

1. Background

The use of response adaptive randomization (RAR) is becoming more common in clinical trials ([Journal of Clinical Oncology. 2011;29\(6\):606-609](#)). Such designs will change the randomization ratio based on information on treatment effect that accumulates within the trial (this is done in the background and not by unblinding the investigators). This has the effect of increasing the number of patients who are assigned to the better performing treatment arm.

Acute care research represents an area where this may be of particular benefit, since few effective treatments exist for many emergency conditions such as stroke. Within such high stakes diseases, it may be advantageous to have a trial designed to improve the overall outcomes (on the average) of the population enrolled by tilting randomization towards the better treatment (which could be the placebo/standard treatment or the experimental treatment) ([JAMA. 2012;307\(22\):2377-2378](#)).

Previous work by this research team focused on the impact of surrogate consent on acute care research. ([BMC Emergency Medicine 2013, 13:18](#)) In the summer of 2011, 400 emergency department patients and their family members at the University of Michigan were interviewed and rated their willingness to participate in 5 treatment and research options in the event of a future, hypothetical stroke. Two of the scenarios described an acute stroke trial with or without response adaptive randomization. While not the primary focus of that research study, 58% of the subjects agreed to the trial with response adaptive randomization, and 21% agreed to the standard clinical trial with fixed randomization. From this previous work, we learned that it would be ideal to more comprehensively describe the research trial to hypothetical patients and simulate the process that is used in actual acute trial enrollments as much as possible.

This informed our follow up study that occurred in the summer of 2012. We presented a hypothetical stroke scenario to 418 subjects presenting to the emergency department for other, non-critical complaints. Half the subjects were presented a hypothetical clinical trial with standard 1:1 randomization, and half the subjects were presented a trial with RAR. There was significantly higher participation in the RAR trial (67.3%) versus the standard trial (54.5%), absolute increase: 12.8% (95% CI: 3.7 to 22.2%). Interestingly, only 62% of the RAR group versus 85% of the standard randomization group were able to accurately identify the allocation procedure when queried at the end of the scenario. The overarching goal of this investigation is to adjust the brief trial description procedure to improve understanding of the trial allocation procedure for the RAR. Improving the communication of the trial procedures within a simulated situation that mimics the rapid discussion regarding an emergency research trial would be beneficial for future interventional research studies in acute stroke and other serious emergent conditions.

2. Specific Aims

1. To measure the impact of adding in brief questions for comprehension into the consent process of a simulated emergency stroke trial with the intent of maximizing understanding of the randomization procedure.

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2. To determine if hypothetical trial participation is increased by the addition of the understanding questions to the consent process.
3. To explore the thematic areas expressed in the questions that the research participants have regarding the hypothetical trial.

3. Design

Cross sectional survey of convenience sample of ED patients and their family members without stroke with random allocation to two hypothetical clinical trials.

4. Inclusion/Exclusion Criteria

Patients or family members must be age 18 or greater. They must agree to participate in study. Patients must be presenting to ED without stroke or alteration in mental status, with stable vital signs and also not located in a resuscitation bay. Patients in any isolation status (contact, droplet, etc) were not approached).

5. Survey Procedures

Patients will be screened in the emergency department based on chief complaint and vital signs from the emergency department information system Centricity or MiChart. If eligible, patients will be asked to participate after a brief description of the study by a co-investigator, consented, and interviewed in the emergency department. In order to better simulate an at-risk stroke population, the oldest patients in the ED at any given time will be screened first.

Verbal consent will be obtained from the patient to participate in the simulation and they will receive a handout regarding their research participation and its voluntary nature. Since this is minimal risk research, and the informed consent form would represent the collection of personal identifiers, formal written informed consent will not be obtained.

If the patient's eligible family member(s) also wish to participate they will be asked to leave the area while the scenario is being administered to the patient.

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After consent is obtained, the patient will be randomized to one of four groups: either receiving a scenario with the RAR trial or the standard clinical trial with or without the addition of comprehension questions. (The two groups without the addition of the comprehension questions will be exposed to the same procedure as the 418 patients from the 2012 study.)

Group	Trial Type	Video Type	Proportion	N from 2012	N from 2014
1	RAR	Uninterrupted	25%	208	75
2	Standard	Uninterrupted	8.33%	210	25
3	RAR	Comprehension	50%	0	150
4	Standard	Comprehension	16.67%	0	50

Four comprehension questions will be added to the videos for the two groups assigned to this intervention, all addressing research procedures relevant to the consent process and operation of the the trial. One of the questions specifically addresses the method of randomization and allocation. Details are found in [appendix 2](#). The following items will be available to the subjects (depending on scenario): [consent form for standard trial](#), [consent form for RAR trial](#), and risk pictograph for stroke thrombolysis ([Stroke. 2010; 41\(2\): 300–306](#)).

