Recruitment and Retention

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Three Aspects of Subject Selection

A. Selection: determining who is eligible
B. Recruitment: inviting eligible individuals
C. Retention: retaining enrolled participants

I will focus on recruitment and retention

Need to Recruit and Retain

- To be ethical, clinical trials need to collect socially valuable data.
- To collect socially valuable data, clinical trials need to enroll and retain a sufficient number of participants.
- Hence, enrolling and retaining enough participants is ethically important!

Many Trials Fall Short

- Delays and failures to recruit enough participants undermine many trials.
  Treweek et al Cochrane Database Syst Rev 2018;2:MR000013
- Almost half of NCI trials fail to enroll enough subjects for meaningful results.
  Kolata. Lack of Study Volunteers Hobbles Cancer Fight. NY Times. 2009
- 44% of randomized trials in the UK fail to enroll a sufficient number of subjects.
  Walters et al. BMJ Open 2017;7:e015276

IRB Dilemma

- Stopping studies that are not recruiting adequately risks wasting the efforts to date.
- But, continuing trials that are not recruiting adequately risks increasing the number of wasted efforts.

Need to be Proactive

- To avoid this dilemma, researchers and IRBs need to pay more attention to recruitment and retention.
- It's not anybody's job; It's everybody's job!
- Trials need to plan in advance how to recruit and retain enough participants.

Finding the Right Balance

- There is a strong ethical incentive to increase recruitment and retention in clinical trials.
- At the same time, participation is voluntary.
- Moreover, overly aggressive recruitment and retention can be ethically problematic.

The Wrong Response

- For example, one way to improve retention would be to forbid participants from withdrawing for any reason.
- That would be problematic.
- What are ethically better methods of recruitment and retention?

SUBJECT RECRUITMENT

Subject recruitment involves active attempts to attract specific individuals within the pool of eligible participants.

Recruitment for good reasons

- Do not focus recruitment on individuals who are (or appear to be) vulnerable.
- Ensure participants are recruited for reasons of science, not compromised (nor privileged) position.

Belmont Report

Site Impact

- Where a study is conducted can have a significant impact on who enrolls.
- Low inclusion of minority groups in some studies likely traces more to inconvenient study sites than more widely discussed concerns regarding trust in researchers.

Choosing a Site

- When choosing study sites, researchers should consider the impact on recruitment and retention, and consider how they can go to participants.
- NIH institutes have had study sites at clinics in DC, including the Unity Health Care Upper Cardozo Health Center.

Methods of Recruitment

Once the sites have been identified, researchers need to recruit participants:

- Incentives for researchers to recruit
- Incentives for clinicians to refer
- Incentives for participants to refer others
- Targeted recruitment
- Advertising

Incentives to Enroll Participants

- Researchers may receive payments for fast enrollment.
- Clinicians may receive payments for referring patients to trials.

Concerns about Incentives

- Do incentives to refer and recruit patients pose a conflict of interest?

→ To what extent might the incentives encourage investigators to refer/enroll inappropriate participants?

Incentives to Participants

- Some studies offer participants incentives to refer others to the trial.
- This approach has been effective at increasing enrollment from difficult to reach populations.

Possible Concerns

- Concern that this approach might undermine the privacy of participants.
- Participants also might pressure others, especially if payment is tied to others actually enrolling.

Role of Advertising

- Advertising plays an increasingly important role in recruiting research participants.
- However, there is significant concern about the ethics of advertising, and not much guidance.

FDA Guidance

- Advertising is "the start of the informed consent and subject selection process."
- IRBs should determine Ads are: not unduly coercive; do not promise a cure; use appropriate font size and visual effects; explain that test articles are investigational; do not emphasize payment or the amount

http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm

Proposed T.V. Ad

- Thumping music, swirling tie-dye colors: "Attention alcohol users…you are a candidate for a new research study.
- We are enrolling men and women, 18-40, to study how alcohol affects the brain.

Effect of Ads

- Does advertising affect which groups enroll?
- Does advertising affect understanding?
- Does advertising affect subject motivations (does it matter?)?

Payment

- What role should payment play in recruiting research participants?
- To what extent is it acceptable to advertise payment?
- What does "do not emphasize" payment mean in practice?

Proposed Bar Coaster

Research Participants Wanted

Earn $50-$1295

Call
555-555-5555

Old Worry

- Many commentators and IRB members express ethical concern over payment.
- In particular, they worry that payments may undermine voluntariness, understanding, or altruism.

Gelinas et al. *NEJM* 2018;378:766-771

Largent, Lynch. *Yale J Health Policy, Law, Ethics* 2017;17:61-82

Data

- Empirical studies find: individuals who focus on payment are more likely to understand; greater payment does not lead to greater willingness to take risks; payment does not undermine altruism.

