Can Response-Adaptive Randomization Increase Participation in Acute Stroke Trials?

Jason S. Tehranisa, MPH; William J. Meurer, MD, MS

Background and Purpose—A response-adaptive randomization (RAR) trial design actively adjusts the ratio of participants assigned to each trial arm, favoring the better performing treatment by using outcome data from participants already in the trial. Compared with a standard clinical trial, an RAR study design has the potential to improve patient participation in acute stroke trials.

Methods—This cross-sectional randomized survey included adult emergency department patients, age ≥18, without symptoms of stroke or other critical illness. A standardized protocol was used, and subjects were randomized to either an RAR or standard hypothetical acute stroke trial. After viewing the video describing the hypothetical trial (http://youtu.be/cKIWduCaPZc), reviewing the consent form, and having questions answered, subjects indicated whether they would consent to the trial. A multivariable logistic regression model was fitted to estimate the impact of RAR while controlling for demographic factors and patient understanding of the design.

Results—A total of 418 subjects (210 standard and 208 RAR) were enrolled. All baseline characteristics were balanced between groups. There was significantly higher participation in the RAR trial (67.3%) versus the standard trial (54.5%), absolute increase: 12.8% (95% confidence interval, 3.7–22.2). The RAR group had a higher odds ratio of agreeing to research (odds ratio, 1.89; 95% confidence interval, 1.2–2.9) while adjusting for patient level factors. Trial designs were generally well understood by the participants.

Conclusions—The hypothetical RAR trial attracted more research participation than standard randomization. RAR has the potential to increase recruitment and offer benefit to future trial participants. (Stroke. 2014;45:00-00.)

Key Words: cerebrovascular accident, acute ■ emergency medicine ■ stroke, acute ■ tissue plasminogen activator

In time-sensitive emergency conditions, participation in research is limited. Medical care should aim to provide the best possible care for that individual; however, it is important to balance this with research goals of gathering unbiased data regarding the effect of treatment. In standard 2-arm clinical trial designs, each participant has an equal but random chance of receiving either treatment. Response-adaptive randomization (RAR) is one way to address the tension between the medical and research aims. In a trial using RAR, the ratio of participants assigned to each study group is adjusted based on accumulating data while the study is ongoing, using a predetermined defined set of rules. This works to collectively favor the patients within the trial in situations when one treatment is ultimately better than the other.

There is limited knowledge on the extent of use and effectiveness of RAR study designs in the emergency setting. However, some studies have assessed willingness to join research studies in emergency conditions such as ischemic stroke or subarachnoid hemorrhage. These studies have shown that just more than half of participants or their proxies consent to research. Hesitation to join emergency research studies was attributed to the perceived risk of such trials and pre-existing negative attitudes toward research.

Participation in emergency care research may be unattractive to a significant proportion of patients. The influence of trial design on research participation in emergency care has not been studied previously. Therefore, we hypothesized that a hypothetical acute stroke trial that included RAR would be more agreeable to participants than a trial using fixed 1:1 randomization, with all other aspects of the trial design presented exactly the same.

Methods

A more detailed description of the methods is available in the online-only Data Supplement. Briefly, we performed a cross-sectional study of noncritically ill emergency department adult patients, without presenting symptoms consistent with stroke, altered mental status, or alcohol intoxication. Participants were introduced to the study, gave consent, and were randomly allocated to see 1 of 2 videos. They also answered questions about demographics and stroke symptom knowledge. The video was the same across both groups, with the exception of the explanation of the hypothetical study: either described as a standard clinical trial or an RAR study. The RAR video can be
viewed at http://youtu.be/cKlWduCaPZc; the standard trial video can be viewed at http://youtu.be/Sr4FfdCTZ-A. All participants in both groups were informed that the trial had recruited approximately one half of the total planned enrollment and then were asked if they would participate in the stroke trial (primary outcome). Statistical analysis was performed using SPSS version 19. The entire protocol was placed online prior to the analysis or visualization of the data (http://bit.ly/11gTHLU). All hypotheses and main analyses were prespecified prior to any visualization of participant responses. We conducted stratified analyses based on participant understanding based on post hoc review of the results.

Ethics
This study was determined to be exempt by University of Michigan Institutional Review Board under 45 CFR 46.101(b). Participation was voluntary, and verbal consent was obtained from all participants.

Results

Participant Characteristics
Four hundred eighteen participants were enrolled in the study, 208 to the RAR group and 210 to the standard group by randomization. Age, sex, history of stroke, hypertension, diabetes mellitus, atrial fibrillation, heart attack, education, ethnicity, and previous knowledge of stroke were comparable across groups (Table I in the online-only Data Supplement).

Primary Outcome
When patients were presented with the hypothetical acute stroke study, 140 of the 208 (67.3%) in the RAR group chose to participate in the study, versus 114 of the 210 (54.3%) of those in the standard group; an absolute difference of 13% (95% confidence interval, 3.7–22.1).

Additional Results
Self-reported understanding between the standard and RAR groups was not significantly different; however, significantly fewer in the RAR group actually correctly identified the method of trial allocation (Table II in the online-only Data Supplement).

In the multivariable logistic regression model, the RAR group had a higher odds of agreeing to research (odds ratio, 1.89; 95% confidence interval, 1.2–2.9) while controlling for age, sex, ethnicity, education, self-reported understanding of protocol, ability to identify allocation technique correctly, and stroke awareness (Table III in the online-only Data Supplement). In stratified analyses, those indicating complete understanding of the protocol and who correctly identified the allocation method were more likely to agree to research if in the RAR group (Tables IV–VI in the online-only Data Supplement).

Discussion
In this study, we found significant higher participation in the hypothetical acute stroke trial when an RAR design was used compared with the standard clinical trial design. In certain respects, this could be expected as the potential for better outcome is posed as greater (although still subject to random chance) in the RAR scenario. This suggests that the design and potential benefits of the RAR feature were able to attract and recruit more participants to join the research study in an acute stroke trial scenario. Importantly, the participation rate of the standard group was comparable to that of other studies, indicating that the conditions of our hypothetical scenario were likely to be comparable to actual experiences in acute stroke trials.

