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Understanding Preferences Regarding Consent for Pragmatic Trials in Acute Care

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Abstract

Background—There has been debate about the role of consent in pragmatic trials comparing qualitatively similar interventions. Consent preferences may differ in acute care contexts given severe illness, time constraints, and other barriers to consent. In addition, studies have not assessed the impact of disclosing financial considerations as a justification for trials. This study was designed to assess preferences of the general public regarding consent for a pragmatic trial in ST-elevation myocardial infarction.

Methods—This survey was completed using an online, probability-based panel representative of the U.S. population. It incorporated a randomized, experimental (2×2) design assessing: 1)

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preference for written consent versus an alternative (notification after enrollment *or* brief verbal consent); and 2) impact of including cost as a motivating factor for the trial. The survey used a scenario based on a recent pragmatic trial in ST-elevation myocardial infarction. Primary independent variables were personal preference and recommendation as a member of a review board regarding written consent versus the assigned alternative strategy and personal attitude toward trial enrollment. Descriptive analyses were conducted using post-stratification weights. Regression models were created to examine relationships between demographic variables and consent preference and willingness to enroll. Provision of cost information was incorporated into a regression model to examine its impact on consent preference.

Results—The study included 2027 participants. 51.1% vs 45.8% stated a personal preference for written consent versus notification after enrollment; however, 60.0% vs. 35.5% preferred brief verbal consent to written consent. Even among respondents stating they would be unlikely to enroll in the trial if asked, more respondents (50.6%) preferred brief verbal consent. The preference for verbal consent was generally shared across demographic categories, although lower educational attainment was associated with reduced acceptance ($p=0.001$ for trend). Respondents were more likely to support an alternative to written consent when asked their personal preference than when asked their recommendation as a member of a review board. The provision of cost information did not have a meaningful effect on consent preferences, attitudes toward enrollment, or views about the study.

Conclusions—Respondents generally supported prospective involvement in enrollment decisions in the setting of acute myocardial infarction and were particularly supportive of brief verbal consent. This support persisted across demographic categories. The finding that individuals were more likely to support alternatives to written consent when asked for a personal preference rather than as a “committee member” suggests that conservative institutional approaches to consent could hinder implementation of more patient-centered approaches. The role of cost transparency in consent discussions warrants further study.

Keywords

Pragmatic trials; Informed Consent; Research Ethics; Acute myocardial infarction; clinical trials

Background

Pragmatic trials comparing standard medical practices across broad populations and clinical settings minimize selection bias, potentially reduce trial costs, and offer exciting potential for improving health outcomes and efficiency.¹ These trials, however, raise interesting questions related to informed consent, and arguments have been advanced that research consent may be less important in trials comparing standard treatments.^{2–5} Special challenges may emerge when these trials test interventions for acute illnesses in emergency settings.⁶ The debate over the use of “deferred consent” for the Unfractionated Heparin versus Bivalirudin in Primary Percutaneous Coronary Intervention (HEAT-PPCI) trial recently illustrated these issues in cardiology.^{7–10} In this trial, two approved anticoagulant drugs (heparin and bivalirudin) were compared in patients undergoing acute intervention for ST-elevation myocardial infarction (STEMI). The absence of prospective consent was highly controversial.

Some commentators have argued that research consent may not be needed in pragmatic trials, especially when they involve treatment arms that are widely used, present similar risks, and are qualitatively similar.^{4, 7, 11} Reasons to avoid consent may be especially strong in the acute care setting. Many standard acute care interventions that may be subjected to pragmatic trials are not even discussed routinely with patients when delivered in the clinical setting. Anticoagulation choice in STEMI is a good example. It is also widely recognized that consent for trial enrollment is often minimally informed in acute situations. Moreover, lengthy consent processes could delay clinical treatment if the study is testing a component of care that must be delivered quickly.^{7, 12, 13}

