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Research in disenfranchised and vulnerable populations: What are the special challenges?

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Introductions

- A little bit about you and your research
- Your goals for this session / particular issues you would like to discuss as a group

To frame conversation - Meet Mr. B

62 years old, multiracial, homeless man

- **Income** – recycles cans
- **PMHx:** DM2, COPD, CHF
- **Geriatric syndromes:**
  - Falls: 3 in 3 months - doesn't know how or why
  - New onset urinary incontinence
- **Substance use:**
  - Tobacco (scavenged butts), ETOH, crack but "I just don't get the same pop from it anymore"
- **Arrested for public urination and drug possession**
  - When trying to explain health problems to arresting officer was charged with resisting arrest
  - Sentenced to 60 days in jail

Explore challenges in conducting research with vulnerable populations

…Thru the lens of Mr. B's participation in the Healthy Aging SF Study

- **The Healthy Aging SF Study is an epidemiologic longitudinal pilot study to:**
  - Describe symptoms in older jail inmates
  - Assess the relationship between symptoms, functional decline and community ER use over time
- **Basic study design:**
  - Participants are enrolled soon after they arrive in jail
  - Participants check-in one week after release from jail
  - 6 Monthly follow ups (in jail or in the community)

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1. **Define the term “vulnerability”**
2. **Discuss early critical steps in research with vulnerable populations**
   - Anticipate needs for IRB / CHR approval
   - Consider how to build and train a research team
3. **Identify special considerations in study design**
   - Approach and intake
   - Informed consent
   - Use of incentives
   - Other retention strategies
   - Handling unanticipated events
4. **Discuss some challenges and strategies in dissemination of research findings**
5. **Benefits of this research**

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Some questions for you

1. Do you work with “vulnerable populations”?
2. Do you conduct research with “vulnerable participants”?
3. What makes them “vulnerable”?

What are "vulnerable populations?"

Many definitions (they all boil down to access to care/health disparities)

- **The U.S. Centers for Disease Control:**
  - Racial and ethnic minorities, and others defined by SES, geography, gender, age, disability, risk status related to sex and gender, and others who are at-risk for health disparities

What are "vulnerable populations?"

Many definitions (they all boil down to access to care/health disparities)

- **The U.S. Centers for Disease Control:**
  - Racial and ethnic minorities, and others defined by SES, geography, gender, age, disability, risk status related to sex and gender, and others who are at-risk for health disparities

- **How does this differ from the definition of vulnerability in research?**

The history of “vulnerability” in research

Nuremberg Trial (1946-1947)

- Nazi human medical experimentation went on trial
- Led to the Nuremberg Code (1949)
  - Established first international guidelines for treating human research participants

…Code begins the conversation about "vulnerable research participants"…

- **Nuremburg Code (1949)**
  - Marks first introduction of the concept of protecting *vulnerable populations* in research
  - But "Vulnerability" is not defined
    - Simple recognition that some people are not able to give true consent

Over time the need for mandatory research guidelines evolves…

The Tuskegee Syphilis Study spans 1949 (1932-72)

- **Prompts release of Belmont Report (1979)**
- **Outlines mandatory guidelines for research involving human subjects**
  - Focused on 3 core principles:
    - Respect for persons (autonomy)
    - Justice (reasonable, non-exploitative)
    - Beneficence ("do no harm")

The Belmont Report defines "vulnerable research participants"

- **Vulnerable research participants:**

  "Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may be sought as research subjects, owing to their ready availability in settings where research is conducted….have to be protected…

- Emphasizes the importance of significantly limiting research in vulnerable populations

Decade following Belmont Report (1980s) AIDS epidemic spreads in the U.S.

- **AIDS – the "gay plague" stigma and discrimination in a vulnerable population**
- **Medical professionals reluctant to study AIDS**
- **Government ignores epidemic**
- **ACT UP is formed (1986) demanding:**
  - Access to experimental drugs
  - More patients with HIV in more clinical trials…

"Vulnerable" population advocates for their inclusion in research

Legacies:

1. **Push for liberalized access** to potentially life-saving but experimental (high-risk) drugs

1. **Relaxation of protective stance towards "vulnerability" in participants since it can cause** inequities in availability of medical treatments (e.g., no children in research = no pediatric drugs)

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Where we are today

- **The current NlH definition of vulnerability**

  "Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectations of benefits associated with participation or of a retaliatory response from senior members of a hierarchy in case of refusal to participate"

How do we operationalize the NIH definition of vulnerability?