Previous work has demonstrated that most clinical research participants are uncomfortable with treatment allocation determined by random chance. A trial design with RAR has the potential to be a viable alternative because it preserves the random element and a participant’s chance of getting an ultimately better treatment is increased. Other trial goals may also be incorporated via similar designs, such as balance of prognostic factors using covariate adjusted response-adaptive allocation.

Our study has several limitations. First, the participants in the study had a mean age of 43. Although the presentation of strokes is typically at an older age, it has been shown that the proportion of patients declining acute care research (either by patient or proxy) was similar in the adult (18–64) and geriatric age (>65) groups, supporting the generalizability of our results with regard to age. Second, the fact that the scenarios presented to the patients were hypothetical is another limitation. In the hypothetical acute stroke scenario used in our study, the patient would not be able to answer for themselves because the symptoms of the stroke would have left the patient cognitively impaired. However, given that our study showed a significant number were in favor of RAR over the standard randomization, it is likely that this preference would extend to the surrogates as well under the 2 likely situations: (1) the surrogate is expected to select the treatment that the patient would have wanted or (2) existing knowledge that surrogates tend to make decisions for care that they themselves would choose. Finally, the generalizability of the study has its limitations. The study population was from a single suburban academic center, and thus, the results may not be generalizable to other regions, countries, or hospital types. Also, we only explored 1 type of RAR design, the play-the-winner design, and it is unknown whether our findings would be applicable to other adaptive designs incorporating RAR such as multiple arm dose finding trials.

Conclusions
In summary, our results show that the RAR trial design attracted a higher research participation rate than standard randomization for a hypothetical acute stroke trial. Implementing the RAR trial design could increase recruitment and also offer the overall trial population added benefit compared with a fixed randomization trial. Future studies aimed at learning more about why RAR was preferred, or what specific components of RAR were viewed favorable, would be valuable in gaining a better understanding of RAR and allow for optimizing its implementation. In addition, improving the rapid communication of adaptive clinical trial designs in the emergency setting with potential research subjects is an important area for future work.

Acknowledgments
Dr Meurer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Disclosures
None.

References
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http://stroke.ahajournals.org/content/suppl/2014/06/10/STROKEAHA.114.005418.DC1

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SUPPLEMENTAL METHODS:

I. Study Consent and Study Information
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:
   Alfred Taubman Health Care Center
   1500 East Medical Center Drive
   Room B1354
   Ann Arbor, MI 48109-5303
   Phone: 734-615-2766
   Email: wmeurer@umich.edu
II. Study Scenarios Presented to Participants
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.

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.

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.

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.

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.

This is the end of the video. You will now be asked some questions by the research assistant.
III. Hypothetical Consent Form for Response-Adaptive Randomization Group
UNIVERSITY OF SALINE
CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

1.1 Study title: XPA in acute stroke trial

1.2 Company or agency sponsoring the study: NIH/NINDS

1.3 Names, degrees, and affiliations of the researchers conducting the study:
William Meurer, M.D., Stroke Program, University of Saline

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

The purpose of this research study is to find out what effects (good and bad) of a drug used to dissolve blood clots called XPA has on you and your stroke when compared to a drug called rt-PA. The rt-PA is already an approved treatment for patients who have stroke due to blockage of an artery in the brain if given within three hours from the onset of stroke symptoms. This study is being done to see if XPA is better and safer than rt-PA.

XPA has not been approved for the treatment of acute stroke and its use is investigational. XPA is an approved drug by the Food and Drug Administration for the treatment for blood clots causing heart attack and chest pain.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely voluntary. You do not have to participate if you don't want to. Your medical treatment will not be affected if you choose not to participate. You will still be given standard medical care. You may also leave the study at any time. If you leave the
study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

You are being asked to take part in this research study because you have been diagnosed with acute stroke. Your stroke is likely due to a blood clot in an artery delivering blood to your brain. When a blood clot blocks an artery supplying blood to the brain, the area of the brain which usually receives the blood may not get enough blood and oxygen to survive. As a result, permanent damage can be done to your brain, which can affect your ability to walk, talk, and function independently. In order to reduce the risk of permanent damage, it is important to restore blood flow as quickly as possible to the brain.

3.1 Who can take part in this study?

Persons aged 18-105 who have been diagnosed with a recent acute stroke likely due to a blood clot in an artery delivering blood to their brains may be able to take part in this study.

This study may not be safe for everyone. It is very important that you provide the investigators with complete and accurate health information. The following are conditions that may stop you from being able to participate due to safety risks:

- You are younger than 18 or older than 105 years of age
- You have a known allergy to XPA

If you have any of the conditions listed above, please tell the investigators. You will not be eligible to participate in this study.

3.2 How many people (subjects) are expected to take part in this study?

700 people are expected to participate, 35 at the University of Saline and 665 at other sites around the United States.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

You will be "randomized" into one of the two groups described below. Randomization means that you are put into a group completely by chance. It is like flipping a coin.

<table>
<thead>
<tr>
<th>Standard medicine group</th>
<th>Study medicine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard dose rt-PA®</td>
<td>XPA</td>
</tr>
</tbody>
</table>

Neither you nor the doctors or nurses conducting this study will choose what group you will be in. At the beginning of the overall trial participants will have a one out of two chance of being placed in the study medicine group. As data accumulates, the central study computer will determine which treatment is performing better and your chance of being placed in the study medicine group could range from one in three (in the event rt-PA appears better) to two in three
(in the event XPA appears better.) The investigators do not know if and when this change in the chances you get randomized to one group or the other has occurred.

In the event of an emergency, your study doctor will be able to find out which treatment you are receiving.

