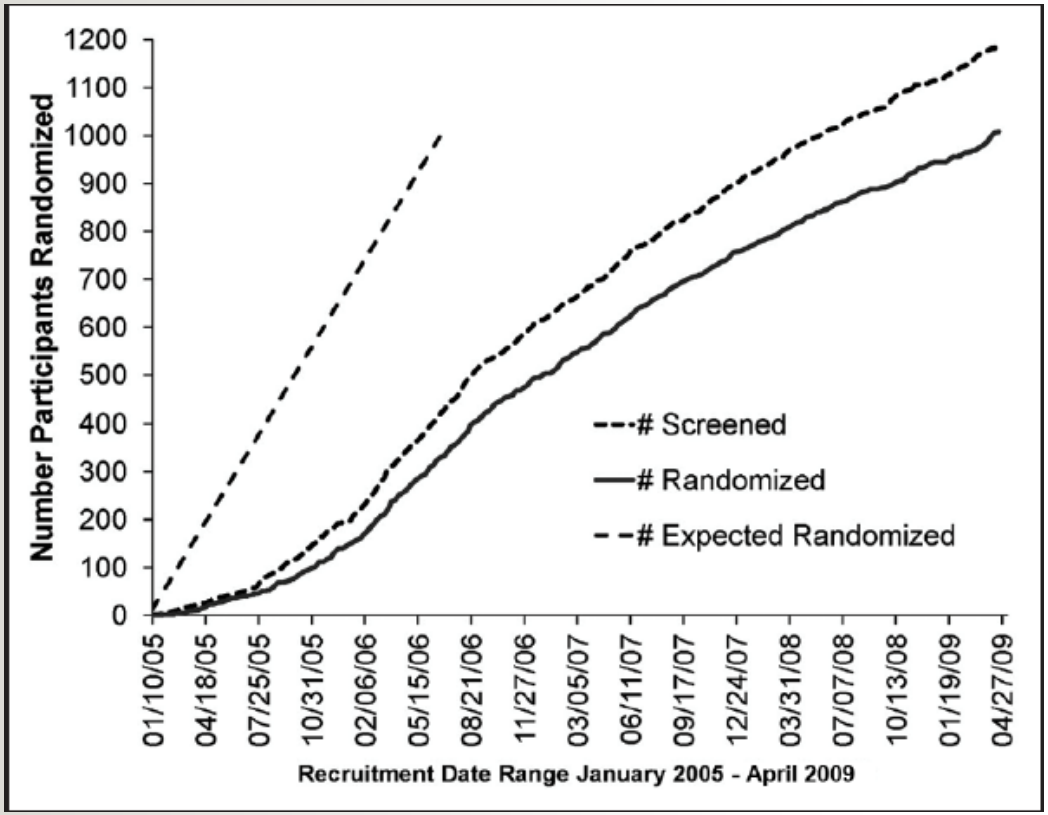
The Science of Recruitment and Retention



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Disclosures

- No disclosures related to this presentation
- Site investigator for clinical trials sponsored by Biogen Idec, Eli Lilly, Genentech, Janssen, the Alzheimer's Disease Cooperative Study, and the Alzheimer's Therapeutic Research Institute
- Consultant to Cogniciti and Flint Rehab

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Lecture Agenda

- Why are recruitment and retention important?
- Recruitment
  - Design choices and strategies to maximize recruitment
- Inclusive recruitment
  - The challenge, the solutions (?), some recommendations
- Retention
  - Design choices and strategies to maximize retention

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Trials Face Challenges to Recruitment

- The most common reason for trial failure is inadequate recruitment
- The majority of trials fail to meet recruitment goals
  - Delays learning/treatment advances
  - Threatens internal validity
  - Raises concerns about generalizability of results
  - Could lead to disparities in disease treatment

Kasenda et al. JAMA 2014.

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The Ethics of Recruitment and Retention

- Trials that fail to recruit a full sample *or* that experience greater than anticipated dropout may be underpowered
- Underpowered trials put patients at risk without the possible benefit of scientific learning and are, therefore, unethical
  - Failure to conduct appropriate sample size calculation equates to negligence
  - Failure to adequately recruit may stem from barriers to participation and investigators should inform themselves and plan appropriately

Halpern et al. JAMA 2002.

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Year	Intervention	Location	N	Sites	n/center/month
1990	Nimodipine	Europe	1215	17	2.86
1992	Nimodipine	North America	1064	53	0.69
1994	Monosialoganglioside GM-1	Multiple	792	16	1.42
1994	Nimodipine	Europe	350	3	1.83
1995	Streptokinase/Aspirin	Europe	622	70	0.20
1995	Alteplase	North America	624	36	0.39
1995	Alteplase	Europe	620	75	0.55
1995	Nadroparin	Other	312	4	3.73
1996	Triilazad Mesylate	North America	660	27	1.29
1996	Streptokinase	Europe	310	48	0.27
1996	Flunarizine	Europe	331	25	0.55
1996	Streptokinase	Other	340	40	0.29
1997	Aspirin	Other	21,106	413	1.28
1997	Piracetam	Europe	927	55	0.45
1997	Heparin/ Aspirin	Multiple	18,456	467	1.04
1998	Ebselen	Other	302	68	0.15
1998	Alteplase	Multiple	800	108	0.49
1998	Danaparoid Sodium	North America	1281	36	0.43
1999	Citicoline	North America	1281	36	0.43
1999	Alteplase	North America	613	140	0.08
2000	Nalmefene	North America	368	45	0.40
2000	Gavestinel	Multiple	1804	173	0.75
2000	Dalteparin	Europe	449	45	0.30
2000	Lubelozole	Multiple	1786	131	0.62
2000	Ancrod	North America	500	48	0.20
2001	Citicoline	North America	899	118	0.49
2001	Gavestinel	North America	1646	132	0.69
2001	Tinzaparin	Multiple	1499	100	0.65
2001	Aptiganel	Multiple	628	156	0.28
2001	Enlimomab	North America	625	67	0.47
2003	Aspirin	Europe	441	4	1.02
2004	Magnesium	Multiple	2589	99	0.40

Elkins et al. Stroke 2006.

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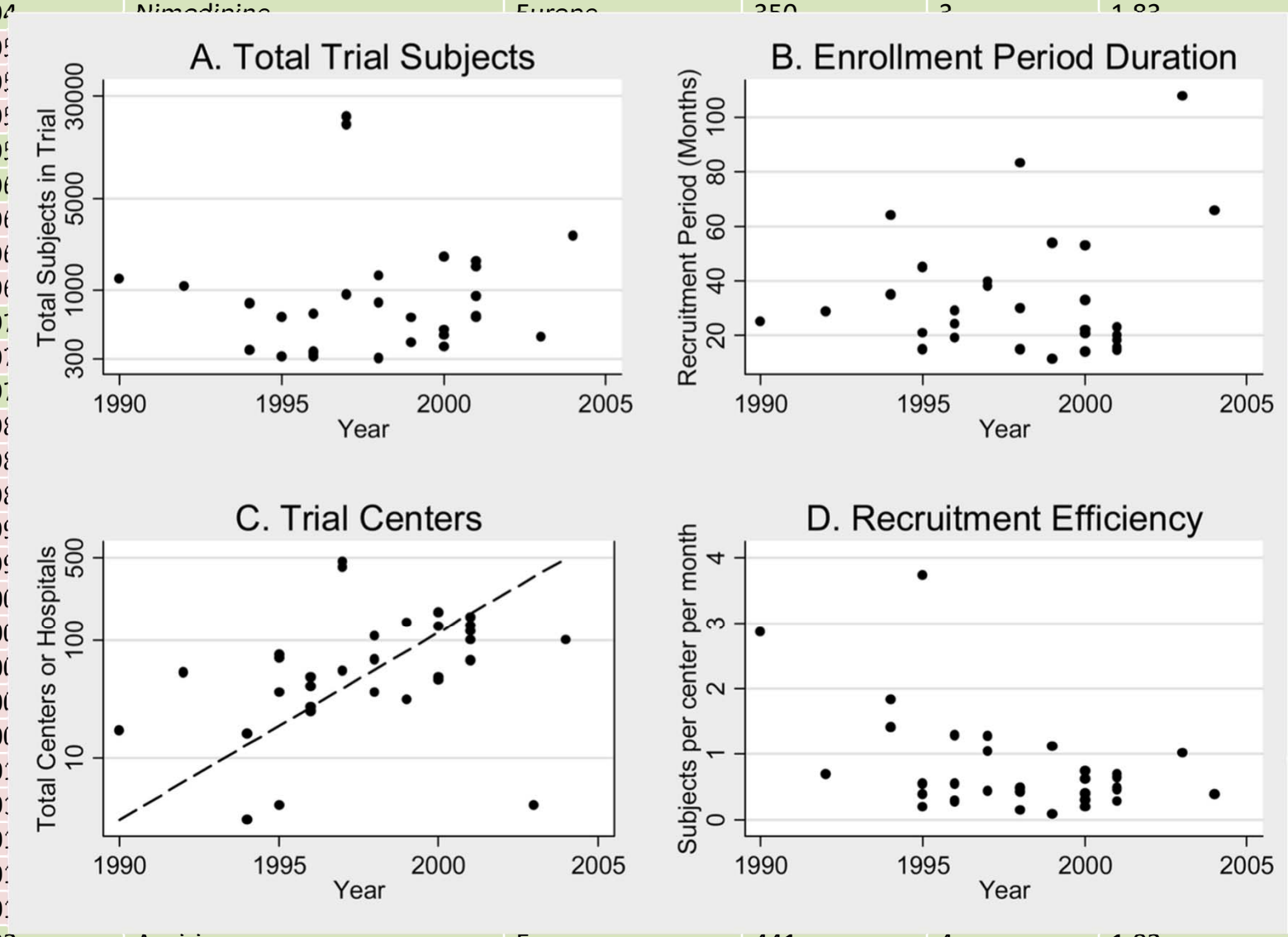

Elkins et al. Stroke 2006.

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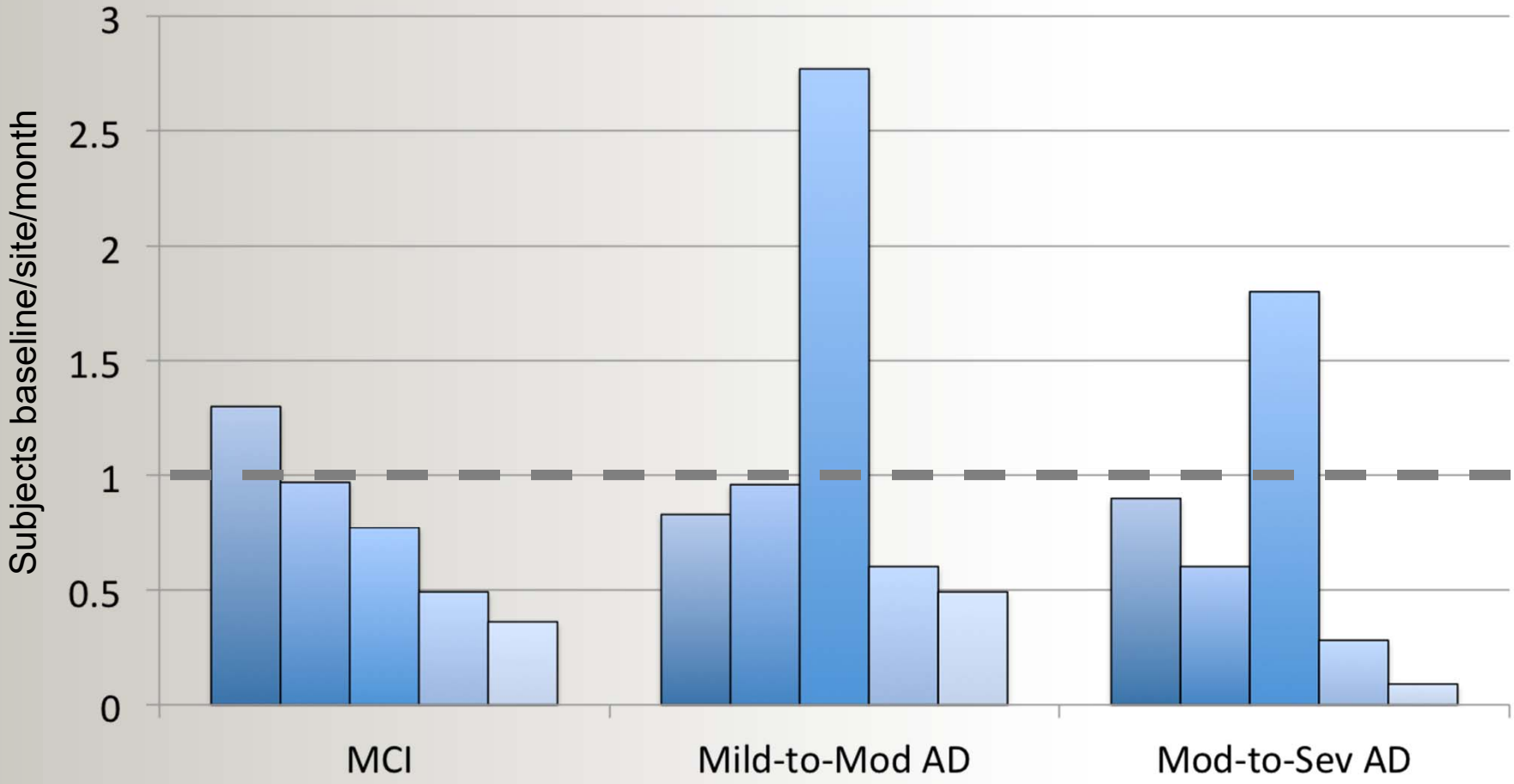
Recruitment Rates for AD Trials



Grill and Karlawish, Alz Res Ther. 2010.