The clinical scenario and all other aspects of the trial will be exactly the same. The patient will be told during this scenario that “time is of the essence” and that a decision needs to be made quickly, in an attempt to simulate the acute trial enrollment process for stroke. Randomization will occur in blocks of 4 and 8, in order to maintain general numerical balance between the groups throughout the study. In addition, if the patient has a family member or other visitor present they will be asked to refrain from discussing the decision with the patient until after the scenario and data collection are completed.

A detailed hypothetical trial protocol will be available to the investigators as a reference regarding questions that the research participant may ask; however the interviewer(s) will have reviewed the protocol extensively and have pilot tested the scenario and should be well equipped to answer nearly all potential questions regarding the hypothetical clinical trial. Notes will be taken regarding the patient’s questions regarding the research trial. In addition, the amount of time spent on questions will be captured as a continuous variable.

A structured survey will be administered which asks whether the patient agrees to the hypothetical trial, along with demographics, stroke warning signs, along with a modified version of the ICQ-4 (which

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excludes the fourth item which asks whether the study met expectations which would not be applicable for this hypothetical study – since they did not participate) instrument to assess adequacy of informed consent ([Journal of Clinical Epidemiology. 2006;59\(6\):608-614](#)). The participant will receive a [handout](#) on stroke warning signs at the end of the research procedures.

At the end of this survey participation in the research will end and no follow up contact will be conducted.

No protected health information or any other specific identifiers will be collected from the patients.

The data collection / scenario instrument will be pilot tested in the spring and adjusted as necessary.

Data collection for the project will proceed over the summer months.

The research assistant (medical student) who is collecting the data will not have access to results within the database during the data collection phase.

6. Analysis Plan

Aim 1: The primary outcome will be difference in proportions for correct identification of the hypothetical trial allocation method between the comprehension questions (intervention) group versus the uninterrupted video group limited to the subjects assigned to the RAR groups. For the primary analysis, the 218 subjects from the 2012 study assigned to the RAR group will be included in the analysis. These 218 subjects will be fully weighted unless a chi-square test comparing the proportion correctly identifying the allocation methods from the 2012 study versus the “uninterrupted video” group from the 2014 study indicates a significant difference between groups. In this case, for the primary analysis, each of the 2012 subjects will be weighted as 0.25 of an observation, thus placing approximately equal weight on the 2014 and 2012 subjects. Since these subjects are being exposed to exactly the same research procedure, we anticipate that there will not be heterogeneity and the subjects will be fully included in this analysis. As a pre-planned secondary analysis we will use multivariable logistic regression to estimate the adjusted odds of correctly identifying the allocation method within the RAR group, and include the following covariates based on our a priori belief about potential confounders: age, sex, ethnicity, and education.

Aim 2: The pre-planned secondary outcome will be a difference in differences analysis. The outcome of interest here will be participation in hypothetical trial (same primary outcome as 2012). Proportions and 95% confidence intervals for each of the four groups will be calculated with 2014 and 2012 groups (uninterrupted video) combined. The subjects from each of the 2012 groups included in this analysis will be fully weighted, unless a chi-square test indicates heterogeneity. (RAR uninterrupted 2014 versus RAR 2012; Standard-uninterrupted 2014 versus standard 2012). Logistic regression will be conducted with the following indicator variables as covariates: RAR trial versus standard, comprehension video versus uninterrupted, and interaction term. In addition, an adjusted model will be fitted including additional covariates were all included in the model based on our a priori belief about potential confounders: age, sex, ethnicity, education, self-reported understanding of protocol, ability to correctly identify allocation

technique and stroke awareness.

Descriptive statistics for demographics and stroke knowledge will be calculated.

Summary scores based in the ICQ-4 scale will also be calculated and comparisons will be made for trial accepters comparing the standard group and the RAR trial group.

7. Sample Size

We plan to enroll approximately 300 subjects. This should be feasible as 418 interviews were conducted during the previous summer and the current protocol is not significantly lengthened in terms of time.

The correct identification proportion in the 2012 study was about 62%. If we have 150 new subjects in the comprehension questions group, and 75 new subjects in the uninterrupted video group (added to the 208 from 2012), we will have 90% power at the 0.05 significance level to detect an increase in the correct identification proportion to 77%, which would be clinically meaningful. (For reference, the standard randomization or “coin-flip” group correctly identified the randomization technique 85% of the time.)