If you take part in this study, you will receive the same basic care given to all stroke patients including the following tests and procedures:

1. An intravenous line or IV will be started to give you fluids into a vein in your arm or hand and (if possible) a second intravenous line will be started which can be used to give the research study medications.
2. A physician will examine you. The physician will perform a few simple neurologic tests to look for problems with your brain. A CT or MRI scan, a special type of brain x-ray, will be done to determine if your stroke is a result of a blood vessel blockage or from a tear in the blood vessel that is bleeding into the brain. If your stroke is a result of bleeding, you will not be allowed in this study.
3. In the emergency room and later in the intensive care unit or stroke unit your blood pressure and heart rhythm will be monitored. You will be examined several times for changes in your neurological condition, before and after the study medication is given. Study personnel will be involved in your care during the entire period.
4. Like all patients treated with standard rt-PA therapy you will be taken to X-ray to have a head CT scan (a special x-ray of the brain) between 18 and 30 hours after the onset of stroke symptoms as a safety check for bleeding. If you were to have any worsening in your condition during the first 24 hours, or at any other time, a head CT scan will be done as soon as possible.
5. While you are in the hospital your care will be under the direction of the admitting physician in consultation with members of the Neurology service. During your hospitalization, you may have other brain imaging studies and other tests that are routinely carried out for patients with a stroke to determine the cause of the stroke.
6. At 5 days post receiving study drug or on the day you are to be discharged from the hospital you will be visited by study personnel. You will also receive a phone call or a visit by study staff to evaluate your condition at 6 to 8 days after your stroke.
7. Three months after your stroke and discharge from the hospital, you will have a follow-up appointment or a home visit by study personnel. At this visit you will have a medical and neurologic examination and be asked questions about the quality of your life at that time.

4.2 How much of my time will be needed to take part in this study?

While you are hospitalized, you will be examined several times for changes in your neurological condition, and have a head CT between 18 and 30 hours after receiving medication. These examinations will take 5-15 minutes each, and the CT scans can take up to 30 minutes. On day 5 or your day of discharge, you will be given a brief neurological examination lasting 5-15 minutes. Six to eight days after your stroke, you will receive a phone call or visit from study personnel that will last approximately 10 minutes. Your final visit at 90 days will last approximately one hour.
4.3 When will my participation in the study be over?

Your participation in the study will be over approximately 3 months from the time you receive the study medication.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

Because the approved dose of rt-PA and XPA both act to dissolve blood clots, both treatments have a risk of bleeding complications. Bleeding into a stroke damaged brain can occur and can be serious since it can make the symptoms of stroke (for example, your ability to walk, talk, and function independently) worse and it sometimes may cause permanent disability or death.

In other studies of stroke patients who received rt-PA given through a vein into the arm using the standard FDA approved dose, about six patients out of 100 had bleeding into the brain that made their condition worse or was life threatening. Stroke patients receiving the study medicine XPA may have a lower or higher risk of bleeding into the brain that might make them worse or be life threatening but the actual risk is unknown.

With both the standard and study treatments there is also a risk of serious internal bleeding that may require blood transfusion or could be life threatening. In patients studied with heart attack the rate of serious internal bleeding was not significantly different between the patients who received XPA and patients receiving rt-PA alone. In stroke patients who receive IV rt-PA alone, about six out of 100 persons treated will have serious internal bleeding that requires a transfusion.

As with any drug, there is some chance of allergic reaction, such as rash. One in 100 persons treated with rt-PA experiences swelling of the tongue and inside the mouth. This swelling is usually mild and easily treated with medication, but rarely difficulty with breathing develops and a tube may need to be inserted into the mouth or nose to keep the airway open.

Finally, with both standard and study treatments there may be minor bleeding from gums or at sites where a puncture has been made to obtain blood samples or to give medicine or fluid into a vein.

Severity of Bleeding Complications and Side Effects

The known or expected risks are:

Because both rt-PA and XPA dissolve blood clots, they have a risk of bleeding complications. Bleeding into the damaged brain can occur and can be serious in some patients since it can aggravate the symptoms of stroke (for example, your ability to walk, talk, and function independently) and it sometimes may cause permanent disability or
death. There is the potential for a higher risk of serious bleeding into the brain, in the range of 6 to 11 people out of 100 having this complication occur.

The researchers will try to minimize these risks by watching you very carefully for any signs that indicate bleeding problems. The CT scan of your brain will be done to check for bleeding in your head between 18 and 30 hours after the start of your stroke. If serious bleeding develops while you are being given the study medication, the study medication will immediately be stopped. If serious bleeding does occur you also will likely be given blood products through your vein to help stop the bleeding. You will be monitored and treated appropriately if any allergic reaction should develop.

**Severity of Radiologic Procedure Side Effects**

A single CT of the brain is about the same as the amount of radiation that the average person living on earth is exposed to in the environment over 8 months. This study requires one additional CT scan of the brain over and above what you would receive as part of your normal stroke care. The precise risk for these tests is unknown but is thought to be very small.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 **What happens if I get hurt, become sick, or have other problems as a result of this research?**

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors. In the event that you become ill or injured from participating in this research study, emergency medical care will be provided to you.

5.3 **If I take part in this study, can I also participate in other studies?**

*Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies.* You should not take part in more than one study without approval from the researchers involved in each study. Tell the researchers if you are involved in any other research studies currently or if you have been involved in research studies within the past 90 days.

5.4 **How could I benefit if I take part in this study? How could others benefit?**

You may not receive any personal benefits from being in this study. We hope the information learned from this research study will help medical professionals understand how to help patients with stroke in the future.
Potential benefits to you may be that the new treatment XPA may be more effective at dissolving the blood clots that cause stroke than the use of rt-PA. XPA has been shown to be effective in dissolving blood clots in patients with blood clots in the arteries to the heart muscle (heart attack). In heart attack patients, XPA has been shown to dissolve blood clots faster than rt-PA alone. The results of the studies using the XPA to treat patients with heart attack were encouraging enough to justify a study of patients with blood clots in their brain arteries causing stroke. However, it is also possible that persons receiving XPA may have less improvement than persons who receive the standard rt-PA therapy or they may have no benefit at all.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?

Instead of being in this research study, you have the following options: 1) Treatment with standard dose 
rt-PA 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.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 “Contact Information” (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

If you decide to discontinue participation in this study, you should contact one of the people listed in the contact information below, as well as your treating doctor. Continued participation in this study allows you to be monitored closely for the development of possible complications. If you discontinue participation, your treating doctor may want to perform additional tests.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

✓ The researcher believes that it is not in your best interest to stay in the study.
✓ You experience side effects from the study medications and it is in your best interest to stop.
You become ineligible to participate.
✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
✓ You do not follow instructions from the researchers.
✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers’ number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Treatment of complications
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan’s medical reviewer.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

You will not be paid or given anything for taking part in this study.

8.3 Who could profit or financially benefit from the study results?

The research 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.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION
The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?

