Panel 1: Options for Altered Consent and the Importance of Minimal Risk Determination

"Waiver" of Consent for the TiME Trial: *Regulatory and Ethical Considerations*

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TiME

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- DSMB member – Proteon Therapeutics
- Consultant – Bellus, GlaxoSmithKline
- Co-Editor – AJKD, National Kidney Foundation

Outline

- TiME Trial design and implementation
- Approach to consent
- Minimal risk and practicability criteria
- Views of patients and physicians

Dialysis-Dependent End-Stage Renal Disease

- Life-long dependence on dialysis unless transplanted
- High comorbidity burden, reduced quality of life
- High mortality rate
  - 21% at 1 year
  - 48% at 3 years

Many Unanswered Questions about Fundamental Aspects of Dialysis Care

- Duration of hemodialysis sessions?
- Dialysis solution potassium concentration?
- Blood pressure target?
- Phosphorus target?
- Hemoglobin target?
- Preventive health care?
- Anticoagulation for atrial fibrillation?

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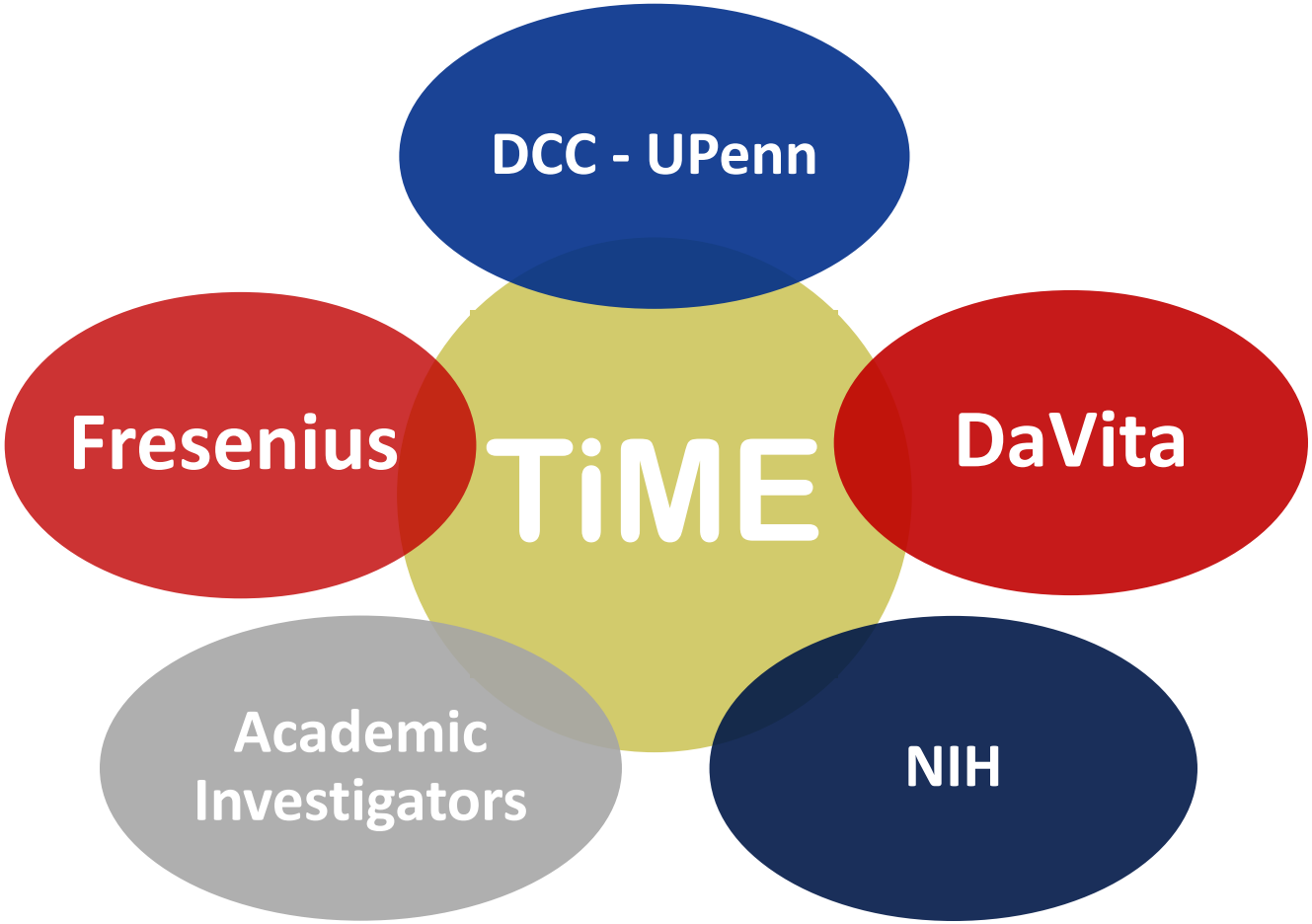
Time to Reduce Mortality in End-Stage Renal Disease (TiME)