There is no pre-specified maximum number of subjects as this is a time-limited summer project. At the end of the 9th week (out of ten) enrollment of new subjects will terminate, unless the total sample size is not at least 300 subjects.

The patients will be randomized in randomly permuted blocks (sizes 12 and 24) to ensure ongoing balance between the 4 groups. The randomization scheme was generated by using the Web site Randomization.com <http://www.randomization.com>. The research assistant will only be able to access the assignment of the current patient, in order to properly administer the scenario.

Appendix 1: Recruitment Script

Study Title: Consent in Hypothetical Acute Stroke Treatment

Study Information

We are conducting a research study to determine your preferences regarding acute stroke treatment and research. This study is completely voluntary and you can choose not to participate without any loss of potential benefits.

There is no compensation for this study. You will receive a brief review of stroke warning signs as part of your participation.

This study will take about 15 minutes of your time. You can choose not to answer any questions you are not comfortable answering. ---We will ask you to identify stroke warning signs. We will describe a situation in which you have a stroke, and then we will present a hypothetical research study. We will ask you whether you would participate in this research study. We will also allow you to ask questions about the hypothetical research study and then ask you some questions regarding the adequacy of the informed consent process for the hypothetical stroke study.

We will then ask you several questions on demographics. At the end of the discussion, your participation will be completed. We will not collect any data which is personally identifiable to you. To ensure there is no chance that we inadvertently disclose documents that can identify you, we will NOT have you sign a consent form for this study (as this would create a document that has your identity). We will review stroke warning signs and provide you with an informational handout from the American Stroke Association. This study is funded by the University of Michigan Medical School.

For questions about this study, please contact Dr. William J. Meurer, MD, MS:

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Appendix 2: Script for video

The added elements for the new comprehension questions are underlined below and only subjects randomized to these scenarios will be exposed to the comprehension questions. The RAR video can be viewed at <http://youtu.be/cKIWduCaPZc>; the standard trial video can be viewed at <http://youtu.be/Srl4FdCTZ-A>.

Scenario

After agreeing to participate, the participant will be randomized to being offered RAR versus standard trial.

Overview

Part 1: Introduction

You have just suffered a stroke. Without warning, you are unable to move the right side of your body (arm or leg) and are unable to talk. You are also unable to understand what others are saying. You have been taken to the nearest emergency department and doctors have done tests and determined that this condition has been caused by a clot in one of the blood vessels in your brain. We will now describe several possible treatment options. We want you to consider participating in this hypothetical trial, and ask questions that you would need answered if this was really occurring. We will provide an overview of the study and the alternative, standard treatment. We will also go over the hypothetical consent form for this study with you. You will then tell us whether you would want to participate in this study. Even though this scenario describes a situation in which you will not be able to talk, please answer the questions we will ask at the end regarding research participation and your understanding of the research protocol.

IMPORTANT: *If you have visitors with you, you may ask them to leave while we do this if you wish. However, it is important that you do not consult with your family members or friends during the scenario. Your family members and friends are also NOT allowed to ask questions regarding the protocol while we are collecting data. When the scenario is finished and we have completed data collection, we encourage you to talk with your family members or friends regarding these types of decisions, and we will attempt to answer any questions. We do recognize that in the event we are attempting to simulate, your family members would likely be very involved in the decision making process – however their task would be helping the researchers and physicians with choosing the treatment or research participation that YOU would want – which is why we are focusing on your opinions in this study.*

You should have a copy of the consent form for this study with you for your reference.

Part 2: Overview – Standard Treatment Drug tPA

Following the stroke, you are a candidate for the standard treatment for a stroke, a drug called tissue plasminogen activator (tPA). This drug, tPA, has been FDA approved to reduce disability following stroke since 1996 and has been used extensively. It works by dissolving clots in the blood vessels of the brain. The original trial was funded by the U.S. government, and it is now recommended by the American Heart Association.

When tPA is administered, for every 100 patients treated, about 13 extra patients would be left with no disability at 3 months when this drug is compared to receiving no acute treatment. By no disability we mean you would be able to walk on your own, care for yourself and return to work or other leisure activities that you enjoy. However, there is a small risk: about 6 out of every 100 patients treated with tPA will develop serious bleeding. Serious bleeding may include bleeding in the brain that could make symptoms worse or other bleeding that may require a transfusion. Still, there is no difference in the chance of dying whether you receive tPA or not.