1. **At its core, definition is about willingness to volunteer and protecting those who are**:
   - Unduly influenced by expectation of benefits
   - Unduly influenced by expectation of retaliation

2. **According to NIH, 1 factor alone rarely defines vulnerability except for:**
   - Pregnant women, human fetuses and neonates
   - Prisoners
   - Children

3. **Some IRBs will identify "special" research populations:**

   Students; investigator's staff; dementia; terminally ill

Instead of pre-determined "vulnerable populations,"

researchers are encouraged to consider

all potentially relevant factors

intrinsic (participant)

and extrinsic (environmental)

to make their own determination of vulnerability

Examples of *potentially relevant* intrinsic and extrinsic factors in determining vulnerability

Vulnerability

Willingness to volunteer unduly influenced by:

- Expectation of benefits
- Expectation of retaliation

Intrinsic:

Extrinsic:

Examples of *potentially relevant* intrinsic and extrinsic factors in determining vulnerability

Vulnerability

Willingness to volunteer unduly influenced by:

- Expectation of benefits
- Expectation of retaliation

Intrinsic:

- Race/ethnicity, gender identity, sexual orientation, Income, educational attainment, SES
- Low literacy / low health literacy
- Health status / serious illness
- Vocation, housing, legal status

Extrinsic:

- What does the study require?
- Where does the study take place?
- Who is conducting the study?
- Could participation put an individual at risk of retaliation?
- How does the research relate to the standard of care?

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First critical steps - special IRB subject sections for vulnerable populations

Inclusion of Children in Research

This study will enroll children who can legally consent for themselves:

○ Yes ○ No

If **yes,** explain why they can consent for themselves in the research setting:

If you will **ONLY** be enrolling children who can legally consent for themselves, press **SAVE and CONTINUE** to skip the rest of this section.

Select all the regulatory categories that apply:

- ☐ No greater than minimal risk (45 CFR 46.404, 21 CFR 50.51)
- ☐ Greater than minimal risk but presenting prospect of direct benefit (45 CFR 46.405, 21 CFR 50.52)
- ☐ Greater than minimal risk (though only a minor increase over minimal risk) and no prospect of direct benefit but likely to yield generalizable knowledge about the subjects disorder or condition (45 CFR 46.406, 21 CFR 50.53)
- ☐ Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407, 21 CFR 50.54)

Explain why the research in this study falls under the above category or categories:

Special IRB subject sections

Children Who Are Wards of the State

It is appropriate to enroll wards in this study because:

Inclusion of Non-English Speaking Subjects

Indicate which method(s) you will use to consent non-English speaking subjects:

- ☐ Preferred Method—Consent form and other study documents will be available in the subject's primary language Personnel able to discuss participation in the patient's language will be present for the consent process.
- ☐ Short-Form—A qualified interpreter will translate the consent form verbally, and subjects will be given the Experimental Subject's Bill of Rights in their primary language, following instructions in Those Who do not Read, Speak or Understand English for required witnessing and signatures

Explain how you will maintain the ability to communicate with non-English speakers throughout their participation in the study:

Inclusion of Pregnant Women, Fetuses, and/or Neonates

Review the regulatory categories and identify all sections of 45 CFR 46 Subpart B under which you believe the research falls and provide study-specific information showing why the research falls within those sections:

Most restrictive rules in special populations: Inclusion of prisoners

Inclusion of Prisoners

Select all the regulatory categories that apply:

- ☐ Study of the possible causes, effects, and processes of incarceration, and of criminal behavior. The study must present no more than minimal risk and no more than inconvenience to the subjects. (45 CFR 46.306(2)(a))
- ☐ Study of prisons as institutional structures or of prisoners as incarcerated persons. The study must present no more than minimal risk and no more than inconvenience to the subjects. (45 CFR 46.306(2)(b))

- ☐ Research on conditions particularly affecting prisoners as a class (e.g., vaccine trials and other research on hepatitis; or research on alcoholism, drug addiction, and sexual assaults, which are all more prevalent in prisons than elsewhere). Special approval must be granted by DHHS. (45 CFR 46.306(2)(c))
- ☐ Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners to control groups which may not benefit from the research, special approval must be granted by DHHS. (45 CFR 46.306(2)(d))
- ☐ HHS Waiver, Federal Register June 20, 2003 (68 FR 36929): Prisoners may be included in epidemiologic research in which the sole purposes are to describe the prevalence or incidence of a disease by identifying all cases or to study potential risk factor associations for a disease. The study must present no more than minimal risk, present no more than inconvenience to the subjects, and prisoners must not be a particular focus of the research.