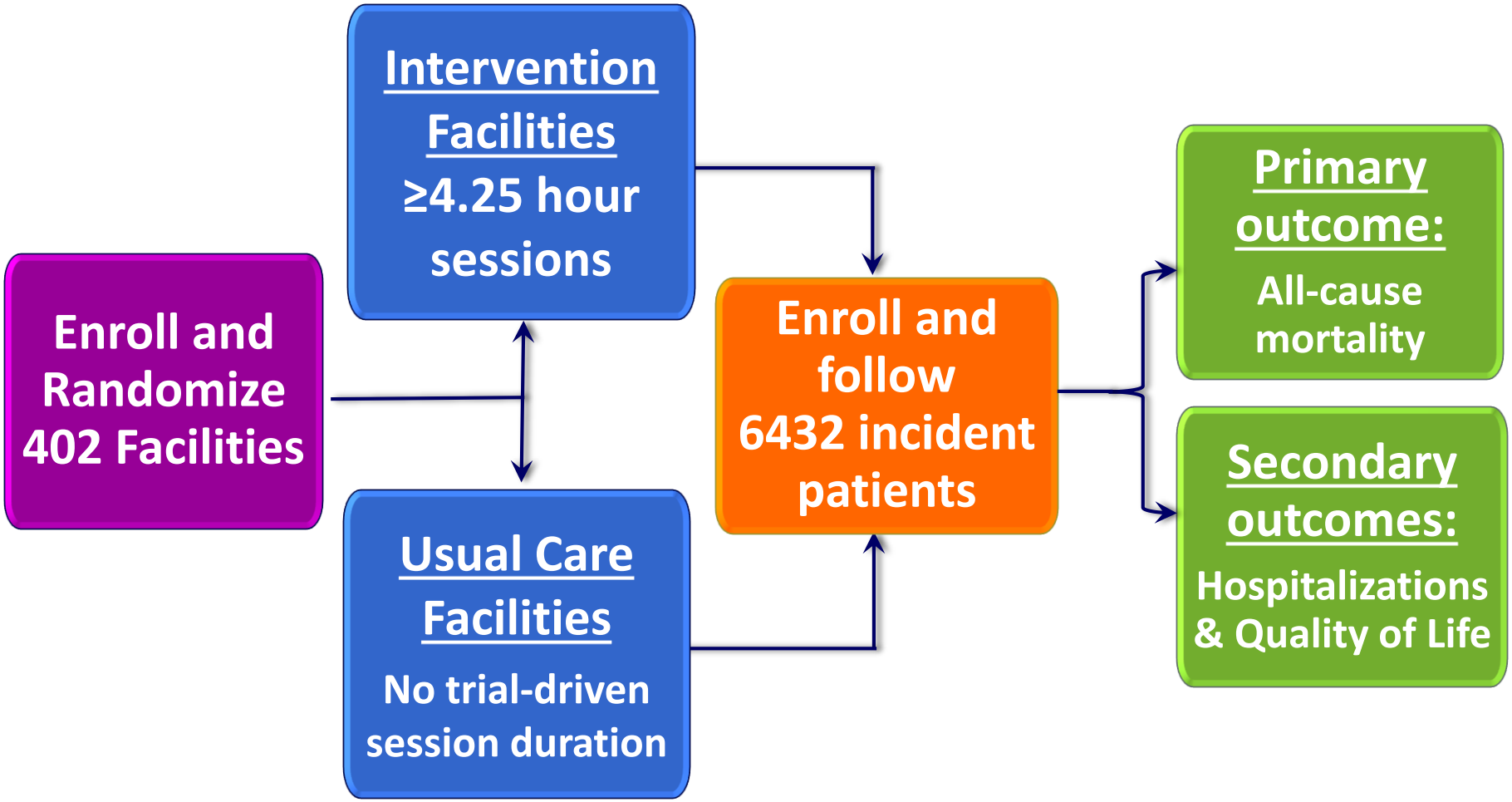
Hypothesis

Facility implementation of ≥4.25-hour dialysis session duration improves outcomes compared with usual care.

TiME Trial Team



Trial Design



Follow-up: 2-3 years

Approach to Consent

- Patients starting dialysis at participating facilities are given a brief information document with:
  - Purpose of the trial
  - How session duration will be affected by the trial
  - Toll-free telephone number to obtain additional information from the research team and to *opt-out* of participation
- Informational posters in participating dialysis facilities throughout the duration of the trial

TiME

Information about the TiME Trial

- This dialysis facility is participating in a national research study called the TiME Trial, sponsored by the National Institutes of Health (NIH). This facility is participating in this clinical trial along with many other dialysis units throughout the country.
- The purpose of
- Because this fac
- Your dialysis fac
- Thank you for r

DaVita.

Frequently Asked Questions About Research and About the TiME Trial

What is a clinical trial?

A clinical trial is a research study in which treatments are evaluated to determine what is best for patients. In order to best compare treatments, clinical trials often involve assignment of patients or treatment centers to a specific treatment approach. Clinical trials help doctors answer a variety of questions about

Whom can I contact if I have questions about this clinical trial?

If at any time you have questions or concerns about this trial, please contact the research team at DaVita using this toll free telephone number: **1-855-557-5813.**

Required Elements of Consent Forms

All Consent Forms

- A statement that the study involves research
- Purpose of research
- Duration of participation
- Description of experimental procedures
- Risks or discomforts
- Benefits
- Available alternatives
- Confidentiality protection

Greater than Minimal Risk Studies

- Compensation for injury
- Research rights
- Voluntary participation

TiME

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Greater than Minimal Risk Studies

- Compensation for injury
- Research rights
- Voluntary participation √

From a Regulatory Standpoint....

Altering Consent = Waiving Consent

Regulatory Criteria for Waiving Consent

1. The research involves no more than minimal risk to the subjects
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects
3. The research could not practicably be carried out without the waiver or alteration
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation

45 CFR Part 46

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45 CFR Part 46

Key Factors for Minimal Risk Determination

- Intervention does not add medical risk
- Physician and patient autonomy are maintained
  - Physicians write dialysis prescriptions
  - Patients have ongoing, frequent contact with physicians
  - Treatment time can be modified at any time
- Research does not change care for patients in Usual Care arm

Two Challenges to Minimal Risk Categorization

1. “How can a trial have minimal risk if the outcome is mortality?”
2. “Randomization always imparts risk because the physician’s contribution to the treatment decision is removed.”

Can the Trial be Minimal Risk if Outcome is Mortality?

Hypothesis: Longer dialysis will improve outcomes

Intervention Facilities

- Intervention might not decrease mortality but there is no expectation that it will increase mortality
- So trial outcome of mortality should not, in and of itself, render the research as greater than minimal risk

Usual Care Facilities

- Trial has no effect on session duration or any other aspects of care
- So, mortality outcome should not render the research as having greater than minimal risk.

Does Randomization Create Risk Regardless of the Intervention?

Concern: physician's contribution to treatment decisions is removed through randomization

<u>Context is important:</u>

- Opportunity for individualization of session duration is preserved in the TiME Trial
- In practice, session durations are driven to a large extent by facility operational considerations rather than physician perspective
  - Facilities have agreed to accommodate longer treatment times for new patients in order to participate in the TiME trial. Perhaps the TiME trial is *increasing*, rather than decreasing, physician's contribution to treatment decision.