In contrast, it may be the case that abandoning prospective consent in acute care pragmatic trials is particularly problematic. First, stakes are high in acute illness, and many studies are designed to detect differences in outcomes such as mortality and major morbidity.^{6, 14} Second, available data suggest patients generally prefer to be asked permission prior to research enrollment, even for acute conditions.^{12, 13, 15} Third, surveys of the public have suggested a preference for prospective consent in pragmatic trials in less acute settings, even when treatment-related risks are low and treatments are similar.^{16, 17} Fourth, failure to obtain research consent could potentially undermine public trust. This may be of particular concern when trials are motivated in part by cost considerations, as many pragmatic trials are. Finally, there are multiple ways to involve individuals in enrollment decisions that do not involve in-depth written consent. These range from opt-out or assent procedures to verbal consent processes.^{6, 10, 18, 19}

These considerations have driven support for alternatives to traditional, in-depth research consent. One recent registry-based trial in STEMI used a brief oral consent process, and HEATPPCI used “deferred” consent, in which patients were automatically enrolled but were asked later for consent for data use.^{8, 20} An earlier report from the present study suggests alternative approaches, especially brief verbal consent, may be highly acceptable to many potential patients.²¹ However, it is important to understand the potential impact of different approaches on different patient groups, potential drivers of consent preferences, and potential implications for public perceptions and trust in the context of acute care pragmatic trials in a U.S. population. In addition, given sensitivity about cost as a driver of medical decisions, it is important to examine the impact on consent preferences of transparency about cost as a motivation for a trial.²²

Methods

Design Overview

We conducted an online survey during December, 2016. The study used the HEAT-PPCI trial, a pragmatic trial comparing heparin versus bivalirudin for anticoagulation in STEMI, as the case scenario.⁸ It described key elements of HEAT-PPCI and assessed respondents’ attitudes toward that study and consent preferences. The study was deemed exempt by the Emory University Institutional Review Board and the National Institutes of Health Office of Human Subjects Research Protections (NIH OHSRP).

Setting and Participants

We used the GfK KnowledgePanel, an online probability-based panel representative of the U.S. population. Panel members are selected through a combination of address-based sampling and random-digit dialing in order to account for individuals without landlines, with unlisted telephone numbers, and without internet access. For the latter group, computer and internet access are provided. Panelists receive non-survey-specific payment through a points-based system administered by GfK.²³ The KnowledgePanel has been used in prior studies regarding consent for clinical research.^{16, 17} This study was distributed using the Omnibus service, which distributes several surveys (with non-overlapping content) together to a national sample from the KnowledgePanel to ensure approximately 1000 respondents per week. Our survey was run on two consecutive weeks to achieve the sample of 2000.

Survey Development and Administration

We adapted primary survey questions from a previous study examining consent preferences for pragmatic trials.¹⁶ We developed a script describing key elements of HEAT-PPCI. GfK staff provided input on the script and questions. We conducted 100 pilot surveys using the Amazon Mechanical Turks platform to assess comprehension of the script and gain feedback on questions. After each section of the script, respondents were asked closed-ended questions about content, and there was an opportunity for open-ended feedback. We conducted five rounds of pilot surveys and altered language after each round in order to address areas of misunderstanding. By the last round, the rate of correct answers to content questions was 100%.

The survey (Appendix 1) was conducted using a 2×2 factorial design (Figure 1). All panelists were presented with the same description of the trial. This included basic information about reasons for randomized trials, background information about heart attack and use of anticoagulants, and information about the two drugs in HEAT-PPCI (bivalirudin and unfractionated heparin). They were informed about the trial design, features of traditional written research consent, and potential advantages and disadvantages of an alternative to written consent in the STEMI setting.

The first layer of randomization involved the consent alternative that respondents were asked to consider. Half the panelists were asked to give their personal preference and recommendation (as a member of the ethics review board) regarding whether the study should be conducted with traditional written consent or with notification after enrollment (no prospective informed consent). The other half were asked to give their personal preference and recommendation (as a member of the ethics review board) regarding whether the study should be conducted with traditional written consent or brief verbal consent.