Comprehension question 1 is presented:

Please choose the most appropriate option:

tPA was previously demonstrated to do what?

A. Reduce disability in selected stroke patients

B. Save lives

C. I don't know

The research subject is provided feedback on the correct answer after making a selection. (Answer A.)

Part 3: Overview – Experimental Drug XPA

The drug that is being investigated by this clinical research trial is an experimental drug, called XPA, or experimental plasminogen activator. It has been used extensively for patients with heart attacks and is just now being investigated in patients with stroke. tPA (the standard treatment for stroke) was also previously used in heart attack patients prior to being approved for use in stroke. This trial is being funded by the U.S. government, and it is designed to answer the question of whether XPA is potentially better and safer than the current standard treatment tPA. The reason we are doing the trial is because we are truly uncertain whether XPA is better than tPA. We have studied

this drug in other people with stroke in a smaller trial. It appeared as safe as tPA in stroke patients and was promising – we are doing this larger trial to determine if it is actually better.

Comprehension question 2 is presented:

Please choose the most appropriate option:

Who is providing the money to do this research study on stroke?

A. The drug company

B. The U.S. government

C. Medical insurance companies

D. The hospital

E. I don't know

The research subject is provided feedback on the correct answer after making a selection. (Answer: B)

Part 4a: Standard Trial Script (skip to RAR trial Script if subject randomized to this)

If you are watching this, the investigators in the hospital have reviewed your medical history and performed a complete neurological exam to ensure that you are a candidate for this study.

If you choose NOT to enroll in the clinical research trial of XPA, you will instead have the following options: 1) Treatment with standard dose tPA given by IV; or 2) No immediate treatment for the stroke. You will still be admitted to the hospital and receive all other appropriate stroke therapies including physical therapy and speech therapy as necessary.

If you choose to enroll in the clinical research trial of XPA, you will have a 50:50 chance of either receiving tPA (the standard treatment) or XPA (the new treatment). This will be determined by a computer and is similar to flipping a coin. This type of randomization is important to make sure that the groups receiving each of the medications are similar in every way, other than which treatment they receive.

Comprehension question 3a is presented:

Please choose the most appropriate option:

Who or what decides what treatment I get (xPA or tPA) in this trial?

A. Randomization (something like a coin flip, with equal 50% chance of getting either for any individual in the trial including me)

B. An algorithm informed by how well previous patients have done in this study, that still has some randomness (but might be like flipping a coin with an 80% chance of heads)

C. The team of doctors and researchers caring for me will evaluate all available information and decide.

D. I don't know

The research subject is provided feedback on the correct answer after making a selection (The correct response in this case is A.)

In addition, in this trial, there will be a 3 month follow up to track how you are doing. You will be free to leave the study at any time, without penalty, but your reasons for leaving may be kept as part of the study record. The study will pay for research-related items and services. However, you will not receive any compensation or benefits from participating, but we hope the information learned from this research study will help medical professionals understand how to help patients with stroke in the future.

Part 4b: RAR Trial Script (don't read if subject randomized to standard trial script)

If you are watching this, the investigators in the hospital have reviewed your medical history and performed a complete neurological exam to ensure that you are a candidate for this study.

If you choose NOT to enroll in the clinical research trial of XPA, you will instead have the following options: 1) Treatment with standard dose tPA given by IV; or 2) No immediate treatment for the stroke. You will still be admitted to the hospital and receive all other appropriate stroke therapies including physical therapy and speech therapy as necessary.

If you choose to enroll in the clinical research trial of XPA, you will either receive tPA (the standard treatment) or XPA (the new treatment). The chances of you receiving tPA or XPA will vary depending on which treatment has shown so far to be the best in reducing disability in patients similar to yourself so far in our study. If no difference has been shown between the treatments so far in the study, you will have a 50:50 chance of receiving XPA versus tPA. However, depending on how much better either treatment is

doing within those patients in whom we already have results, you may have as high as an 80:20 chance of receiving the better performing treatment. At this point in time, across the U.S. approximately half of the total planned 700 patients have been enrolled. All of the researchers are blinded from the data of patients already enrolled, and the distribution of the better treatment is being determined by a computer that analyzes the ongoing results.

Comprehension question 3b is presented:

Please choose the most appropriate option:

Who or what decides what treatment I get (xPA or tPA) in this trial?

A. Randomization (something like a coin flip, with equal 50% chance of getting either for any individual in the trial including me)

B. An algorithm informed by how well previous patients have done in this study, that still has some randomness (but might be like flipping a coin with an 80% chance of heads)

C. The team of doctors and researchers caring for me will evaluate all available information and decide.

D. I don't know

The research subject is provided feedback on the correct answer after making a selection (The correct response in this case is B.)