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Study Design Choices

- Consider recruitment and retention as early in the process as possible
  - Don't design a trial that is not feasible
  - Appreciate the patient's perspective (and any other perspectives necessary for the trial to be successful – e.g., parents or caregivers).

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Study Design Choices – Eligibility Criteria

- Patients who truly suffer from the disease
- Patients who are most likely to benefit from therapy
  - Patients in whom, if benefit occurs, the investigator will be able to detect it
- Patients who represent the greater disease suffering population
- Patients who are likely to complete the trial

Leber PD, Davis CS.. *Control Clin Trials 1998,* 19:178-187. Friedman et al. Fundamentals of Clinical Trials. Third Edition. 1998.

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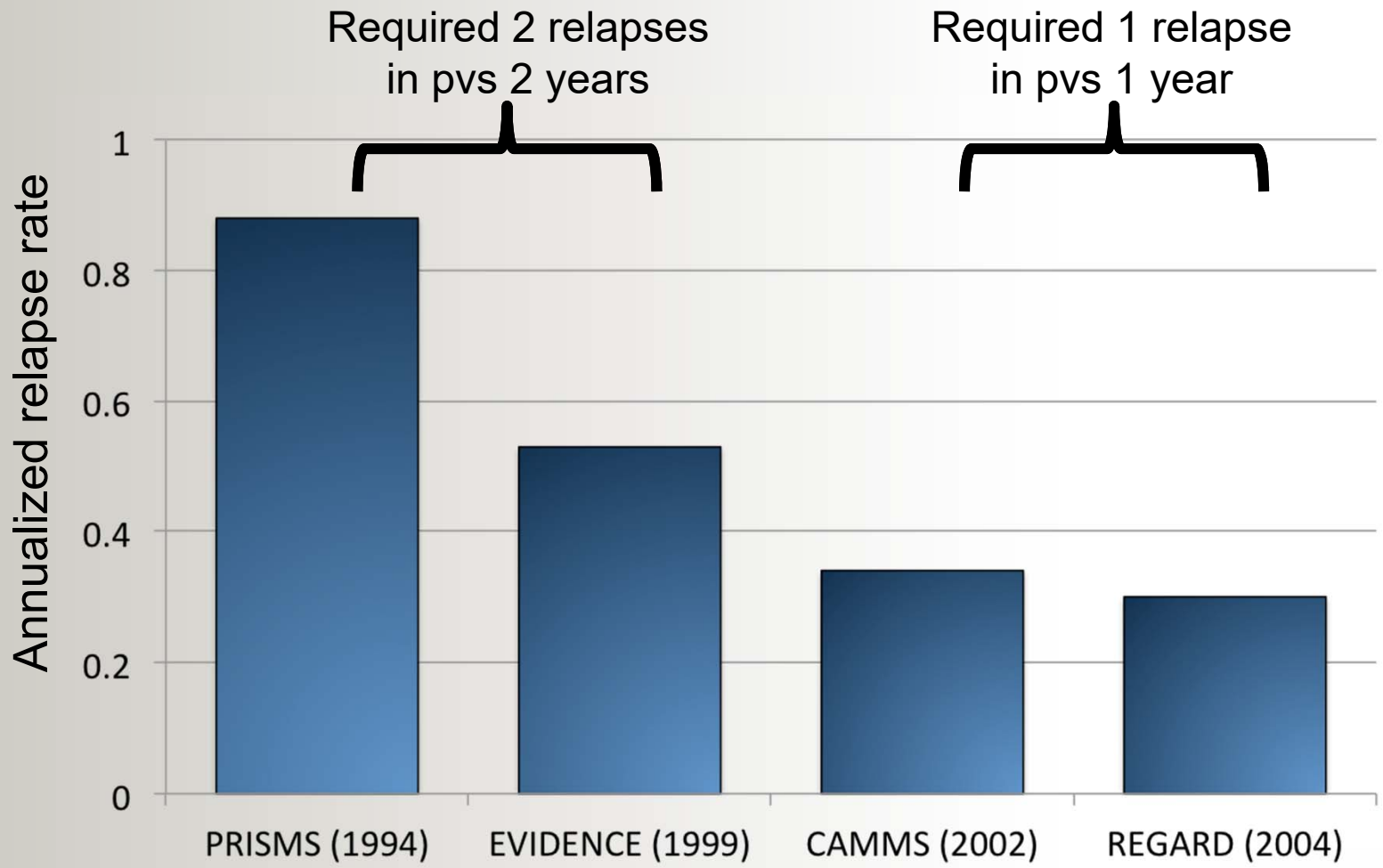
Study Design Choices – Eligibility Criteria



Uitdehaag et al. Curr Med Res Opin. 2011.

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What About in the Acute Neurologic Setting?

- Meta-Analysis of recruitment to acute stroke trials
- Inclusion criteria strongly associated with recruitment success
  - Maximum allowed time from symptom onset
  - Inclusion of mild strokes

Elkins et al. Stroke 2006.

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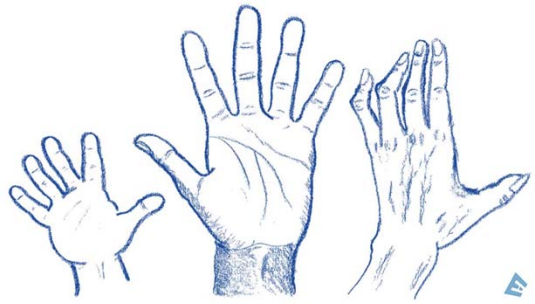
Inclusion Across the Lifespan



June 1–2, 2017 Workshop Summary

- Trials frequently exclude patients who make up the bulk of potential treatment users
  - E.g., cancer patients >65 years
  - Age of puberty onset can vary by group
- A thoughtful approach is required
  - Don't simply adopt previous or standard age limits
  - Consider physiologic measures that are warranted by safety
- *Protection from research* can be replaced by *protection through research*

https://report.nih.gov/UploadDocs/NIH%20Inclusion%20Across%20the%20Lifespan%20Workshop%20Summary%20Report%20_FINAL_508.pd

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Why Do Patients Participate?

Parkinson's Disease[1]

- Advance science (63%)
- Access to treatments (56%)
- Neurologist's recommendation (52%)
- Benefit others (52%)
- Severity of disease (44%)
- Receive quality care (37%)
- Reputation of investigator (23%)
- Request of neurologist (16%)
- No other options (15%)
- Prestige of institution (15%)

Hypertension[2]

- Personal health benefit (40%)
- Help others (37%)
- Contribute to scientific knowledge (14%)
- Access to care (12%)
- Trust in hospital or individual (7%)
- Money (6%)
- Other (8%)

Alzheimer's disease prevention[3]

- Altruism (56%)
- Desire to lower risk for AD (54%)
- Learn lifestyle information about AD (34%)
- Family history (26%)
- Convenience (20%)
- Learn diagnostic risk (16%)
- No reason not to (14%)
- Protect future generations (12%)
- Free medical care (12%)
- Access to investigational drugs (10%)
- Reputation of investigator/institution (10%)
- Incentives/payments (8%)
- Social support (4%)

[1]Valadas et al. *Parkin Rel Disord* 2011; [2]Halpern et al. *Am Heart J* 2003; [3]Grill et al. *Alz & Demen* 2013.

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What About in the Acute Neurologic Setting?

Reasons for Positive Views of EFIC	%
Direct medical benefit	88
Unable to get consent	39
Risks are low/no harm	35
Contribute to science/help patients	32
Other people agreed (family/community leaders)	26
Trust in researchers	24
In case of emergency, do what needs to be done	21
Patient is so badly injured it could not hurt	14
Research is important	11

Dickert et al. Crit Care Med 2015.

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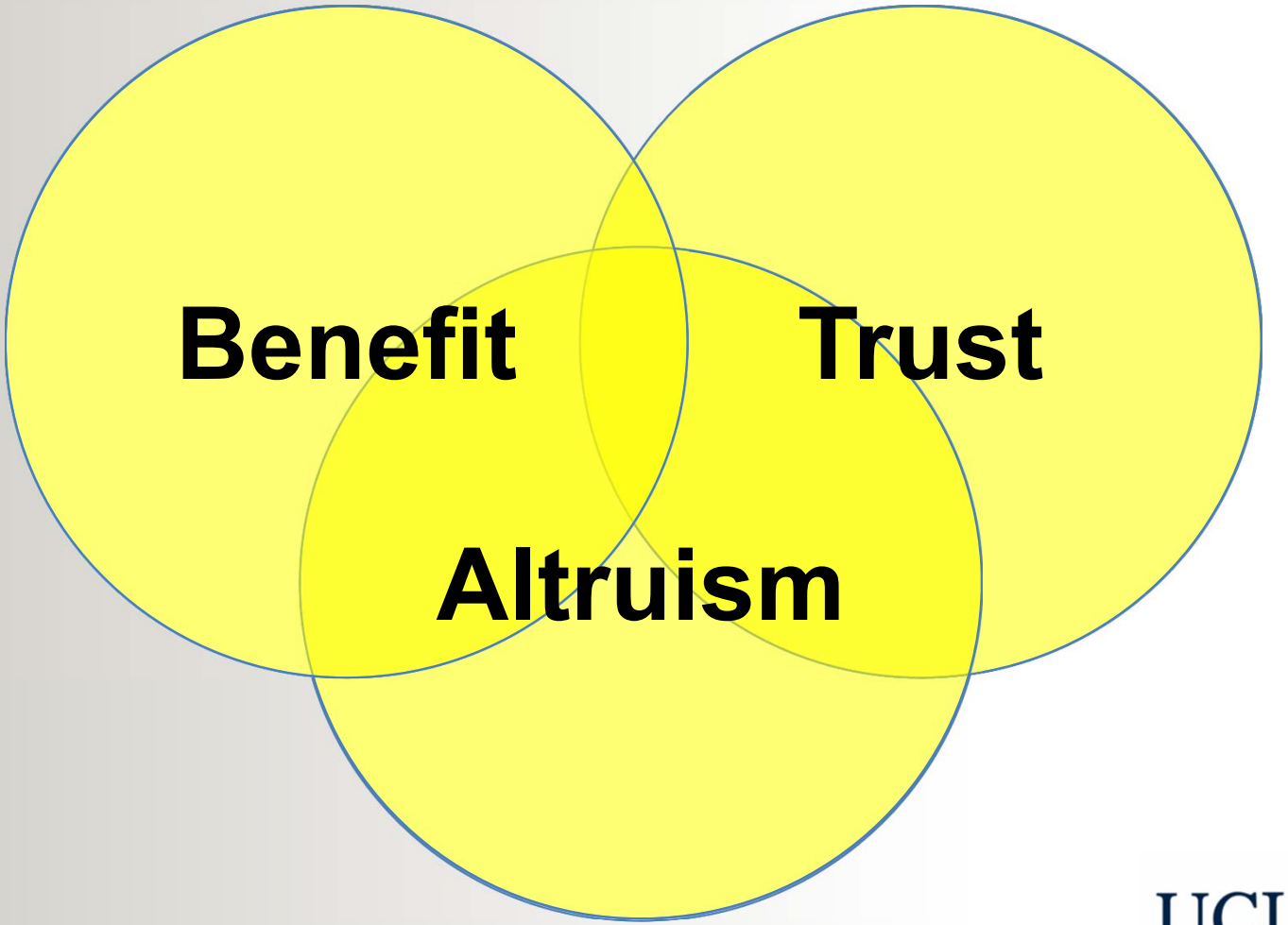
Patient Perspective



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Why Don't Patients Participate?

Parkinson's Disease[1]

- Fear of AEs (50%)
- Aggressiveness of treatment (35%)
- Inconvenience (34%)
- None (24%)
- Distance from hospital (19%)
- Possibility of placebo (11%)
- Hospitalization (8%)
- Number of visits (8%)
- Data privacy (6%)

Hypertension[2]

- Having to stop current meds (56%)
- Inconvenience (38%)
- Fear of known AEs (35%)
- Possibility of placebo (24%)
- Skeptical of research (13%)
- Fear of unknown AEs (12%)
- Progression of other illnesses (10%)
- Other (15%)

Alzheimer's disease prevention[3]

- Fear of investigational drugs (48%)
- Fear of medical procedures (22%)
- Lack of time (18%)
- Travel (8%)
- Lack of personal need (12%)
- Skepticism toward research (12%)
- Hopelessness/denial (8%)

[1]Valadas et al. *Parkin Rel Disord* 2011; [2]Halpern et al. *Am Heart J* 2003; [3]Grill et al *Alz & Demen* 2013.