Bentley, Thacker. *J Med Ethics* 2004;30:293-298; Halpern et al. *Arch Intern Med* 2004;164:801-803; Cryder et al. *Soc Sci Med* 2010;70:455-464; Halpern et al *Ann Intern Med* 2010;152:358-365

New Worry

- The potential to make money may result in participants not being truthful.

Devine et al. *Clin Trials* 2013;10:935-948

Dickert. Clin Trials. 2013;10(6):840-841

- For example, they may misreport their history to enroll, or fail to report side effects to stay enrolled.

Possible Safeguards

- Rely on objective measures in the study.
- Use pro-rated and sequential rather than lump sum payments.
- Don't disclose inclusion/exclusion criteria.

McCaul, Wand. *Alcohol Clin Exp Res* 2018; 42:230–237

Devine et al. *Contemp Clin Trials Commun* 2017;5:67–71

Other Challenges

- Data suggest that many problems recruiting participants trace to practical concerns: awareness of studies, transportation, parking, child care.
- Who addresses these concerns?

Difficult to Reach Participants

- Given all the challenges, recruitment efforts may focus on those who are most easy to identify and recruit.
- Yet, more difficult to recruit individuals may differ in scientifically relevant ways.

Goldman et al.

Cl Trials 2018; 15: 543-550

Learning Health Care

- Some argue that difficulties recruiting participants trace to current reliance on a "segregated" approach to clinical trials.
- Learning healthcare systems have been proposed as a way to address this concern.

Olson et al. The learning healthcare system. IOM report 2007
https://rethinkingclinicaltrials.org/

Increased Recruitment?

- Conducting research in the course of providing health care has the potential to increase enrollment.
- To further increase enrollment, some argue consent should be replaced with notification for low risk studies.

Cumyn et al. https://doi.org/10.1002/lrh2.10206
Asch et al. Healthcare 2020; 8:100462

Research Cohorts

- Alternatively, some have proposed to invite patients to consent to being entered into a pool of potential participants.
- Those who are eligible for a trial will be enrolled, possibly without notification.

Kim et al. Clin Trials 2018 Feb;15(1):9-16

eStudies

- During COVID, use and acceptance of telehealth has increased significantly.
- More reliance on virtual participation might improve research enrollment.

Naito et al. NPJ Parkinsons Dis. 2021;7(1):34.

Need for Data

- Many trials do not describe their recruitment methods and few studies have assessed which methods are effective.
- Trials that use new methods should evaluate them systematically.

Rosser et al. Cl Trials. 2022;19:239-250

Assessment of 4 Methods

Real time screening in electronic medical record: effective

Defer consent for EEG if parents not in the hospital: controversial but effective

Weekend screening: expensive

Expand sites: very effective

McBain et al. Pediatr Crit Care Med. 2016;17(3):246-50

SUBJECT RETENTION

Subject retention involves attempts to keep enrolled participants in the study.

Retention of participants

- To collect valid data, recruited participants need to be retained.
- Data suggest that enrolled participants can experience problems in their personal lives as a result of their participation in clinical research.

Lazovski J, et al. *JERHRE* 2009; 4:89-97

Obligations

- Some argue that regarding individuals as having an obligation to participate might increase enrollment and retention.

Schaefer et al JAMA 2009; 302: 67–72

- Others worry this approach may actually decrease participation.

Subjects versus Participants

- Alternatively, to encourage retention it might help to turn research *subjects* into research *participants*?
- Do research WITH individuals, NOT on them.

Encouragement?

- Participants make vital contributions to research.
- We need to find ways to emphasize this fact, and encourage retention, without undermining voluntariness.

Results from NIH Participants

- Yes: they tell me that I can withdraw.
- But: they never explain why I shouldn't!

How do we ethically address this concern?

Treatment and Treats

How people are treated affects their willingness to contribute to joint activities.

- Explain importance of contribution?
- Add perks, like good meals?
- Throw parties?

Payment Schedules

- Some studies modify their payment schedules to encourage participants to stay in the study: pay more for later procedures; completion bonuses.
- These practices raise their own ethical concerns.

Some Data

- Regular phone calls and sending cards did not increase retention.

Glassman et al. Clinical Trials 2020;17:195-201

- Payment, in-person contact, and study flexibility increased retention.

Grape et al. J Adolesc 2018;65:123-132

Summary

- Recruitment and retention are vital to ethical clinical research.
- The challenges they raise have not received the attention they deserve.

Further Reading

- Ewing et al. Dev Cogn Neurosci 2018;32:130-137
- Robinson et al. Trials 2016;17(1):294
- Schoeppe et al. Int J Behav Med 2014;21(5):794-803
- Tobler, Komro, Eval Programm Plan 2011;34(2):87-96
- Zook et al. Clin Trial 2010;7(4):400-410
- Robinson et al. J Clin Epidemiol 2007;60(8):757-765
- Villarruel et al. J Spec Pediatr Nurs 2006;11(4):244-250