Every effort will be made to maintain the confidentiality of your study records. Agents of the United States Food and Drug Administration, the University of Saline, designates of the National Institute of Neurologic Diseases and Stroke, Saline Ann Arbor Pharmaceuticals and the XPA Stroke Trial Clinical Coordinating Center will be allowed to inspect sections of your medical and research records related to this study. The data from the study may be published; however, you will not be identified by name. Your identity will remain confidential unless disclosure is required by law.

You will be assigned an identification number which will be used on forms filled out about you instead of your name. These forms, your consent form, and other information about you will be kept in a locked cabinet. Computer files pertaining to you will be kept on password-protected files, such that only study personnel will have access to this information.

Information collected about you for research will be reported to the study Clinical Coordinating Center through a secure website. Only authorized members of the study team will have access to this password-protected site. Research data collected about you and sent to the Clinical Coordinating Center will have personal identifiers removed except for your assigned study ID number and dates (including your date of birth; dates of admission and discharge; and dates of other events, treatments or procedures during your hospital stay).

A copy of this consent form will also be placed in your medical record. If the researcher orders any tests, the order and results will also become part of your regular medical record. When you are seen by investigators during your inpatient visit, progress notes related to the study will also be placed in your medical record. This is done so that if you have other health problems or need other treatment during the study, the doctors caring for you will be able to obtain sufficient information about what drugs or procedures you are receiving in the study and can treat you appropriately.

You have been told that when the study is completed, you will not be given specific results of the study, such as to which treatment group you were assigned to. You do have the option of receiving overall study results.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from the University of Saline Health System or any other hospital, doctor, or health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
• Mental health care records (except psychotherapy notes not kept with your medical records)
• Alcohol/substance abuse treatment records
• Your AIDS/HIV status
• All records relating to your stroke, the treatment you have received, and your response to the treatment
• Demographic information
• Personal identifiers
• Billing information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

• The researchers may need the information to make sure you can take part in the study.
• The researchers may need the information to check your test results or look for side effects.
• University, Food and Drug Administration (FDA), and/or other government officials may need the information to make sure that the study is done in a safe and proper manner.
• Study sponsors or funders, or safety monitors or committees, may need the information to:
  o Make sure the study is done safely and properly
  o Learn more about side effects
  o Analyze the results of the study
• Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
• The researchers may need to use the information to create a databank of information about your condition or its treatment.
• Information about your study participation may be included in your regular University of Saline medical record.
• If you receive any payments for taking part in this study, the University of Saline accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.

• Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to
continue to be used or disclosed, even after you have canceled your permission or the study is over. Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Saline Health System, it is protected by the Health System’s privacy policies. For more information about these policies, ask for a copy of the University Of Saline Notice Of Privacy Practices. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: William Meurer, MD
Mailing Address:
University of Saline Health Systems
Department of Emergency Medicine
100 E. Ann Arbor Saline Rd
Saline, MI 48139
Telephone: 734-555-2766
You may also express a concern about a study by contacting the Institutional Review Board listed below, or by calling the University of Saline Compliance Help Line at 1-888-555-2481.

IRB - Saline
1800 Ann Arbor Rd.
Building 201, Room 2486
Saline, MI 48199-2810
Telephone: 734-555-4768
Fax: 734-555-1622
e-mail: irb@saline.edu

If you are concerned about a possible violation of your privacy, contact the University of Saline Health System Privacy Officer at 1-888-555-2481.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRB number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.
12. SIGNATURES

**Research Subject:**

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _________________________________. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that if I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Signature of Subject: ___________________________ Date: ________ Time: _____

Name (Print legal name): ________________________________

Patient ID: ___________________________ Date of Birth: ______________

**Legal Representative (if applicable):**

Signature of Person Legally Authorized to Give Consent ___________________________ Date: ________ Time: ________

Name (Print legal name): ___________________________ Pho: ______________

Address: ___________________________

Check Relationship to Subject:

Parent  Spouse  Child  Sibling  Legal Guardian  Other: __________________

*If this consent is for a child who is a ward of the state (for example a foster child), please tell the study team immediately. The researchers may need to contact the IRBMED.*

Reason subject is unable to sign for self: ___________________________________

**Principal Investigator (or Designee):**

I have given this research subject (or his/her legally authorized representative, if applicable) information about this study that I believe is accurate and complete. The subject has indicated that he or she understands the nature of the study and the risks and benefits of participating.

Name: ___________________________ Title: ___________________________

Signature: ___________________________ Date and Time of Signature: ___________________________

**Witness (optional):**

I observed the above subject (or his/her legally authorized representative, if applicable) sign this consent document.

Name: ___________________________

Signature: ___________________________ Date and Time of Signature: ___________________________
IV. Hypothetical Consent Form for Standard Group
UNIVERSITY OF SALINE
CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

1.1 Study title: XPA in acute stroke trial

1.2 Company or agency sponsoring the study: NIH/NINDS

1.3 Names, degrees, and affiliations of the researchers conducting the study: William Meurer, M.D., Stroke Program, University of Saline

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

The purpose of this research study is to find out what effects (good and bad) of a drug used to dissolve blood clots called XPA has on you and your stroke when compared to a drug called rt-PA. The rt-PA is already an approved treatment for patients who have stroke due to blockage of an artery in the brain if given within three hours from the onset of stroke symptoms. This study is being done to see if XPA is better and safer than rt-PA.

XPA has not been approved for the treatment of acute stroke and its use is investigational. XPA is an approved drug by the Food and Drug Administration for the treatment for blood clots causing heart attack and chest pain.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely voluntary. You do not have to participate if you don't want to. Your medical treatment will not be affected if you choose not to participate. You will still be given standard medical care. You may also leave the study at any time. If you leave the
study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

You are being asked to take part in this research study because you have been diagnosed with acute stroke. Your stroke is likely due to a blood clot in an artery delivering blood to your brain. When a blood clot blocks an artery supplying blood to the brain, the area of the brain which usually receives the blood may not get enough blood and oxygen to survive. As a result, permanent damage can be done to your brain, which can affect your ability to walk, talk, and function independently. In order to reduce the risk of permanent damage, it is important to restore blood flow as quickly as possible to the brain.

3.1 Who can take part in this study?

Persons aged 18-105 who have been diagnosed with a recent acute stroke likely due to a blood clot in an artery delivering blood to their brains may be able to take part in this study.