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What About in the Acute Neurologic Setting?

Survey of Opt-Out Bracelet Requesters for Cardiac Arrest Study with EFIC

- 70% agreed that medical research in emergency care is important
- 63% disagreed that there are times when individual rights should be limited for the benefit of public health
- 87% agreed that “it is never okay to conduct research without the consent of the participant.”
- 82% agreed that “the right to make my own choice is more important than the interests of the general community.”

Nelson et al. *Resuscitation* 2013.

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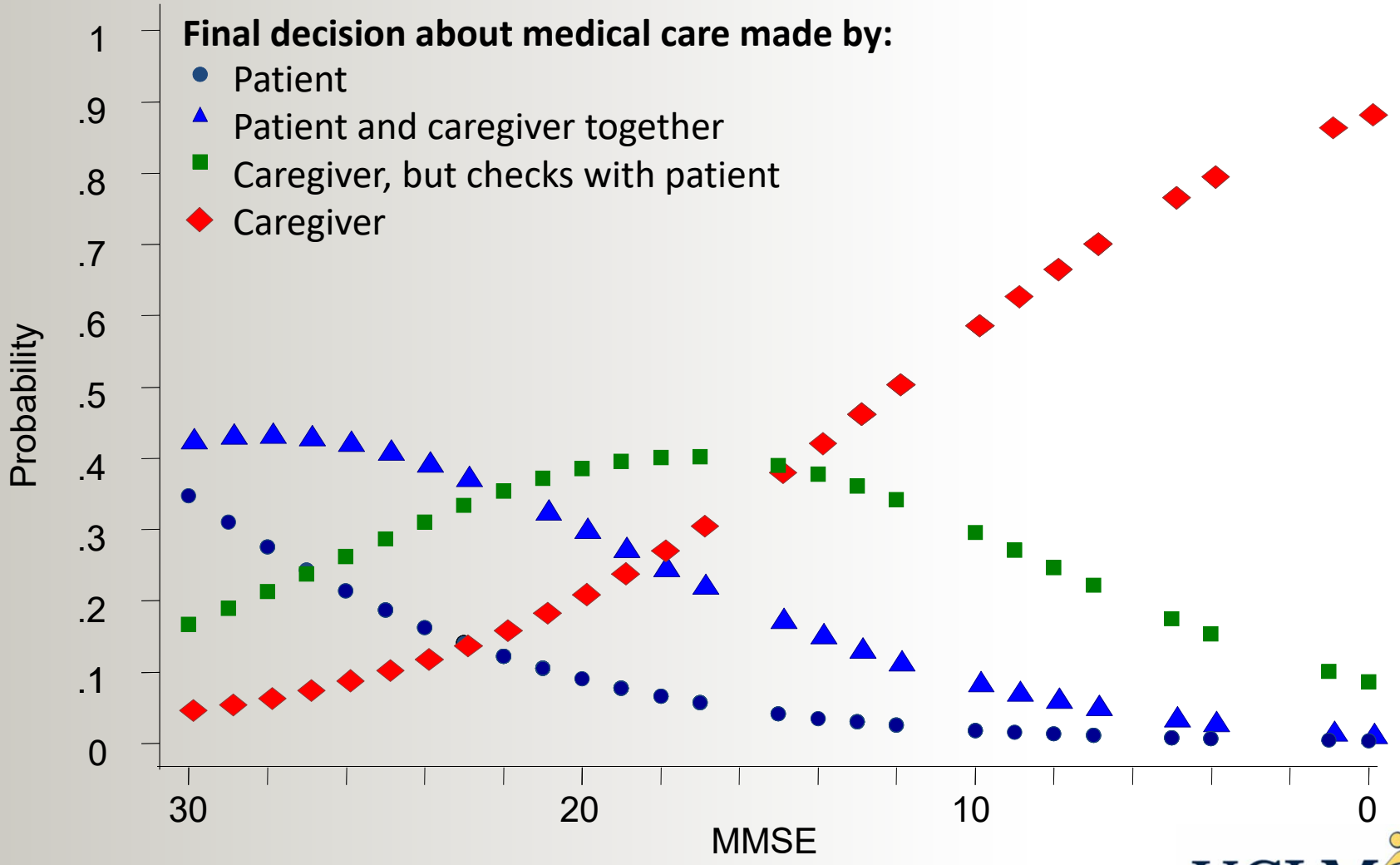
Medical Decision Making Through AD



Karlawish et al, *J Geriatr Psych & Neurol* 15:68-72, 2002

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Study Design Choices – Visit Number

- Telemedicine safety visits, instead of in-person visits, may reduce participant burden and increase willingness to participate
  - Enroll at a medical Center but complete safety visits at a local clinic
- Using telephone visits may suffice in some trials for assessing safety and reducing the overall burden of participation
  - MS Ibudilast trial

Shprecher et al. Telemed J E Health 2012.

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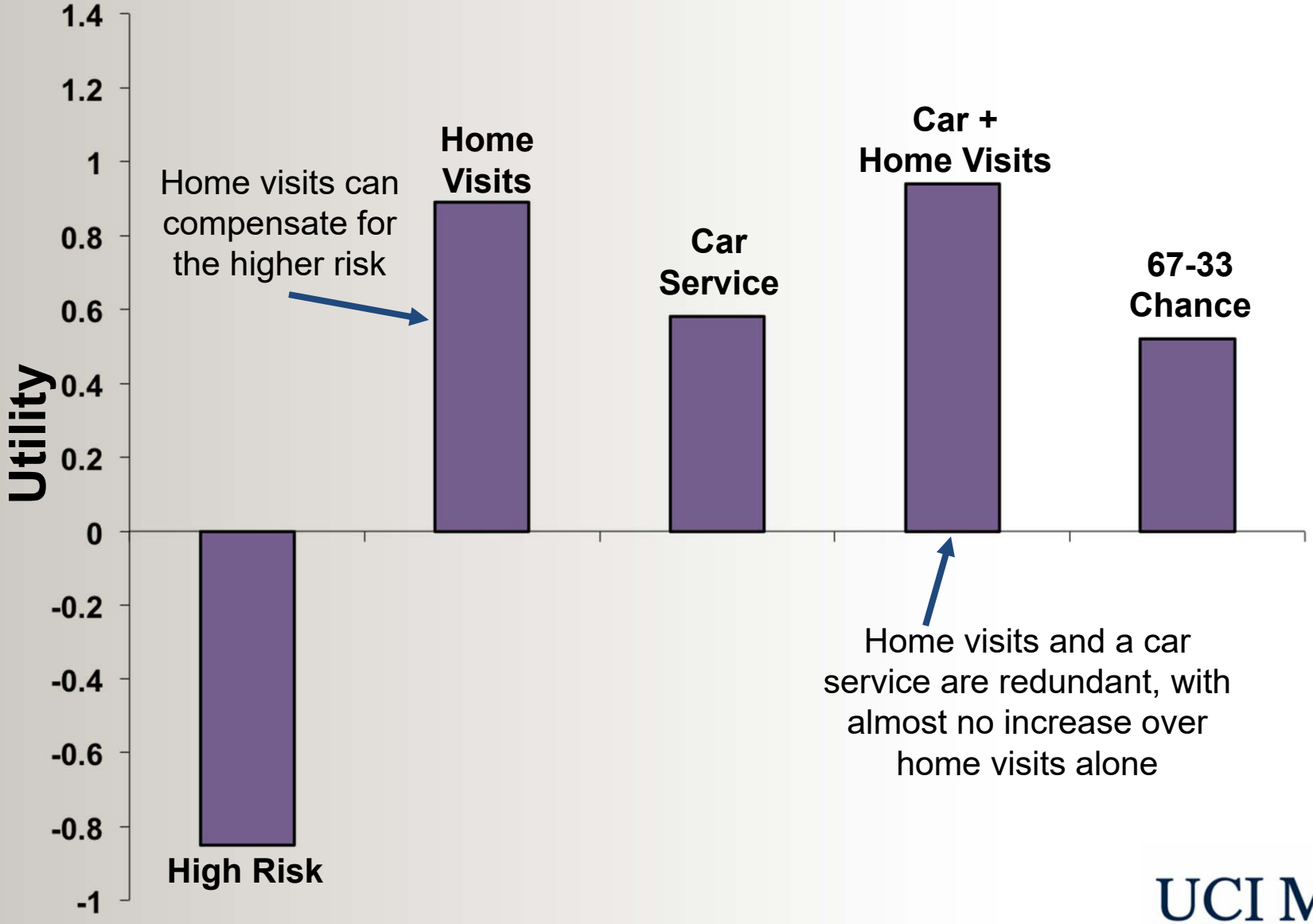
Redesigning Alzheimer's disease Trials



Karlawish et al. Neurology 2008.

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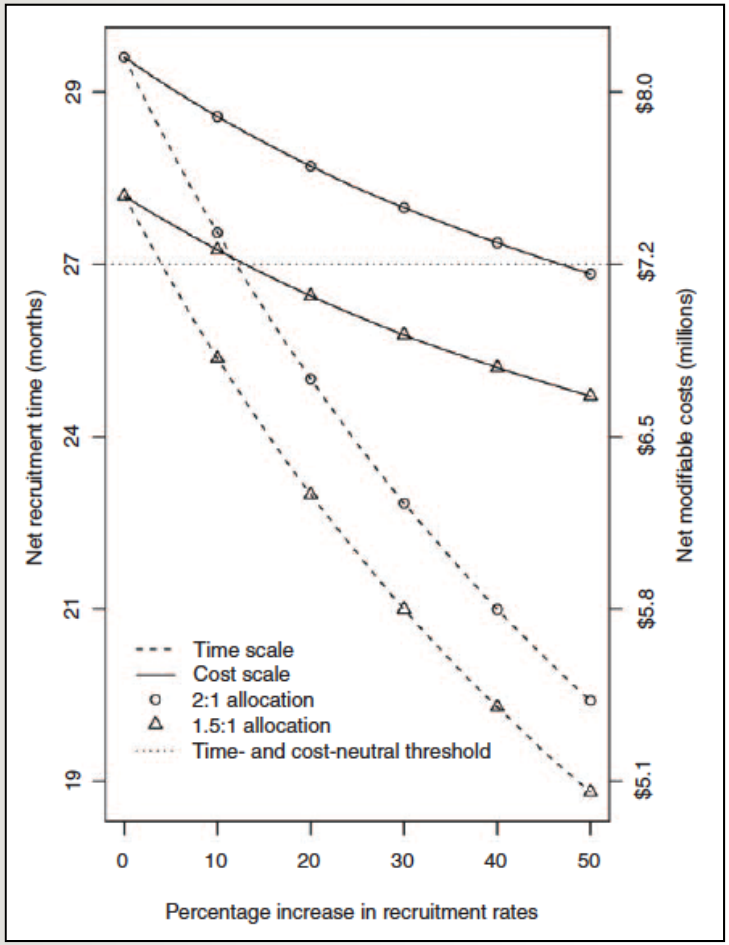
Alternate Allocation

Drug/Placebo Ratio	% increased recruit. rate needed to abbreviate
1 to 1	-
1.5 to 1	4%
2 to 1	12%

Drug/Placebo Ratio	% increased recruit. rate for cost
1 to 1	-
1.5 to 1	13%
2 to 1	47%



Pros

- Relatively low improvement in recruitment rate to improve trial
- Increased access to drug
- Dose information
- Increased knowledge of rare AEs

