CLINICAL TRIALS RETENTION

Demystifiying Subject Withdrawl

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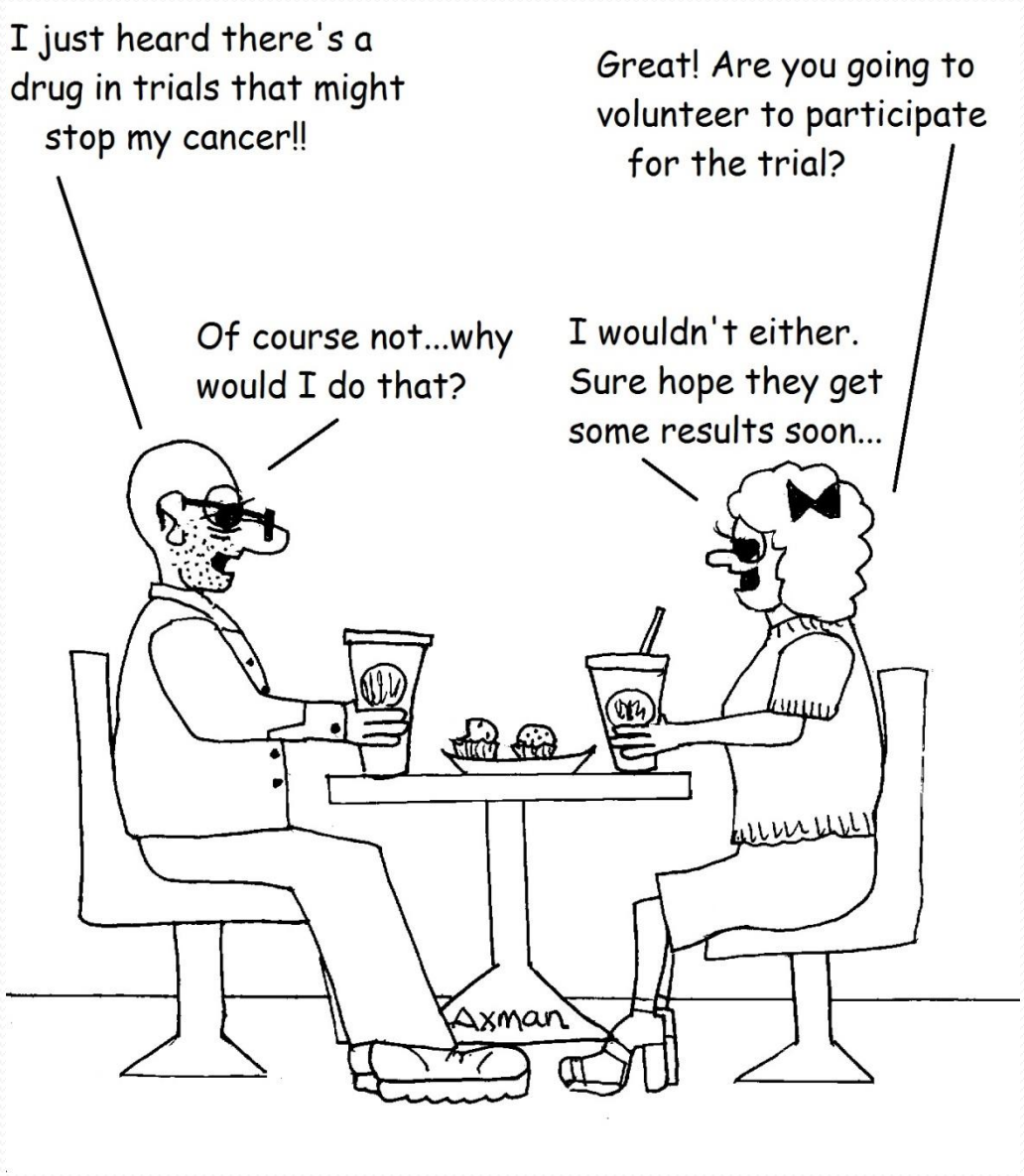
Objectives

Describe circumstances that may change a subject's level of participation / subject status.
Analyze appropriate withdrawal pathways to ensure subject safety.
Reflect how successful team communications during a subject withdrawal ensures subject safety.
Assess how subject withdrawal impacts study procedures and success.