The second layer of randomization involved whether participants received cost information. The study description for half the panelists within each group included the following statement: “(bivalirudin) costs a lot more than (heparin), but doctors would use (bivalirudin) if it were clearly shown to be better than (heparin) in a head-to-head study.” Cost was not mentioned in the study description for the other panelists. This statement was designed to

test whether learning that cost was a motivating factor for the trial would impact perceptions of the study or consent preferences.

All panelists were asked a series of questions about their views of the trial. These questions included: the value of the study, whether patients in the study face greater risks than standard care, whether patients in the study are likely to receive better treatment, and whether the respondent would personally enroll in the study if eligible and asked to enroll. They were also asked their level of personal experience with heart attacks. Demographic data are maintained by GfK for all panelists.

Outcome and Measurements

The primary outcome measure was response to the following question: “If you were a patient having a heart attack and being treated in this health system’s emergency room, would you personally prefer written consent before enrollment or [verbal consent/ notification after enrollment]?” Panelists were asked to respond to this question on a 4-point scale, with the option to indicate whether they would “definitely” or “probably” choose that practice. For comparison, they were asked the same question from the perspective of an ethics review board member. Further questions regarding attitudes toward the study were assessed using a 7-point Likert scale.

Statistical Analysis

Sample size was calculated based on a priori assumptions of percent preference for written consent for each group (written vs. alternative, with or without cost information) using simulations. Specifically, we assumed 70% preference for written consent vs. no prospective consent and hypothesized an absolute 10% reduction in preference for written consent versus verbal consent. We hypothesized that people receiving cost information would prefer written consent more frequently than those not receiving cost information (10% difference). A sample size of 2000 panelists was chosen (n=500 per group) in order to provide 100 % power to detect an absolute difference of 10% between consent preferences and 78% power to detect an interaction effect of 10% between cost and consent preference at a 2-sided α level of 0.05.

All analyses were conducted using SAS 9.4 (Cary, NC) and R (version 3.2.2). All tests were 2sided. Statistical significance was defined by $p < 0.05$. In order to adjust for noncoverage or selection bias, analyses were conducted using post-stratification weights supplied by GfK based on 2016 Census data. Unweighted descriptive data are displayed in Table 1 and appendices for assessment of representativeness. Except where noted, all other reported data are weighted. A report of an unweighted analysis of the primary independent variable was published previously.²¹

Descriptive statistics were tabulated for all questions. Bivariate analyses were conducted to examine relationships between demographic variables (including experience with MI) and questions regarding consent preference and likelihood of personal enrollment in the trial. Because we were interested primarily in large effects with potential practical or policy implications, we dichotomized responses to consent preference questions and collapsed the

Likert scale regarding likelihood of personal enrollment into categories of disagree, neutral, and agree.

The relationship between demographic variables and the primary outcome was examined using logistic regression. Associations between demographic variables and attitude toward personal enrollment in the trial (1– Strongly Disagree to 7 – Strongly Agree) were examined using ordinal logistic regression. In order to examine whether the relationship between outcomes and demographic covariates was affected by provision of cost information, an interaction term with each covariate was incorporated into the regression model (one at a time) while adjusting for other demographic covariates. This exploratory analysis was adjusted for multiple comparisons.

Results

Respondents

The survey was sent to 6106 panelists (3000 in week 1 and 3106 in week 2, Figure 1). 2027 individuals completed the survey. Response rate was 33.2%, which is the norm for this mechanism. Respondents had higher educational attainment and household income than the general population, and there was slight under-representation of women and persons of Black race and Hispanic ethnicity (Table 1). Demographic characteristics in the two consent groups (written vs. notification after enrollment and written vs. brief verbal) were similar, as were characteristics of individuals randomized to receive or not receive cost information (Appendix 2). Most respondents (86.7%) did not report prior experience with emergency care for myocardial infarction.

