



Consenting for Acute Stroke Clinical Trials

Jennifer Juhl Majersik, MD

Associate Professor, Neurology

Chief, Division of Vascular Neurology

Director, University of Utah Stroke Center & Telestroke Network

PI, UT StrokeNet

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Presenter Disclosure Information

FINANCIAL DISCLOSURES:

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UNLABELED/UNAPPROVED USES DISCLOSURES:

None

OTHER DISCLOSURES:

NIH StrokeNet Executive Council member, lead of the working group on this subject.

Over-Arching NIH StrokeNet Goal

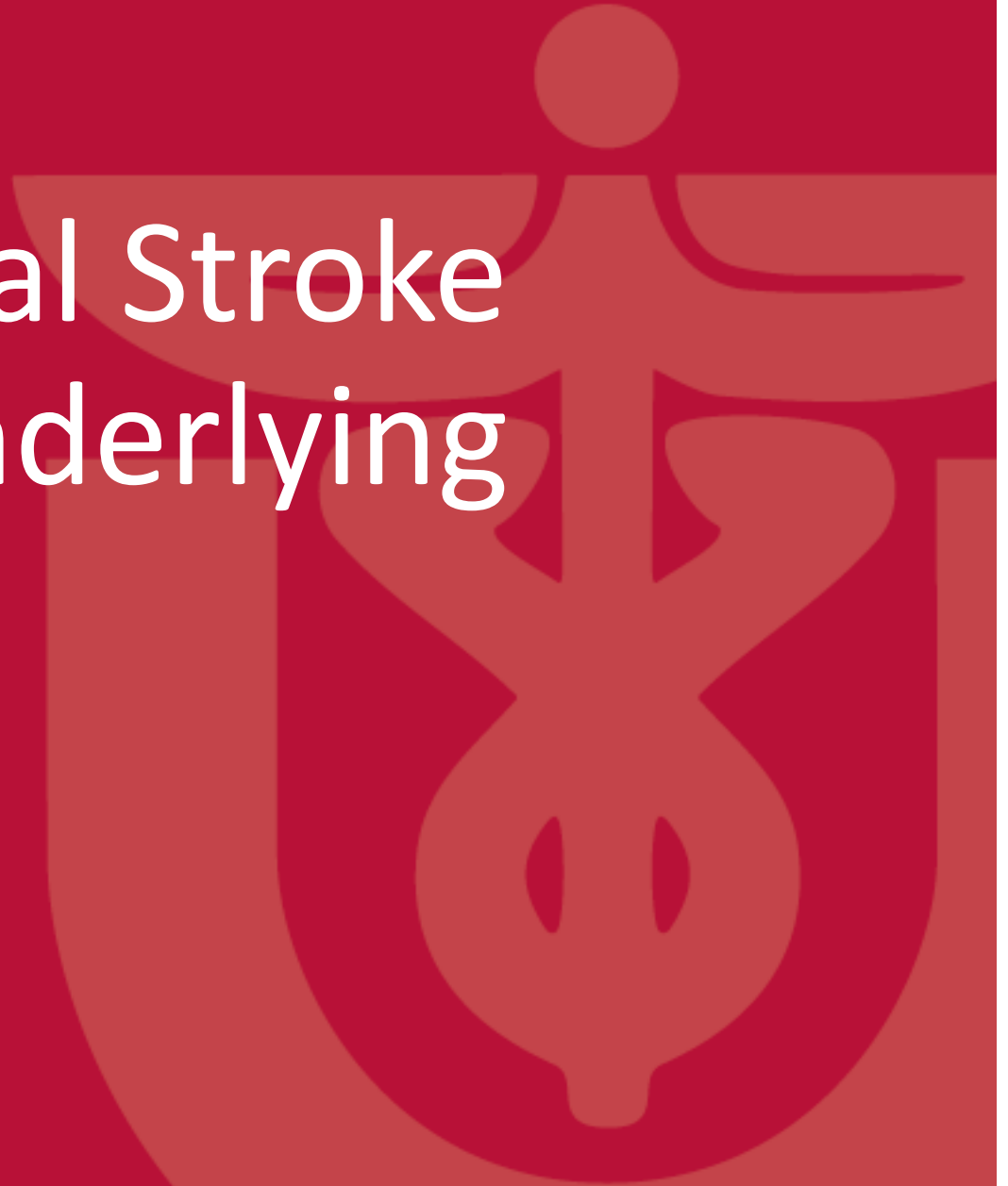
**Discover better treatments to
reduce stroke incidence,
treat acute stroke,
and improve stroke recovery**

*Requires enrolling as many patients
into high quality clinical trials as possible
While minimizing bias
And maintaining ethics*

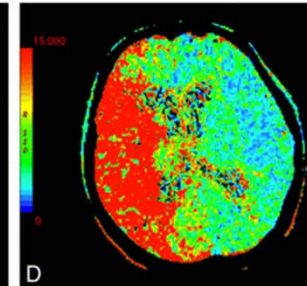
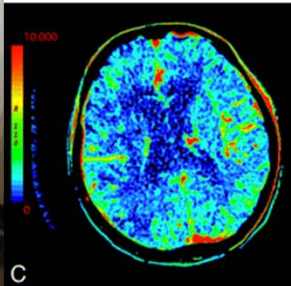
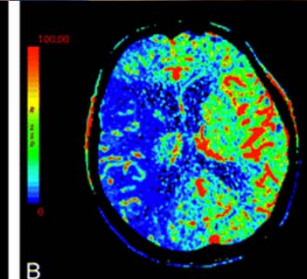
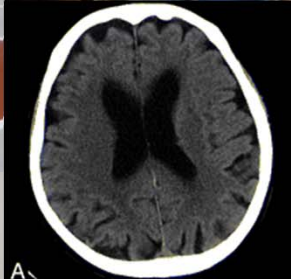
Today's Goals

- Learn the 3 ethical principles of research
- Learn the required elements of informed consent and their barriers in acute stroke trials
- Learn how alternate forms of consent can reduce these barriers
- Provide practical tips for informed consent