IRB may sometimes require special panels to review vulnerable population research

Prisoner example:

1. **A majority of the IRB shall have no association with the prison(s) involved.**

2. **At least <u>one member of the IRB must be a prisoner, or a prisoner representative</u>**

3. **Additional OHRP (Office of Human Research Protection) review for NIH-funded prison health studies** - Certification to make sure that regulatory provisions are met

IRB may ask for a Certificate of Confidentiality

- **Document issued by the NIH**
- **Allow investigator to refuse to disclose information on research participants in any:**
  - Civil
  - Criminal
  - Administrative
  - Legislative, or other proceeding, whether at the federal, state, or local level
- **Goal is to promote participation in studies by helping assure confidentiality and privacy to participants**

The bottom line: IRBs and vulnerable populations

- **IRB requires special steps for a few predetermined "vulnerable populations"**
  - But vulnerability is not limited to these populations
  - The trends in IRBs is that there is greater and greater concern with vulnerability in research
  - Many IRBs consider persons with serious or terminal illness to be a "vulnerable" or at least a "special" research population
- **As we develop studies for IRB approval, we need to be constantly thinking through how to mitigate vulnerability in study design**

First critical steps - Building and training a research team

Objectives in building a team:

- Rapport/relate-ability, Comfort discussing difficult topics, active listening skills, etc.

Training a team:

- Real world, practical experience prior to study:
  - Senior Ex-Offenders Program staff conducted practice interviews with our research staff
  - Feedback to staff on what they need to change or unexpected landmines

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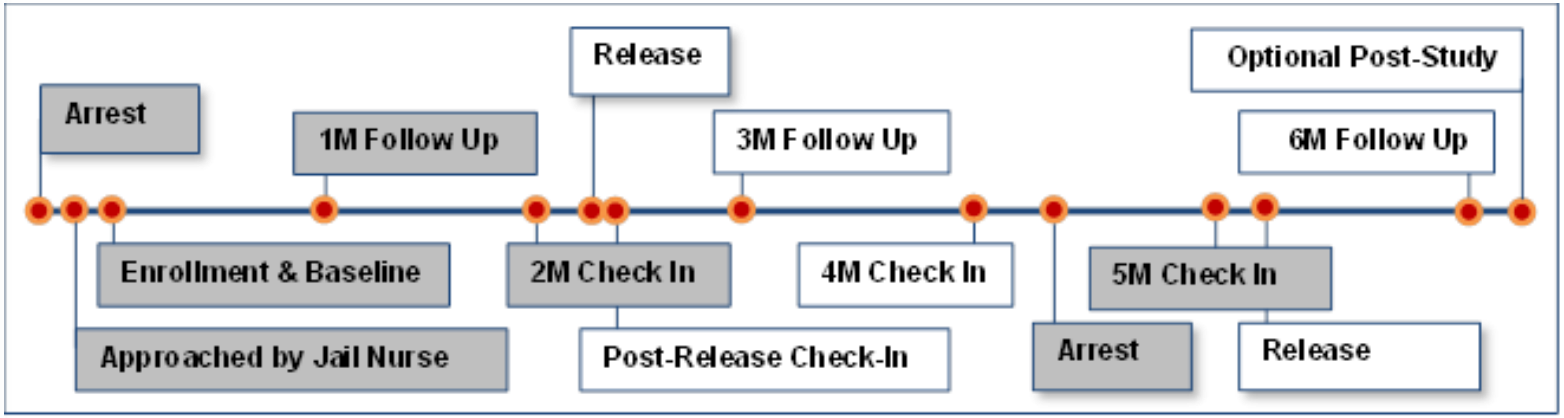
4. Discuss some challenges and strategies in dissemination of research findings
5. Remind ourselves that research with vulnerable populations is often worth the effort

Designing a study for vulnerable subjects

Mr. B's 6 months in the Healthy Aging SF Study



Study design: approach and intake Questions for you

- **<u>Timing</u> of approaching participant about study**
  - *"Timing is everything"*
  - What are some special considerations in the timing of approaching potential participants about a study?
  - How do you identify those considerations before launching the study?

