trial

- Randomized trial of care management and online skills training vs usual care to prevent self-harm in people at high risk
- Interventions delivered by research personnel outside of clinical encounters
- Patients could receive care from overlapping and changing mix of providers
- SO, individual patients randomzied

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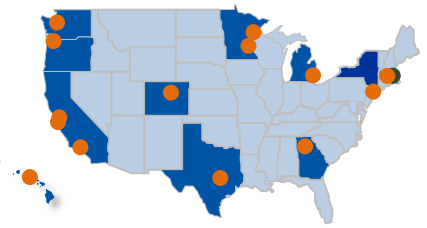

One “wrong” reason for a cluster deisgn

- Sometimes chosen as a way to dodge questions about informed consent
- There are better (and more honest) ways to address that – more later

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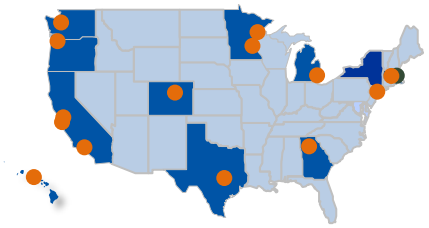

Mechanisms of assignment

- Parallel-group randomization
- Randomized cross-over or stepped wedge
- Naturalistic rollout (retrospective or prospective)

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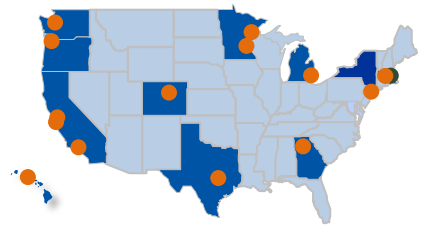

Stepped-wedge crossover: Thou shalt…

- Practical considerations require “staging” of implementation
- Intervention is highly desirable (or inevitable)
- Potential for harm is low
- The intervention can be “turned off” if needed

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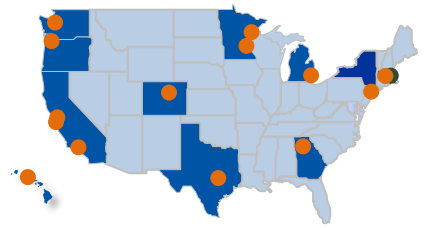

Stepped wedge crossover: Thou shalt not

- Significant temporal effects in processes or outcomes
- Clusters appear/disappear or change in size
- Risk or harm of intervention is not well known

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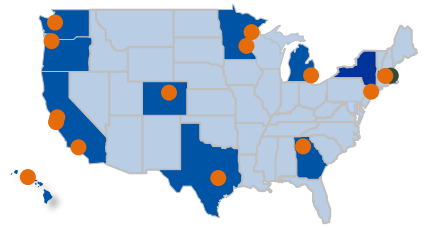

Is parallel group randomization ever wrong?

- Parallel group randomization never reduces internal validity
- BUT parallel group randomization can certainly interfere with external validity

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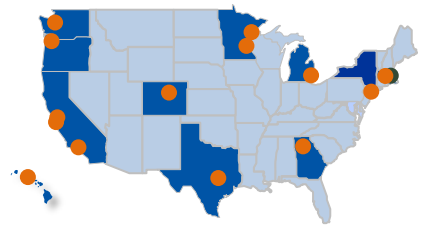

Who could be “blinded”:

- Patients or participants
- Treating clinicians
- Outcome “assessors”
- Analysts

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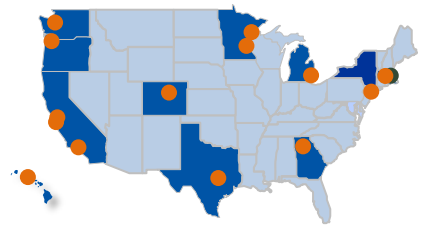

Who should be “blinded”:

- Patients or participants - Sometimes
- Treating clinicians - Sometimes
- Outcome “assessors” – Always (if possible)
- Analysts – Always

Key point: When would blinding distort the intervention or change the study question?