Acute Clinical Stroke Care: the underlying landscape



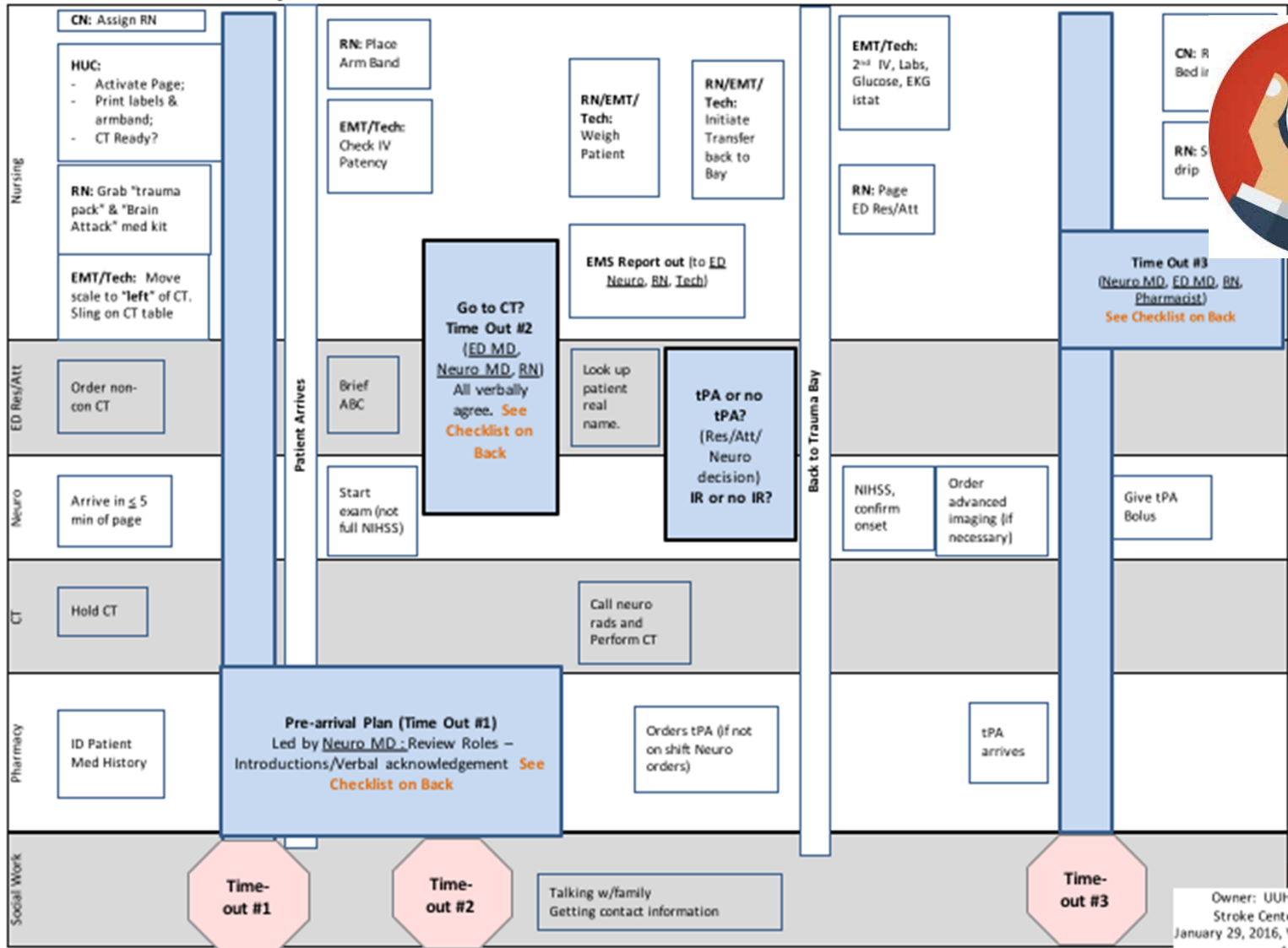
Acute Stroke Care at UUH



Acute Stroke Care at UUH

Neuro

Brain Attack - ED Expedited CT Protocol

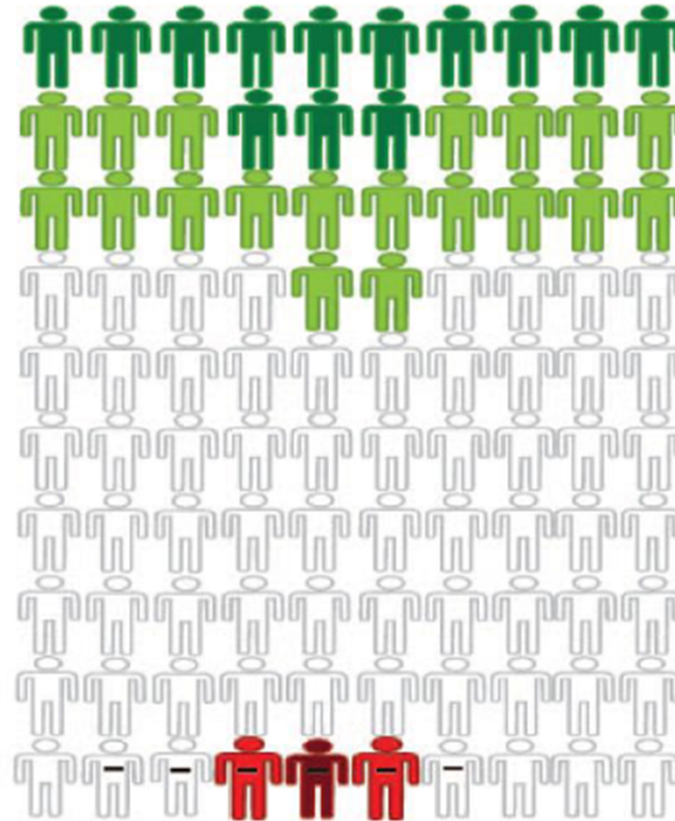


Emotional Distress in Patients / Families too



Decisional Paralysis

TPA for Cerebral Ischemia within 3 Hours of Onset-Changes in Outcome Due to Treatment



Changes in final outcome as a result of treatment:

- Normal or nearly normal
- Better
- No major change
- Worse
- Severely disabled or dead

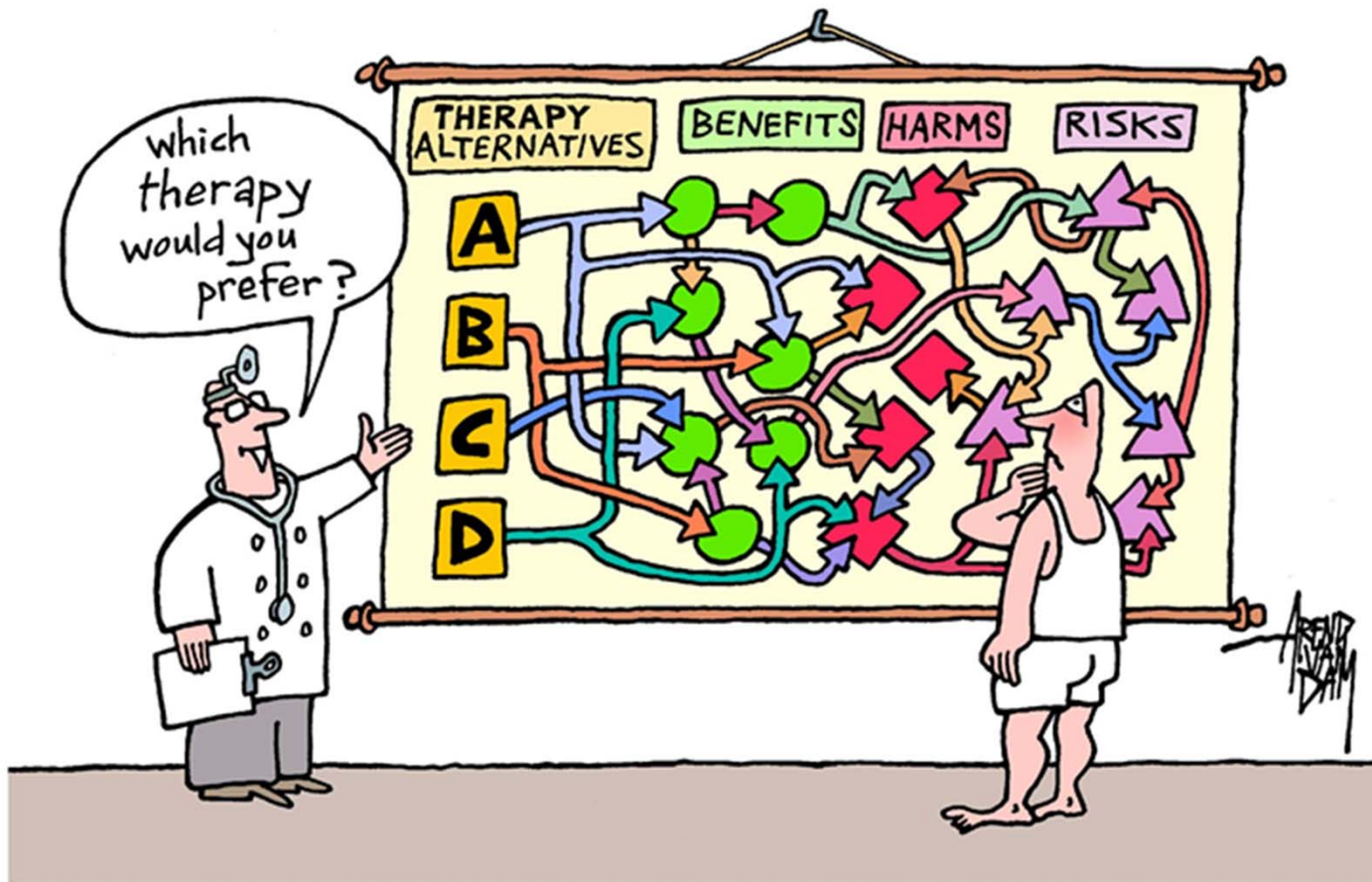
Early course:

- No early worsening with brain bleeding
- Early worsening with brain bleeding

Stroke. 2010;41:300–306

Basics of Informed Consent





informed consent

3 Main Ethical Principles of Clinical Research

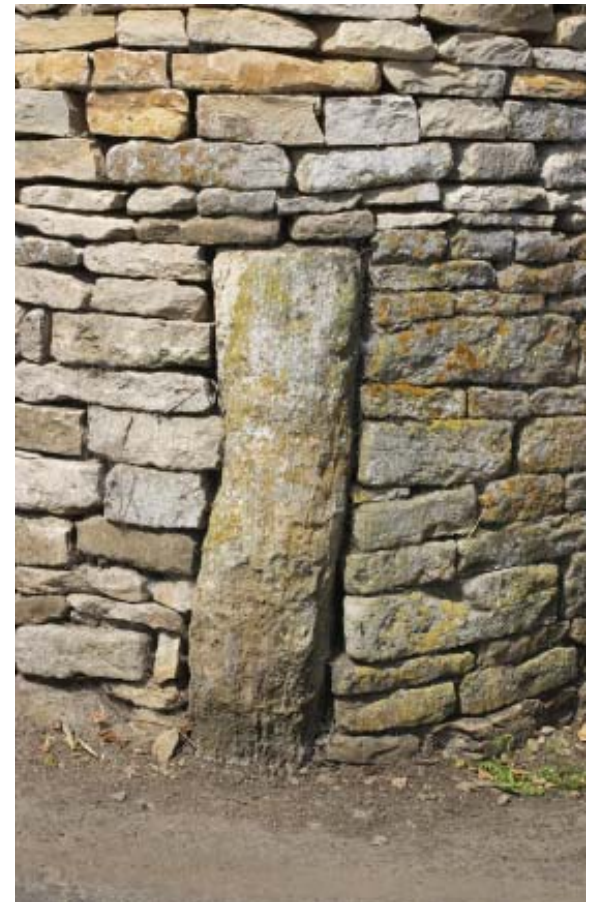
Originally outlined in the Belmont Report in 1979

- 1. Respect for persons:** people should be informed and free to choose whether or not to participate in research
 - Opposite is “paternalism”
- 2. Beneficence and non-maleficence:** the goal to maximize possible benefits and minimize possible harms
- 3. Justice:** the burdens and benefits of research should be equitable distributed among groups of patients
 - meant to prevent repeating prior abuses of disadvantaged groups such as minorities and prisoners

Informed Consent: Cornerstone of RCT Ethics

A process, not a document

- Patients are provided an oral description of the study
- Adequate time
- Consent document is usually signed but not always
- To provide informed consent, the participant must be:
 - ≥ 18 years old
 - Have capacity to clearly understand the facts, implications, and future consequences of their decision
 - Children can provide *assent* with parental consent. Same for cognitively impaired persons.

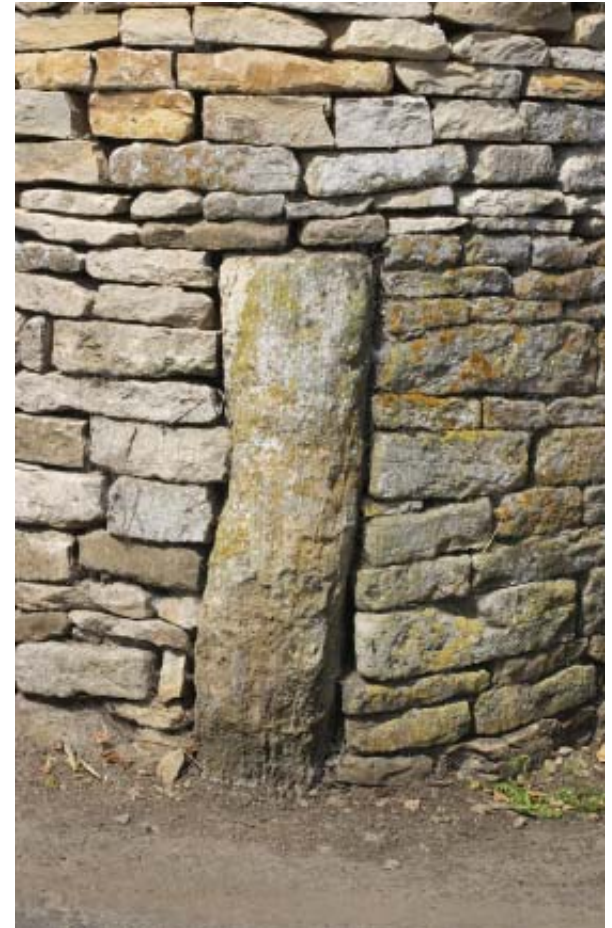


Informed Consent: Cornerstone of RCT Ethics

A process, not a document

Legally required to include:

- RCT objectives
- Methods and procedures
- Potential risks and benefits
- Liability in case of injury
- Alternatives to participation including options for discontinuation
- Investigator plans for use of private information

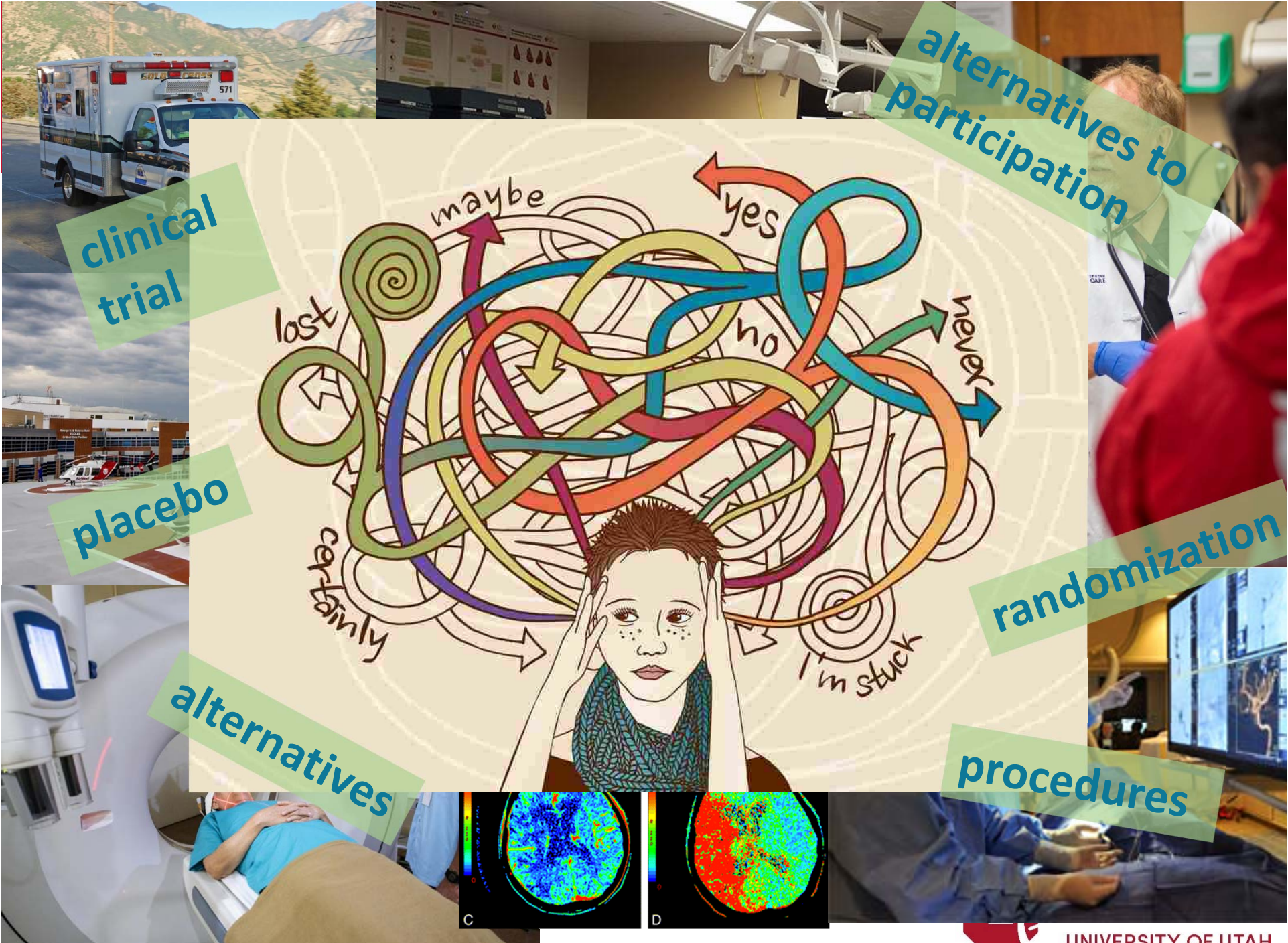


Barriers to Informed Consent in all Fields

- Low literacy and numeracy
 - 5th - 10th grade reading level recommended
 - Avoid decimals, percentages
- Low health literacy
 - Basic concepts of pathophysiology
 - Avoid medical jargon
- Low “trial literacy”
 - Placebo, Randomization, Inclusions / Exclusions
- Foreign languages
- Low trust between patients and investigators
 - Disenfranchised groups
 - Profit motives of investigators

Acute Stroke & Clinical Trials: a doomed marriage?





clinical trial

alternatives to participation

placebo

randomization

alternatives

procedures

Quotes from “the Field” during Informed Consent

“You just want my mom to be a guinea pig.” (distrust)

“I understand drugs need to be tested in people,
but I’m not up for that being on me.” (fear)

*“Why can’t I just have the new drug if it’s so
great?” (trial illiteracy)*

*“I’m in. Sounds like a sure thing.” (therapeutic
misconception)*

“I never would have consented if I’d known there was
risk!” (said the next day)

[What isn’t being said?]

Signs of a Failed Consent Process



Cartoon from the 2019 Bioethics Ethics Cartooning Contest at the Morgridge Research Institute, Univ of Wisconsin – Madison

Signs of a Failed Consent Process

WWW.ANDERSTOONS.COM



"You want informed consent, I want more pudding.
Let's make a deal."

Specific Barriers to Informed Consent in Acute Stroke

- Stress from acute life-threatening situation
- Tight time constraints
 - Inability to contact families
 - Limited time to improve trial illiteracy
- Acute cognitive impairment limiting ability to provide informed consent

Time Constraints + Trial Illiteracy

- 2010 focus group study of patient attitudes towards trials in acute neurologic illness:
 - Patients with previous stroke or brain injury or at risk for TBI
 - **Participants felt that placebos were unfair and unnecessary. Randomization is not right.**
 - Therapeutic misconception: the experimental treatment must be better than nothing. Little understanding that supportive care is the standard of care.

Time Constraints + Trial Illiteracy

- 2010 focus group study of patient attitudes towards trials in acute care

- **Doctors**

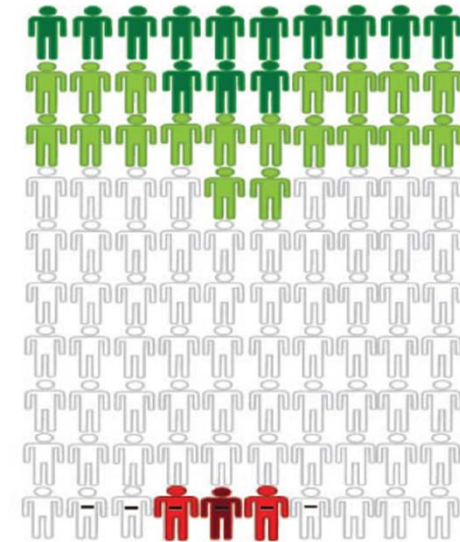
“I don’t want my health to be randomized. I want the best treatment that my caregivers can give me and that’s based on their experience, that’s based on their knowledge. So if the people who are caring for me think treatment A’s the best, I want treatment A. If they think treatment B’s the best, I want treatment B, but I don’t want a computer randomly assigning me a treatment independent of what doctors think is best for you.”

...nothing. Little
standard of care.

Time Constraints + Trial Illiteracy

- Decisional visual aids:
 - Data is still being accrued for utilization in RCT consent process
 - A cancer study found increased recruitment, with decreased decisional confusion, and increased trial knowledge in subjects who used a visual aid.
- Could such visual aids be useful in stroke trials??

TPA for Cerebral Ischemia within 3 Hours of Onset-Changes in Outcome Due to Treatment



Changes in final outcome as a result of treatment:

- Normal or nearly normal
- Better
- No major change
- Worse
- Severely disabled or dead

Early course:

- No early worsening with brain bleeding
- Early worsening with brain bleeding

Decker C, et al. Circ Cardiovasc Qual Outcomes 2015;8:S109-116
Sundaresan P, et al. Radiother Oncol 2017;125:124-129

Acute Stroke & Cognitive Impairment

In the ED: acute cognitive impairment

Aphasia: failure to make or understand speech

Severe dysarthria: impedes intelligible communication

Coma: frank reduction in level of consciousness

Neglect: inability to grasp the gravity of the situation



Loss of autonomy: inability to self-provide informed consent

across several ischemic stroke trials, including the original tPA trial, only ~ 30% of patients have been capable of providing their own consent in the acute

stroke setting

Acute Stroke & Cognitive Impairment

- Patients who lose autonomy are:
 - Older
 - Have more severe strokes
 - Have left-hemispheric strokes
 - And have higher rates of in-hospital mortality
- To exclude patients without autonomy:
 - Reduces generalizability by creating a study population that isn't representative of the whole (*increases bias*)
 - Doesn't benefit the widest population of patients (*violates the principle of justice*)
- Alternate forms of informed consent are absolutely necessary to conduct ethically sound and scientifically valid studies.

Alternate Forms of Consent:

Surrogacy

Tele

EFIC



Legally Authorized Representative (LAR)

- FDA definition: an individual or judicial body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research
- Who can act as an LAR?
 - Not necessarily the same as for clinical care
 - Varies considerably across the US and world
 - Utah:
 - Spouse
 - Adult child (18 years of age or over) for his or her parent
 - Individual with power of attorney
 - Guardian appointed to make medical decisions for incapacitated persons

How do you know if you need an LAR?

- Many trials provide no guidance, leaving it up to the investigator
- 2012 Survey by Liera: the definition of loss of autonomy varies
 - NIH Stroke Scale score:
 - deemed adequate to establish decisional capacity based on the language subscore by most (62%) of the co-investigators
 - but the minority (36%) of the IRBs
- Some trial protocols specify a screening cognitive questionnaire to establish competency prior to consent
- Due to these variances, investigators should take advantage of their local IRBs to interpret local laws when designing stroke studies.