This study may not be safe for everyone. It is very important that you provide the investigators with complete and accurate health information. The following are conditions that may stop you from being able to participate due to safety risks:

- You are younger than 18 or older than 105 years of age
- You have a known allergy to XPA

If you have any of the conditions listed above, please tell the investigators. You will not be eligible to participate in this study.

3.2 How many people (subjects) are expected to take part in this study?

700 people are expected to participate, 35 at the University of Saline and 665 at other sites around the United States.

<table>
<thead>
<tr>
<th>4. INFORMATION ABOUT STUDY PARTICIPATION</th>
</tr>
</thead>
</table>

4.1 What will happen to me in this study?

You will be "randomized" into one of the two groups described below. Randomization means that you are put into a group completely by chance. It is like flipping a coin.

<table>
<thead>
<tr>
<th>Standard medicine group</th>
<th>Study medicine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard dose rt-PA®</td>
<td>XPA</td>
</tr>
</tbody>
</table>

Neither you nor the doctors or nurses conducting this study will choose what group you will be in. You will have a one out of two chance of being placed in the study medicine group.

In the event of an emergency, your study doctor will be able to find out which treatment you are receiving.
If you take part in this study, you will receive the same basic care given to all stroke patients including the following tests and procedures:

8. An intravenous line or IV will be started to give you fluids into a vein in your arm or hand and (if possible) a second intravenous line will be started which can be used to give the research study medications.
9. A physician will examine you. The physician will perform a few simple neurologic tests to look for problems with your brain. A CT or MRI scan, a special type of brain x-ray, will be done to determine if your stroke is a result of a blood vessel blockage or from a tear in the blood vessel that is bleeding into the brain. If your stroke is a result of bleeding, you will not be allowed in this study.
10. In the emergency room and later in the intensive care unit or stroke unit your blood pressure and heart rhythm will be monitored. You will be examined several times for changes in your neurological condition, before and after the study medication is given. Study personnel will be involved in your care during the entire period.
11. Like all patients treated with standard rt-PA therapy you will be taken to X-ray to have a head CT scan (a special x-ray of the brain) between 18 and 30 hours after the onset of stroke symptoms as a safety check for bleeding. If you were to have any worsening in your condition during the first 24 hours, or at any other time, a head CT scan will be done as soon as possible.
12. While you are in the hospital your care will be under the direction of the admitting physician in consultation with members of the Neurology service. During your hospitalization, you may have other brain imaging studies and other tests that are routinely carried out for patients with a stroke to determine the cause of the stroke.
13. At 5 days post receiving study drug or on the day you are to be discharged from the hospital you will be visited by study personnel. You will also receive a phone call or a visit by study staff to evaluate your condition at 6 to 8 days after your stroke.
14. Three months after your stroke and discharge from the hospital, you will have a follow-up appointment or a home visit by study personnel. At this visit you will have a medical and neurologic examination and be asked questions about the quality of your life at that time.

4.2 How much of my time will be needed to take part in this study?

While you are hospitalized, you will be examined several times for changes in your neurological condition, and have a head CT between 18 and 30 hours after receiving medication. These examinations will take 5-15 minutes each, and the CT scans can take up to 30 minutes. On day 5 or your day of discharge, you will be given a brief neurological examination lasting 5-15 minutes. Six to eight days after your stroke, you will receive a phone call or visit from study personnel that will last approximately 10 minutes. Your final visit at 90 days will last approximately one hour.

4.3 When will my participation in the study be over?

Your participation in the study will be over approximately 3 months from the time you receive the study medication.

5. INFORMATION ABOUT RISKS AND BENEFITS
5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

Because the approved dose of rt-PA and XPA both act to dissolve blood clots, both treatments have a risk of bleeding complications. Bleeding into a stroke damaged brain can occur and can be serious since it can make the symptoms of stroke (for example, your ability to walk, talk, and function independently) worse and it sometimes may cause permanent disability or death.

In other studies of stroke patients who received rt-PA given through a vein into the arm using the standard FDA approved dose, about six patients out of 100 had bleeding into the brain that made their condition worse or was life threatening. Stroke patients receiving the study medicine XPA may have a lower or higher risk of bleeding into the brain that might make them worse or be life threatening but the actual risk is unknown.

With both the standard and study treatments there is also a risk of serious internal bleeding that may require blood transfusion or could be life threatening. In patients studied with heart attack the rate of serious internal bleeding was not significantly different between the patients who received XPA and patients receiving rt-PA alone. In stroke patients who receive IV rt-PA alone, about six out of 100 persons treated will have serious internal bleeding that requires a transfusion.

As with any drug, there is some chance of allergic reaction, such as rash. One in 100 persons treated with rt-PA experiences swelling of the tongue and inside the mouth. This swelling is usually mild and easily treated with medication, but rarely difficulty with breathing develops and a tube may need to be inserted into the mouth or nose to keep the airway open.

Finally, with both standard and study treatments there may be minor bleeding from gums or at sites where a puncture has been made to obtain blood samples or to give medicine or fluid into a vein.

Severity of Bleeding Complications and Side Effects

The known or expected risks are:

Because both rt-PA and XPA dissolve blood clots, they have a risk of bleeding complications. Bleeding into the damaged brain can occur and can be serious in some patients since it can aggravate the symptoms of stroke (for example, your ability to walk, talk, and function independently) and it sometimes may cause permanent disability or death. There is the potential for a higher risk of serious bleeding into the brain, in the range of 6 to 11 people out of 100 having this complication occur.

The researchers will try to minimize these risks by watching you very carefully for any signs that indicate bleeding problems. The CT scan of your brain will be done to check for bleeding in your head between 18 and 30 hours after the start of your stroke. If serious bleeding develops while you are being given the study medication, the study medication
will immediately be stopped. If serious bleeding does occur you also will likely be given blood products through your vein to help stop the bleeding. You will be monitored and treated appropriately if any allergic reaction should develop.

**Severity of Radiologic Procedure Side Effects**

A single CT of the brain is about the same as the amount of radiation that the average person living on earth is exposed to in the environment over 8 months. This study requires one additional CT scan of the brain over and above what you would receive as part of your normal stroke care. The precise risk for these tests is unknown but is thought to be very small.

As with any research study, there may be additional risks that are unknown or unexpected.

**5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?**

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors. In the event that you become ill or injured from participating in this research study, emergency medical care will be provided to you.