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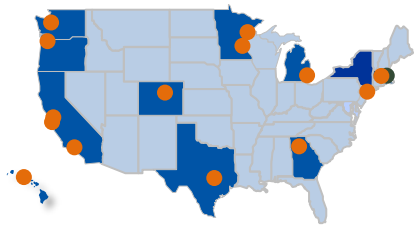

Example:
PRIDE trial of LAI antipsychotics

- Randomized trial of LAI antipsychotics vs. oral medication to prevent hospitalization or incarceration in people with psychotic disorders
- Blinding patients would require placebo pills in those assigned to LAI “sham” injections in those assigned to oral medication
- SO patients and treating clinicians were not blinded

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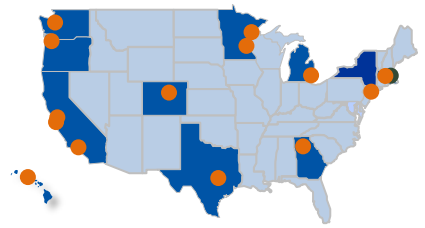

Example:
Suicide Prevention Outreach Trial

- Randomized trial of care management and online skills training vs usual care to prevent self-harm in people at high risk
- Patients and treating clinicians cannot be blinded
- Outcome based on self-harm diagnoses (usually from ED or inpatient care)
- ED or inpatient clinicians unlikely to be aware, but likelihood of seeking care could be affected

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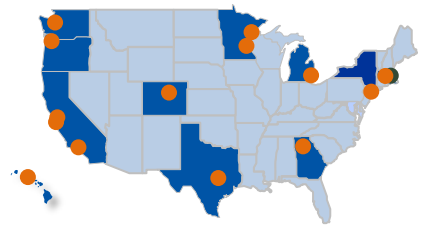

Should interventions be standardized or controlled?

- It depends on:
  - How much will effectiveness (or safety) vary with resources and expertise?
  - What resources and expertise will be available where results will be applied?

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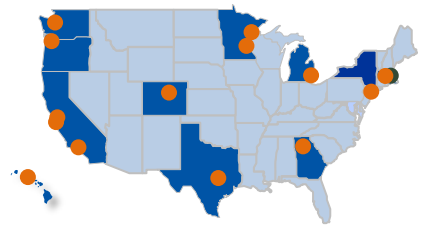

Should usual care or control condition be standardized or controlled?

- It depends on:
  - What is the setting or population where you would apply these results (Who is your customer)?
  - Is there an ethical obligation to assure some level of quality or safety?

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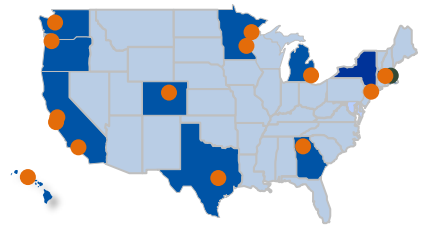

Example:
PRIDE trial of LAI antipsychotics

- Randomized trial of LAI antipsychotics vs. oral medication to prevent hospitalization or incarceration in people with psychotic disorders
- Assuring perfect adherence to oral medication would probably guarantee a null result
- BUT investigators had some obligation to protect participants from preventable crises
- SO protocol established a “floor” level of follow-up frequency and outreach

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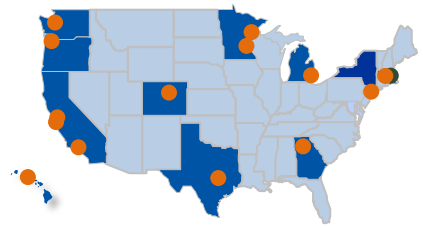

The informed consent decision tree

- Is this research involving human subjects?
- Does the research create more than minimal risk?
- Can the usual requirement for informed consent be waived?
- Is some abbreviated consent or notification appropriate?

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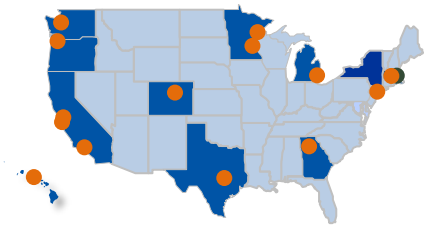

Is this research involving human subjects?