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Effect of Consent on Practicability of Research

- Consent would move trial toward determination of efficacy rather than effectiveness
  - We'd end up with highly selected, non-representative patient population
- Since treatment assignment is known at time of participant enrollment opt-in consent would create imbalances in participant characteristics across treatment groups

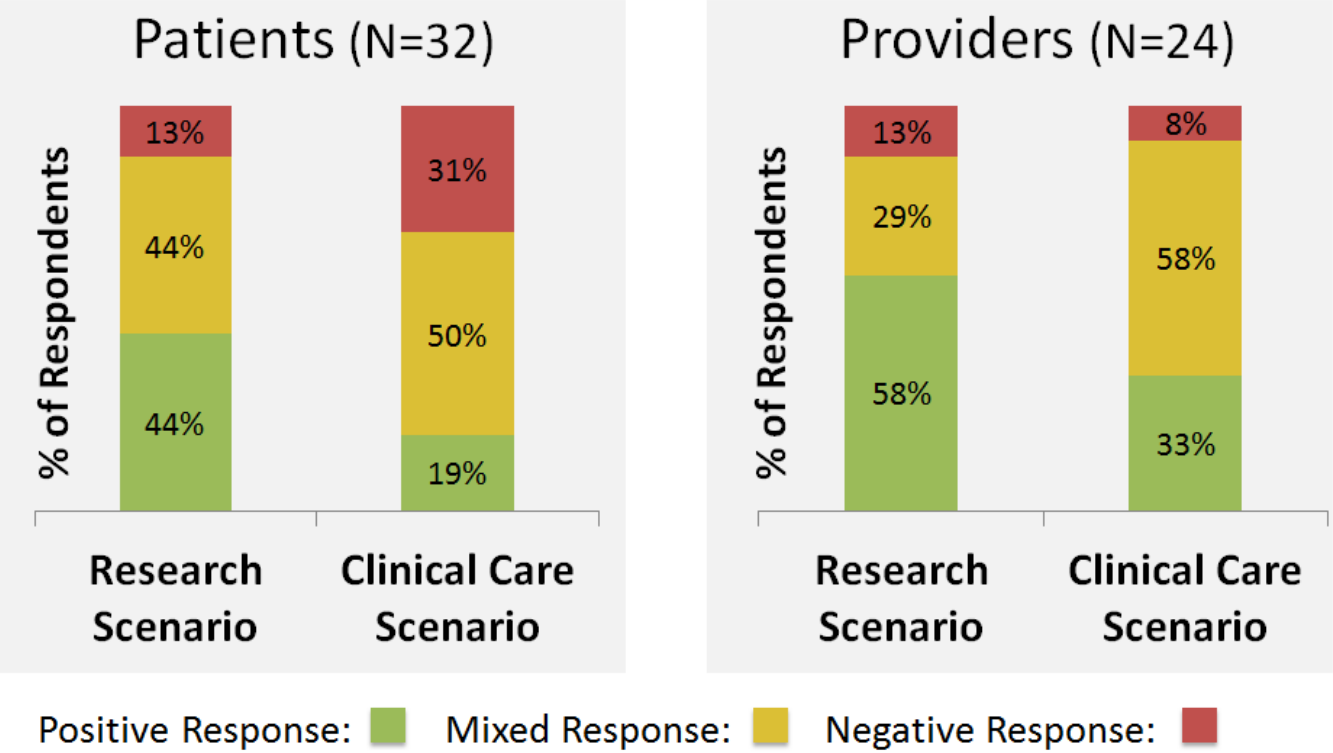
Conclusion: Research is not practicable without the waiver (alteration) of consent

Ethical Considerations

Perspective of investigators, dialysis providers, and IRB

- Informing participants is important
- Goal is to change the default session duration in a way that preserves physician and patient autonomy

What Do We Know From Empirical Ethics Research?



Patients and physicians were as (if not more) willing to relinquish autonomy in the context of research as in clinical care and were comfortable with allowing limitations on decision-making at the individual patient level in research studies

Kraybill, A et al. AJOB Empirical Bioethics 7:106-115, 2016

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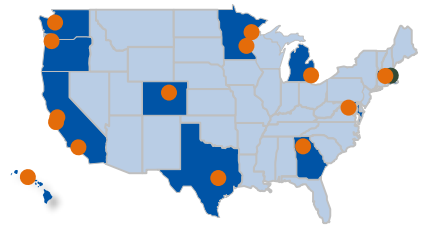

Suicide Prevention Outreach Trial

Defining minimal risk and reasonable informed consent

Gregory Simon MD MPH

Group Health Research Institute

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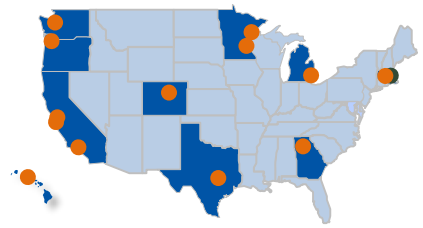

Outline

- Brief description of SPOT pragmatic trial
- How could this trial change or increase risk?
- Our abbreviated/modified consent procedure
- Experience to date
- Lingering questions

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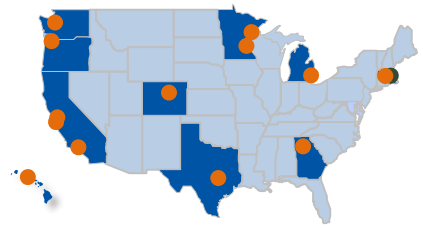

Background

- Suicide is 10th-ranked cause of death – and increasing.
- Increasing use of standard depression scales means we can identify those at risk.
- Moderate evidence for effectiveness in high-risk (tertiary prevention) populations:
  - Care management and risk-based care pathways
  - Behaviorally-oriented skills training
  - Periodic “caring messages” of concern and support
- Increasing attention from health system leaders

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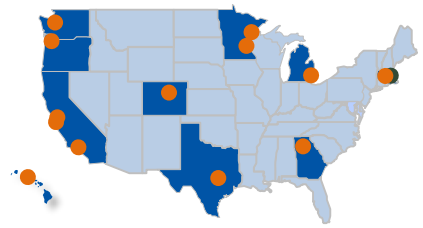