Cons

- Longer trial
- Modest increase in cost
- Increased subject burden

Vozdolska et al. Clin Trials 2009

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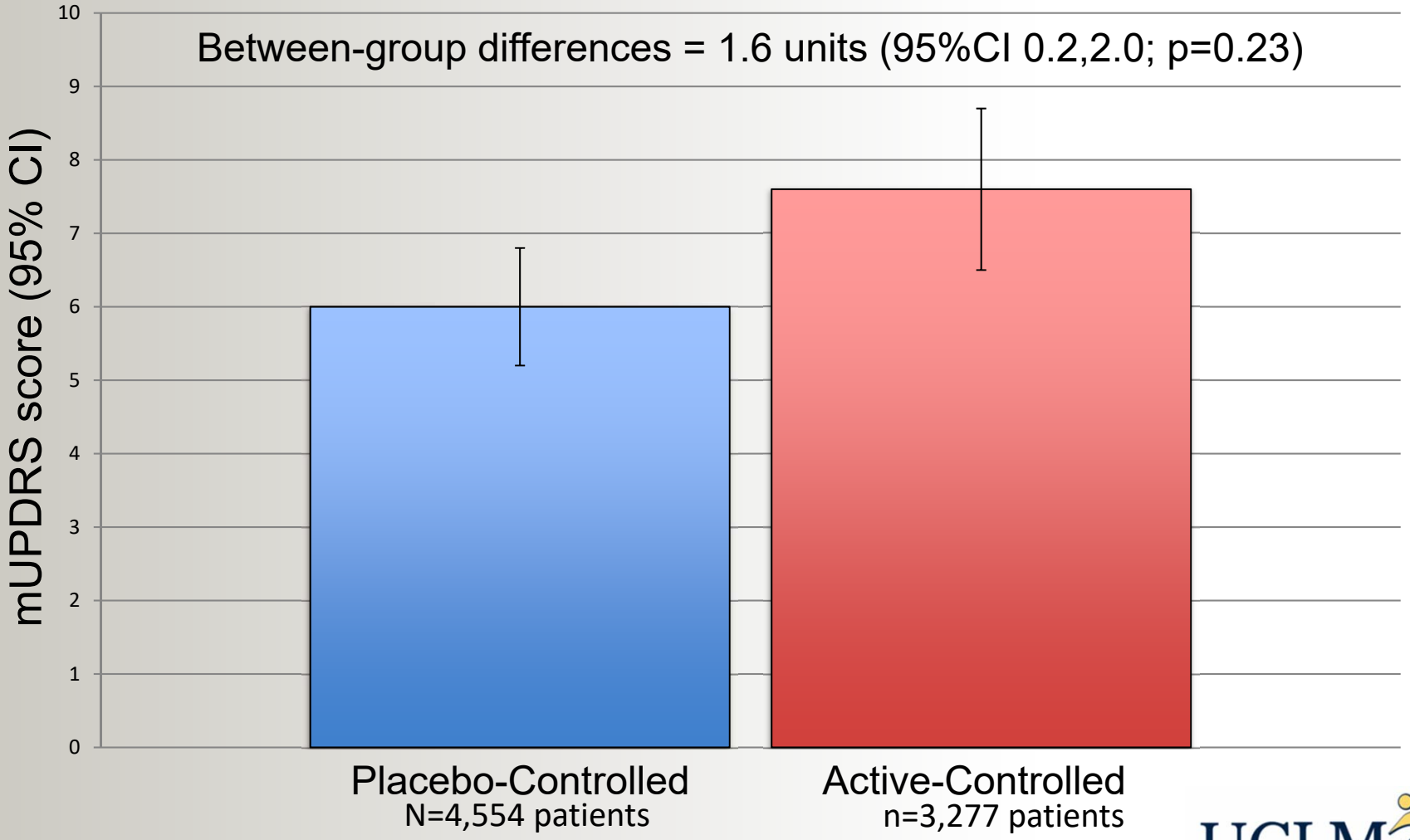
The Lessebo Effect



Mestre et al, Neurology 2014. Hey and Kimmelman, Neurology 2014.

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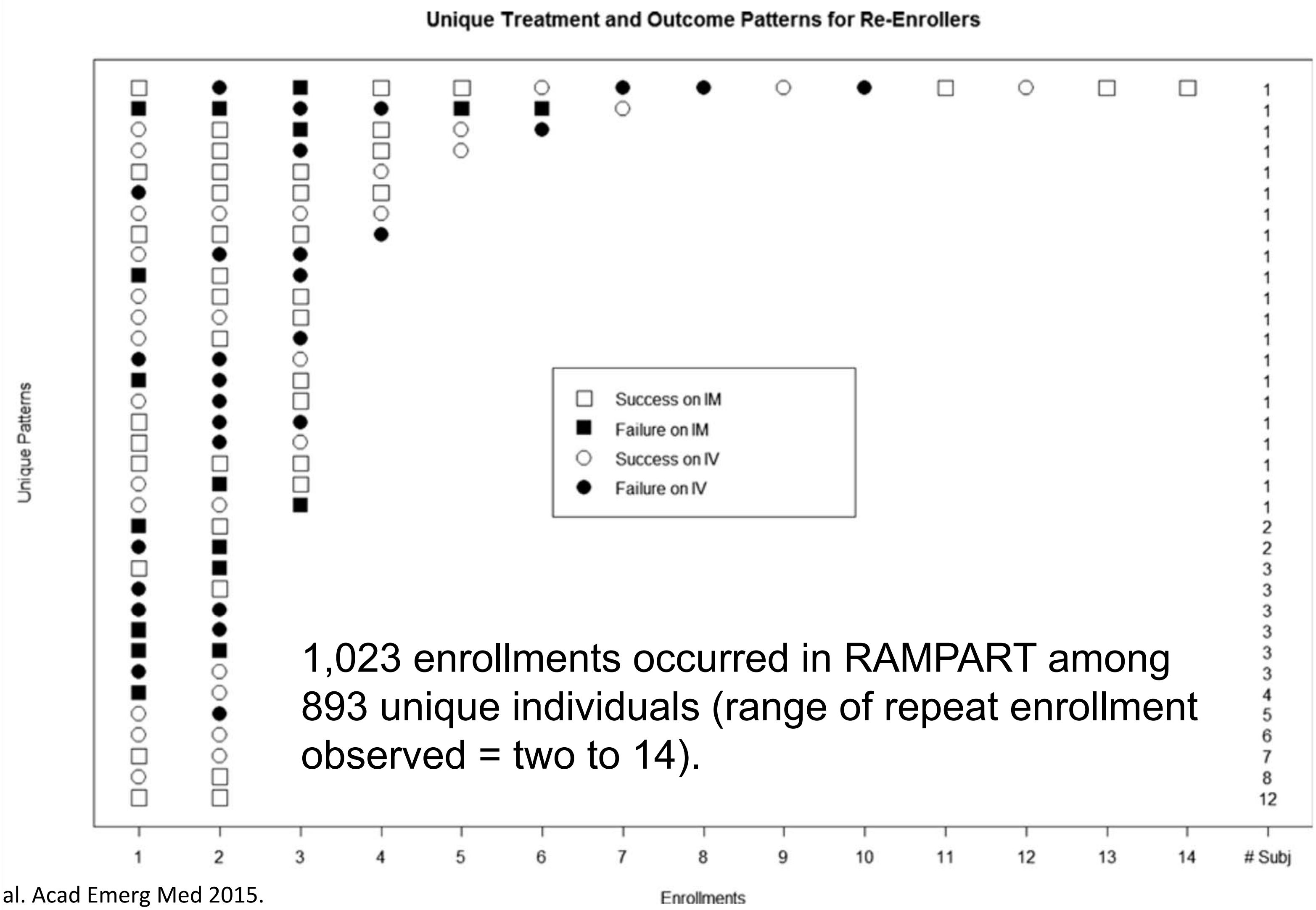
Study Design Choices – Rescreening

- Many (if not most) patients will be ineligible for trial criteria.
- Will you allow previous screen failures to be reassessed (e.g., after washout of excluded therapy)?
- 55 of 59 (93%) participants rescreened for the Combination therapy in relapsing-remitting MS trial were enrolled

Schneider et al JAGS 1997. de Los Rios la Rosa et al. Stroke 2012. Grill et al. Dementia Geriatric Cognitive Disord 2012. Elm et al Clinical Trials 2014. Bhanushali et al. Clin Trials 2014

Study Design Choices – Re-Enrollment in EFIC Trials

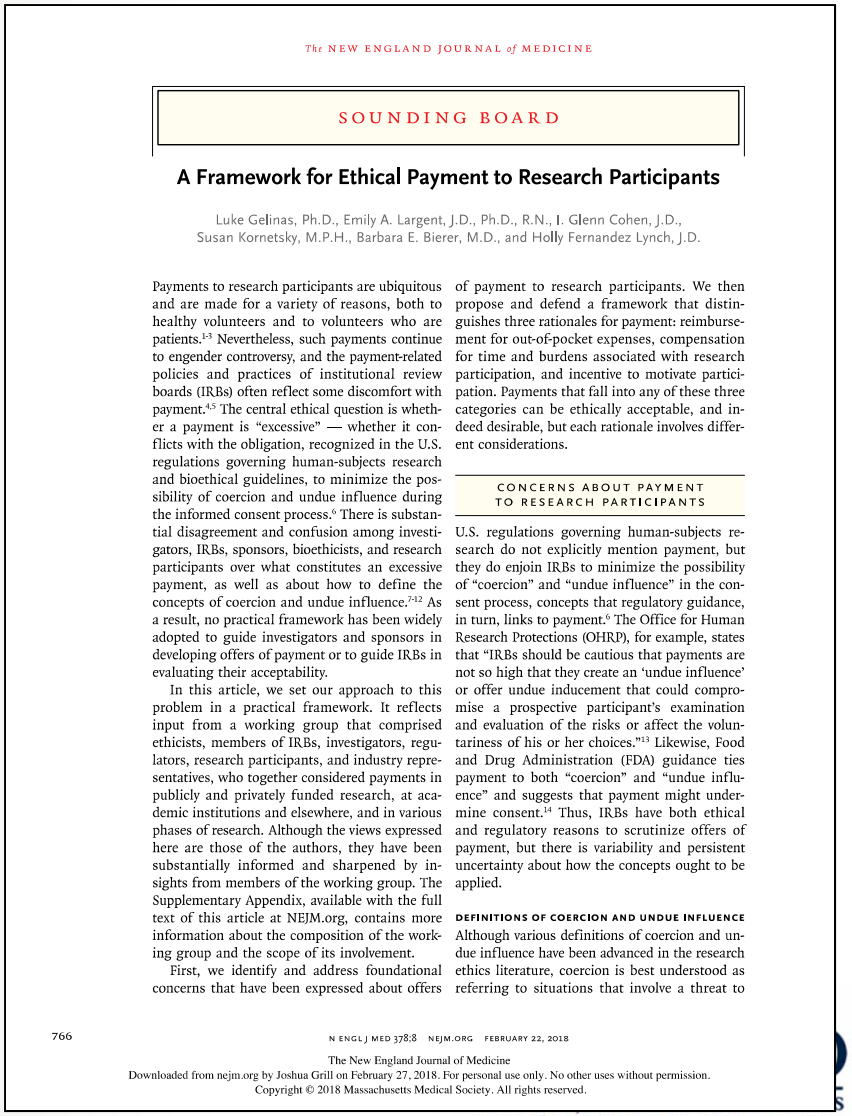


1,023 enrollments occurred in RAMPART among 893 unique individuals (range of repeat enrollment observed = two to 14).

Meurer et al. Acad Emerg Med 2015.

Defining Incentives

- Reimbursement
  - Covering out of pocket costs
- Compensation
  - Fair wage for time spent
- Incentive
  - Above fair wage to induce participation



The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

A Framework for Ethical Payment to Research Participants

Luke Gelinas, Ph.D., Emily A. Largent, J.D., Ph.D., R.N., I. Glenn Cohen, J.D., Susan Kornetsky, M.P.H., Barbara E. Bierer, M.D., and Holly Fernandez Lynch, J.D.

Payments to research participants are ubiquitous and are made for a variety of reasons, both to healthy volunteers and to volunteers who are patients.[1-3] Nevertheless, such payments continue to engender controversy, and the payment-related policies and practices of institutional review boards (IRBs) often reflect some discomfort with payment.[4,5] The central ethical question is whether a payment is "excessive" — whether it conflicts with the obligation, recognized in the U.S. regulations governing human-subjects research and bioethical guidelines, to minimize the possibility of coercion and undue influence during the informed consent process.[6] There is substantial disagreement and confusion among investigators, IRBs, sponsors, bioethicists, and research participants over what constitutes an excessive payment, as well as about how to define the concepts of coercion and undue influence.[7-12] As a result, no practical framework has been widely adopted to guide investigators and sponsors in developing offers of payment or to guide IRBs in evaluating their acceptability.

In this article, we set our approach to this problem in a practical framework. It reflects input from a working group that comprised ethicists, members of IRBs, investigators, regulators, research participants, and industry representatives, who together considered payments in publicly and privately funded research, at academic institutions and elsewhere, and in various phases of research. Although the views expressed here are those of the authors, they have been substantially informed and sharpened by insights from members of the working group. The Supplementary Appendix, available with the full text of this article at NEJM.org, contains more information about the composition of the working group and the scope of its involvement.

First, we identify and address foundational concerns that have been expressed about offers of payment to research participants. We then propose and defend a framework that distinguishes three rationales for payment: reimbursement for out-of-pocket expenses, compensation for time and burdens associated with research participation, and incentive to motivate participation. Payments that fall into any of these three categories can be ethically acceptable, and indeed desirable, but each rationale involves different considerations.