- Calling it “quality improvement” doesn’t answer the question
- Common Rule definition of research: “a systematic investigation… designed to develop or contribute to generalizable knowledge”
- Common Rule definition of human subjects research: “physical procedures by which information or biospecimens are gathered and manipulations of the subject or the subject's environment that are performed for research purposes”
- Just in case that’s not clear, OHRP adds: “a quality improvement project may constitute non-exempt human subjects research”
- SO – many activities are quality improvement AND research

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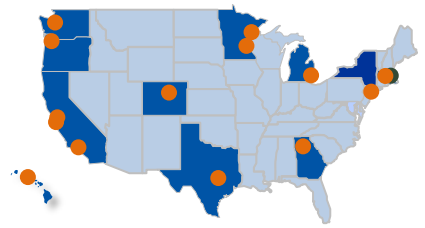

Does the research create more than minimal risk?

- The question concerns the risk created by the research (not risk that already existed)
- When research is embedded in practice, must consider effects of specific research activities:
  - Use of records data
  - Assignment of alternative interventions or treatments
  - Delivery of new or “experimental” interventions

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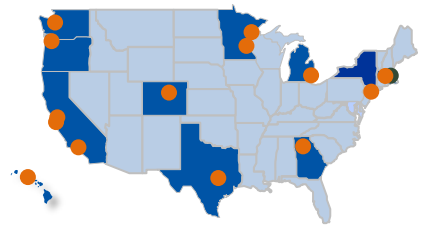

The requirement for informed consent be waived if:

- Research is not practicable without a waiver
- Research does not create more than minimal risk
- Waiver does not abridge rights or privileges
- (If appropriate) notification is provided

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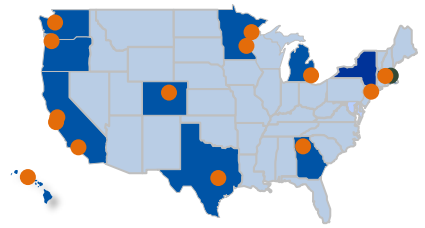

Example:
Suicide Prevention Outreach Trial

- Randomized trial of care management and online skills training vs usual care to prevent self-harm in people at high risk following Zelen design
- Waiver of consent to use records to identify participants
- Waiver of consent to randomly assign to usual care or OFFER of interventions
- Notification/abbreviated consent procedure at time of initial offer
- Waiver of consent to use records to identify outcomes

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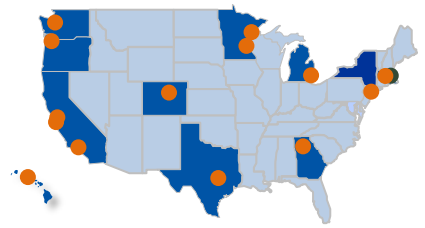

But…

Objecting to experiments even while approving of the policies or treatments they compare

Patrick R. Heck[a,b,1], Christopher F. Chabris[b], Duncan J. Watts[c], and Michelle N. Meyer[a]

[a]Center for Translational Bioethics and Health Care Policy, Geisinger Health System, Danville, PA 17822; [b]Autism and Developmental Medicine Institute, Geisinger Health System, Lewisburg, PA 17837; and [c]Annenberg School for Communication, University of Pennsylvania, Philadelphia, PA 19104

Random assignment involves issues of rights as well as risks.

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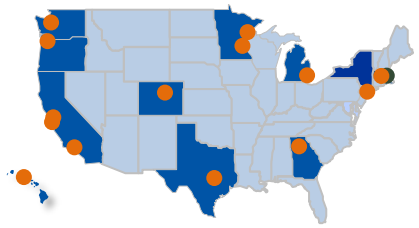

Why intent-to-treat analysis?