Study design: approach and intake

- **Timing of approaching participant about study**
  - A jail nurse called our study offices, “Mr. B said he wasn’t interested then, after a day in jail, he said he was interested ONLY if it didn’t mess with his court case.”
  - We found the vast majority get through court within 48 hours
  - Designed our study so that intake starts at 48 hours after admission to jail

Study design: approach and intake Questions for you

- **Location of interview**
  - *"Location, location, location"*
  - Can mean the difference between an in-depth response to questions or simple yes/no answers and shrugs
  - Has this been an issue in your studies? How have you addressed this issue?

Study design: approach and intake

- **Location of interview**
  - The nurse says Mr. B wants to hear more about the study
  - Mr. B only wants to be interviewed if other inmates cannot see him speaking to a study staff member
  - Clear that we needed both a confidential, private room and also a closed-door interview room out of view of any other inmates

Study design: Informed consent Questions for you

- **Consent form**
  - How do you approach consent in your studies?
  - Have you used modified consent forms in your studies?
  - What was your experience? Was it time consuming? Useful?

Teach-to-Goal Modified Informed Consent is used to address poor comprehension

- **Iterative, educational process**
  - To assess and improve consent comprehension in vulnerable populations with limited literacy
- **The basic steps:**
  1. Participants are read consent form (usu 6th grade level)
  2. Asked to describe procedures or answer questions about study
  3. Misperceptions are corrected before consent
- **Promoted by National Quality Forum and Agency for Healthcare Quality and Research**

McCrady, Bux, 1999; Zetola, et. al, 2008; Coyne, et. al, 2003; Sudore, et. al, 2008.

Study design: Informed consent

Consent form – written at less than 6th grade level

- Interviewer reads form to Mr. B
- Then interviewer asks Mr. B 10 true / false questions... "To make sure I explained everything I need to explain. If you get one wrong, it's because I didn't go over it well enough and we'll go over it again."

job in explaining the study well enough.

Ask all the questions and record the participant's "1st try" responses (T, F, or IDK). When you have finished asking all of the questions once, return to questions that were answered incorrectly. Review the relevant sections of the consent forms and then repeat the question(s). Repeat for 2nd and 3rd tries.

If a participant is unable to answer one or more of the questions correctly on their 3rd try (i.e. after reviewing the correct answer twice), say: "**I am sorry but only patients who can correctly tell us what this study is about can be in it. But thank you for taking the time to hear about the study.**"

Before each statement, be sure to say the phrase: "True, False, or I Don't Know."

1. **True, False, or I Don't Know: The reason for this study is to know what kind of healthcare services older people need when they're leaving jail and reentering the community.**

   Answer: *TRUE*

1st Try	2nd Try	3rd Try	Could Not Complete

   Relevant section from the Consent Form: *Why is this study being done? (Page 1).*

2. **True, False, or I Don't Know: Anybody can participate in this study.**

   Answer: *FALSE*

1st Try	2nd Try	3rd Try	Could Not Complete

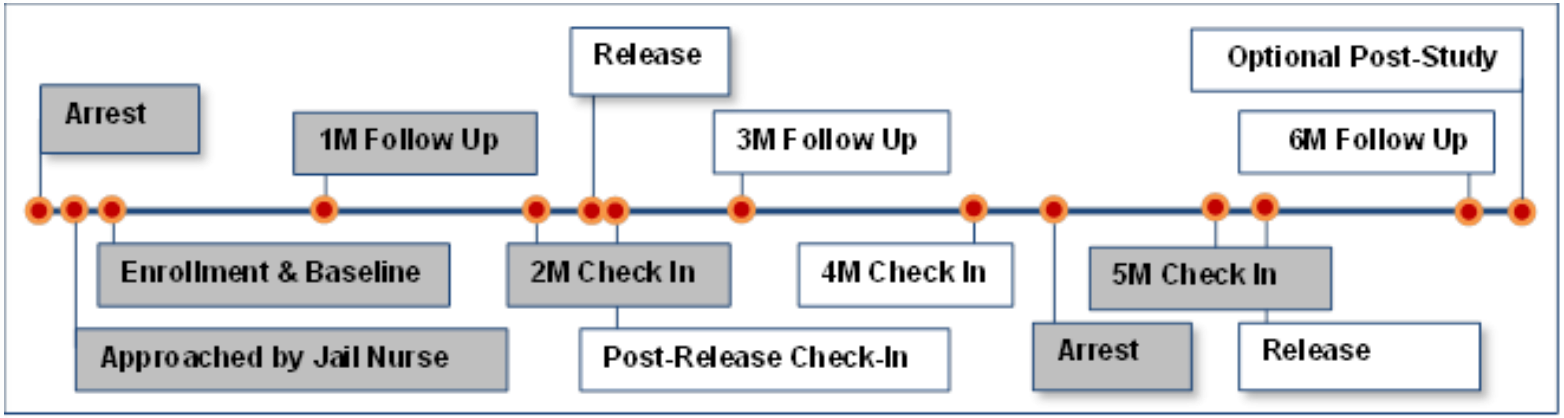
   Relevant Section from the Consent Form: *Introduction (Page 1), You are being asked to take part in this study because....*