Consent preferences and recommendations

In the group (Group A) asked to choose between written consent and notification after enrollment, 51.1% vs 45.8% stated a personal preference for written consent (Figure 2). When asked their recommendation as a member of the ethics review board, 56.7% vs. 40.7% stated they would recommend written consent. Less than half (41.5%) chose written consent as *both* their personal preference *and* their recommendation as an ethics review board member. Among respondents with discrepant answers to these two questions, it was more common to have a personal preference for notification after enrollment but board member recommendation for written consent (14.3%) than the reverse (8.6%, see Appendix 4). After adjustment, significant predictors of a lower odds of choosing written consent as a personal preference included household income over \$75,000, having a high school degree or “some college” education, and being disabled (Table 2).

Among the group (Group B) asked to choose between written consent and brief verbal consent, 35.5% stated a personal preference for written consent vs. 60.0% for verbal consent (Figure 2). When asked their recommendation as a member of the ethics review board, 47.2% would recommend written consent vs 45.9% verbal consent. Only 21.2% of respondents in this group chose written consent as *both* their personal preference *and* their recommendation as an ethics review board member. Among respondents with discrepant answers to these two questions, it was more common to have a personal preference for

verbal consent but board member recommendation for written consent (25.2%) than the reverse (12.7%, see Appendix 4). After adjustment, the only significant demographic predictor of lower odds of choosing written consent as a personal preference was education beyond high school. Significant predictors of higher odds of choosing written consent as a personal preference included living in the West and being unemployed (Table 2).

Attitudes toward the trial

Overall, 56.7% agreed that the pragmatic trial described was valuable; 25.3% agreed that patients in the study faced greater risks than in usual care; and 24% agreed that patients in the study were more likely to get better treatment than those receiving usual care. Respondents who were white, had higher educational attainment and income, and who were employed or retired were numerically more likely to agree that the study is valuable (Appendix 3).

Approximately half (46.7%) of participants stated that they would likely give a doctor permission to include them in the trial if they were to experience a heart attack and become eligible for enrollment. Almost a third (34.8%) were neutral, and 15.1% stated they would be unlikely to give permission to be included (Table 3). After adjustment, the only significant predictor of a lower odds of being willing to enroll was race other than white, black, or Hispanic ethnicity. Significant predictors of a higher odds of being willing to enroll included higher education (Bachelor's degree or more) and having personal experience with MI in the emergent setting (Table 2).

Relationships between attitudes toward the trial and consent preferences

In general, there was an increase in preference for the alternative to written consent (either notification after enrollment or verbal consent) as personal willingness to enroll in the trial increased (Table 3). Among individuals who were unlikely to agree to enrollment in the trial, there was a significantly greater preference for written consent as opposed to notification after enrollment (77.5% vs 20.9%). However, when asked to choose between written and brief verbal consent, half of those who were unlikely to agree to enrollment in the trial preferred verbal consent (50.6% vs. 47.4%).

Effect of cost information on consent preferences and attitudes toward the trial

The presence of cost information in the study description did not have a pronounced effect on consent preferences, attitudes toward trial enrollment, or views about the study (Table 4). The provision of cost information appeared to modify several associations between demographic covariates and consent preference and likelihood of trial enrollment. For example, the provision of cost information was associated with an increase in preference for written versus verbal consent among black respondents as compared to white respondents (OR 0.65 without cost vs 1.87 with cost, $p=0.017$ for interaction) and among unemployed as compared to employed respondents (OR 0.94 without cost vs. 2.56 with cost, $p=0.018$ for interaction). In contrast, compared to respondents with income $< \$25,000$, cost disclosure decreased preference for written versus verbal consent among individuals with income $\$50,000$ – $74,499$ (OR 1.47 without cost vs. 0.52 with cost, $p=0.029$ for interaction) and income over $\$75,000$ (OR 1.79 without cost vs. 0.66 with cost, $p=0.012$ for interaction).