Pragmatic Trial Design

- Weekly automatic identification of patients at risk (using questionnaire data in health system EHRs).
- Automatic assignment to usual care (no contact) or to the **offer** of one of two outreach programs:
  - Care management: assessing risk and facilitating follow-up
  - Skills training: online training program supported by coaching reminders
- Interventions delivered primarily by health system EHR patient portal messaging
- Subsequent suicide attempts ascertained from health system EHR and insurance claims data
- Comparison by original assignment, regardless of level of intervention participation

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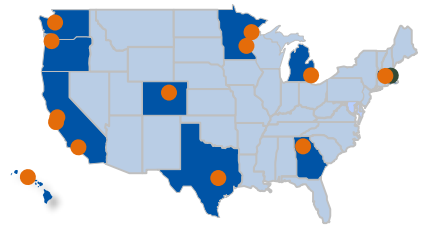

Why a traditional consent procedure won't work

- Our question is about effectiveness of population-based outreach (not effectiveness in those interested in outreach)
- Variable participation is expected and central to the question (It's a feature, not a bug!)
- The pre-consent randomization (modified Zelen design) is not about efficiency – it's scientifically necessary.

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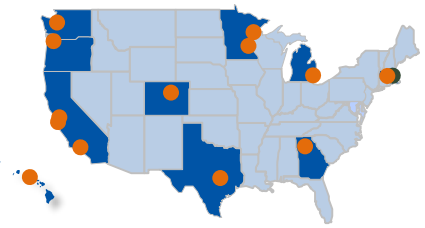

We could have avoided lots of grief….

"We considered and rejected the option of group- or cluster-level randomization (such as randomizing providers or clinics to intervention or usual care conditions). The proposed interventions are applied at the level of the individual patient rather than the provider or clinic, so cross-over or spill-over of intervention effects within clinics or providers should not occur. Consequently, there is no scientific advantage in cluster-level randomization. Cluster-level randomization could, however reduce statistical power. While cluster-level randomization would seem to avoid ethical concerns regarding pre-consent randomization, it only obscures (rather than resolves) the ethical concern. "

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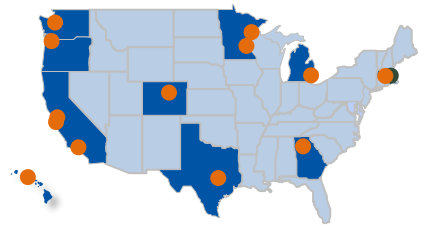

How could this design cause harm or increase risk?

- Use of records data to identify patients at risk
- Random assignment to usual care
- Random assignment to offer of intervention
- Delivery of intervention programs
- Use of records data to ascertain outcomes

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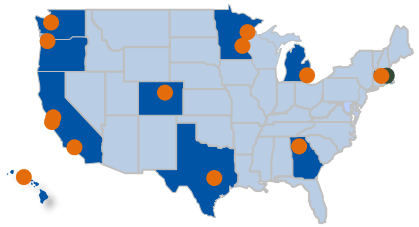

Use of records to identify patients at risk

- IRBs routinely grant waivers for more intrusive use of records data – but affected patients are not informed.
- Some people may object to research use of sensitive info, but how could we know without contacting them?
- The initial invitation is really part of the intervention (a form of “caring message”).
- Completely automating the invitation would increase privacy protection, but isn’t “automated caring” an oxymoron?

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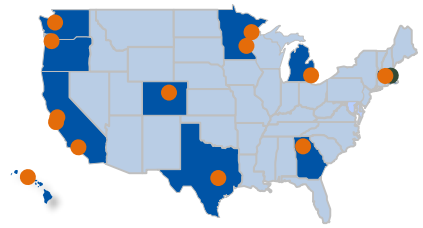

Assignment to usual care

- Concern among various reviewers (IRG, IRB, etc.) about assigning high-risk patients to control or “placebo” group.
- BUT usual care is, by definition, the treatment that would have otherwise occurred.
- Key Point: No treatment usually available would be withheld (or even modified).
- Important to distinguish ethical responsibilities from liability or public relations concerns.

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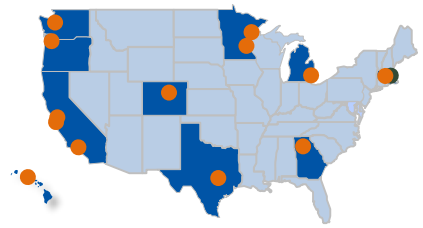

Assignment to offer of intervention

- Intervention contents are based on best-practice recommendations.
- BUT we must acknowledge that average best practice isn't optimal for every individual.
- Key Point: What's randomly assigned is the OFFER of intervention. Participation is voluntary, and content is very transparent.

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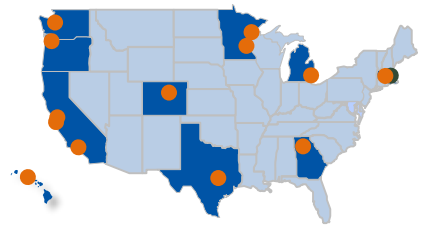

Delivery of intervention programs

- Intensity of outreach must balance beneficence against autonomy/privacy interests.
- Must acknowledge that care of people at risk for suicidal behavior can sometimes be coercive.
- Flexibility and personalization are essential, and that's inherent in pragmatic trials.

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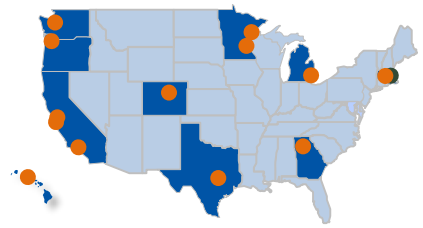

Use of records to ascertain outcomes

- Retention of identifying information is necessary to extract data regarding suicide attempts and suicide deaths.
- Essential to ascertain outcomes for participants declining intervention services.
- IRB required strict separation of data streams for intervention delivery and outcome ascertainment.

