CLINICAL TRIALS RETENTION

Demystifying Subject Withdrawal
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Objectives

<table>
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<tr>
<th>Description</th>
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<td>Describe circumstances that may change a subject’s level of participation / subject status.</td>
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<td>Analyze appropriate withdrawal pathways to ensure subject safety.</td>
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<td>Reflect how successful team communications during a subject withdrawal ensures subject safety.</td>
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<td>Assess how subject withdrawal impacts study procedures and success.</td>
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General principles

- Considering clinical trials should be the norm, not the exception
- We should raise awareness and access and do all that we reasonably and safely can to ensure adherence and completion of participation
- Clinical trials can improve not only individual patient lives but also have collective benefit for the greater community.
I just heard there's a drug in trials that might stop my cancer!!

Of course not... why would I do that?

Great! Are you going to volunteer to participate for the trial?

I wouldn't either. Sure hope they get some results soon...
Effect of Trial Type

- Treatment trials
  - All phases of trials and all points of disease
- Non treatment trials
  - Symptom management and quality of life
- Long-term observational studies
  - Hypothesis generation
  - Helpful to disease population
Decision to participate

- Motivation
- Benefits
- Altrusim
- Vulnerability
- Ethics
  - Depends on disease, study phase, prognosis, socioeconomic and cultural environment
Barriers to Trial Continuation

- Fear about not receiving treatment
  - Confusion about the term “placebo-controlled”
- Fear of being a “guinea pig”
  - Fear they will derive harm from an experimental agent
    - There will always be inherent risk
    - Trials are designed to minimize risk
      - Preclinical testing, continuous safety evaluation, phase I trials
    - Patients may withdraw for any reason at any time
I was not sure if he has to be 'blinded' or 'masked'. 
Really Good Clinical Trials

I hate blinded studies!

Is that you, Liz?

Double blind is a curse when you're the Dr.!

A slight downside of blinded studies...
Elements of Success

- Regular interactions of research personnel
- Discussion with nurse coordinators about implementation, progress, problems and solutions
  - Contact data, don’t “write off” subjects easily
  - Engage families and educate them
  - Work on mobility, transportation
- Questions to protocol subcommittees to enhance design or operations.
Other factors in retention

- Distance
- Income
- Culture
- Age
Reasons for dropout

- Moving away
- Personal obligations
- Loss to f/u
- Non-compliance
- Monetary/financial

- These are likely to be different than reasons for involuntary removal of subjects by investigators
Barriers to enrollment

- Uncomfortable/Distrust
- Low compensation
- Lack of study partner
- Low level of education
- Lack of transportation
- Lack of interest
- Time commitment
- Missed appointment
- Privacy/confidentiality concerns
- Personal health issues
- Distance to study site
- Prejudice of study medication
- No contact information
- Lack of health insurance
- Misinformed

Reasons for dropout

- Participant re-location/moving
- Personal obligations
- Lost to follow-ups
- Non compliance
- Low compensation
- Student Graduating
- Lack of interest
- Difficulty with scheduling
- Changing doctors
- Deceased
- Incarceration

Important Retention Strategies

- Rapport
- Telephone calls before and after visits
- Fair compensation
- Scheduling flexibility
- Frequent reminders
- Attentive personnel
- Showing sensitivity and respect
A structured format to check in regularly

- Design study visits to coincide with other visits
- Allow patients to go to other centers for standard of care procedures
- Providing a budget for transportation reimbursement
- Non-coercive incentives such as child care, gift cards for out of pocket expenses.
Strategies to improve retention in randomized trials

- Scant literature
- Most has to do with return of surveys/questionnaires
  - Monetary incentive
  - Monetary incentive based on receipt
  - Non-monetary incentive, prize drawings
  - Postal packages, priority delivery not effective.
  - Length and relevance not that important

- Less research regarding retention in trials that involve return to study sites
  Brueton VC BMJ Open 2014
Retention Strategies Through the Years

Retention Strategies

- Most common are “contact and scheduling methods (83% of studies had this)
- Financial incentives increase retention in population based cohort studies and increase questionnaire response rates
- The number of strategies correlated positively with retention rates
- Cited lack of comparative studies, heterogeneity in study populations and study designs as barriers to understanding this