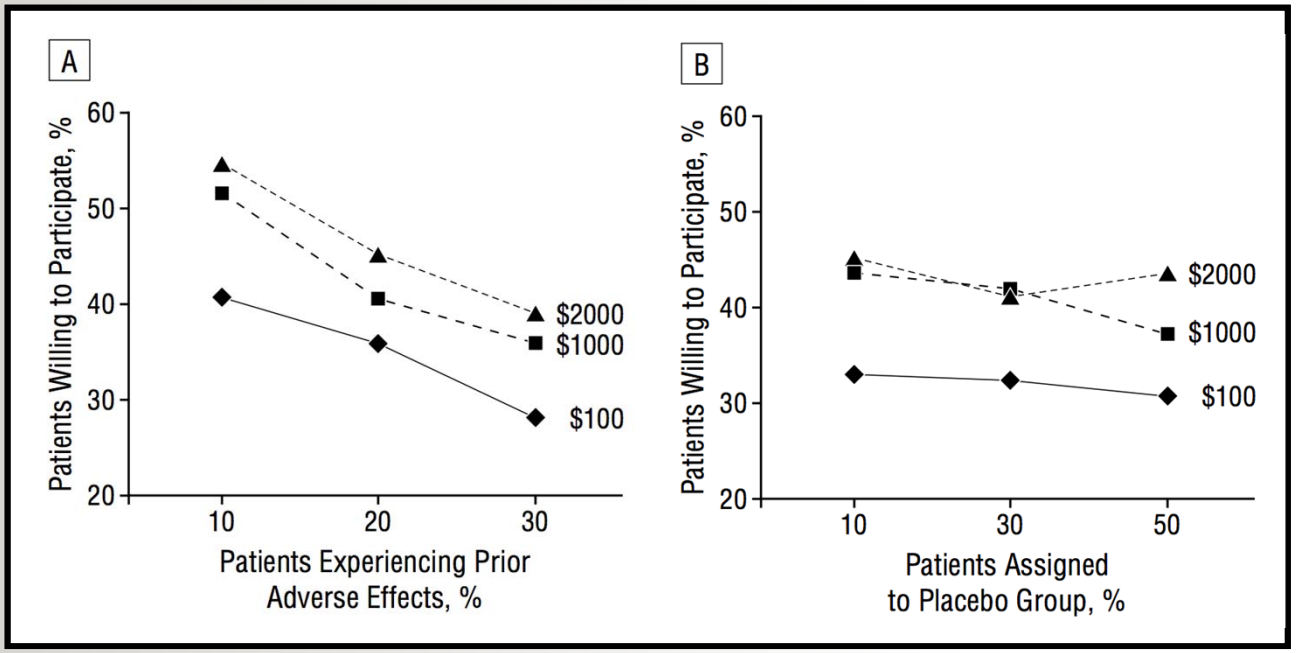
CONCERNS ABOUT PAYMENT TO RESEARCH PARTICIPANTS

U.S. regulations governing human-subjects research do not explicitly mention payment, but they do enjoin IRBs to minimize the possibility of "coercion" and "undue influence" in the consent process, concepts that regulatory guidance, in turn, links to payment.[6] The Office for Human Research Protections (OHRP), for example, states that "IRBs should be cautious that payments are not so high that they create an 'undue influence' or offer undue inducement that could compromise a prospective participant's examination and evaluation of the risks or affect the voluntariness of his or her choices."[13] Likewise, Food and Drug Administration (FDA) guidance ties payment to both "coercion" and "undue influence" and suggests that payment might undermine consent.[14] Thus, IRBs have both ethical and regulatory reasons to scrutinize offers of payment, but there is variability and persistent uncertainty about how the concepts ought to be applied.

DEFINITIONS OF COERCION AND UNDUE INFLUENCE

Although various definitions of coercion and undue influence have been advanced in the research ethics literature, coercion is best understood as referring to situations that involve a threat to

What About Offering Incentives?



	$10 incentive	$5 incentive
Response rate	60.5	52.8*
Cost/response	$18.48	$12.24*

*p<0.01 vs $10

Halpern et al. Med Care 2002. Halpern et al. Arch Intern Med 2004.

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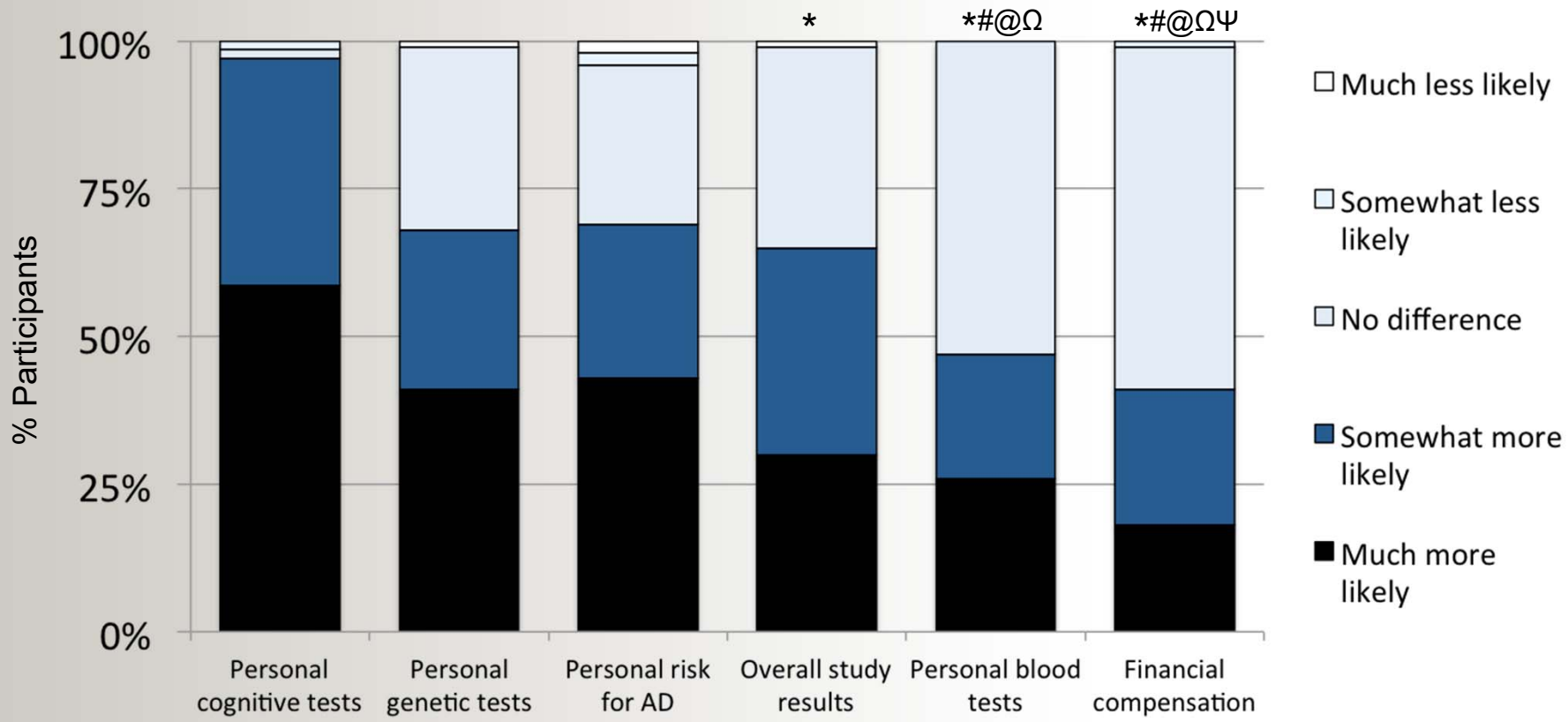
What About Offering Incentives?



*p<0.05 vs cognitive testing results; #p<0.05 vs genetic test results; @p<0.05 vs personal AD risk estimates; Ωp<0.05 vs overall study results; Ψp<0.05 vs personal blood test results.

Grill et al., Neurobiol Aging 2016.

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Participant Sources

- The majority of participants are patients recruited by physician investigators.

Source	Participants, n (%)
Physicians involved in trial, direct recruitment	63%
Other treating neurologists referral	29%
Clinic staff referral	4%
Other physician referral	1%
Site websites	1%
Clinicaltrials.gov	<1%
Friend	<1%
Other patient	<1%
In-clinic advertising	<1%

Bhanushali et al. Clin Trials 2014

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Increase Potential Participant Awareness

- Increase referrals
  - Physicians
  - Advocacy groups
- Distribute well designed brochures
- Internet
- Advertising
- Media
- Utilize committed participants as advocates for studies
- Utilize available registries

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New Opportunities with Electronic Medical Records

Table 1 Clinician versus automated notification system

	April 15–June 14 Clinician page	June 15–August 14 Automated
Number of women aged 15–30 years	1701	1713
Number of ankle injuries	44	41
Number of contacts by page	7	23
Number not eligible	6	16
Number of eligible subjects missed	16	0
Number enrolled	1	6
Sensitivity	5.9% (95% CI 3.1% to 30.8%)	100% (95% CI 56.1% to 100%)
Specificity	77.7% (95% CI 57.3 to 90.6%)	52.9% (95% CI 35.4 to 69.8%)
Positive predictive value	14.2%	30.4%

Cardozo et al. Emerg Med J 2010.

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New Opportunities with Social Media

- Should be held to the same ethical standards as “offline” recruitment
- Particular areas of emphasis
  - Respect for privacy
  - Investigator transparency
  - Terms of agreement
  - Recruiting networks
  - Participant communication

Gelinas et al., Am J Bioethics 2017

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Finding a way to predict seizures with Apple Watch.

Researchers hope Apple Watch could eventually help predict seizures before they happen. Since its launch, the EpiWatch app has enabled people to accurately track the onset and duration of seizures in real time, creating a correlation between episode history and medication. Participants sensing an impending seizure launch the app by tapping a custom complication on

Brochures

- Illustrations and Photos
- Large fonts (especially when recruiting older participants)
- Answer the reader's questions
  - What are the symptoms of the disorder?
  - What is the purpose of the study?
  - Why is the study meaningful or important?
- List financial or other incentives
- Say who is eligible
  - Be careful to not cause a potentially eligible participant to mistakenly assume that they are not eligible.

Brochures

- Uses
  - May facilitate discussion with patients
  - Can be shared with advocacy groups
  - Can be left in medical office waiting rooms, by other clinicians and in community outreach
  - Can also be used by participants to recruit other participants
- Alternatively, video brochures may be equally, if not more, effective in communicating the purpose and importance of a study and have the additional advantage of the potential to go viral

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Video Brochures Engage and Educate

https://player.vimeo.com/video/112942312

Paula Hunter is giving something very precious to help Alzheimer's fight - her brain

July 13, 2015 | Updated 9:52 p.m.

Nurse Diane Capobianco, left, waits while Paula Hunter receives a monthly infusion at UC Irvine as part of the A4 study

MOST POPULAR

- Disneyland employee accused of trying to sell admission tickets in exchange for sex with
- 'Hoax' no more: Man arrested in Vallejo-to-Huntington Beach kidnapping; woman told FBI sh
- Lakers' young players struggle against Knicks

The Orange County Register, July 13, 2015.

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Utilize Registries

- Repository of individuals willing to consider participating in studies
- Contact immediately upon study initiation, rather than serially enrolling
- Registrants have
  - Provided medical information so that queries are enriched for eligibility
  - Expressed a willingness to participate in research
  - May have defined the types of studies in which they are/are not interested in participating

Grill and Galvin, Alz Dis Assoc Disord 2014.