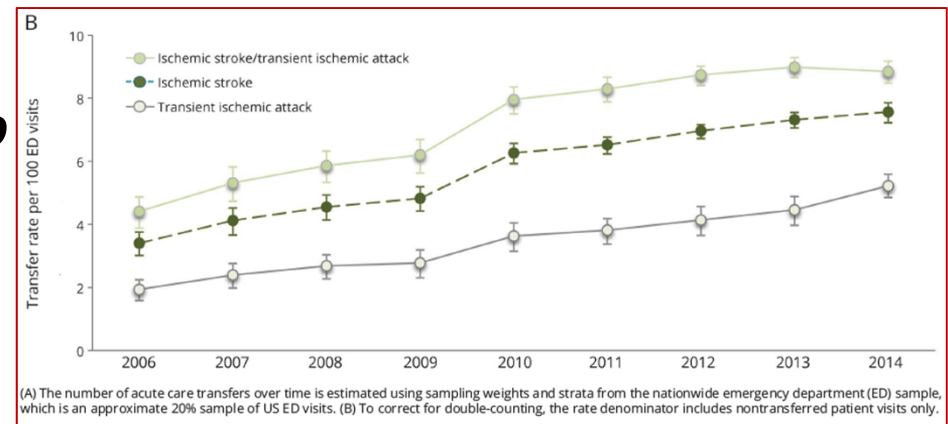
Remote Consent

Interfacility transfers for acute IS/TIA are rising:

- more than doubled from 2006 to 2014 (3.4-7.6%)
- rural facilities particularly likely to transfer - 45% of IS patients transferred



Can we use this epidemiologic trend as a unique opportunity to reduce geographic bias and get these patients into our acute stroke trials?



Considerations:

- Transfers are facilitated via a doctor-to-doctor phone call or a patient-to-doctor telestroke consult
- Studies are typically performed at the larger centers
- Family typically are not transported with the patient

Alternatives to In-Person Consent in Acute Stroke: Remote Consent



- 2 options: phone & telestroke
 - Neither has been broadly implemented
- **Phone-Based Consent :**
 - 18% of surveyed international IRBs allow consent by phone.
 - Phone-based consent was successfully used in a large pre-hospital stroke study (FAST-MAG)
 - EMS personnel briefly explained the study and then called the on-call study MD to obtain oral consent
 - Subsequent signed consent upon arrival to ED
 - Dramatically reduced onset-to-enrollment times.

Alternatives to In-Person Consent in Acute Stroke: Remote Consent



Telestroke-Based Consent:

- US: many systems are hub-and-spoke – ideal for trial enrollment
- Allows the provider to speak directly to the patient or surrogate
 - Provides face-to-face consent
 - Potential for display of graphics
 - Likely improves communication and understanding vs phone
- Can reduce time to enrollment by providing “heads up” to study team, including research pharmacy, ahead of transfer
- Implementation is spotty:
 - Some trials allowed phone + fax but not video-enabled consent
 - One ICH trial used telemedicine consent: increase in enrollments and reduction in time from patient arrival at hub to study drug
- **SN cIRB considers local tele-consent processes**
- For UUH: we can use telestroke system, email, phone and fax

Exception from Informed Consent (EFIC)

- Enrollment in a clinical trial *without* informed consent
- Title 21, Code of Federal Regulations, Section 50.24 (21 CFR 50.24)
- Developed to address the data-free zone that exists in our ED's
- Can be utilized when:
 - a) subjects have a life-threatening medical condition that necessitates urgent intervention (also conditions with morbidity endpoints)
 - b) for which available treatments are unproven or unsatisfactory
 - c) and who, because of their condition, cannot provide informed consent
- The research must:
 - a) have the prospect of direct benefit to the patient
 - b) involve an investigational product that to be effective has to be administered before informed consent can be obtained, and
 - c) be unable to be conducted without the waiver

EFIC in the Pre-Hospital Setting

Very few stroke studies in the pre-hospital setting:

- 1) Brain imaging not readily available in the field
 - Thus any investigational drug or device tested in the pre-hospital setting has to be safe for patients with intracerebral hemorrhage, infarct, and stroke mimics.
- 2) There may not be time for informed consent in the field, whether by the patient or a surrogate.

A 2017 international meta-analysis of consent methods in pre-hospital trials across multiple countries:

- Multiple types of consent are used internationally
- *EFIC was the model of choice in the US*

How to Utilize EFIC?

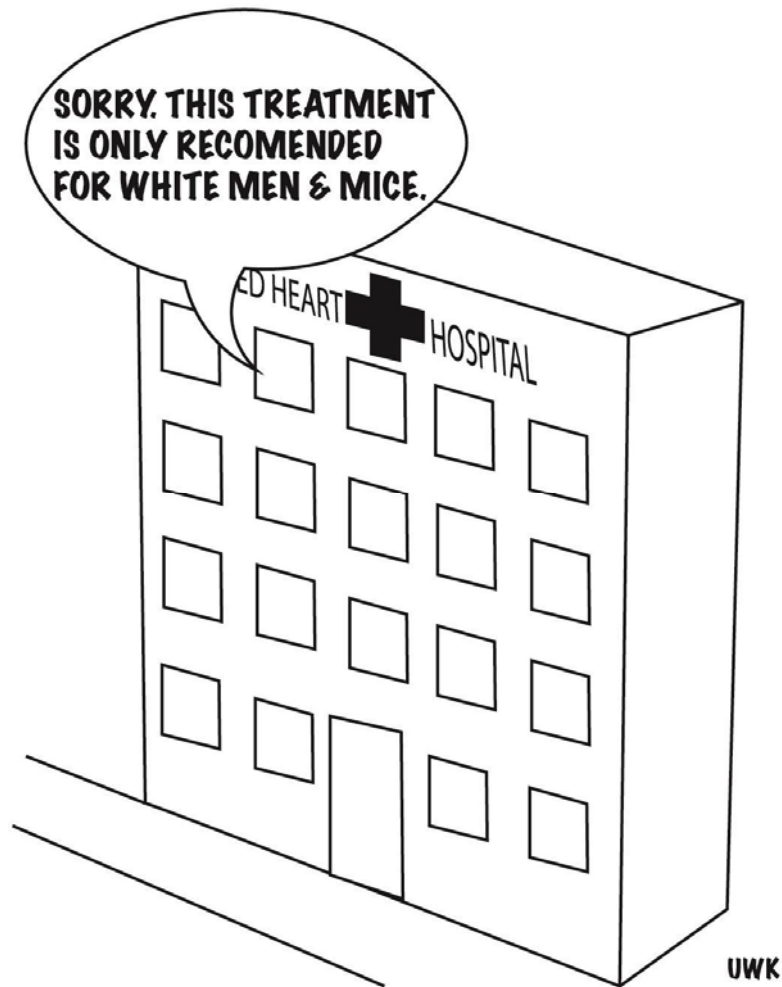
Additional responsibilities on the IRB and investigators

- Investigators must **consult with representatives** of the community in which the research will take place and the subjects will be drawn.
- Community discussion can have several forms:
 - meetings specifically organized to discuss the research
 - local radio and/or television talk shows or interactive websites
 - conducting surveys or convening focus groups
- The FDA clearly lays out the required content
- The goals are to provide the opportunity for discussions with, and soliciting opinions from, the representative community, including providing input into the IRB decision-making process.

Bias and Generalizability in Stroke Trials



Representative Study Populations: the data



**Stroke trial populations
historically not
representative of women,
minorities, and extremes of
ages**

*Winning cartoon from the 2019 Bioethics
Ethics Cartooning Contest at the
Morgridge Research Institute, Univ of
Wisconsin – Madison*

Representative Study Populations: the data

WOMEN:

- A 1990's study of 15 RCT of secondary prevention of statins (with stroke as one endpoint) found that only 23% of 31,683 patients were female.
- Stroke trials specifically: only 37.8% of participants are female
- But enrollments of women *are* increasing.
- In 51 NINDS-funded multi-gender phase III trials: women enrollment increased from 34% (1985-1994) to 43% (1995-2000)

Representative Study Populations: the data

RACE:

- 80% of NINDS-funded clinical trials report some race info. But...
 - 32% only dichotomize between white and non-white
 - Of those that report non-white races:
 - 48% report only AA
 - Only 23% report any information on Hispanic ethnicity
- % of AA in neurologic trials has increased in last 2 decades
- 2011: NINDS-funded multi-race trials reporting on race/ethnicity
 - AA: 14.5% of all trials, 22.7% of stroke trials (US pop = 12.9%)
 - Hispanics are less represented: 5.8% of subjects (US pop = 12.5%)
 - Representation decreased: 7.4% (1985-1994), 5.0% (1995-2000)
 - True numbers difficult to know due to lack of reporting

Representative Study Populations: Solutions?

- NIH:
 - requires PIs to describe strategy for equitable inclusion of women and minorities in the research plan and in yearly progress reports.
 - In 2019, implemented the *Inclusion across the Lifespan* policy: requires the addition of age
- NIH StrokeNet:
 - working group to assist potential investigators in creating a women and minorities inclusion plan
- National Initiative for Minority Involvement in Neurological Clinical Trials (NIMICT):
 - seeks to understand investigator-level barriers to increased minority recruitment and retention in neurological trials
 - creating evidence-based toolkits to address these challenges

Representative Study Populations: Solutions?

NIMICT interviewed trial PI's and research coordinators to determine barriers to effective minority recruitment and retention.

- PI's identified leading barriers to minority recruitment:
 - Mistrust of research and medical system
 - Lack of awareness about trials
 - Communication issues
- Research coordinators identified
 - Translation, literacy, Spanish dialect differences
 - Family composition, patients' demographics, symptom severity
 - Culturally-appropriate non-verbal cues, immigration status (Hispanics)
 - Social legacy related to disparate racial treatment
- 36% of PI's said they require cultural competency training for staff
- Coordinators did not identify such training as useful, preferring:
 - Hiring process that includes competency assessments
 - "on-boarding" including how to handle the emotional pitfalls of the job

Stroke 2015;46:2232-2237

J Racial Ethn Health Disparities 2017;4:1225-1236

J Racial Ethn Health Disparities 2018;5:322-332



Representative Study Populations: Solutions?

- NINDS encourages investigators to include and engage patients and advocacy groups early in study design process
- Investigators should plan:
 - outreach and education to enhance research awareness (especially in diverse communities)
 - creation of toolkits
 - training in gender, age, and culturally sensitive communication techniques.
- Consider using “new” tools such as social media and mobile health applications to enhance study efficiency, engagement, and retention.
- Marketing should be planned proactively and in parallel with protocol design.