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!!
Great! Are you going to volunteer to participate for the trial?
Of course not...why would I do that?
I wouldn't either. Sure hope they get some results soon...
Axman

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


CLINICAL TRIALS: BLINDING / MASKING
BY: SHIVENDRA PAL
I WAS NOT SURE IF HE HAS TO BE 'BLINDED' OR 'MASKED'
MRP
Placebo
Std.
© shivendra
www.clinicalresearchcartoons.in
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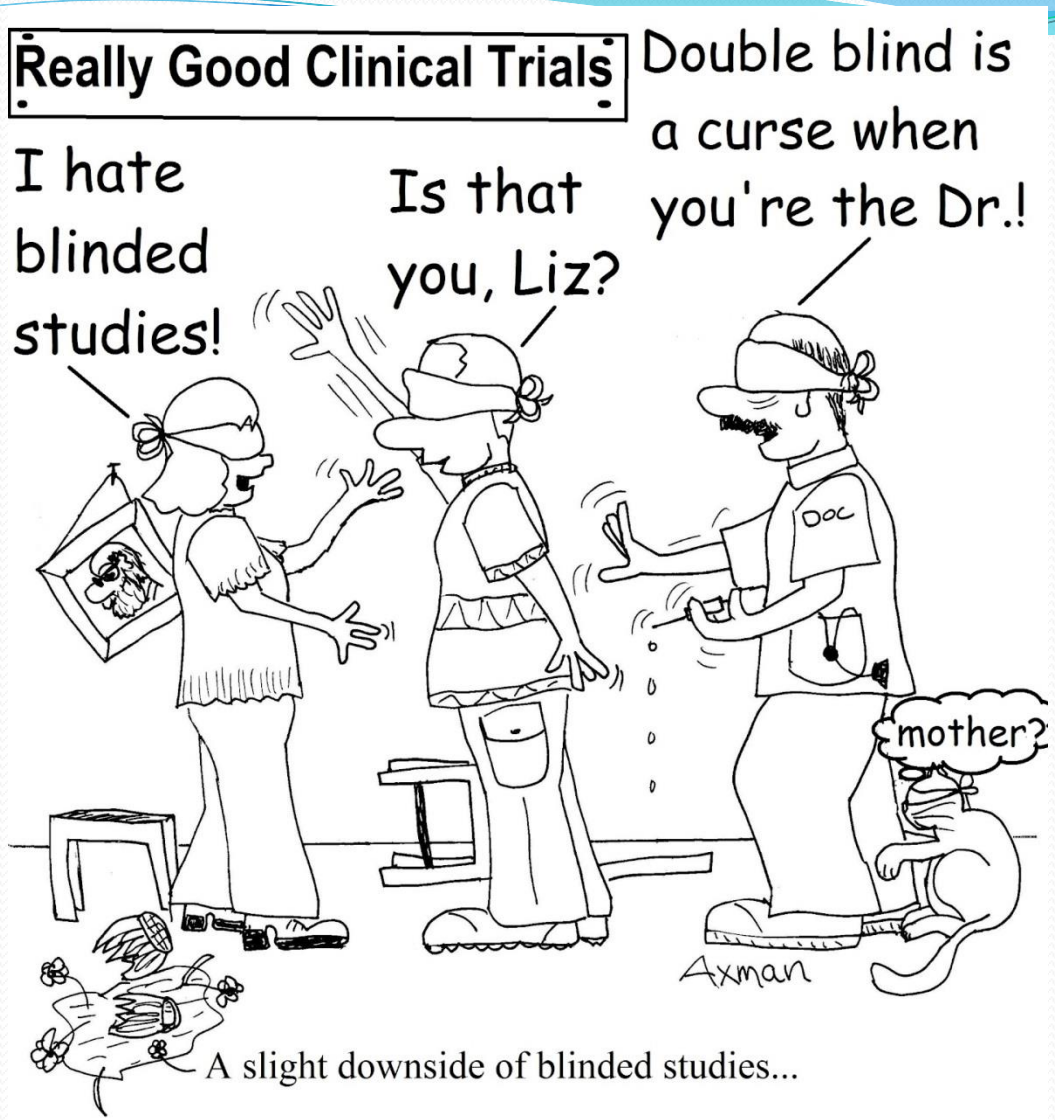

Really Good Clinical Trials
I hate blinded studies!
Is that you, Liz?
Double blind is a curse when you're the Dr.!
Doc
mother?
Axman
A slight downside of blinded studies...