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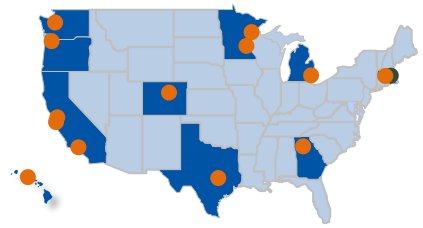

Patient/consumer engagement

- Anonymous surveys of mental health service users
- Online surveys via the Depression and Bipolar Support Alliance
- Research team includes people with lived experience of suicidal ideation and behavior

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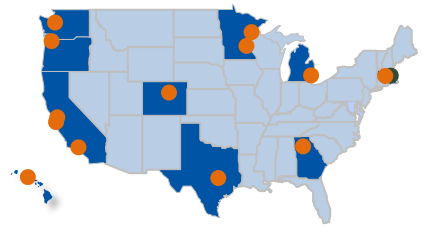

Overall consent process

- Waiver of consent for use of records to identify participants
- Waiver of consent for assignment to usual care or intervention conditions
- Abbreviated consent information at time of invitation to intervention conditions
- Continuing notice that participation is voluntary – with guidelines about intensity of outreach
- Waiver of consent for use of records to ascertain outcomes

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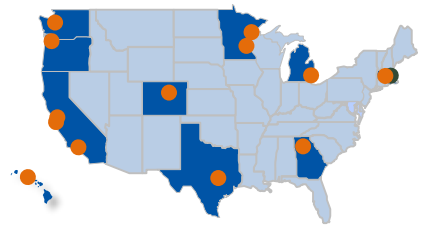

Abbreviated consent with intervention invitation

- Inform that intervention is part of research
- Description of intervention procedures
- Description of incremental risks
- Inform that effectiveness is not proven
- Clear process for declining participation

BUT – Always includes expression of caring and concern:

"I hope you find this program helpful, but if you find it unhelpful or upsetting, you can decide not to participate at any time."

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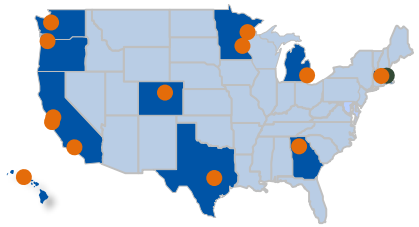

Invitation process:
Balancing beneficence and autonomy

- Invitation message via EHR portal messaging
  - Includes options for agree or decline
  - Reminder if no response after 1 week
- If no response, 2nd invitation 4 weeks later
- If no response, 3rd invitation 4 weeks later
- If no response, do not contact again

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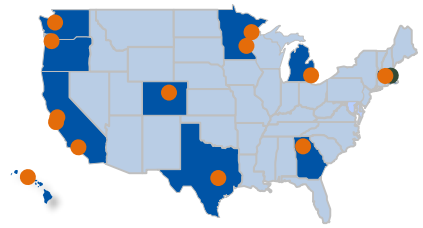

Experience to date

- Approx. 1800 invited to intervention programs
  - 45% actively agree to participate in intervention
  - 20% actively decline
  - 35% do not respond after 3 cycles of invitation

  (recall that invitation really is an intervention)
- Approx. 1% upset by or complain about invitation
  - But about half of those agree/join after explanation

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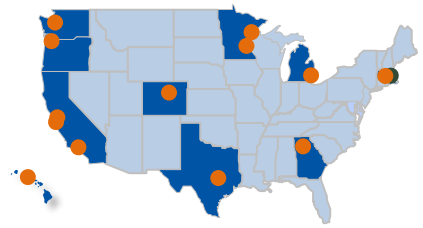

Will the abbreviated consent procedure bias estimates of intervention uptake or effectiveness?

- Invitation messages are less “inviting” than they would be in an actual implementation.
- Abbreviated consent process also introduces some technological “clunkiness”
- Ideally, this would be an empirical question – but it won’t be for now.

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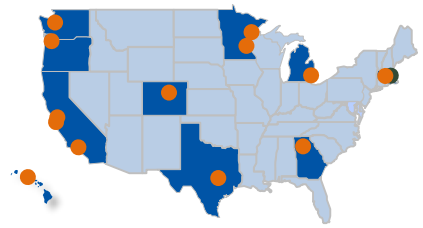

How should we consider average effects vs. distributional effects?

- We hope to demonstrate that intervention programs reduce risk of suicide attempt?
- We already know that some people assigned to interventions perceive harm from use of records data.
- Those benefits and harms accrue to different people.
- Does that matter?

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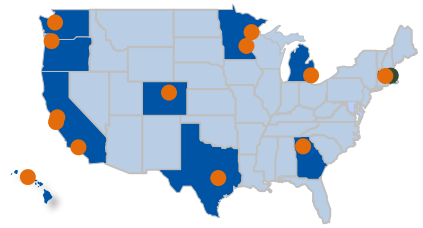

How do we consider the “harm” from using records?

- Harm or injury seems unrelated to random assignment or nature of interventions.
- Does the harm come from the knowing – or the telling?
- How should we balance autonomy/privacy interests against risk of suicide attempt?
- How do autonomy interests apply to de-identified data?

Philosophical and Regulatory Ambiguities

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Children's Mercy Hospital
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Oversight

- HHS/OHRP Common Rule
- FDA
- Single-site IRBs/Central IRBs
- Tort law and criminal law

Ambiguity in many key concepts

- Minimal risk
- Attributable risk
- Altered consent
- Equipoise
- Research vs QI

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)

Key questions

- Is it the risk of daily life for *a particular child?*
  - Sick kids' daily lives are full of risk
    - PK studies on kids with cancer
  - Kids who live in dangerous neighborhoods face greater risks than those in safer neighborhoods.
    - Kennedy-Krieger lead abatement study
  - Some activities are riskier than others
- Or is it some sort of "average" risk?

IRBs must make judgments

- Well-studied differences in how IRBs judge "minimal risk."
- Differences in assessment of
  - Venipuncture
  - MRI
  - Passive consent
  - Many other research interventions

Studies of IRB variability

- Khan et al. Variability of the institutional review board process within a national research network. Clin Peds;2014: 53:556-60.
- Higgerson RA et al. Variability in IRBs Regarding Parental Acceptance of Passive Consent. Pediatrics, 2014
- Hirshon JM et al. Variability in Institutional Review Board Assessment of Minimal-risk Research. Acad Emer Med 2002; 9:1417–20.

What are the risks of daily life?