**5.3 If I take part in this study, can I also participate in other studies?**

*Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies.* You should not take part in more than one study without approval from the researchers involved in each study. Tell the researchers if you are involved in any other research studies currently or if you have been involved in research studies within the past 90 days.

**5.4 How could I benefit if I take part in this study? How could others benefit?**

You may not receive any personal benefits from being in this study. We hope the information learned from this research study will help medical professionals understand how to help patients with stroke in the future.

Potential benefits to you may be that the new treatment XPA may be more effective at dissolving the blood clots that cause stroke than the use of rt-PA. XPA has been shown to be effective in dissolving blood clots in patients with blood clots in the arteries to the heart muscle (heart attack). In heart attack patients, XPA has been shown to dissolve blood clots faster than rt-PA alone. The results of the studies using the XPA to treat patients with heart attack were encouraging enough to justify a study of patients with blood clots in their brain arteries causing
stroke. However, it is also possible that persons receiving XPA may have less improvement than persons who receive the standard rt-PA therapy or they may have no benefit at all.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?

Instead of being in this research study, you have the following options: 1) Treatment with standard dose rt-PA 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.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 “Contact Information” (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

If you decide to discontinue participation in this study, you should contact one of the people listed in the contact information below, as well as your treating doctor. Continued participation in this study allows you to be monitored closely for the development of possible complications. If you discontinue participation, your treating doctor may want to perform additional tests.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- The researcher believes that it is not in your best interest to stay in the study.
- You experience side effects from the study medications and it is in your best interest to stop.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is suspended or canceled.
8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers’ number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Treatment of complications
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan’s medical reviewer.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

You will not be paid or given anything for taking part in this study.

8.3 Who could profit or financially benefit from the study results?

The research 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.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?
Every effort will be made to maintain the confidentiality of your study records. Agents of the United States Food and Drug Administration, the University of Saline, designates of the National Institute of Neurologic Diseases and Stroke, Saline Ann Arbor Pharmaceuticals and the XPA Stroke Trial Clinical Coordinating Center will be allowed to inspect sections of your medical and research records related to this study. The data from the study may be published; however, you will not be identified by name. Your identity will remain confidential unless disclosure is required by law.

You will be assigned an identification number which will be used on forms filled out about you instead of your name. These forms, your consent form, and other information about you will be kept in a locked cabinet. Computer files pertaining to you will be kept on password-protected files, such that only study personnel will have access to this information. Information collected about you for research will be reported to the study Clinical Coordinating Center through a secure website. Only authorized members of the study team will have access to this password-protected site. Research data collected about you and sent to the Clinical Coordinating Center will have personal identifiers removed except for your assigned study ID number and dates (including your date of birth; dates of admission and discharge; and dates of other events, treatments or procedures during your hospital stay).

A copy of this consent form will also be placed in your medical record. If the researcher orders any tests, the order and results will also become part of your regular medical record. When you are seen by investigators during your inpatient visit, progress notes related to the study will also be placed in your medical record. This is done so that if you have other health problems or need other treatment during the study, the doctors caring for you will be able to obtain sufficient information about what drugs or procedures you are receiving in the study and can treat you appropriately.

You have been told that when the study is completed, you will not be given specific results of the study, such as to which treatment group you were assigned to. You do have the option of receiving overall study results.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from the University of Saline Health System or any other hospital, doctor, or health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records)
- Alcohol/substance abuse treatment records
- Your AIDS/HIV status
- All records relating to your stroke, the treatment you have received, and your response to the treatment
• Demographic information
• Personal identifiers
• Billing information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

• The researchers may need the information to make sure you can take part in the study.
• The researchers may need the information to check your test results or look for side effects.
• University, Food and Drug Administration (FDA), and/or other government officials may need the information to make sure that the study is done in a safe and proper manner.
• Study sponsors or funders, or safety monitors or committees, may need the information to:
  o Make sure the study is done safely and properly
  o Learn more about side effects
  o Analyze the results of the study
• Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
• The researchers may need to use the information to create a databank of information about your condition or its treatment.
• Information about your study participation may be included in your regular University of Saline medical record.
• If you receive any payments for taking part in this study, the University of Saline accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.

• Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over. Examples of reasons for this include:

• To avoid losing study results that have already included your information
• To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
• To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Saline Health System, it is protected by the Health System’s privacy policies. For more information about these policies, ask for a copy of the University Of Saline Notice Of Privacy Practices. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

• Obtain more information about the study
• Ask a question about the study procedures or treatments
• Talk about study-related costs to you or your health plan
• Report an illness, injury, or other problem (you may also need to tell your regular doctors)
• Leave the study before it is finished
• Express a concern about the study

Principal Investigator: William Meurer, MD
Mailing Address:
University of Saline Health Systems
Department of Emergency Medicine
100 E. Ann Arbor Saline Rd
Saline, MI  48139
Telephone: 734-555-2766

You may also express a concern about a study by contacting the Institutional Review Board listed below, or by calling the University of Saline Compliance Help Line at 1-888-555-2481.

IRB - Saline
1800 Ann Arbor Rd.
If you are concerned about a possible violation of your privacy, contact the University of Saline Health System Privacy Officer at 1-888-555-2481.

*When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRB number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.*
12. SIGNATURES

Research Subject:
I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with __________________________. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Signature of Subject: _______________________________ Date: _________ Time:_____

Name (Print legal name): ________________________________

Patient ID: _______________________________ Date of Birth: _______________________

Legal Representative (if applicable):
Signature of Person Legally Authorized to Give Consent ___________________________ Date: _________ Time:_____

Name (Print legal name): ________________________________ Phone: ________

Address: ___________________________________________

Check Relationship to Subject:
Parent  Spouse  Child  Sibling  Legal Guardian  Other: ______________________

If this consent is for a child who is a ward of the state (for example a foster child), please tell the study team immediately. The researchers may need to contact the IRBMED.

Reason subject is unable to sign for self:_________________________________________

Principal Investigator (or Designee):
I have given this research subject (or his/her legally authorized representative, if applicable) information about this study that I believe is accurate and complete. The subject has indicated that he or she understands the nature of the study and the risks and benefits of participating.