## Retention strategy themes

<table>
<thead>
<tr>
<th>Contact and Scheduling Methods</th>
<th>Multiple contacts</th>
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<tbody>
<tr>
<td>Visit Characteristics</td>
<td>Flexible, unhurried</td>
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<tr>
<td>Study Personnel</td>
<td>Consistent, culturally competent</td>
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<tr>
<td>Non-financial incentives</td>
<td>Parking</td>
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<tr>
<td>Financial incentives</td>
<td>Cash, gift certificates</td>
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<tr>
<td>Reminders</td>
<td>Postcards</td>
</tr>
<tr>
<td>Special tracking methods</td>
<td>Search engines</td>
</tr>
<tr>
<td>Study description</td>
<td>Visit numbers and times</td>
</tr>
<tr>
<td>Benefits of study</td>
<td>Education of patient/family</td>
</tr>
<tr>
<td>Reimbursement</td>
<td>Taxi, child care during visit</td>
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<tr>
<td>Study identity</td>
<td>T-shirts; inform about progress</td>
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<tr>
<td>Community involvement</td>
<td>Present pilot results to group</td>
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Why retention and withdrawals are important

- Validity of longitudinal studies
- Studies with high drop out rates are thought to be inferior because of increased risk of selection bias
- Those remaining may differ from those who left
- May be differential attrition across study groups being compared.
Missing data

- Important to address how missing data will be handled
- Assume failure
- Last observation carried forward
  - Most likely to have biases
- Maximum likelihood estimation
- Multiple imputation approaches
  - Least likely to have biases
Clinical equipoise

- Allows investigator to continue a trial until there is enough statistical evidence to convince others of the validity of results
- No loss of ethical integrity
- Individual MD vs medical community
- Affects randomization and cross-over
Premature discontinuation

- Dropout due to treatment (no benefit or toxicity)
- Dropout unrelated to treatment (moved away)
- Lost to follow up
Voluntary withdrawal

- Subjects may leave study at any time
- No penalty or loss of benefits occurs
- Should not affect how study personnel view the subject

- Return study drug
- Complete follow-up procedures
- Determine whether consent for follow-up is also being withdrawn; no contact; no information; public records can be accessed regarding survival status
Being taken off study without consent

- Medication needed not allowed by study
- Study MD decides continuing study harmful
- Serious side effect to study drug occurs
- The study is stopped by sponsor, FDA, IRB, or study doctor before completion
- Non-adherence to study visits or procedures
- Pregnancy
- Subject does not consent to continue in study after being told of changes in research that might affect them
Not so good reasons for withdrawal

- Enrollment errors
- Randomization effect
Once withdrawal occurs, what then?

- Communication with primary care team or subspecialty clinical team
  - Referrals in place
  - No lapse of necessary therapy
  - Continued observation for adverse events
- What routine labs or other evaluations need to revert to the “standard of care” mode?
- Will the subject allow f/u for survival/outcomes or further contact?
- How important are the end of trial evaluations?
Important Considerations

- Can data already collected by used?
- Can more data be obtained?

- Withdrawl from interventional component
  - Can have F/U interviews, PE, blood draws, etc.
  - Information can be obtained from records, health care provider

- Withdrawl from all components
  - No contact related to study
  - No use of identifiable private information
Important things to do at withdrawal

- Document withdrawal and why
  - IRB reporting?
- Communicate
- Assure ongoing treatment as appropriate
- Understand rules about data retention
  - FDA, HIPAA
  - Understand rules regarding biospecimens
- HHS.gov (2010 guidance)
Post-trial follow up

- Prolonged follow up can provide important information about efficacy and safety outcomes
- Can be logistically challenging and costly
- Will only be as good as in trial follow up
  - Face to face
  - Telephone
  - Postal service
  - Web
  - Use of routine health records
Reporting Outcomes Data

- Trial registration
- Procedures for recruitment and retention
  - Important to note why a subject dropped out or was removed
- Procedures for reporting on randomization and intervention
- Statistical methods used to assess treatment efficacy
“There is a peculiar paradox that exists in trial execution—we perform clinical trials to generate evidence to improve patient outcomes; however, we conduct clinical trials like anecdotal medicine; (1) we do what we think works; (2) we rely on experience and judgement and (3) there are limited data to support best practices.”