Mr. B's teach-to-goal consent process

Mr. B gives wrong answer to: *"Are their risks to participating in this study?"*

- **Mr. B:** "Those aren't real risks to me"
- **Interviewer:** "OK, but I have to make sure that I've reviewed all the important information with you. Let's look back at the Consent Form where they talk about risks."
- **Interviewer:** "Here," (she points to the text). "We're saying information about you and your health could get out if you join this study. If that happens, it's possible that people will know things about you that you might not want them to know. Even if you're not worried about it, we think this is real risk. Do you want to talk about this or do you have any questions about this?"
- **Mr. B** says no. Interviewer asks question again, Mr. B says "there are risks even if I'm not bothered by them" and he selects "True"

Study design: Incentives



- **Incentives to participate**
  - Considerable debate about the ethics of this issue
  - What do you do in your studies?
  - Do you find incentives to be fair? Problematic? When?

Ethical considerations offering incentives in vulnerable populations research

Incentives:

- A benefit to motivate to action (employee bonus for productivity)
- A compensation which makes up for a loss (per diem for jury duty service)
- Considered alternative to other forms of power –
  - Persuasion (undue influence)
  - Coercion (threat of harm)
- **Incentives *themselves* are not considered an ethical problem per se but they can become problematic…**

How should we think about incentives?
An ethical framework for considering incentives

Altruism is the ideal

- A free gift of time to unknown others
- Rare – the supply of these types of volunteers do not meet demands of medical research

Think about incentives using 3 established principles that guide research (Belmont Report):

- Respect for persons (autonomy)
- Beneficence (Do no harm)
- Justice (reasonable non-exploitative)

QUESTION TO ASK YOURSELF:

Does using incentive alter ethical judgments in any of these areas?

Grant RW, Sugarman J. Ethics in Human Subjects Research: Do Incentives Matter? Journal of Medicine and Philosophy, 29(6): 717–738, 2004

A framework for considering incentives – Respect for persons

Respect for persons: Autonomy, focus - decisions are made that are free of undue/coercive influence

- Generally framed in the example of offering monetary incentives to homeless participants
  - **Coercion**: Even a small amount of money could operate like coercion (make a judgment against his/her will). Therefore, be wary of offering incentives to vulnerable populations
  - **Free choice**: Coercion side of the debate is paternalistic. The scenario is about inequality not coercion. The desire to have the money more than anything else is free choice. To deny the destitute an opportunity offered to wealthy denies their liberty (and their autonomy)
- Most hotly debated / unresolved ethical debate
  - Little motion in recent years – choose your side!

A framework for considering incentives – Beneficence

Beneficence: "Do no harm." Focus - level of risk (harm) of study is reasonable in relation to the prospect of benefit

- Have concern when: participants will only consent to a study if the incentive is relatively large because their aversion to the study is strong
  - NO GOOD: Aversion to the study and/or risk is so great that you are calibrating the incentive to overcome it…

A framework for considering incentives - Justice

Justice:

1. **Protection from exploitation**
2. **Fair access to participate in research**

- **Protect from exploitation:** Wrong if want to spend least amount so you preferentially recruit poor participants
- **Fair access:** It is important to consider importance of including participants who might benefit from research even if they are historically hard to recruit and retain