Practicum



Tips for Recruitment Success

- Work with your IRB to find legal, ethical ways to include the broadest population of patients and allow the most straightforward consent
- Work with your CTSA / Office of Clinical Trials Research to create an unbiased, representative enrollment plan
- Monitor your enrollments for diversity of age, sex, race, ethnicity
- Determine *ahead of time* how you'll determine autonomy
- Practice your consent in group settings (esp with new hires)
 - We created a short script for each study to keep on hand
 - Consider the use of visual aids
 - “short-form” translated consent forms
- Prepare local processes ahead of time

Study script

DO NOT GIVE TO PATIENTS- FOR INTERNAL USE ONLY!

As you know, the University of Utah is an academic medical center and we are involved in numerous clinical trials. You/ your relative specifically qualify for the XXX clinical trial sponsored by XXX

You qualify for this trial because you had a stroke and EXPLAIN STUDY. We will let a computer randomly select your group. You and your study physician will be blinded to your treatment assignment. The physician can be unblinded in case of an emergency.

Would you be interested in hearing more about this study and potentially participating?

There will be XXX patients included in this trial nationally, XXX at Utah.

I must tell you that participation is absolutely voluntary and you may withdraw from the study at any time without any consequences. You will still receive the best standard of care treatment at the University of Utah.

You will not be compensated/ you will be compensated XXX to participate in this trial. Anything that is being done per standard of care, things that you would get whether you are in the study or not, will be billed to you or your insurance. Anything additional that we will do for study purposes only, will not be billed to you/ your insurance, we will pay for these with study funds.

Treatment: The duration of this study is XXX. EXPLAIN WHAT WILL HAPPEN DURING STUDY

Risks: EXPLAIN RISKS

In addition to the risks listed above, you may experience a previously unknown risk or side effect.

Benefits: you may or may not see any direct benefits from participating in this study. Others may benefit in the future from what we learned from this trial.

Alternative procedures: By not signing the consent you would not have the opportunity to participate in the trial and to receive the study treatments. If you choose not to participate, during your hospitalization, you will receive standard care for stroke patients.

Injury: If you are injured from being in this study, medical care is available to you at the University of Utah as it is to all sick or injured people. The University of Utah has not set aside any money to pay the costs for such care. The University will work with you to address costs from injuries. Costs would be charged to you or your insurance company (if you have insurance). Since this is a research study, some health insurance plans may not pay for the costs. Compensation for research-related injury is not available from the study sponsor. STUDY SPECIFIC, CHECK IF SPONSOR PAYS FOR POTENTIAL INJURIES

Confidentiality: We will keep your medical records confidential, only individuals working with us on this trial will have access to your records. If the results of the trial are published, your identity will remain confidential. If and when get audited, monitored by a regulatory agency (local IRB, FDA, study monitor)

Streamline Local Processes



Streamlining the Enrollment Process in Acute Stroke Trials: Reducing Enrollment Times while Maintaining Quality

Kinga Aitken MD, MPH, CCRP, Ka-Ho Wong BS, Crystal Neate BS, Michael Dela Cruz BA, Lee S. Chung MD, Adam H. de Havenon MD, L. Dana Dewitt MD, Peter M. Hannon MD, Chelsea Meyer DO, Jerdan Ruff MD, Jana J. Wold MD, and Jennifer J. Majersik MD, MS
 Division of Vascular Neurology, Department of Neurology, University of Utah Health, Salt Lake City, UT

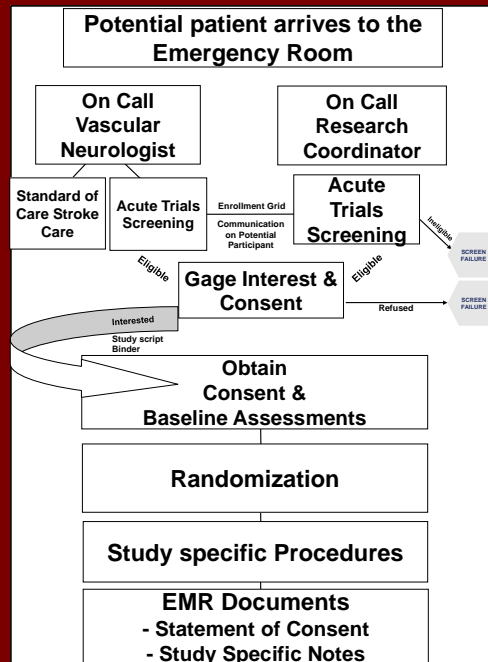
Objective & Background

Acute stroke is a stressful time for patients, families, and medical staff. Adding potential clinical trial enrollment to this mix further complicates the situation, and can result in chaos, delaying randomization, or losing potential patients due to time constraints. Streamlining processes can decrease enrollment time and improve flow, compliance, and data quality.

Design and Methods

- Due to an increase in the number of acute studies through StrokeNet as well as non-StrokeNet trials, we identified a need for streamlined enrollment processes.
- After input from multiple stakeholders as well as identifying multiple opportunities for improvement, we designed a new enrollment process and implemented it on 1/1/2017.
- Enrollments were analyzed from 2 acute stroke trials that were enrolling between 1/1/16-1/1/18, split into two cohorts of pre- vs post-process implementation.
- Mean enrollment times (patient arrival to signed consent form) were calculated by trial and overall, and compared using the paired t test.

Results: Process Development



We developed an enrollment grid that details which trial to offer to patients who qualify for multiple acute trials

- allows for equitable opportunity to enroll in all trials without bias
- Enrollment binders are housed in the emergency room
- Includes documents to be completed during enrollment, tabbed by research member (MD vs coordinator).
- Also include protocol reminders, drug orders, and references to a secure shared drive with additional helpful documents.

Consent: Yearly consenting practice sessions are held for new fellows and research team members. Binder includes:

- Current study specific consent forms with consent version verification cover sheets
 - study specific scripts to ensure uniform presentation of information and consent elements.
- Data Entry: Electronic health record "smart phrases" were created to help streamline documentation needs.

- Major improvements were found in internal workflow and consistency while staying compliant with regulatory requirements.
- Overall data quality remained excellent with an error rate well below <1%

Results: Enrollment Times

	Trial 1 (n=5)	Trial 2 (n=6)	All (n=11)
Pre-Implementation, hrs (mean, SD)	3.5 (1.7)	3.1 (1.7)	3.2 (1.5)
Post-Implementation, hrs (mean, SD)	0.9 (0.2)	1.1 (0.1)	0.99 (0.1)
P-Value	< 0.005	< 0.005	< 0.005

Conclusions

The new processes support the University of Utah Stroke Center's vision of efficient trial conduction in the acute setting with **reduction of enrollment times and maintenance of excellent data quality**. These processes are now being implemented and disseminated to our spokes and telestroke sites.

Funding Source

Stroke Trials Network (StrokeNet): NIH/NINDS 1U24NS107228



Practical Tips to Informed Consent in Stroke

PREPARATION

- Know the trial
- Have a script and practice ahead of time
- Yearly training with new team members and consent practice prior to start of each new trial
- Determine ahead of time what you (site investigator) will go over versus the coordinator
- Have an answer prepared for the common questions:
 - *Do you recommend this trial?*
 - *Would you enroll your parents in it?*
 - *Why can't I just get the best treatment?*
 - *Will you make \$ off of me?*

Practical Tips to Informed Consent in Stroke

AT TIME OF CONSENT

- Have the coordinator with you if possible.
- Find a quiet spot and sit down.
- Speak without rushing while acknowledging the stress of the situation and the time constraints. Allow time to ask questions.
- Use simple language, define both research and medical terms
- Be aware of cultural differences
- Watch for and respond to non-verbal and verbal cues of discomfort, mistrust
- Explain their participation is totally voluntary, no repercussions

POST CONSENT

- Talk to coordinator, and, later, the patient and family about how it went so you can learn from the experience

Final Thoughts



Future Research

A call to scientifically evaluate methods to improve stroke trial recruitment and retention

- Recruitment Top Priorities:
 - Short and illustrated patient information leaflets
 - Non-written consent
 - Reimbursement for new interventions only within a study
 - Can we co-enroll?
 - Trial designs that include acute + recovery or acute + prevention
- Retention Top Priorities:
 - Involvement of patient groups
 - Remote and central follow-up
 - Use of mobile devices
 - Reminders to patients about their consent to participate

Future

Need to improve our population's understanding of research

...Preferably when time limits aren't so dire

- Community education on clinical research
 - At-risk populations
 - Schools
 - Community fairs
 - Community leader
 - Get creative!

- Advanced directives for research participation?



PechaKucha Night-Salt Lake City Volume #22 Curated with the University of Utah Center for Clinical + Translational Science

Our final event for 2017 will be a first for PechaKucha Night-Salt Lake City! We're partnering with the University of Utah Center for Clinical and Translational Science to **feature people/organizations/projects that promote wellness through collaborations between academic research, arts, and the public.**

Presenter Lineup:

Kyl Myers HER Salt Lake Contraceptive Initiative

Carl Moore Peaceful Advocates for Native Dialogue

Fahina Pasi National American Tongan Association

Steve Alder Health2Go U of U Dept. of Family & Prev Med

Deanna Kepka HPV Vaccination

Scott Summers_ Nutrition & Integrative Physiology, UU

Ed Napia_Urban Indian Center

Heather Coulter Collaboration & Engagement Team

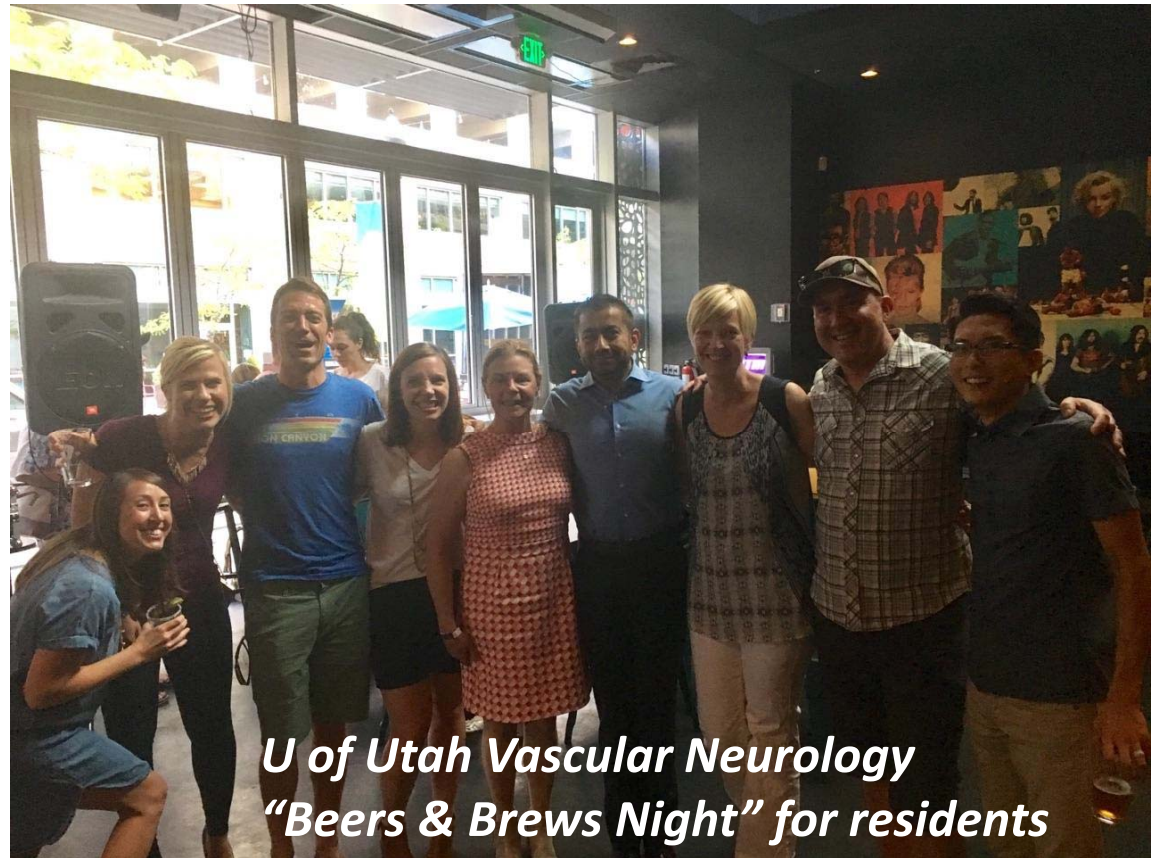
Jenny Majersik UT StrokeNet & Telestroke

Allie Miraglia HealthInsight

Sarah Beesley ICU Intermountain

Thank you!

Questions?



Randomized Clinical Trial (RCT)

Widely considered the most rigorous method of determining efficacy of interventions

- A prospective study of human subjects
- Random allocation to either the intervention under study or a control intervention or placebo
- Goal is to create comparable subject groups - in the characteristics which may affect the outcome
 - sex, age, race
 - presence of vascular risk factors, stroke severity
- Ultimate goal: allow the outcomes to be attributed to the intervention and not baseline patient differences.

Threats to Clinical Research

- Random error:
 - Results from sampling variability
 - Decreases as sample size increases
- Bias: a form of systematic error that affects research and distorts the measurement process
 - Independent of sample size & statistical significance
 - Multiple forms, can occur in trial planning, implementation, analysis
 - 3 main types: information bias, selection bias, confounding
 - Causes association estimates to be either larger or smaller than the true association.
 - “Its presence is universal” but we can work to minimize it.

Selection & Channeling Bias in Stroke Trials

- Selection and Channeling Bias:
 - Occurs during identification of the study population
 - Not uncommon in retrospective studies. In prospective studies, it occurs when enrolling.
 - Selection bias: when the criteria used to recruit and enroll patients into separate study cohorts are inherently different
 - Channeling bias: when patient prognostic factors or degree of illness dictates the study cohort into which patients are placed
- Less common in RCTs but *can occur* by only enrolling certain patients or groups of patients

Selection & Channeling Bias in Stroke Trials

Utmost importance that stroke trial subjects be representative of the population being studied

➤ Stroke incidence, mortality, subtypes vary by sex, age, race, ethnicity

Two Problems if we differentially enroll one group over another (frail elderly versus healthy young)

1. Our measured outcomes may reflect that decision rather than the intervention being tested
2. Under-enrollment of certain populations reduces generalizability

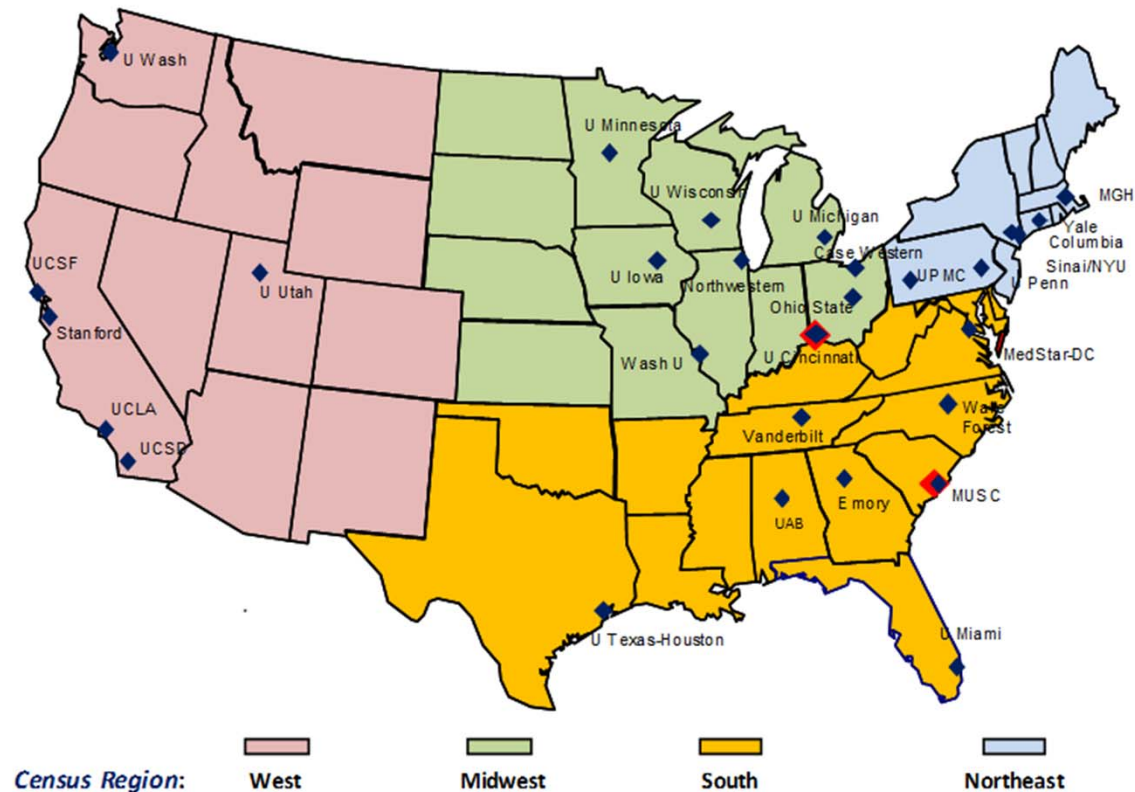
Study results need to be applicable to “real world” patients, not just highly selected sub-populations

Bias and Ethics of Competing Trials



National and Regional Coordinating Centers

- National stroke trials network, funded by the NIH in 2013
- 25 Regional Coordinating Centers all with satellite hospitals
- Acute, subacute, recovery trials
- Formed a working group to suggest best practices: experienced trialists, research coordinators, and ethicists



An “Embarrassment of Riches” (Jeff Saver)

- Competing trials are multiple trials with overlapping entry criteria
- Result in patients eligible for multiple trials
- Represents a unique problem in stroke centers with large trial portfolios
- How do we approach a patient when eligible for multiple trials?
- If there are too many trials, all may under-enroll (ethical problem)

Options for Disclosure of Competing Trials

1. Disclose all trials to patient; let the patient decide
 - a. Maximizes respect for persons?
 - b. Impractical
 - c. May increase malfeasance (stress in ED)
2. Let the clinicians decide, using whatever criteria they want
 - a. Minimizes respect for persons
 - b. Introduces scientific bias
3. Randomize the choice
 - a. Won't solve the under-enrollment problem
 - b. Difficult to institute
 - c. No ethical difficulties
4. Institution intentionally prioritizes
 - a. Improves the under-enrollment problem
 - b. Can lead to investigator difficulties

So which trial do you offer?

Offer the trial:

- the investigator thinks will work best for this patient (clinical factors)
- clinical coordinator availability
- sponsored by the foundation you've just submitted a grant to
- a random trial determined at patient presentation (coin flip)
- Based on **pre-determined non-patient based criteria**
 - Equal Chances: Day of week
 - Unequal Chances:
 - Opening or closing enrollment window
 - Renumeration of trial
 - Internal pre-grant trial
 - Last one up goes to the bottom

Concerns

- Potential enrollment bias
- Ethical concern
- No bias, no ethical concern
- No ethical concern
- No ethical concern. May result in under-enrollment of some trials.
- No ethical concern