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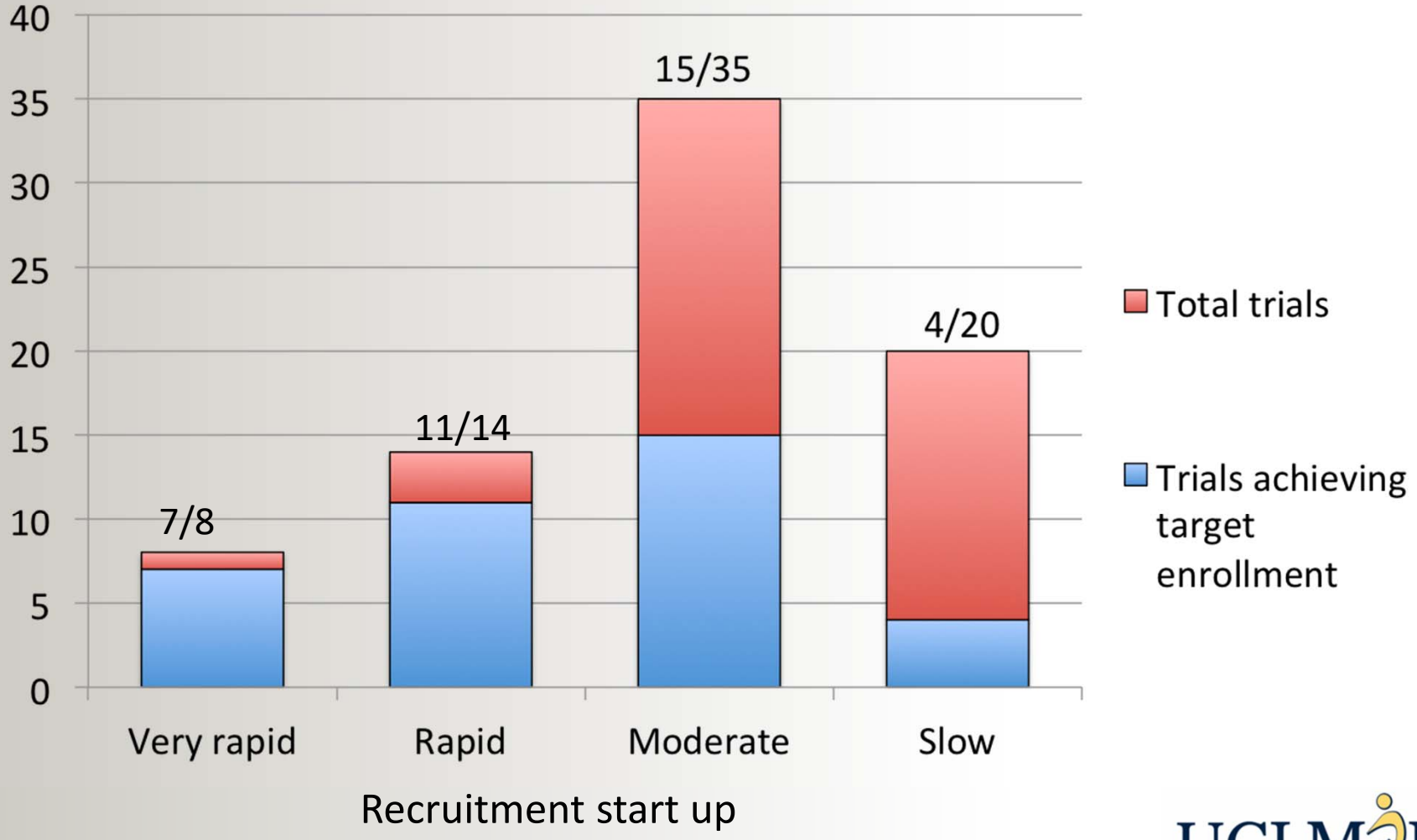
Initial Recruitment Rate Predicts Overall Success



Haidich and Ionnidis, J Clin Epidemiology 2001.

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Why Is Diverse Participation Important?

- Social justice
  - Health disparities persist and are perpetuated through research with non-generalizable samples
- Scientific rationale
  - Race/ethnicity are cultural constructs with genetic underpinnings
    - Treatment safety and efficacy may differ among races/ethnicities

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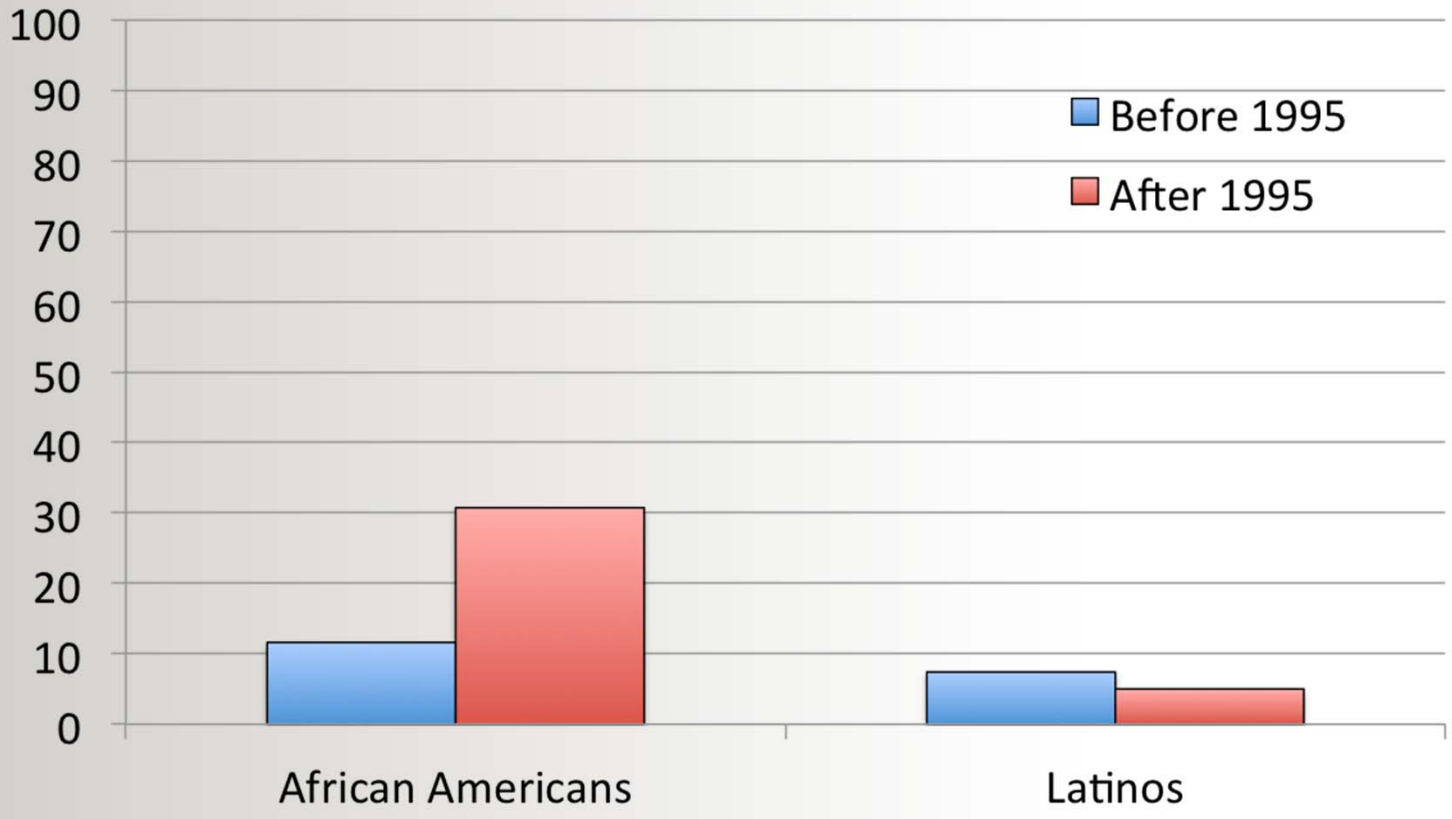
Race and Ethnicity Can Impact Treatment Effects

Trait	Findings
Breast cancer	Differences in Native American ancestry at the estrogen receptor locus led to discovery of a genetic variant that was protective against breast cancer in Latinas.
Heart failure	A post-hoc analysis of clinical trials of fixed-dose combination of hydralazine and isosorbide dinitrate suggested that black, but not white patients had a significant reduction in mortality compared to placebo.
Increased preterm birth rate	Exposures to endocrine disrupting chemicals such as bisphenol-A (BPA) are more common among minorities who live in low socioeconomic strata. BPA causes epigenetic alterations of the germ line resulting in increased preterm birth rate; these alterations can pass down to future generations.
Stevens-Johnson syndrome	The risk of carbamazepime-induced Stevens-Johnson syndrome due to HLA-B*1502 is highest in populations of Southeast Asian and East Asian ancestry.
Kidney disease	Genetic variants of APOL1 have been associated with kidney disease in individuals of African ancestry whose ancestors lived in regions of Africa endemic with trypanosomiasis; these renal risk variants are largely absent in individuals of European or Asian ancestry.
Response to efavirenz	Blood levels and treatment response to this antiretroviral drug are influenced by individual ancestral make up, which can be accounted for by polymorphisms of cytochrome 2B6 and genetically defined ancestry.

Oh et al. PLOS Med, 2015.

URG Participation in NINDS-Sponsored Clinical Trials



Burke et al. Neurology 2011.

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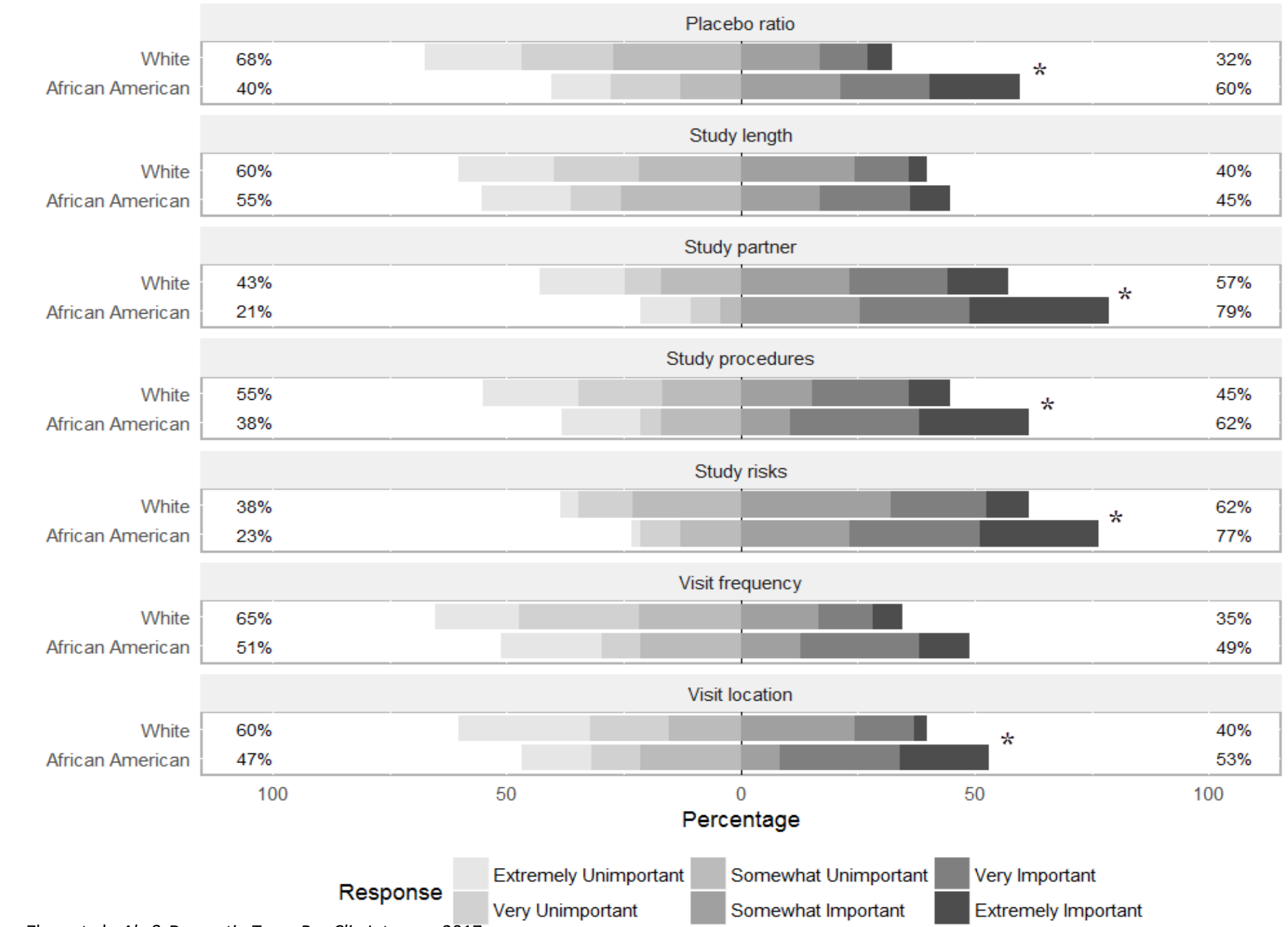

Zhou et al., *Alz & Dementia Trans Res Clin Interven*. 2017.

Recommendations to Improve Trial Diversity

- Invest and be present in the community through education and partnerships with community leaders and organizations
  - Practice transparency, describe research procedures, allay fears; involve participants
- Hire promotoras and community liaisons
- Partner with community providers
- Maintain staff diverse in appearance and spoken language
- Reduce logistical barriers by offering flexible visit times, transportation assistance, childcare, etc.

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Trial Sample Diversity

- What should be the goals?
  - Local or national representation (e.g., census data)
  - Scientific representation (i.e., sufficient for secondary analyses of efficacy or safety)
- How to budget?
  - Diverse costs more than convenient recruitment
  - But reviewers may “raise eyebrows” at higher budgets
- Some RFAs for diversity research exist
- Site selection may be critical
- Mandates can create unenviable positions for PIs

Oh et al. PLOS Med, 2015.

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What Should You Do If Recruitment is Slow?

- Understand the challenges
  - High screen fail rate vs low enrollment
- Previous successes as guidance?
  - New sources
  - Advertisement
  - Recruitment coordinator
- In multisite trials
  - Can successful signs instruct improvement at slower sites?