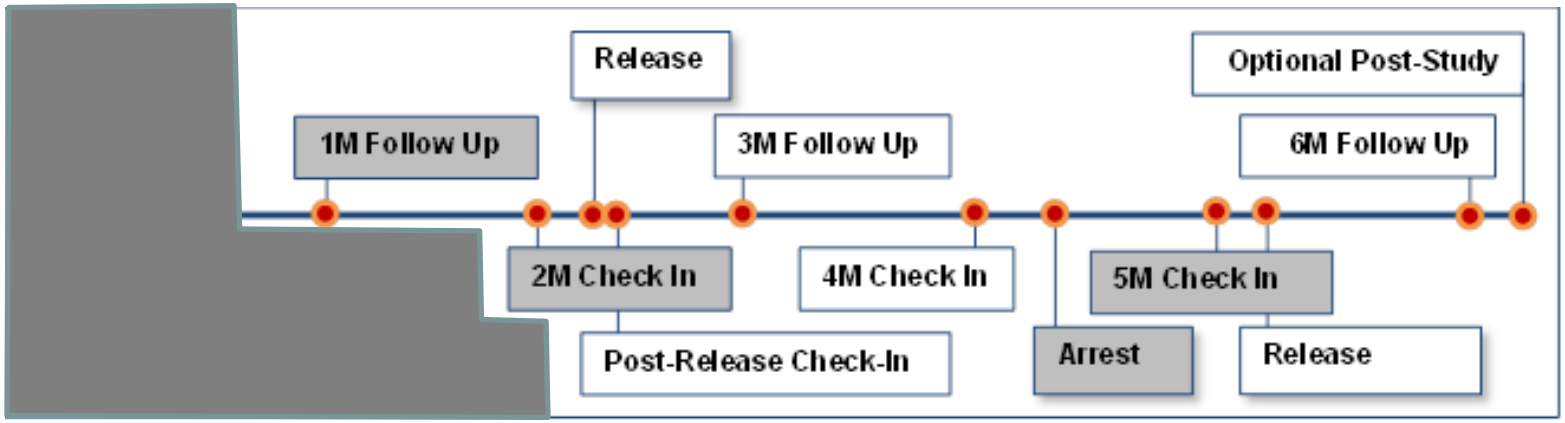
Sum up slide on incentives

Always consider the points of concern:

- Where the subject is in a dependency relationship with the researcher (student, patient)
- Where the risks are particularly high
- Where the research is degrading
- Where the participant will only consent if the incentive is relatively large because the participant's aversion to the study is strong

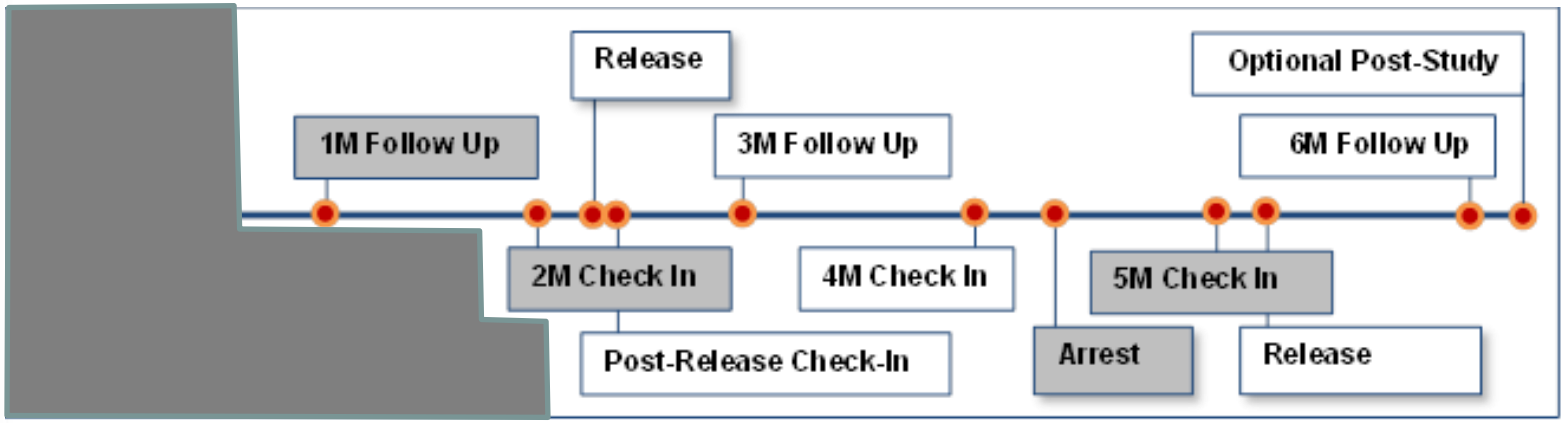
When these conditions are present, use of incentives highly questionable

Study design: Retention
Questions for you



- **Retention Strategies**
  - Incentives
  - Other retention strategies you have used in your research studies?