Name: _______________________________ Title: _______________________________

Signature: _______________________________ Date and Time of Signature: _______________________

Witness (optional):
I observed the above subject (or his/her legally authorized representative, if applicable) sign this consent document.
Name: _______________________________

Signature: _______________________________ Date and Time of Signature: _______________________

33
V. Tissue Plasminogen Activator (tPA) Risk Pictograph
Supplemental Figure I

About 1 in 4 patients will be normal without any treatment at all.

For every 100 patients treated, about 13 will change from being disabled to being normal.

Many patients will be disabled no matter what.

About 1 in 5 patients will die. This risk is the same with or without tPA because stroke is a serious disease.

Outcome about three months after stroke.

- Normal or nearly normal.
- Severely disabled (nursing home) or dead.
- Some disability. Likely unable to work.
- Early worsening with brain bleeding.

Adapted from appendix of Stroke 2010 Feb;41(2):300-6
VI. Data Collection Form for Hypothetical Trial
RAR-Hypothetical Survey Question Set

Q1: Enter Subject Number

Q2: 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)

Q3: Research Group: (filled out by research assistant)
   Standard CT (1)
   RAR (2)

Q4: Would you agree to participate in this clinical trial? (If unsure attempt to answer additional questions)
   Yes (1)
   No (2)

[If NO is selected]

Q5: Would you wish to have the standard treatment rt-PA or no treatment at all?
   rt-PA (1)
   No Treatment (2)

Q6: Did you understand the study when you decided to participate?
   Yes, completely (1)
   Mostly (2)
   Somewhat (3)
   Not at all (4)

Q7: Did you understand the potential benefits as they were explained?
   Yes, completely (1)
   Mostly (2)
   Somewhat (3)
   Not at all (4)

Q8: Did you understand the potential risks as they were explained?
   Yes, completely (1)
   Mostly (2)
   Somewhat (3)
   Not at all (4)

Q9: 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)

Q10: What is your age?
Q11: What is your gender?
   Male (1)
   Female (2)
   Prefer not to answer (3)
Q12: How many brothers and sisters do you have?
Q13: Have you had a stroke before?
   Yes (1)
   No (2)
   Prefer not to answer (3)
Q14: Do you have high blood pressure?
   Yes (1)
   No (2)
   Prefer not to answer (3)
Q15: Do you have diabetes?
   Yes (1)
   No (2)
   Prefer not to answer (3)
Q16: Do you have atrial fibrillation?
   Yes (1)
   No (2)
   Prefer not to answer (3)
Q17: Have you had a heart attack before?
   Yes (1)
   No (2)
   Prefer not to answer (3)
Q18: What is the highest level of education you have achieved?
   Some high school (1)
   High school graduate (2)
   Some college (3)
   College graduate (4)
   Post-graduate degree (Master's, PhD, MD, JD, MSW, etc) (5)
   Prefer not to answer (6)
Q19: 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)
Q20: 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)
SUPPLEMENTAL TABLES:

Supplemental Data Tables

The full dataset in SPSS is publically available at http://dx.doi.org/10.6070/H42R3PNK
**Supplemental Table I:** Demographic information by hypothetical trial design.

<table>
<thead>
<tr>
<th></th>
<th>Standard (n = 210)</th>
<th>RAR (n = 208)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>42.60 (14.55)</td>
<td>44.35 (16.28)</td>
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<td>Male, No. (%)</td>
<td>108 (51.4)</td>
<td>94 (45.2)</td>
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<tr>
<td>History of stroke, No. (%)</td>
<td>10 (4.8)</td>
<td>12 (5.8)</td>
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<td>Hypertension, No. (%)</td>
<td>63 (30.0)</td>
<td>73 (35.1)</td>
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<td>Diabetes, No. (%)</td>
<td>31 (14.8)</td>
<td>35 (16.8)</td>
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<tr>
<td>Atrial Fibrillation, No. (%)</td>
<td>15 (7.1)</td>
<td>20 (9.6)</td>
<td>0.362</td>
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<tr>
<td>Myocardial Infarction, No. (%)</td>
<td>18 (8.6)</td>
<td>9 (4.3)</td>
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<td>Education, No. (%)</td>
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<td>0.560</td>
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<td>Some HS</td>
<td>11 (5.2)</td>
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<td>High School</td>
<td>44 (21.0)</td>
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<tr>
<td>Some College</td>
<td>76 (36.2)</td>
<td>71 (34.1)</td>
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<tr>
<td>College Graduate</td>
<td>51 (24.3)</td>
<td>57 (27.4)</td>
<td></td>
</tr>
<tr>
<td>Post-graduate Degree</td>
<td>28 (13.3)</td>
<td>36 (17.3)</td>
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<td>Race/Ethnicity, No. (%)</td>
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<td>White</td>
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<td>156 (75.0)</td>
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<td>African American</td>
<td>49 (23.3)</td>
<td>38 (18.3)</td>
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<td>Hispanic</td>
<td>5 (2.4)</td>
<td>3 (1.4)</td>
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</tr>
<tr>
<td>Asian</td>
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<td>Other</td>
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<td></td>
</tr>
<tr>
<td>Prefer not to answer</td>
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<td>0 (0.0)</td>
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<td>Stroke Risk Factors Identified, No. (%)</td>
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<td>66 (31.4)</td>
<td>59 (28.4)</td>
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<td>3</td>
<td>43 (20.5)</td>
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<tr>
<td>5</td>
<td>10 (4.8)</td>
<td>10 (4.8)</td>
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</tbody>
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**Table I Legend:** RAR, response-adaptive randomization; tPA, tissue plasminogen activator; XPA, hypothetical experimental fibrinolytic drug.
**Supplemental Table II:** Additional results and self-reported understanding by hypothetical trial design.