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

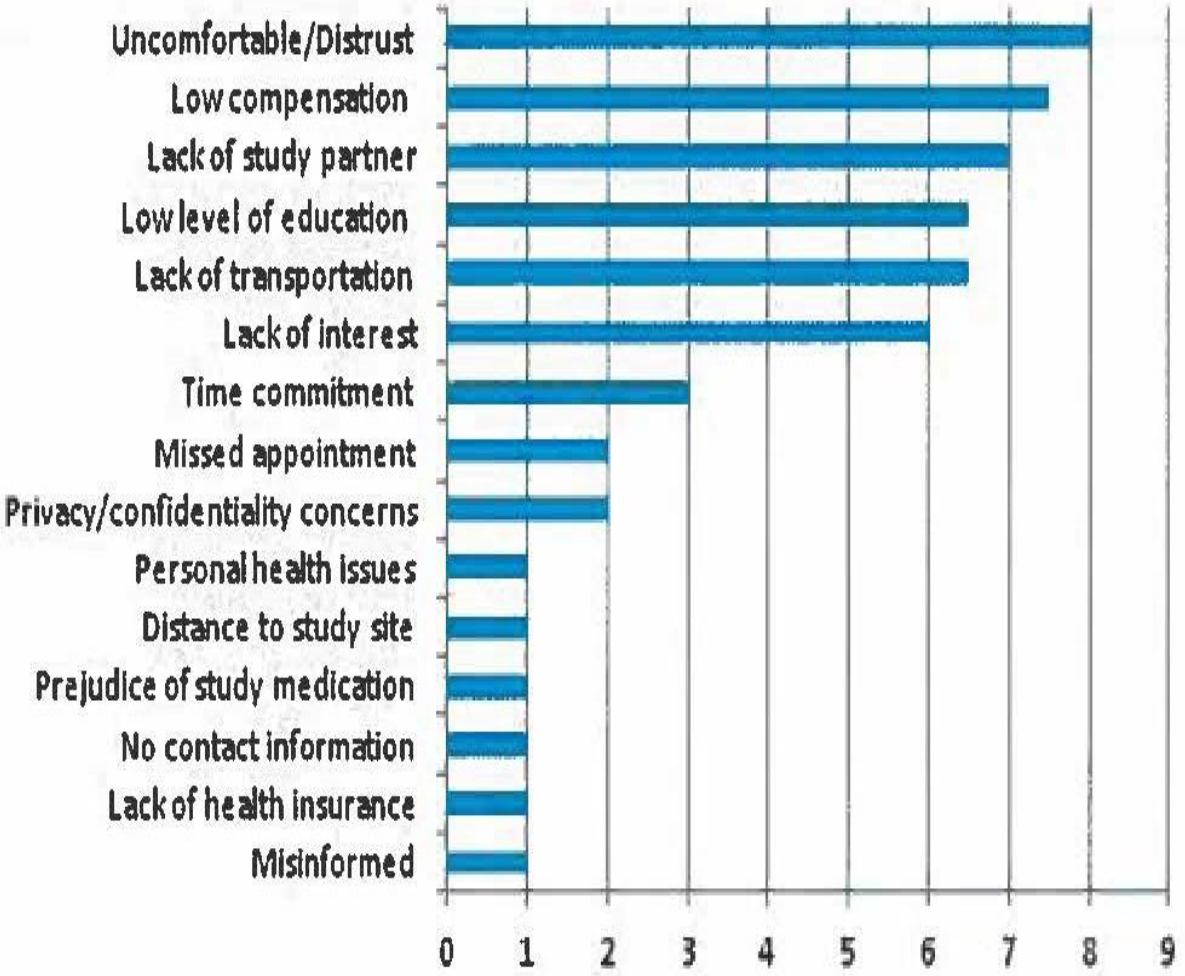
- Distance
- Income
- Culture
- Age

Reasons for dropout

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

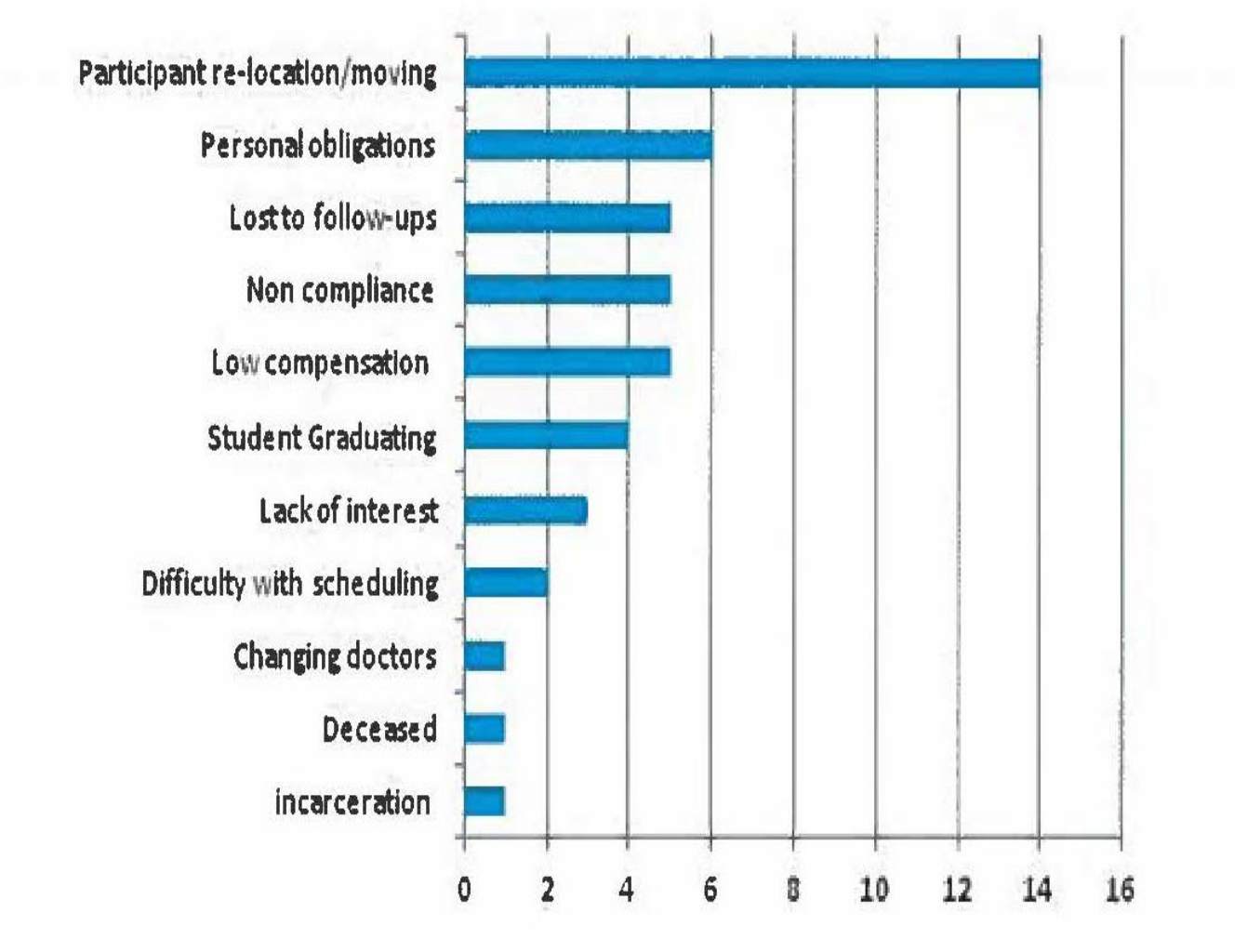
- These are likely to be different than reasons for involuntary removal of subjects by investigators

Barriers to enrollment



Otado et al. Clin TranslSci. 8:460, 2015

Reasons for dropout



Otado et al. Clin Tranl Sci 2015 8:460.

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.