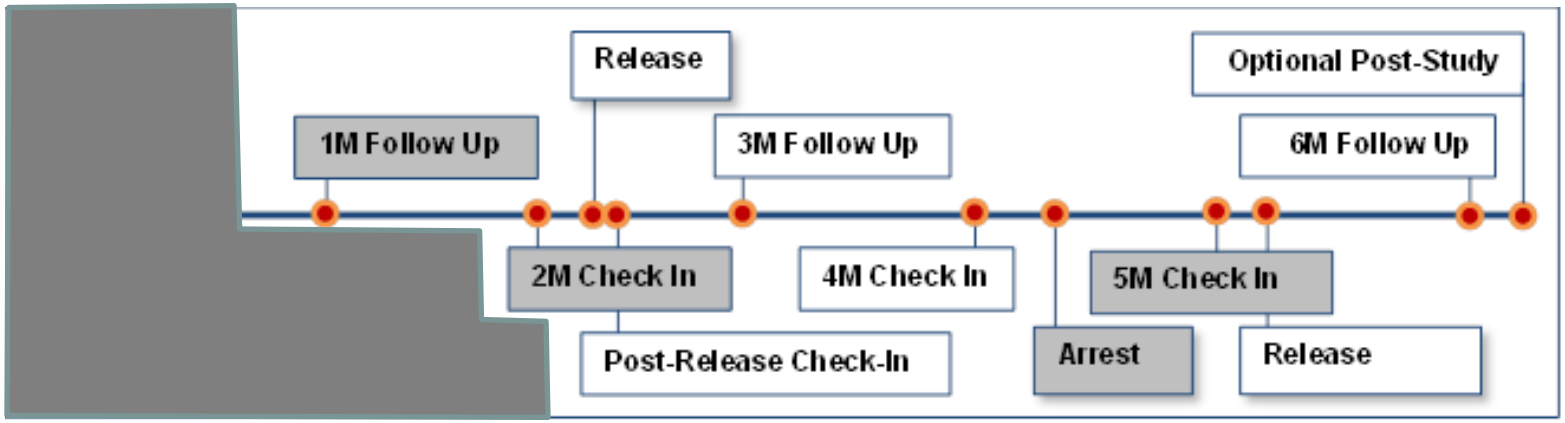
Retention Strategies



- **Retention Strategies: Community-based office**
  - Tenderloin-based office is a safe place with a big lobby where participants can stop by anytime for water, to use restroom, to make local phone calls, or get out of the rain
  - Each interview starts with a snack and informal catch-up; Time is budgeted to let "talkers" talk and be heard

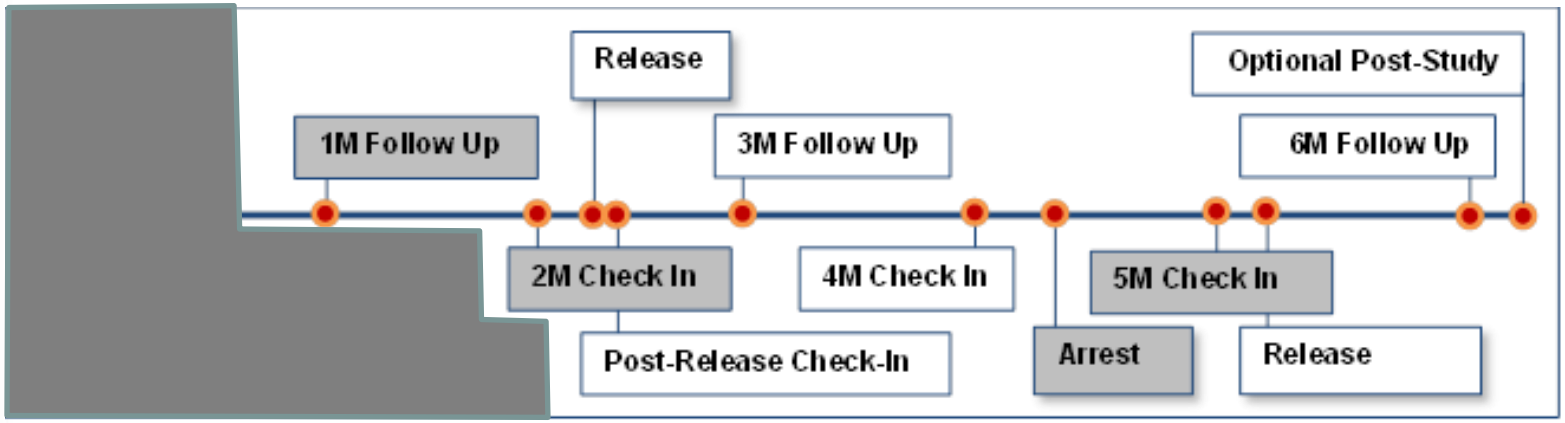
"I'll tell you why I don't like the other places I see doctors. Everybody always has these preconceived ideas about me. Cause of things I've done and all– things in my past. But I like coming here. Here we just talk and it's cool."