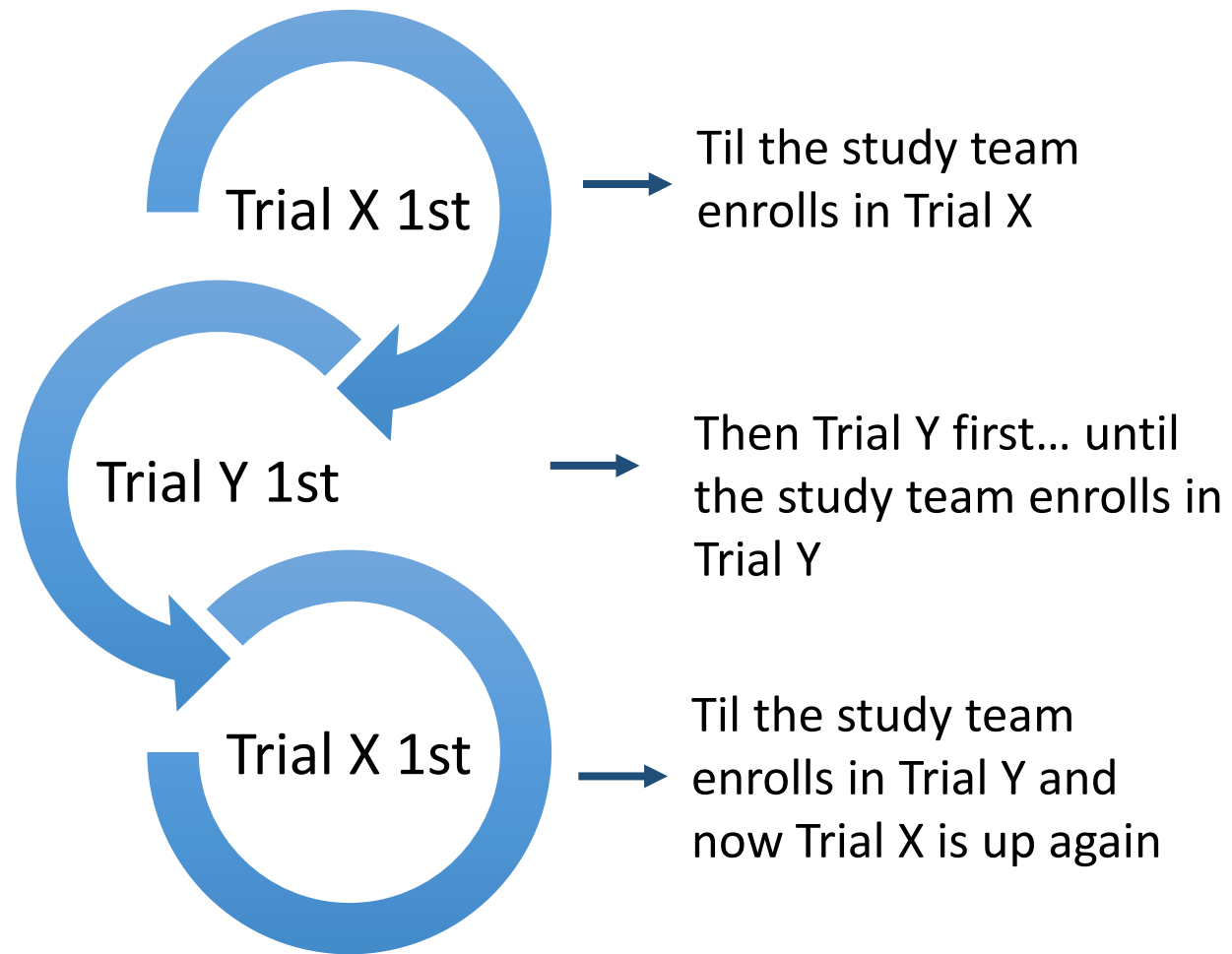
Each center has to have a written policy detailing how they will offer equitable enrollment in competing trials. The guideline states:

- 1) When timeframes permit: present all trials for which a patient is eligible.
- 2) For hyperacute and acute trials: only one trial should be offered to a patient at a time.
- 3) Whether (and how) research personnel disclose to patients the presence of additional, non-offered trials should be determined ahead of time.
- 4) Acceptable methods of determining which trial to present to patients in the hyperacute-acute time period include:
 - a) choosing to conduct no overlapping trials at a given clinical site
 - b) randomized assignment at the time of patient presentation
 - c) utilizing pre-specified allocation grids.

Sample of Enrollment Grid

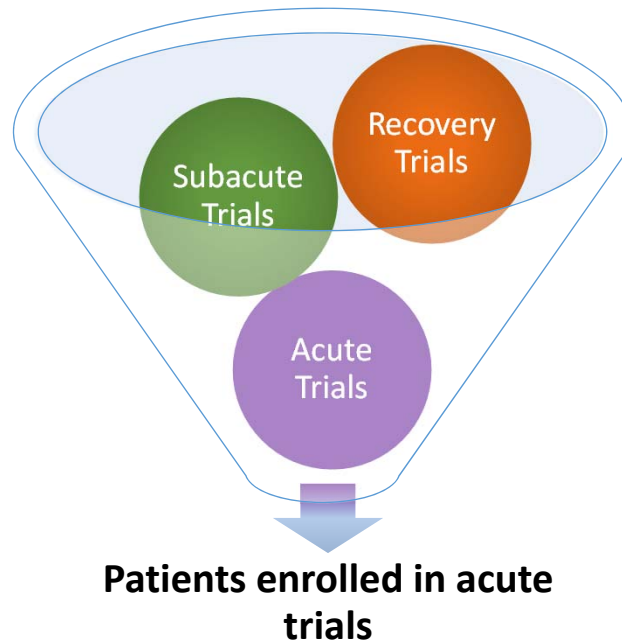
Acute Stroke Studies Enrollment Grid		
NIHSS \leq 5	NIHSS \geq 5	
All Days	Odd Days	Even Days
1-SHINE	1-SHINE	1-SHINE
2-PRISMS	2-Rhapsody	2-GAMES
	3-GAMES	3-Rhapsody
<i>GAMES: 0-10 hrs, NIHSS \geq10</i>		
<i>SHINE: 1-12 hrs, NIHSS 3-22</i>		
<i>Rhapsody: 2 hrs after tPA, NIHSS \geq5</i>		
<i>PRISMS 0-3 hrs, NIHSS \leq5</i>		

Another Sample: Rolling Enrollment Process



Worries in the Stroke Center

- Overlap of secondary prevention and recovery trials with acute stroke trials
- What do the acute stroke trials leave behind?

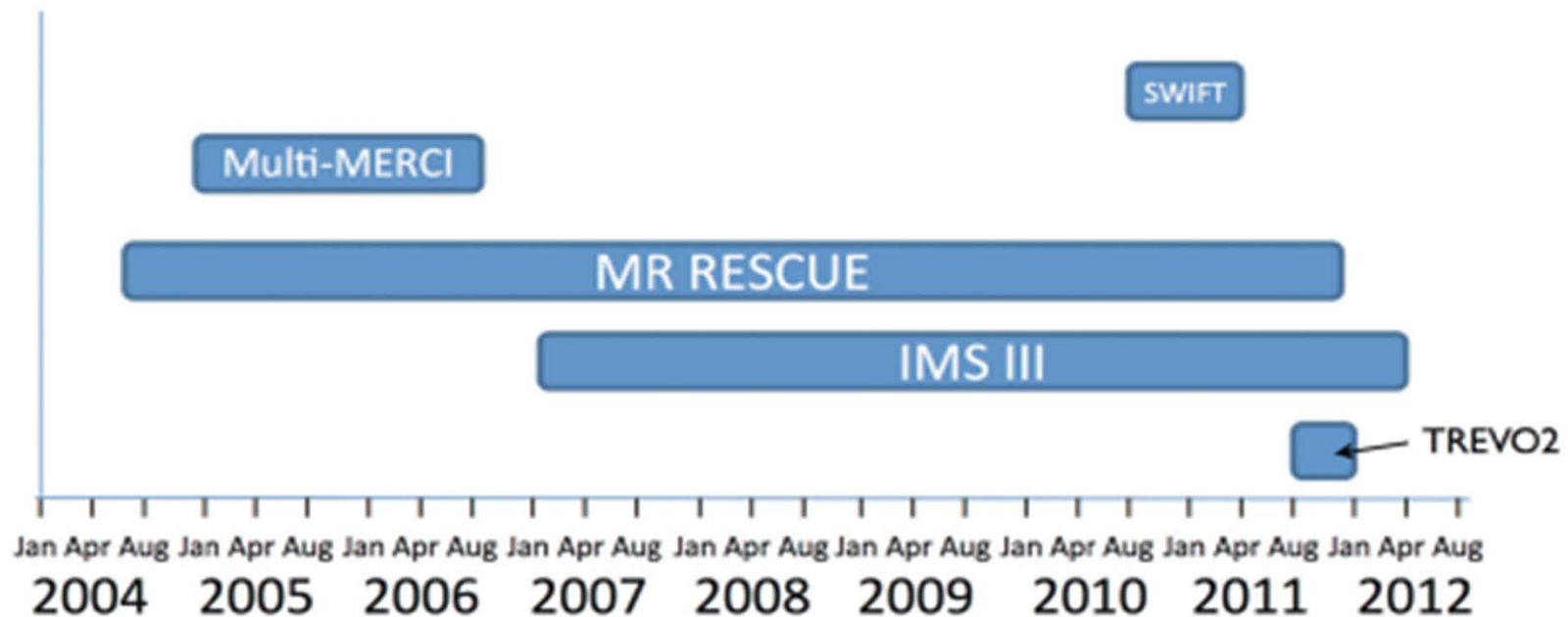


Enrollment bias: frequency and impact on patient selection in endovascular stroke trials

J Neurointerv Surg. 2016 April ; 8(4): 353–359

Examined clinical factors of patients enrolled in endovascular trials at UCLA compared to those who were eligible but not enrolled

They found: less than half were eligible for a formal clinical trial and only half of those were enrolled



Enrollment bias: frequency and impact on patient selection in endovascular stroke trials

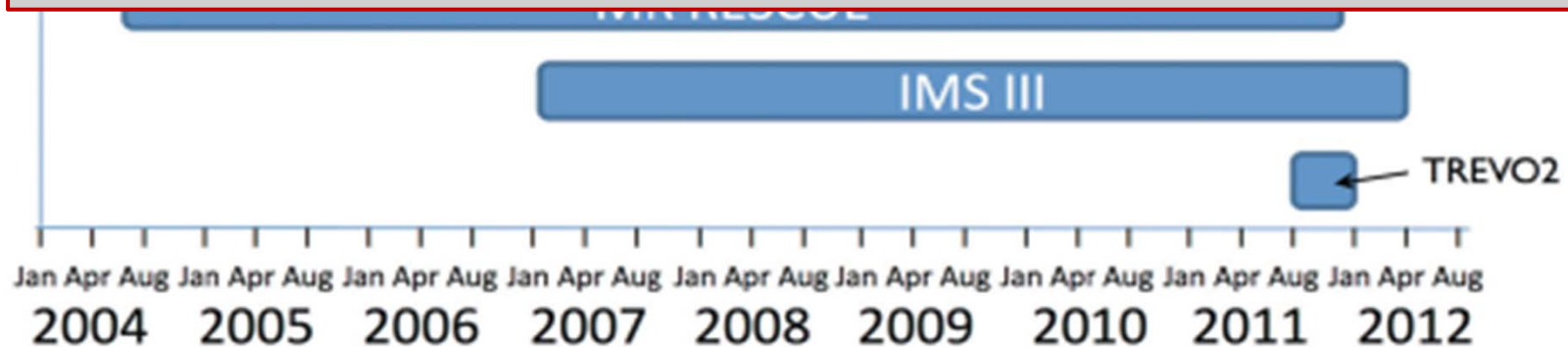
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The primary enrollment obstacles:

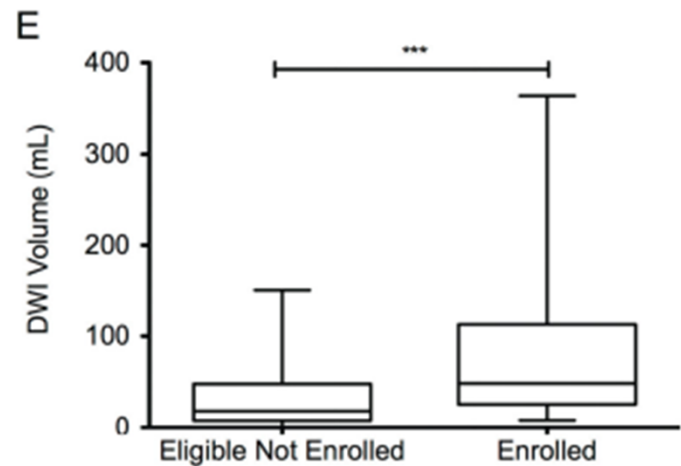
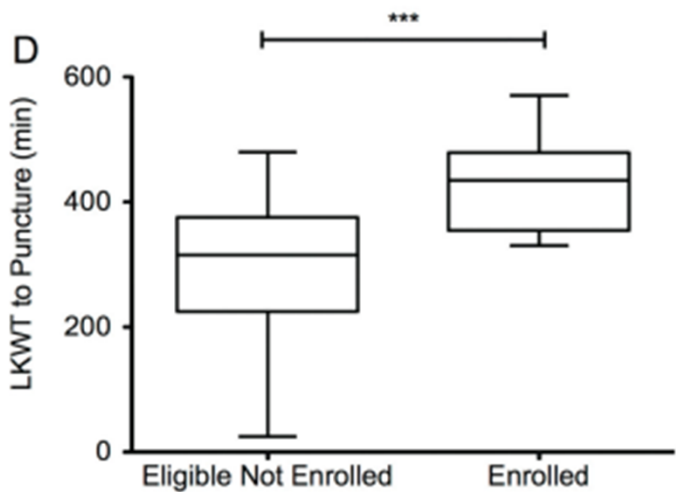
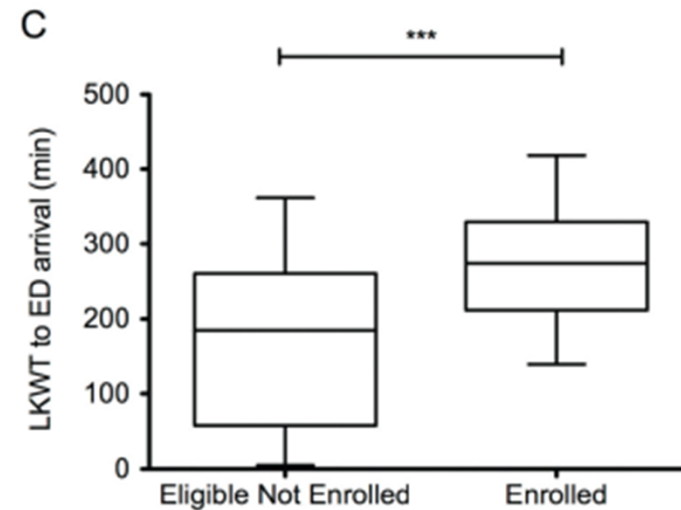
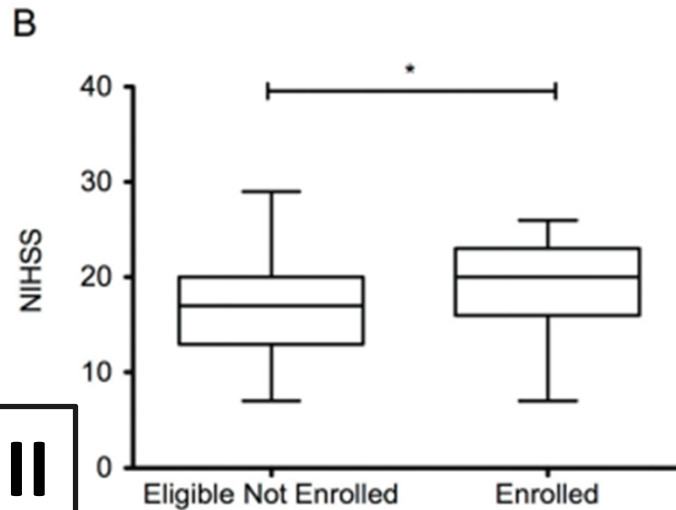
- 1) competing clinical trials
- 2) frequent preference to be treated outside of a trial by patient/legally authorized representative or physician



Enrollment bias: frequency and impact on patient selection in endovascular stroke trials

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IMS III



IF WE DON'T
KNOW WHICH DRUGS
ARE SAFEST AND MOST
EFFECTIVE FOR PREGNANT
WOMEN AND CHILDREN,
WHY DON'T THEY JUST
LET US INTO MORE
CLINICAL
TRIALS?

TO
PROTECT
YOU FROM
UNTESTED
DRUGS.

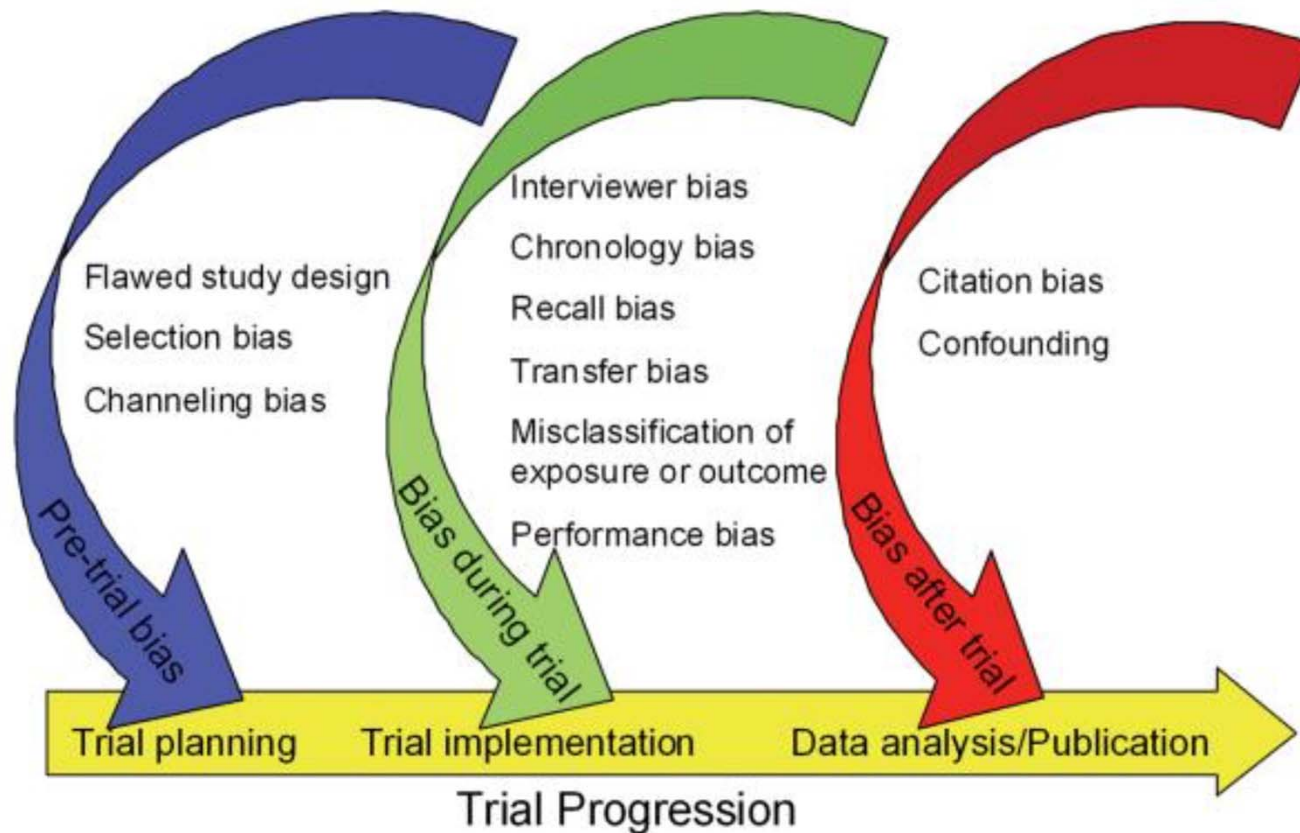
Statistically-Funny.blogspot.com



CATCH-22: CLINICAL TRIAL EDITION

Forms of Scientific Bias in Clinical Trials

Major Sources of Bias in Clinical Research



Can We Offer Co-Enrollment?

- Trials typically require enrollment in only one trial
- But some trials enroll and then screen → then if pass screening → randomize
- Can we enroll in TWO trials and screen for both – then enroll in the one that passes screening – if screens positive for both, patient chooses
- Can we devise ways to allow recovery trials to co-exist with acute and prevention trials?

Representative Study Populations: the data

- Patients may drop out of long duration clinical stroke trials (secondary prevention and recovery trials)
- Introduces scientific bias if low retention rates vary by:
 - demographics of race, sex, or age
 - clinical factors such as disease severity or coexisting risk factors
- Can lead to inconclusive or invalid results
 - particularly of subgroup analyses by race due to low power
- Reasons for drop-out and retention rates by race and sex are under-reported in secondary stroke prevention trials → bias is difficult to detect.
- Low retention leads to premature termination of studies, wasting \$ and resources → ethical concerns of patients who consented without ultimate purpose