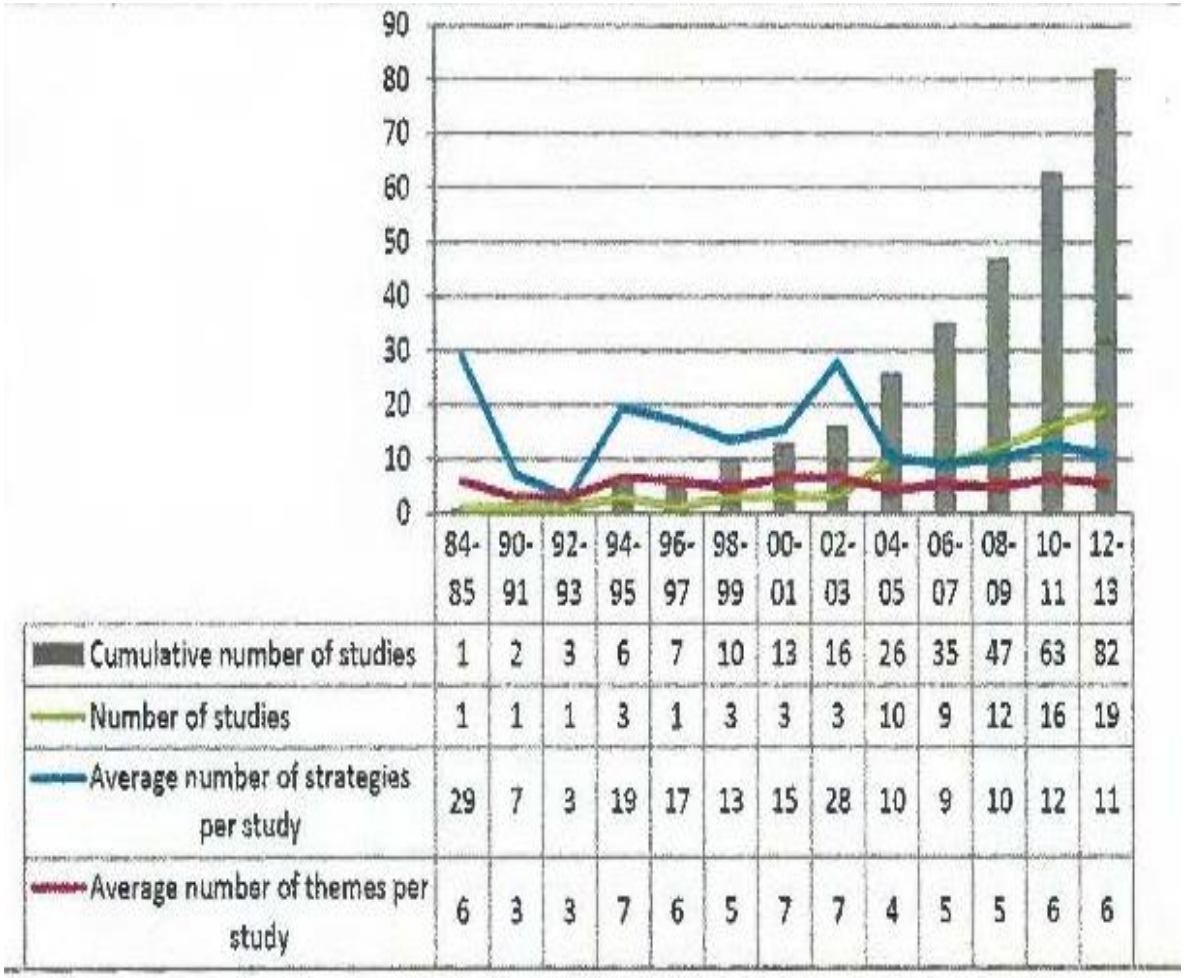
Strategies to improve retention in randomized trials

- Scant literature
- Most has to do with return of surveys/questionares
  - 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



	84-85	90-91	92-93	94-95	96-97	98-99	00-01	02-03	04-05	06-07	08-09	10-11	12-13
Cumulative number of studies	1	2	3	6	7	10	13	16	26	35	47	63	82
Number of studies	1	1	1	3	1	3	3	3	10	9	12	16	19
Average number of strategies per study	29	7	3	19	17	13	15	28	10	9	10	12	11
Average number of themes per study	6	3	3	7	6	5	7	7	4	5	5	6	6

Robinson KA et al. J Clin Epidemiol 63:1481-7, 2015.