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Retention

- Retaining enrolled subjects is just as (if not more) important as recruiting them
  - Loss to follow ups prevent scientific questions from being answered
  - Underpowered trials may be unethical
  - Skewed drop outs can bias results

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The Ethics of Underpowered Trials

Trial	N	Active Completers	Placebo Completers	Overall Retention
Dimebon	183	78/89 =0.88	77/94 =0.82	0.92
Gamma secretase inhibitor	51	32/36 = 0.89	12/15 =0.80	0.86
Rosiglitazone	518	106/122 =0.87	336/389 =0.86	0.85
High dose B vitamin	409	204/240 =0.85	140/169 = 0.83	0.84
Rivastigmine patch	1195	704/893 =0.79	266/302 =0.88	0.82
Estrogen replacement	120	65/81 =0.80	32/39 =0.82	0.81
Galantamine	978	539/692 =0.78	240/286 =0.84	0.80
Rofecoxib	351	179/240 =0.74	88/111 =0.79	0.76
DHA	402	178/241 = 0.74	129/161 =0.80	0.76
Bapineuzumab	234	92/122 =0.75	87/107 =0.81	0.76
AN1792	372	223/299 =0.74	53/73 =0.73	0.74
Idebenone	536	281/407 =0.69	96/129 =0.74	0.72
Atorvastatin	640	207/314 =0.66	245/326 =0.75	0.71
Galantamine	636	266/423 =0.63	172/213 = 0.81	0.69
Tarenflurbil	1684	506/862 =0.59	540/822 =0.66	0.62

Grill and Karlawish, Alz Res Ther 2010

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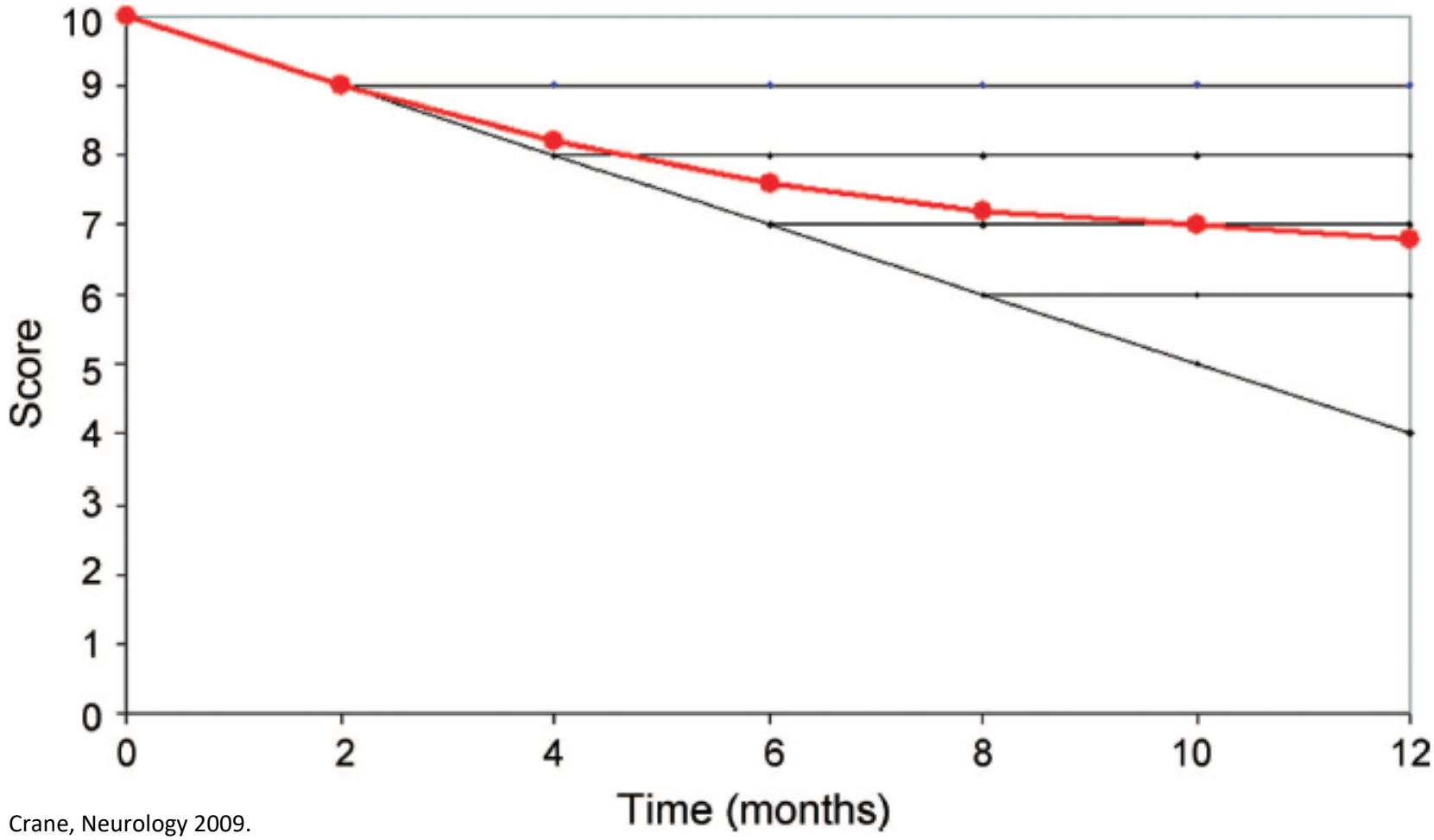
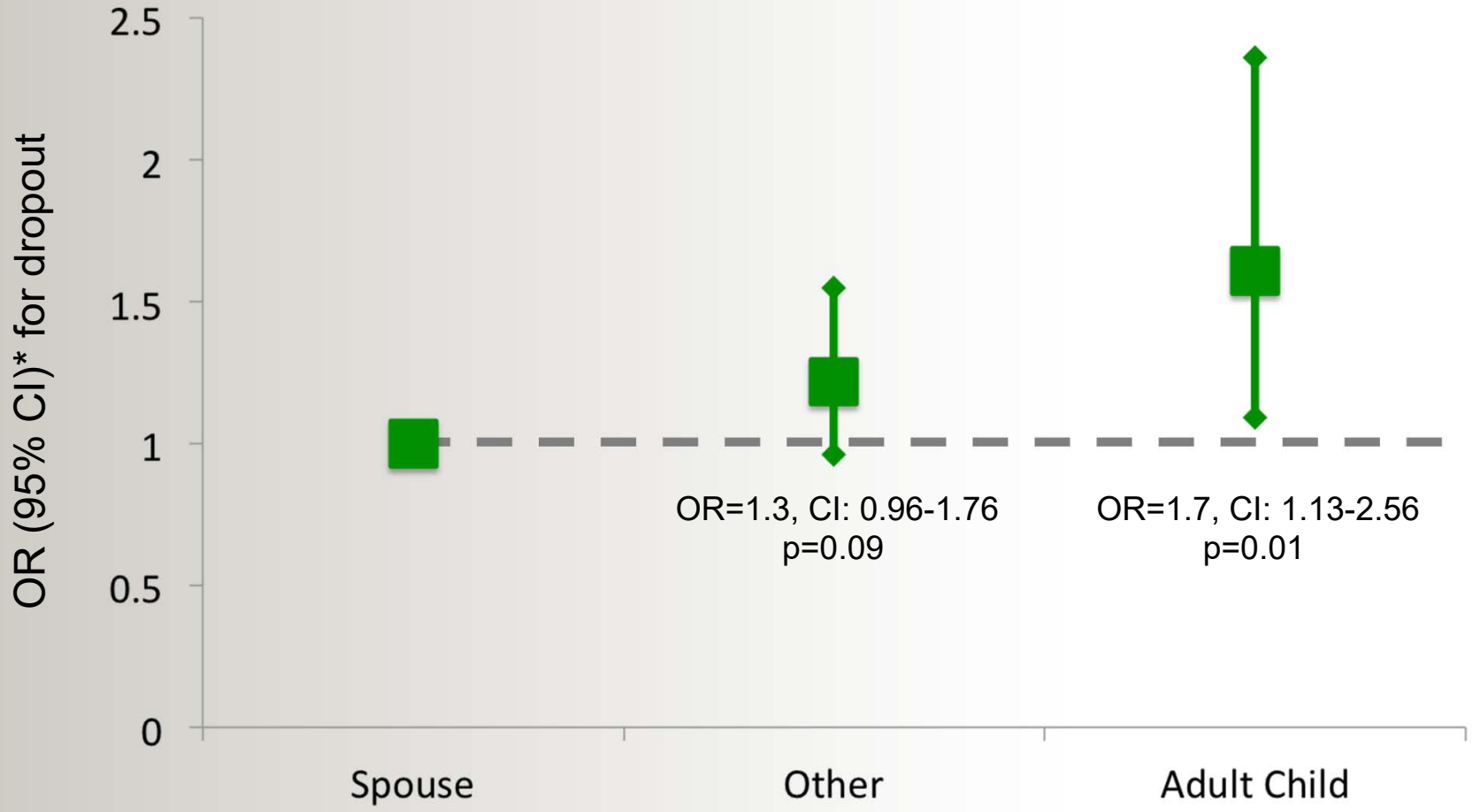
Skewed Drop Out

Figure Effect of the last observation carried forward method for missing data in a hypothetical trial with no difference between active treatment and placebo other than earlier dropout in the active treatment arm



Crane, Neurology 2009.

Study Partner Impact on AD Trial Retention



*Relative to spouse study partner group

Grill et al. Neurology 2013.

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Informant Replacement

Outcome measure	Stable informant, mean±SD	New informant, mean±SD	t-test, p value	Test of equal variance, p value
CDR-SB	2.01±2.57	2.37±3.07	0.10	0.0002*
FAQ	3.45±5.02	4.48±6.39	0.02*	<0.0001*
NPI-Q	0.11±1.14	0.13±1.38	0.81	<0.0001*

CDR-SB, Clinical Dementia Rating Sum of Boxes. FAQ, Functional Assessment Scale. NPI-Q, Neuropsychiatric Inventory-Quick.

Grill et al. Alz Dis Assoc Disord 2015.

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Themes of Retention Strategies

- Community involvement
- Study identity
- Study personnel
- Study description
- Contact and scheduling methods
- Reminders
- Visit characteristics
- Benefits of study
- Financial incentives
- Reimbursement
- Nonfinancial incentives
- Special tracking methods

Robinson et al., J Clin Epi 2007. Robinson et al., J Clin Epi 2015.

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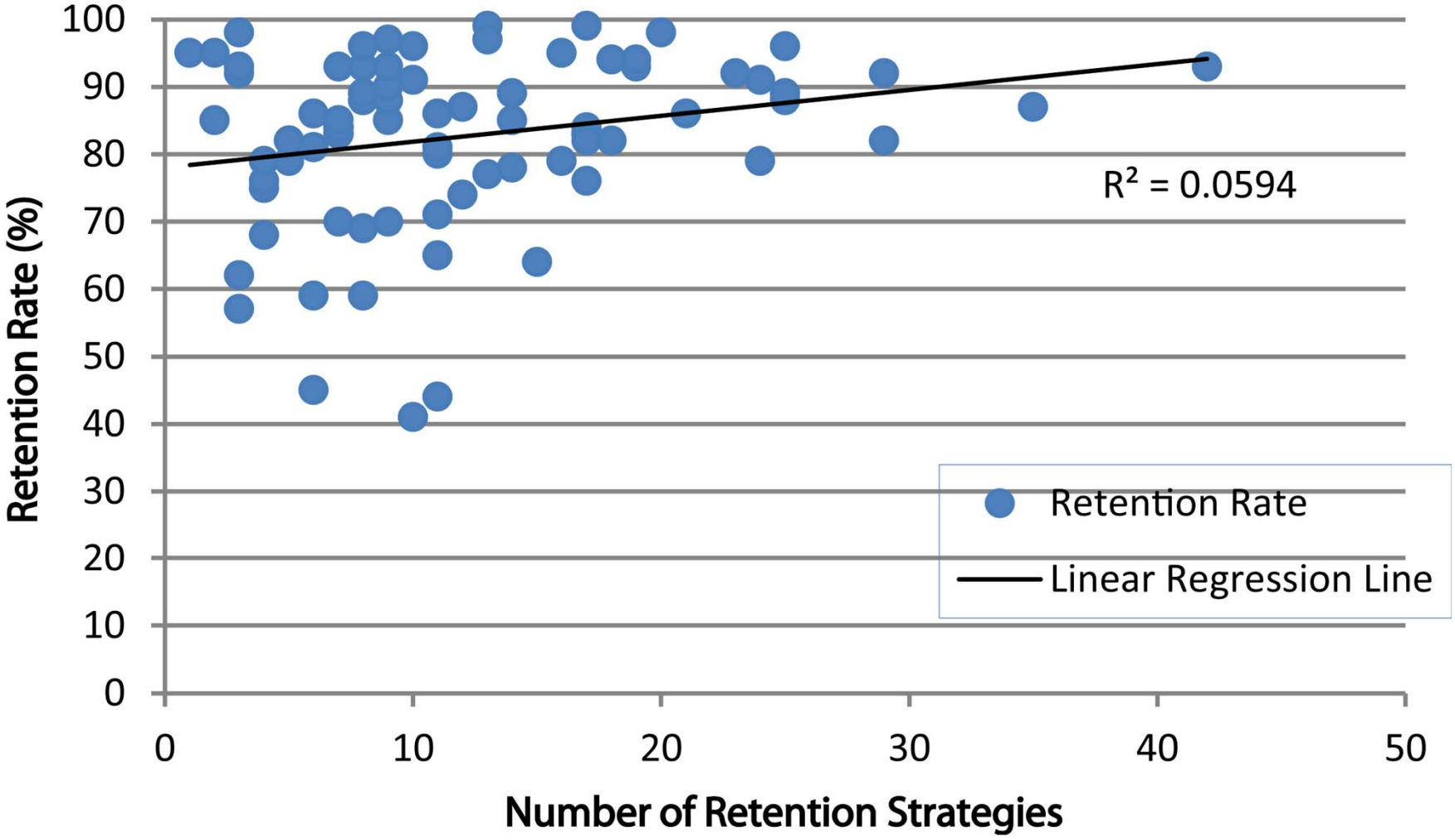
Retention Strategies



Robinson et al., J Clin Epi 2015.