In addition, in this trial, there will be a 3 month follow up to track how you are doing. You will be free to leave the study at any time, without penalty, but your reasons for leaving may be kept as part of the study record. The study will pay for research-related items and services. However, you will not receive any compensation or benefits from participating, but we hope the information learned from this research study will help medical professionals understand how to help patients with stroke in the future.

Part 5: Conclusions

The XPA research study is funded by the National Institutes of Health and was designed by stroke researchers at the University of Saline. The companies whose products are being studied may benefit if the study demonstrates that this treatment combination is helpful. Saline Ann Arbor Pharmaceuticals are providing the study medications, but are not involved in the design of this research or the decision to publish results.

Comprehension question 4 is presented:

Please choose the most appropriate option:

What are the benefits of participating in this trial?

A. The satisfaction of knowing that my participation is informing the care of future patients.

B. Monetary compensation that will be paid directly to me by the researchers.

C. I will definitely receive the superior treatment based on the described study procedures.

D. I don't know

The research subject is provided feedback on the correct answer after making a selection (The correct response in this case is A.)

This is the end of the video. You will now be asked some questions by the research assistant.

Appendix 3: Data Collection

RAR-HypotheticalVersion1

Q26 Enter Subject Number

Q4 Please name as many stroke warning signs as you can. (Up to 5)

- Headache (1)
- Paralysis (2)
- Trouble Speaking/Confusion (3)
- Change in Vision (4)
- Dizziness (5)
- None (6)

Q19 Research Group: (filled out by research assistant)

- Standard CT (1)
- RAR (2)

Group Randomized to

- Standard - Uninterrupted
- RAR - Uninterrupted
- Standard - Comprehension Questions
- RAR - Comprehension Questions

Q-TBA Click done when all the questions have been answered (timed question), notes will be taken on separate paper form and categorized.

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Q2 Would you agree to participate in this clinical trial? (If unsure attempt to answer additional questions)

- Yes (1)
- No (2)

Answer If Would you agree to participate in this clinical trial? (I... No Is Selected

Q3 Would you wish to have the standard treatment rt-PA or no treatment at all?

- rt-PA (1)
- No Treatment (2)

Q16 Did you understand the study when you decided to participate?

- Yes, completely (1)
- Mostly (2)
- Somewhat (3)
- Not at all (4)

Q17 Did you understand the potential benefits as they were explained?

- Yes, completely (1)
- Mostly (2)
- Somewhat (3)
- Not at all (4)

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Q18 Did you understand the potential risks as they were explained?

- Yes, completely (1)
- Mostly (2)
- Somewhat (3)
- Not at all (4)

Q27 If you were in the hypothetical trial, how would the experimental treatment XPA versus the standard treatment tPA be picked?

- The study would use randomization, something like flipping a coin (1)
- The study would use an algorithm that would give me a higher chance of receiving whichever treatment was looking better in the trial so far. (2)
- My doctors would decide (3)
- Don't know / do not remember (4)

Q5 What is your age?

Q6 What is your gender?

- Male (1)
- Female (2)
- Prefer not to answer (3)

Q7 How many brothers and sisters do you have?

Q8 Have you had a stroke before?

- Yes (1)
- No (2)

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- Prefer not to answer (3)

Q9 Do you have high blood pressure?

- Yes (1)
- No (2)
- Prefer not to answer (3)

Q10 Do you have diabetes?

- Yes (1)
- No (2)
- Prefer not to answer (3)

Q11 Do you have atrial fibrillation?

- Yes (1)
- No (2)
- Prefer not to answer (3)

Q12 Have you had a heart attack before?

- Yes (1)
- No (2)
- Prefer not to answer (3)

Q13 What is the highest level of education you have achieved?

- Some high school (1)
- High school graduate (2)

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- Some college (3)
- College graduate (4)
- Post-graduate degree (Master's, PhD, MD, JD, MSW, etc) (5)
- Prefer not to answer (6)

Q14 We are interested in knowing about the composition of the community that you live in and will use census data to collect that information. In order for us to determine this, could you tell us your zip code? (If prefer not to answer, leave blank)

Q15 What is your race / ethnicity?

- White, Non-Hispanic (1)
- African American (2)
- Hispanic (3)
- Asian (4)
- Pacific Islander (5)
- Native American (6)
- Other (7) _____
- Prefer not to answer (8)