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<thead>
<tr>
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<th>Standard (n = 210)</th>
<th>RAR (n=208)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreed to TPA (If declined trial), No. (%)</td>
<td>87 (90.6)</td>
<td>64 (94.1)</td>
<td>0.415</td>
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<td>“Did you understand the study?”, No. (%)</td>
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<td>0.392</td>
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<td>Yes</td>
<td>125 (59.5)</td>
<td>115 (55.3)</td>
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<td>Mostly</td>
<td>63 (30.0)</td>
<td>63 (30.3)</td>
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</tr>
<tr>
<td>Somewhat</td>
<td>21 (10.0)</td>
<td>30 (14.4)</td>
<td></td>
</tr>
<tr>
<td>Not at all</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>“Did you understand the benefits?”, No. (%)</td>
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<td>0.390</td>
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<tr>
<td>Yes</td>
<td>129 (61.4)</td>
<td>139 (66.8)</td>
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<tr>
<td>Mostly</td>
<td>48 (22.9)</td>
<td>41 (19.7)</td>
<td></td>
</tr>
<tr>
<td>Somewhat</td>
<td>29 (13.8)</td>
<td>21 (10.1)</td>
<td></td>
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<tr>
<td>Not at all</td>
<td>4 (1.9)</td>
<td>7 (3.4)</td>
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</tr>
<tr>
<td>“Did you understand the risks?”, No. (%)</td>
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<td>0.812</td>
</tr>
<tr>
<td>Yes</td>
<td>153 (72.9)</td>
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<tr>
<td>Mostly</td>
<td>33 (15.7)</td>
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</tr>
<tr>
<td>Somewhat</td>
<td>18 (8.6)</td>
<td>16 (7.7)</td>
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<tr>
<td>Not at all</td>
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<td>5 (2.4)</td>
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<td>“How would the XPA/tPA treatment be determined?”*, No. (%)</td>
<td>174 (85.3)</td>
<td>10 (5.0)</td>
<td>&lt;0.001</td>
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<tr>
<td>Coin flip</td>
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<td>Study algorithm</td>
<td>5 (2.5)</td>
<td>126 (62.4)</td>
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<td>Doctor’s decision</td>
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<td>Don’t know/Don’t remember</td>
<td>11 (5.4)</td>
<td>39 (19.3)</td>
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<td>Correctly Identified allocation method*, No. (%)</td>
<td>174 (85.3)</td>
<td>126 (62.4)</td>
<td>&lt;0.001</td>
</tr>
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<td>Yes</td>
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**Table II Legend:** Response-adaptive randomization; RAR. * P-value <0.001.
**Supplemental Table III: Full final logistic regression model output**

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<th>Covariate</th>
<th>Odds Ratio</th>
<th>95% CI</th>
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<tr>
<td>RAR group vs. Standard</td>
<td>1.89</td>
<td>1.223 - 2.921</td>
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<tr>
<td>White vs. all other race/ethnicity</td>
<td>1.271</td>
<td>0.777 - 2.079</td>
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<tr>
<td><strong>Education</strong></td>
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<tr>
<td>High school or less</td>
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</tr>
<tr>
<td>Some college</td>
<td>1.185</td>
<td>0.579 - 2.425</td>
</tr>
<tr>
<td>College graduate</td>
<td>1.489</td>
<td>0.769 - 2.885</td>
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<tr>
<td>Post-graduate degree</td>
<td>1.011</td>
<td>0.503 - 2.033</td>
</tr>
<tr>
<td>Reported complete understanding (no vs. yes)</td>
<td>0.812</td>
<td>0.526 - 1.253</td>
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<tr>
<td>Correctly identified randomization (no vs. yes)</td>
<td>1.476</td>
<td>0.889 - 2.451</td>
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<tr>
<td>Correctly identified allocation (no vs. yes)</td>
<td>0.956</td>
<td>0.6 - 1.522</td>
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<td><strong>Age (years)</strong></td>
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<td>&lt;=25</td>
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</tr>
<tr>
<td>26 to 38</td>
<td>0.737</td>
<td>0.314 - 1.731</td>
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<td>39 to 45</td>
<td>1.08</td>
<td>0.491 - 2.373</td>
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<td>46 to 65</td>
<td>1.251</td>
<td>0.532 - 2.942</td>
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<td>66+</td>
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<td>0.258 - 1.174</td>
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**Supplemental Table IV:** Primary outcome stratified by self-reported complete understanding

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<th>Less than complete understanding</th>
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<tr>
<td></td>
<td>Agree N</td>
<td>Refuse N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Group</td>
<td>60%</td>
<td>51</td>
<td>40%</td>
<td>34</td>
<td>0.64</td>
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<tr>
<td>RAR Group</td>
<td>63%</td>
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<td>37%</td>
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<table>
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<th>p value by chi-square</th>
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<td></td>
<td>Agree N</td>
<td>Refuse N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Group</td>
<td>50%</td>
<td>63</td>
<td>50%</td>
<td>62</td>
<td>0.002</td>
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<tr>
<td>RAR Group</td>
<td>70%</td>
<td>81</td>
<td>30%</td>
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**Supplemental Table V:** Primary outcome stratified by correct identification of allocation

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<th>p value by Fisher exact</th>
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<td>Agree N</td>
<td>Refuse N</td>
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<tr>
<td>Standard Group</td>
<td>83%</td>
<td>5</td>
<td>17%</td>
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<td>RAR Group</td>
<td>67%</td>
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<th></th>
<th>p value by chi-square</th>
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</thead>
<tbody>
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<td></td>
<td>Agree N</td>
<td>Refuse N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>17</td>
<td>43%</td>
<td>13</td>
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<td>RAR Group</td>
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<td>43%</td>
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<th>p value by chi-square</th>
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</thead>
<tbody>
<tr>
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<td>Agree N</td>
<td>Refuse N</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Standard Group</td>
<td>53%</td>
<td>92</td>
<td>47%</td>
<td>82</td>
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<td>RAR Group</td>
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<td>26%</td>
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**Supplemental Table VI:** Association between understanding and correct identification

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<th>Complete Understanding</th>
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<th>Yes</th>
<th>N</th>
<th>No</th>
<th>N</th>
<th>p value by chi-square</th>
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<td>Yes</td>
<td>80%</td>
<td>184</td>
<td>20%</td>
<td>45</td>
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<td>&lt;0.001</td>
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<td>No</td>
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<td>116</td>
<td>34%</td>
<td>61</td>
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SUPPLEMENTAL RESULTS:
Supplemental Results

To test for effect modification between the treatment groups all of the interaction terms with group assignment (examples: age*group, understanding*group, etc.) were put into the final logistic regression model (individually and as a group) and none achieved statistical significance of \( p < 0.05 \). We also conducted stratified analyses relating research participation across the RAR and standard groups (stratifying by self-reported complete understanding, accurate identification of allocation method, and also cross tabulating the association between self-reported complete understanding and accurate identification of allocation method – Supplemental Material Tables 2-4).