Sports and minimal risk

Table 2. Physical Risks From Sports in the Daily Lives of Healthy Children Older Than 6 Years*

	Risk per Million Instances of Participation				
Sport	Total Injuries	Permanent Disability	Total Level-IV Injuries†	Surgeries	Broken Bones
Football	3800	42	500	270	910
Soccer	2400	38	300	NA	NA
Basketball	1900	58	300	160	180
Cheerleading	1700	NA	100	NA	NA
Baseball	1400	61	300	120	30
Skateboarding	800	NA	200	20	170

*Data from American Sports Data Inc.

Level IV injury – those resulting in emergency department visit, hospitalization, ongoing physical therapy, or that prevent participation in sports for >1 month.

Wendler et al JAMA 2005

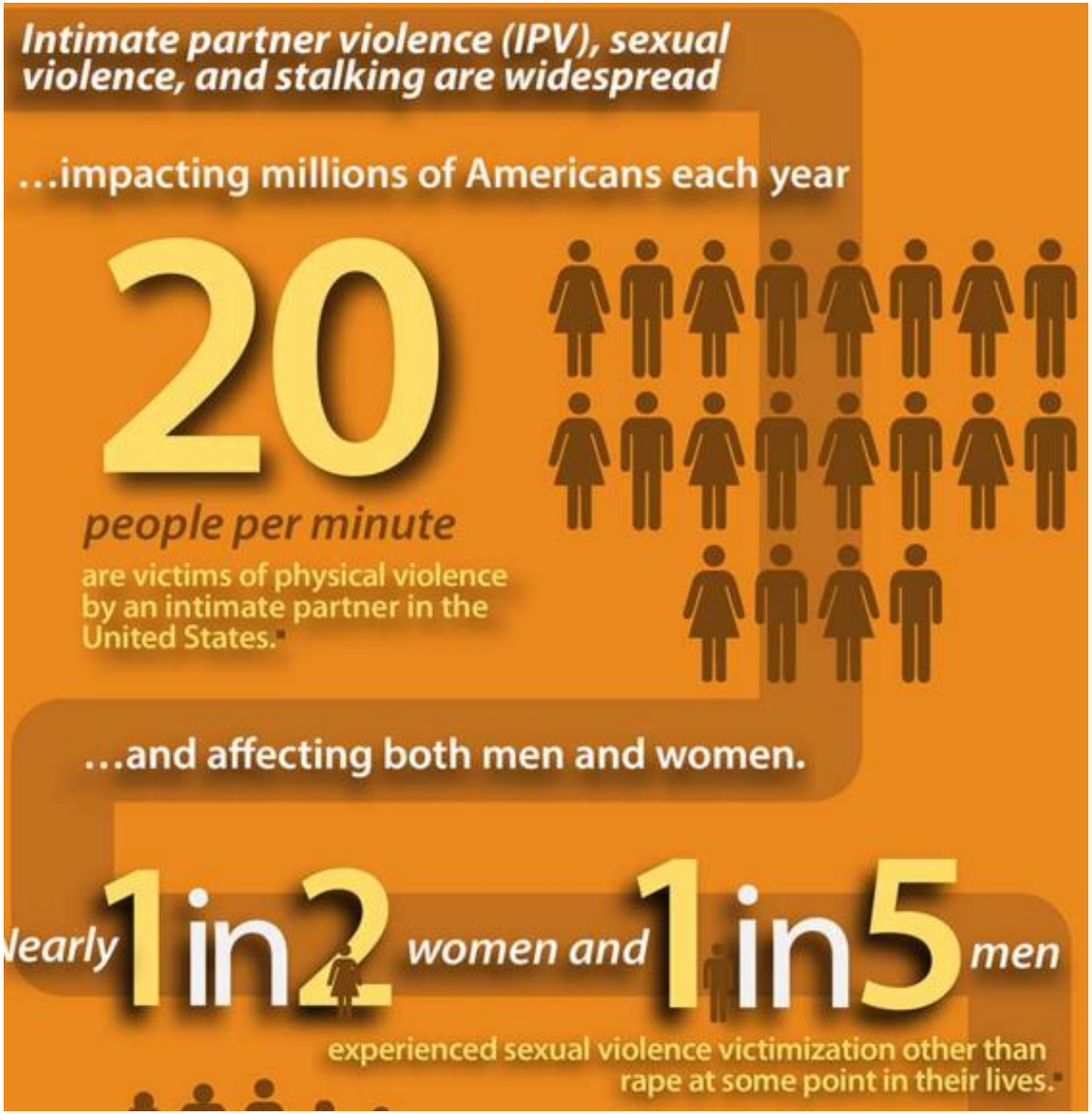
Table 3. Psychological Risks in the Daily Lives of Healthy Children*

Risk	%				
	Never	Almost Never†	Sometimes	Often†	Almost Always
Feel scared or afraid	56.2	13.8	27.4	0.9	1.7
Feel sad or blue	57.7	15.5	25.1	1.0	0.7
Have trouble sleeping	68.6	12.6	15.4	1.4	2.0
Worry what will happen	53.1	13.7	26.2	2.7	4.3

Table 4. Cumulative Risks in the Daily Lives of Healthy Children, by Age Group*

Harm	Cumulative Risk per Million Children per Day				
	<1 y	1-4 y	5-9 y	10-14 y	15-19 y
Death	1.5	1.5	1.4	1.4	10
Hospitalization	1.0	1.3	1.7	2.1	6.0
Emergency department visit	6.4	16.4	26.0	36.1	64

Wendler et al JAMA 2005



http://www.cdc.gov/violenceprevention/nisvs/infographic.html

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Minimal risk

- Whatever “minimal risk” means in the context of research, the threshold is much lower than the actual risk of daily life.

Studies classified as minimal risk

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

Area 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 impossible to do with consent, not because it is minimal risk.

Attributable risk

- In pragmatic research, are the risks of the interventions being studied risks of the research?
  - 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

- "The reasonably foreseeable risks of research include already-identified risks of the standards of care being evaluated as a purpose of the research."