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Retention Recommendations

- Design the protocol to minimize long-term burden on participants
- Ensure all sites are practicing good retention, which begins with enrolling appropriate participants
- Communicate the importance of trial completion to participants
- Show gratitude for participants
- Financial incentives improve retention
  - Save for milestone visits, cash > gift cards, more $ = higher retention
- Use newsletters and other forms of communication to keep site teams and participants engaged and invested in trial success

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Show Gratitude to Participants

- Thank you notes
- Other token gifts (coffee mugs, pens, blankets, magnets can help with appointment reminders)
- Tweets/texts
- See them/talk to them
  - PI visibility has major impact on retention
  - Understand when burden in accumulating

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BRIEF REPORT

Participant Satisfaction With Learning Alzheimer Disease Clinical Trial Results

Aimee L. Pierce, MD,†‡ Chelsea G. Cox, MPH, MSW,*† Huong Nguyen, BSc,* Dan Hoang, BA, BSc,*† Megan Witbracht, PhD,*† Daniel L. Gillen, PhD,*†§ and Joshua D. Grill, PhD*†||¶#*

Key Words: clinical trials, disclosure, engagement

(*Alzheimer Dis Assoc Disord* 2018;00:000–000)

Clinical trials face consistent barriers to recruitment, due in part to skepticism and distrust toward research.[1,2] Improving public trust in research may be essential to expediting achievement of the national goal of developing effective therapies for Alzheimer disease (AD).[3] One mechanism to improve trust is to ensure positive experiences by study participants.

Providing aggregate study results to participants at the conclusion of a trial represents a minimal ethical standard and is an important aspect of trial conduct that improves public trust in the research enterprise.[4] Yet, the consistency with which results are shared with participants and their satisfaction with this process are largely unstudied. To address this need and to better understand how participant satisfaction relates to the manner in which trial results are disclosed, we interviewed participants from a recently completed clinical trial for mild AD.

METHODS

The purpose of this study was to better understand how AD trial participants and study partners learn trial results, whether they are satisfied with this experience, and whether this experience affects their attitudes toward AD clinical research. To do so, we performed a telephone interview study with participants in a recent phase 3 industry-sponsored clinical trial. The UC Irvine Institutional Review Board (IRB) approved this study. Verbal informed consent was performed by telephone and acknowledged in writing by the investigator performing the interview.

The Progress of Mild Alzheimer Disease in Participants on Solanezumab Versus Placebo, EXPEDITION-3, study enrolled mild AD patients (Mini Mental State Exam score range, 20 to 26) to an 18-month study of the monoclonal antibody against amyloid beta, solanezumab, or placebo (https://clinicaltrials.gov/ct2/show/NCT01900665). Participants received monthly infusions of study medication and underwent routine examination including neuropsychological assessment of study outcome measures. All participants were required to enroll with a knowledgeable informant, or study partner.

Individual participants who completed their 18-month double-blind period were invited to rollover into an open-label extension. The final participants in EXPEDITION-3 completed the double-blind portion in October 2016. The open-label extension period continued until November 23, 2016, when a press release announced that development of solanezumab in mild AD would be halted because it did not meet the primary efficacy outcome of the study (https://investor.lilly.com/releasedetail.cfm?ReleaseID=1000871). Several media outlets, including scientific publications, popular press television, radio, and print outlets, and Internet websites, released stories about the announcement.

Immediate formal communication of trial results to study participants was not instructed by the trial protocol or through communication from the sponsor. At our site, we called each of the 11 participants (of whom 10 had enrolled in the open-label study) and their study partners within one week of the press release to inform them of the available trial results. Blinding assignments were not available at the time of these notification phone calls.

To recruit to the current study, we mailed an invitation letter or invited participants verbally at an in-person study closure visit. In addition, an IRB-approved flyer for the interview study was shared with colleagues at 2 nearby EXPEDITION-3 sites. Information about the number of participants at these sites was not available.

A single member of the research team (H.N.) conducted the interviews separately with participants and their study partners. After a brief description of the EXPEDITION-3 study, participants' knowledge and participation in the study were confirmed. We outlined the timeline of events for the announcement of the EXPEDITION-3 results and used forced choice questions to assess the approximate timing and manner through which participants learned results. We examined participants' satisfaction with the manner through which they learned results, preferences for the manner of learning results, overall desire to learn results and randomization assignment, and likelihood of participating in future AD trials. In total, the survey included 16 forced choice questions. Four additional questions collected brief participant demographic information including age, race, ethnicity, and years of education. Completion of the survey took ~15 minutes. A copy of the interview guide is available by emailing the corresponding author. Study data were collected and managed using Research Electronic Data Capture (REDCap).[5]

RESULTS

We interviewed 5 trial participants and 8 trial study partners (Table 1). Two study partners had participated in

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Communicating with participants during the conduct of multi-center clinical trials

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Abstract

Background: Communicating with trial participants is an important aspect of study conduct, relevant for informed consent and respect for participants. Group teleconferences are one means to convey information to trial participants. We used group teleconferences during an ongoing large-scale clinical trial to communicate important trial updates.

Methods: The National Institute of Neurological Disorders and Stroke Exploratory Trials in Parkinson's Disease Longitudinal Study-1 trial studied creatine for treatment of early-stage Parkinson's disease. A total of 1741 participants enrolled at 45 sites in the United States and Canada to take part in a double-blind randomized trial of 5 years of treatment with creatine versus placebo. The study leadership held two teleconferences with study participants and their caregivers after each of two pre-specified interim analyses, for a total of four teleconferences. Each agenda included a presentation by study leadership followed by an open question and answer period. Teleconference recordings were made available to all site personnel and trial participants. Recordings were reviewed and abstracted for themes and topics of the presentations, participant questions, and discussion. Number of participants, connection time for each participant, number of questions, and caller connection time were summarized using descriptive statistics. After the first teleconferences, participants who remained on the call until the end were invited to complete a voluntary, four-question survey about the teleconference process. During the second teleconferences, participants were notified of premature study closure.

Results: There were 258 callers for the first pair of teleconferences and 604 callers for the second pair of teleconferences. Study leaders answered more than 110 questions from study participants and caregivers across all calls. The most frequently asked question themes related to study drug, Parkinson's disease, side effects, future research, and data analysis. The initial teleconferences were well received by participants. Based on responses to the post-call survey, 98% (118/121) of participants found the call useful, 91% (115/127) were interested in future similar calls, 88% stated the call made them more likely to continue in the study (112/128), and 85% (90/106) were satisfied overall with study communications.

Conclusion: Teleconferences provide a convenient way to communicate with trial participants and can be used during the conduct of clinical trials to convey study progress and other information. For multi-site trials, teleconferences enable participants to engage directly with study leadership and to ask questions. Survey respondents were highly satisfied with the group teleconference experience. Future research is needed to determine whether teleconferences improve participants' satisfaction with clinical trial participation and improve retention.

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Show Gratitude to Participants

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Summary

- Recruitment is often slower than anticipated, delaying progress, increasing cost, and utilizing patient resources; at worst, could threaten validity
- Optimal recruitment begins with study planning
- Greater than expected retention can render a trial underpowered
- Retention may be optimized by considering participant perspective, investigator involvement, and effort to retain

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Questions?

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What About in the Acute Neurologic Setting?

Negative Views about EFIC	%
Concerns about consent	26
Other people not as accepting	16
Concerns about side effects	13
Unsure about balance of risks/benefits	8
Believes drug is experimental (guinea pigs)	7
Concerns about placebo	7
Lack of medical benefit	6
Others (family) disagreed	6

Dickert et al. Crit Care Med 2015.

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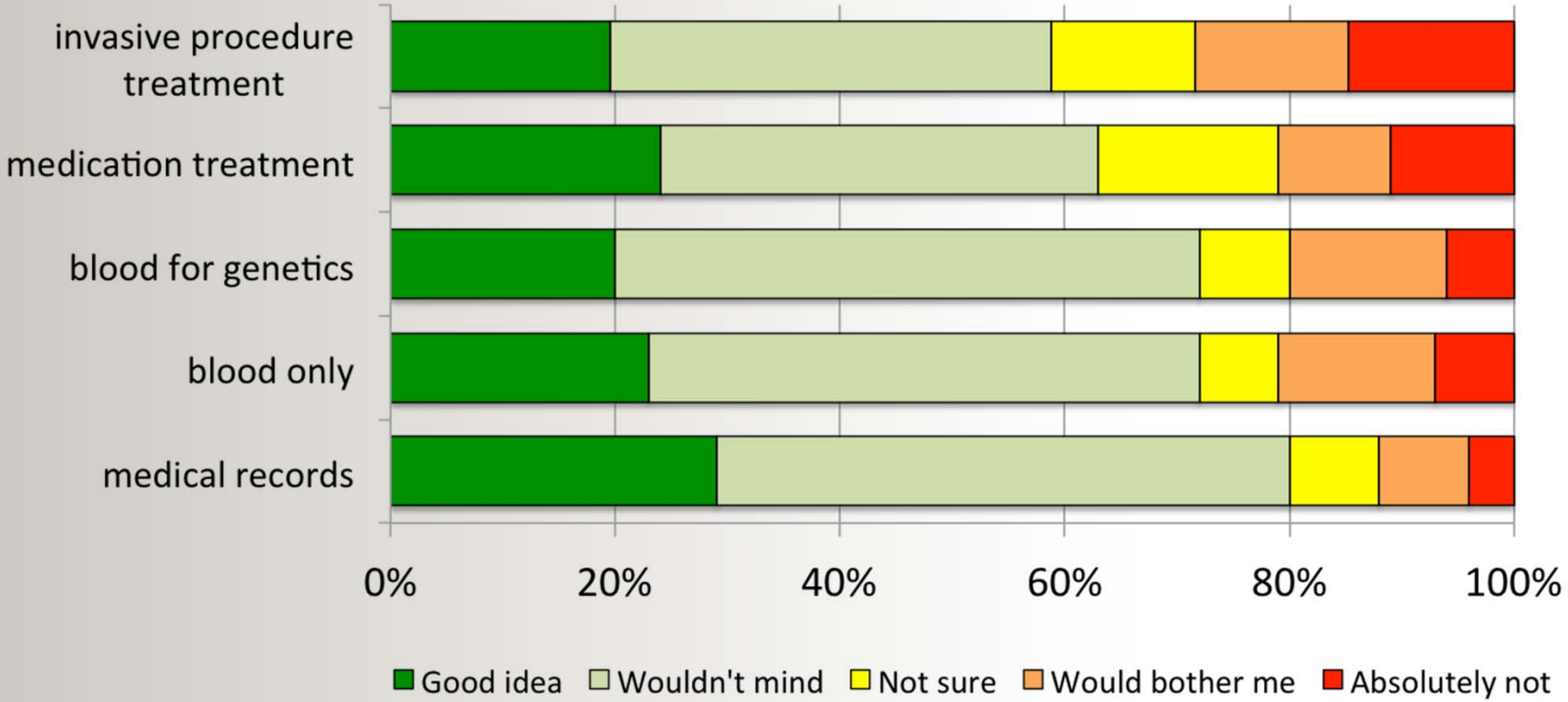
What About in the Acute Neurologic Setting?



- Unacceptability may be more common among minorities, lower education, those with previous negative research experiences
- Opinions can vary by trial specifics

Kleindorfer et al. Cerebrovasc Dis 2011. Smithline and Gerstle. Am J Emerg Med 1998. Dickert et al. Resuscitation 2013.

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EFIC Requirements

- 289 public disclosure activities over 22 months
- Cumulative estimated target audience = 12,978,315
  - Newspaper stories or announcements = 18%
  - Radio and television broadcasts = 10%
    - These accounted for 75% of the estimated target audience.
  - Electronic media including e-mail distributions, on-line postings, and website visits = 19% of activities and contributed 11% of the estimated target audience

→ 14 requests to opt out

Silbergleit et al. Acad Emerg Med 2012.

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