Retention Strategies



- **Retention Strategies: Tracking system**
  - Contact Form includes:
    - Friends and family
    - Frequent hangouts - corners / stores, etc
    - Living spaces - soup kitchen lines / shelters / SROs, etc
  - Daily monitoring of jail census for re-arrests
    - 72% participants lost to follow up at some point
    - 70% “found” (brought back to the study)

Handling unanticipated events



Importance of training and retraining of staff

- **Mr. B remained in jail for 60 days**
  - While in jail another study participant threatened a deputy during his 1 month follow up visit
  - Staff retrained on threatening behavior and new IRB reporting requirements developed based on new event
  - Events → need to develop new protocols and document that staff retraining occurred

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Disseminating results
Some *challenges*

1. **Not everyone views issues of vulnerability same**
   - Submitted a manuscript about the importance of using modified consent forms (the Teach-to-Goal forms)
   - Reviewer called our research exploitative even though our point was to call for greater protections than the status quo

2. **Many research findings have political implications**
   - Published an article on applying palliative care framework to early (compassionate) release laws for prisoners with serious illness
   - Asked to testify in hearings on topic
   - Have to decide where/if to draw line between research and advocacy

3. **Questions about generalizability for mainstream high impact journals**

Disseminating results
Some strategies to overcome challenges

Build broad network of support around work

1. **Raise awareness that your research area matters**
   - May need to think beyond the traditional paths for academic advancement (papers and grants): drum up support with community talks, webinars, even (at times) textbook chapters!!!
2. **Assemble an Advisory Board**
   - Think beyond close contacts
   - Interdisciplinary and outside of academia: attorneys, judges, CMOs, wardens, SW, former prisoners, etc…
3. **Don’t get too hung up on impact factor**
   - Some of best palliative care and prisoner health research published in lesser known journals

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Why research with vulnerable populations is worthwhile

Now a growing NIH priority:

- ACA mandated National *Center* on Minority Health and Health Disparities become National *Institute* on Minority Health and Health Disparities

- Health Disparities Strategic Research Plan
  - Dedicates $2.7 billion annually to reduce disparities
  - Funding spread across 28 NIH centers and institutes

- *"NIH research is aggressively pursuing innovative new hypotheses, while maintaining emphasis on translation of discoveries from laboratory bench to the real world of communities, vulnerable populations, and patient groups."*

Why research with vulnerable populations is worthwhile

Give voice to the voiceless

"I'll be honest with you. In the beginning, it was a little bit more about the money. Sitting in [jail], knowing how hard it is coming out. I was like, damn. Yeah. That money could help. But since I've started your project? It's not about the money anymore. I like coming here. Talking with you guys. Giving something back. I'm gonna miss it."

Resource for working with vulnerable research subjects

- **The US Department of Health and Human Services has a section on Vulnerable Populations under Policy and Guidance:**

  http://www.hhs.gov/ohrp/policy/populations/index.html

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The Nuremberg Code (1949)

1. Requires voluntary agreement of the participant
2. Research must help society
3. Research questions should be based on previous knowledge
4. Research should not cause mental and physical suffering, should avoid risk of injury and death
5. Amount of risk can't exceed importance of problem
6. Researchers must be qualified
7. Participant can stop at any time
8. Researchers must stop if risk of injury, disability, death