  – http://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-disclosing-risk-in-standards-of-care/index.html

Waiver or alteration of consent

Elements of standard consent

- The study involves research
- Purposes of the research
- The expected duration of the subject's participation
- A description of the procedures to be followed
- Identification of procedures which are experimental
- Reasonably foreseeable risks, discomforts, benefits
- Disclosure of alternatives to participation
- A statement of how confidentiality will be maintained
- Any compensation for injury
- A contact person
- A statement that participation is voluntary,

Alterations

- Short form without all elements
- Deferred consent
- Notification/opt-out rather than consent
- Pre-randomization

OHRP criteria for waiver

- No more than minimal risk;
- No adverse affect on rights and welfare;
- Research not practicable without waiver;
- Additional information after participation;

FDA Scenarios For Possible Waiver

- The FDA permits clinical investigation without informed consent in some circumstances:
  - One-time Emergency Exemption for Investigational Drug, Biologics, and Devices
  - Exception for Planned Emergency Research
  - In Vitro Diagnostic Device Studies Using Leftover Human Specimens Not Individually Identifiable
  - The U.S. President may waive informed consent for military personnel

For all practical purposes…

- An alteration of consent first requires a waiver of the standard consent requirements – and so, any alterations must meet the criteria for waiver.
- Standards are strict and somewhat precise, but with significant ambiguities.

QI as minimal risk research

- Project to prevent central line infections.
- Step-wedge design: Different hospitals will implement intervention at different times.
- Each hospital will be its own control,
- Analysis will pool “before” and “after”

Intervention

- MDs/RNs will be taught five procedures:
  - Hand washing,
  - Using gowns, masks, and gloves during CL insertion
  - Cleaning the skin with chlorhexidine
  - Inserting these lines anywhere except the groin if possible
  - Quickly removing the CLs when no longer necessary.
- All currently recommended by CDC.

Intervention

- Five interventions to help staff
  - Educational session about central line infections.
  - A “catheter insertion cart” with instructions and equipment;
  - A checklist for the five activities.
  - RN/RA will ask, every day, whether to remove CL.
  - RNs may stop a CL-insertion procedure if they observe a violation of the guidelines.

Questions

- Is it research?
- Is it minimal risk?
- Is there equipoise?
- Can it be done without IRB approval?
- Can it be done without participant 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

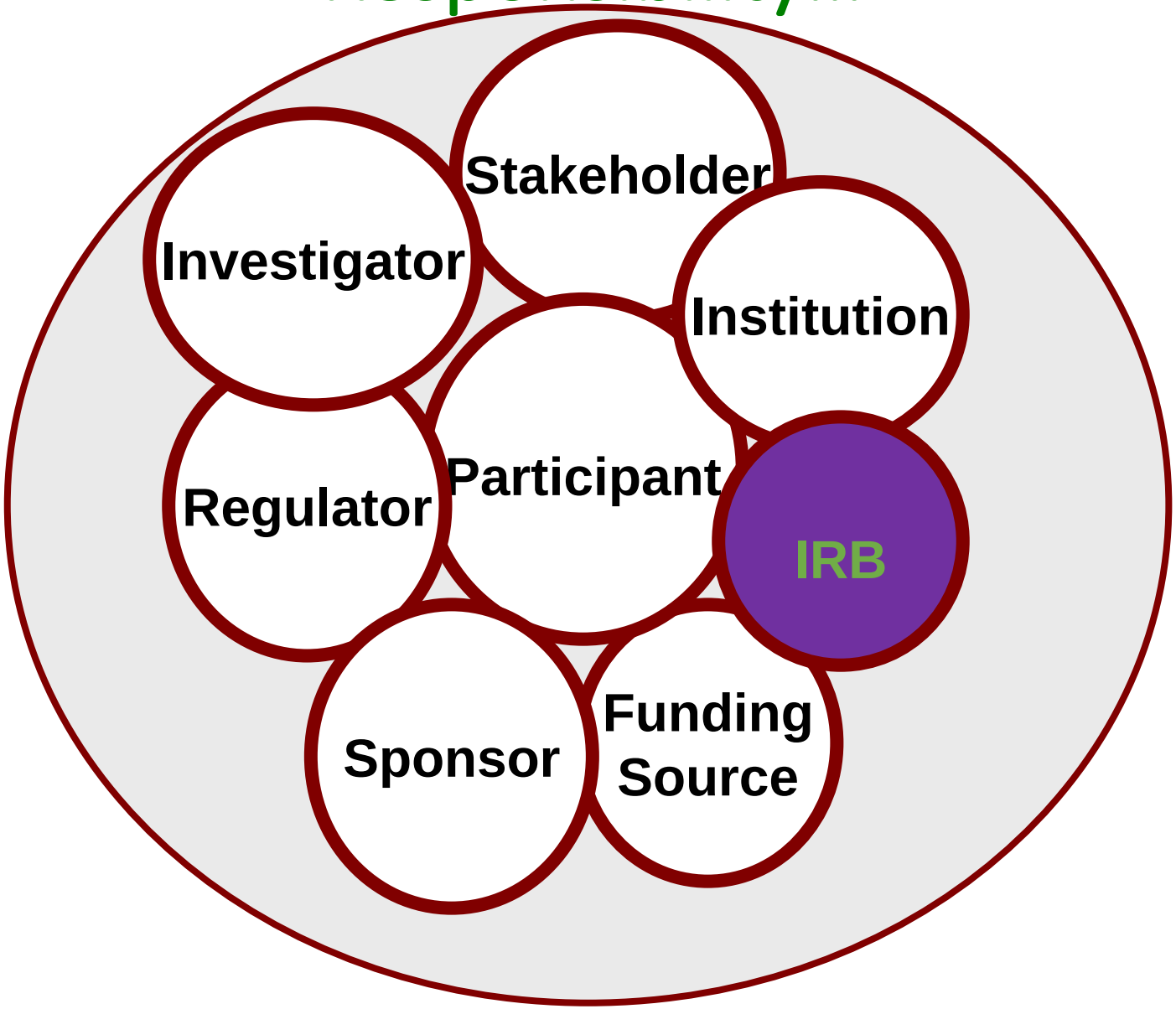
IRB Review of Pragmatic Clinical Trials

Emma A. Meagher, MD

Associate Vice Provost, Human Research

University of Pennsylvania

Human Subjects Protection Is a Shared Responsibility…



The Challenge for IRBs

- Apply regulations (45CFR46 & 21 CFR 50) that were developed for a different environment and are intended to protect participants and provide for data integrity