- Partial uptake or adherence are usually "signal" rather than noise
- We can't identify comparable populations – whether it's usual care or an alternative intervention

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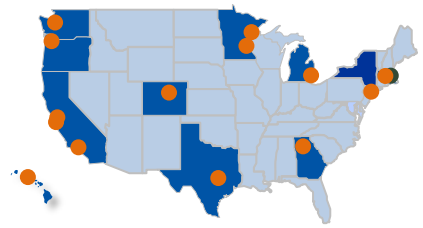

Important sources of bias

- Identification bias or biased enrollment
- Biased ascertainment of outcomes

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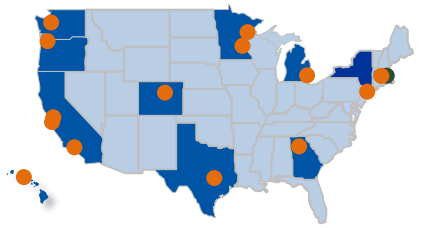

Example:
Suicide Prevention Outreach Trial

- Randomized trial of care management and online skills training vs usual care to prevent self-harm in people at high risk following Zelen design
- Expected low uptake and incomplete adherence for outreach interventions
- Analyze by original assignment, regardless of uptake or adherence
- Avoid any “as-treated” or “per-protocol” analysis
- Interventions may affect care-seeking or identification (but surveys are definitely NOT the solution)

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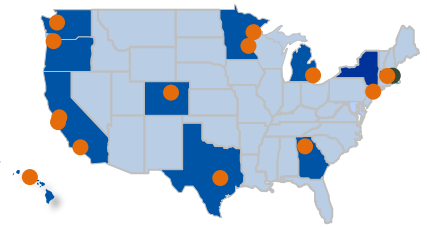
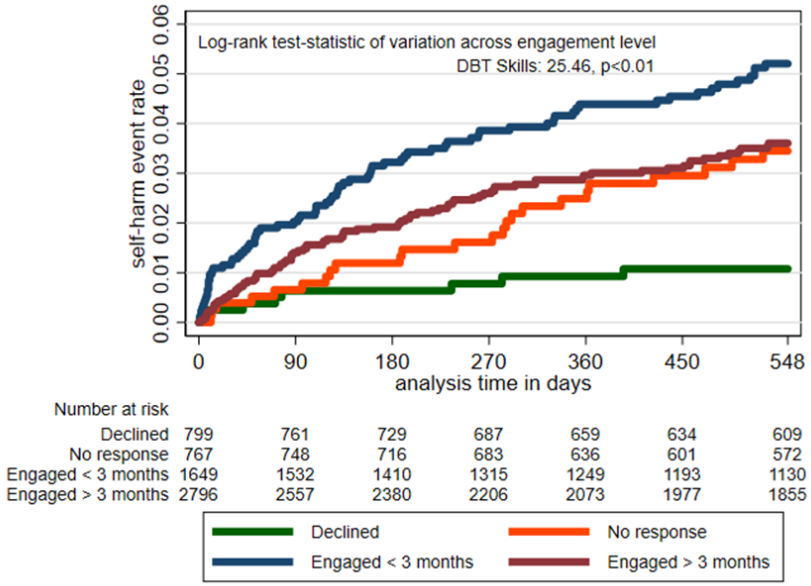


Risk of self-harm by intervention uptake



- Lowest risk in those who decline
- Highest risk in those who leave early
- Comparing any intervention uptake to UC: Intervention increases risk
- Comparing >3 mos intervention to UC: Intervention decreases risk

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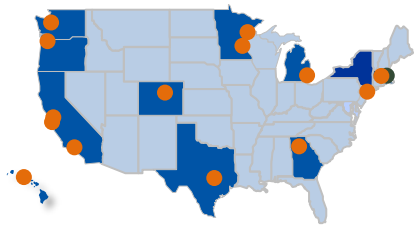

Clarifying the question: Who is your customer?

- What is their role?
- What decision do they face?
- What options are available?
- What are their constraints?
- What is their threshold for action?

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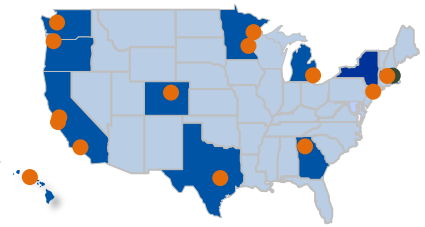

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