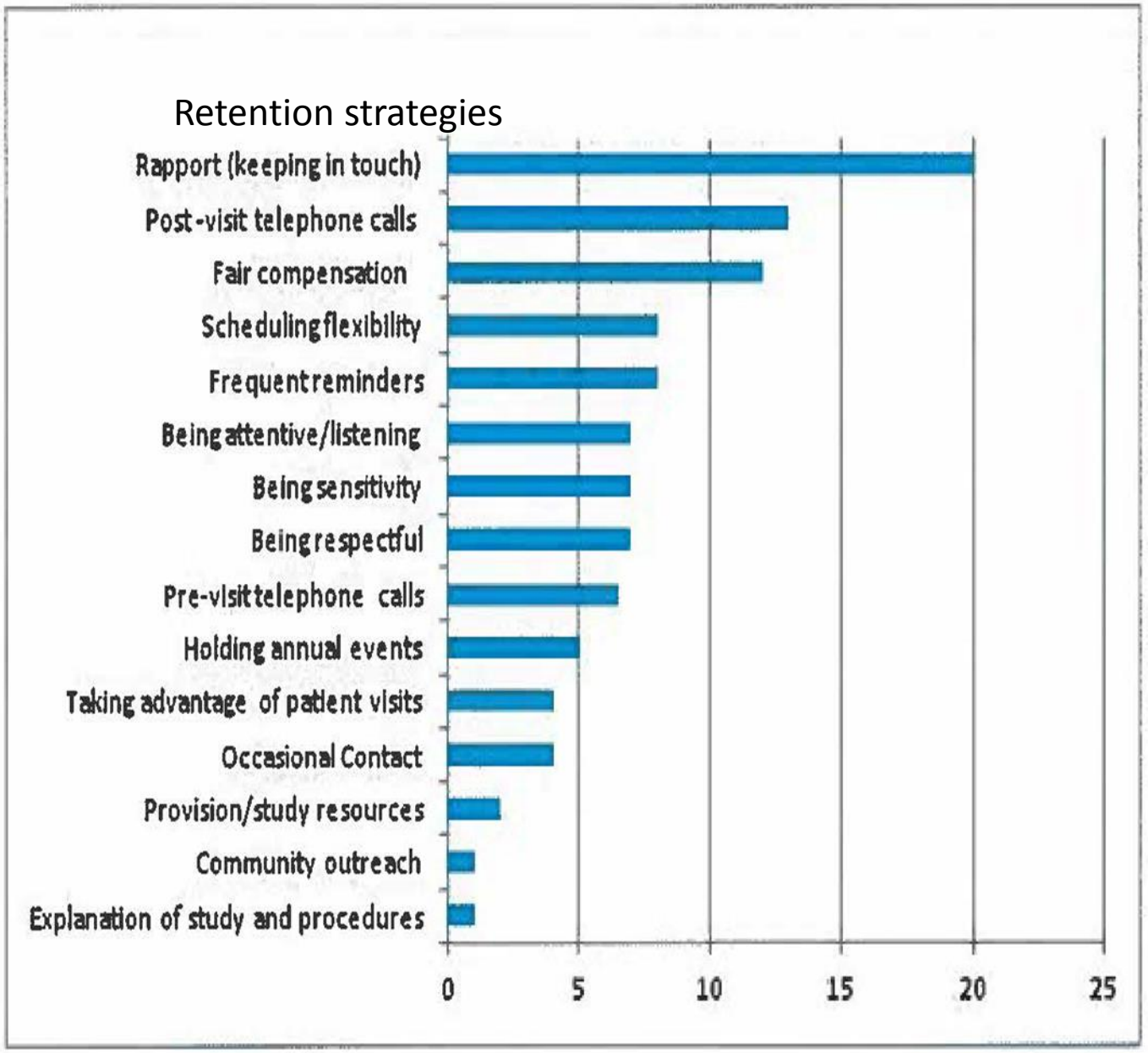
Retention Strategies

- Most common are “contact and scheduling methods (83% of studies had this)
- Financial incentives increase retention in population based cohort studies and increase questionair 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

- Robinson KA et al. J Clinic Epidemiol 2015 68: 1481.

Retention strategy themes

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



Otaldo J et al. Clin Transl Sci 2015 8:460-6, 2015

Why retention and withdrawls 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
    - Witkiewitz et al Alcohol coin Exp Res 2015 39:1571.

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 withdrawl

- 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 withdrawl

- Enrollment errors
- Randomization effect

Once withdrawl 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 withdrawl

- Document withdrawl 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 trails 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.”
    - Monica Shah. Quoted in : Heart Fail Rev 2014 19:135-42.