- PCTs are typically designed by academic clinician scientists in academic health care centers who are striving to identify the best treatment practice, amongst those routinely practiced by health care providers, through the acquisition of rigorous data

- PCTs are dependent upon the evaluation of streamlined clinical care algorithms occurring in the real world setting of patient care and they often deploy cluster randomization

- Recognize that, though the purpose is to validate clinical practice, the patients are research participants who are afforded protections commensurate with risk and have their autonomy preserved

PCTS By Nature Are Diverse – They May Differ In

- Type of intervention
  - Medical
  - Technological
  - Behavioral
- Complexity of study design
- Target of intervention
  - Patients
  - Trainees/healthcare providers
  - Systems/processes/algorithms
  - Direct plus indirect participants
- What constitutes the study team

This necessitates a very careful and rigorous review by experienced IRBs who are required to apply and sometimes interpret the ambiguity of regulation

IRB Decision Matrix

BENEFICENCE

Maximize benefit and minimize harm

Risk/Benefit Analysis
Experimental Design
Qualifications of PI

JUSTICE

Fairness in selection of subjects

Subject selection
Inclusion/exclusion
Population of inference

RESPECT FOR PERSONS

Recognize and respect individual autonomy and protect those with diminished autonomy

Informed Consent Process

Privacy & Confidentiality
Special Protection for Vulnerable Populations

IRB Review of PCTs - Beneficence

- Have investigators established that the interventions are within the limits of accepted clinical practice?
    - How extreme within the limits of practice are the groups?
    - Is affirmation of that assertion by a consultant/expert advisable?
    - Does the experimental design include any titration/alteration of the interventions?
    - Is usual care constrained?
    - Is individual or cluster randomization occurring?

- What are the burdens or harms (attributable risk) and benefits to the participants?
    - If the purpose of the study is to answer the question which treatment is better how can you know this?

- How are participants informed of the nature, harm, burden and benefit of clinical care interventions?
    - Is a clinical consent process occurring?

IRB Review of PCTs – Justice

- Have the investigators justified the study population?
- Is the study population likely to be the target populations?
- Is the burden of the research disproportionally borne by a section of the population?
- Are vulnerable populations being included?

IRB Review of PCTs – Respect for Persons

- How will participants be informed that they are being asked to participate?
  - Is an individual informed consent process planned?
  - Is a waiver of informed consent or an altered consent process being sought and if yes is it acceptable?
  - Is it appropriate to have stakeholder /gatekeeper engagement?
- How will participants be informed of the burdens, potential harms and benefits of participation?
- How will they be informed of the alternatives to participation?
- If patients decline participation and a cluster randomization is being used how will they receive clinical care?

If Individual Consent Is Planned What Should Be Disclosed?

- Purpose
  - Here is what is known, here is what is not known, the purpose of this research is to find out..
- Methods and procedures
  - Here is the experimental approach we will take … this would include a description of the standard care algorithms being compared and for how long participation will last
- Risks, burden and benefits
  - Risk versus attributable risk
- Alternatives
  - Access to care outside of being a participant in this PCT
- Confidentiality provisions

What Does the IRB Consider When a Waiver of IC is Requested?

- Is the research no greater than minimal risk?
- Is obtaining informed consent considered impracticable?
  - Scientific validity
  - Feasibility
- Does the provision of a waiver or alteration adversely affect the rights and welfare of the subjects?
- If appropriate, will participants be provided with additional pertinent information after participation?
- Does the research fall under the purview of FDA?

What About the Options of Altered Consent?

- Altered consent is a confusing term because in essence it means that there exists a waiver of some element of traditional informed consent.

- For example some studies allow for consent to be required for some activities involved in the research plan

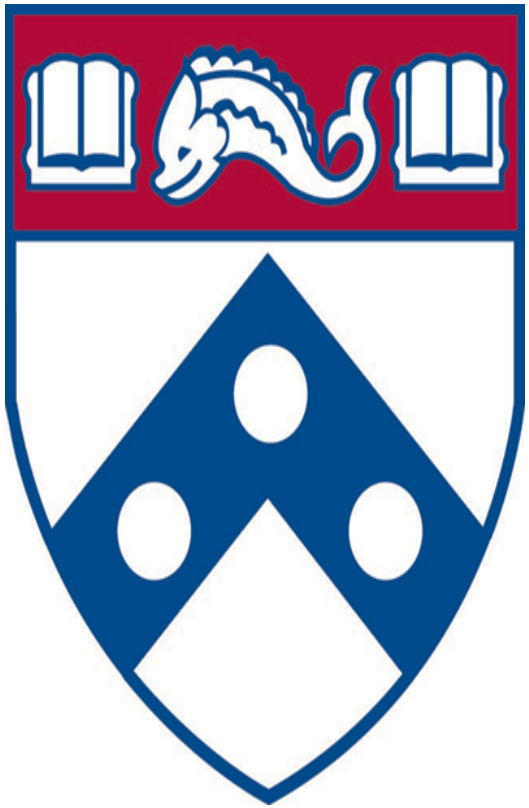
  - Waive consent for access to data
  - Waive consent for access to the EMR for eligibility determination
  - Require consent or an abbreviated consent to access EMR for outcome assessments or at time of randomization

- There are other methods whereby participants can learn about the elements of the study in advance of the study and be provided the opportunity to opt out

Interpretation of Regulations & Guidance Presents Challenges for IRBs

- Beneficence
  - If the purpose is to identify which approach is better how can you assess risk vs. benefit?
  - If a measured outcome is death does it mean the study is greater than minimal risk?
  - Are we correct in assessing risk as a function of attributable risk only?
  - If the multiple IRB reviews are occurring will that lead to differing assessments?
  - Does randomization automatically adversely affects the rights and welfare of participants?
  - If you consider there may be higher risk in one arm can you assume there is by default a lower risk in the other – is that any different from what occurs in clinical practice?
- Respect For Persons
  - Should the concept of “practicability” only consider scientific validity or also consider feasibility
  - Should consideration of the expertise at the site enter into determination of practicability

Thank you!



Questions and Answers

Please submit questions for the panelists to:

EthicsofPragmaticTrialsWkshp@mail.nih.gov