After correction for multiple testing, no interactions between cost and demographic covariates remained statistically significant.

Discussion

Pragmatic trials offer important opportunities to improve quality and efficiency of care and are integral components of a learning health system.²⁴ There has been extensive discussion about the need for consent in pragmatic trials, with many arguing that consent is often unnecessary or less important.^{3, 4} Similarly, there has been substantial attention in the literature to ethical aspects of research in the acute context, where time constraints and other barriers to consent exist.^{25–27} However, there has been little focus on acute care pragmatic trials specifically.^{6, 14} Consent preferences in these trials are important to study, because the trials address “high stakes” outcomes, and prior evidence suggests that acutely ill patients value being asked for permission prior to enrollment. This study addressed these questions using a nationally representative sample and employed a unique experimental design comparing multiple consent strategies and examining the impact of cost on attitudes in key domains.

As noted previously, these data suggest significant support among members of the public for alternatives to traditional written informed consent for this pragmatic trial comparing qualitatively similar treatments in STEMI.²¹ Specifically, 60% of the respondents stated a preference for brief verbal consent, and 46% preferred notification after enrollment (both compared to written consent). In addition, the relative preference for brief verbal consent over notification after enrollment suggests that there may be value from patients’ perspectives in being involved prospectively in enrollment decisions. This would argue against the use of “deferred consent,” as was used in HEAT-PPCI, if brief, simple involvement is possible. Importantly, the comparison of brief verbal consent and notification after enrollment was indirect; respondents were asked to make 1 of 2 head-to-head comparisons with a common comparator (written consent) rather than to choose one of the 3 processes. However, we believe that this comparison is valuable as a hypothesis-generating finding. Moreover, it is highly salient that brief verbal consent was endorsed by half of the individuals who stated they would be unlikely to enroll in this trial (50.6%). Notification after enrollment, in contrast, was endorsed by only 20.9% of these individuals.

Some may argue that a brief verbal consent process lacks meaning. However, it is important to recognize that consent processes serve different functions, some of which may be more achievable in the acute setting than others.²⁸ Even a very brief verbal consent may provide sufficient information about a trial for many people who prefer not to be involved in research, for example, to recognize that they would not want to be included and decline participation. Given that 15.1% of respondents reported that they would be unlikely to join the described trial, giving them this option seems valuable. For other patients, just knowing that both drugs are routinely used and have similar side effects may be sufficiently reassuring that they would want to enroll. The precise reasons for preferring brief verbal consent over other options were not examined in detail. However, the findings reinforce other empirical data suggesting that actual MI patients generally prefer prospective involvement rather than enrollment under an exception from informed consent.^{12, 13, 15}

These data do not necessarily impugn consent forms altogether. While respondents demonstrated a clear preference for brief verbal consent versus traditional written consent, it was described in the scenario that the verbal consent process was brief and focused. A preference for the verbal option could indicate a distaste for having to sign a consent form in an acute situation. Alternatively, it may indicate a preference for brevity and simplicity rather than an objection to written materials. Highly simplified, short forms designed around typical consent conversations are reasonable to consider and study; they also may be simpler to implement from a regulatory perspective than waiver of written consent. Most importantly, these data suggest public support for consent approaches that differ from what is commonly implemented. Members of the public seem to be sensitive to clinical context and do not seem to endorse the position that respect for subjects in acute conditions requires in-depth consent processes and forms.

An important focus of this analysis was the examination of associations between demographic and socioeconomic variables and attitudes toward consent practices. There was numerically greater objection to notification after enrollment among lower income respondents, respondents with lower educational attainment, and black respondents, though most of these differences were not statistically significant. These effects were less pronounced in the group asked to consider verbal consent. While there was significantly greater preference for written consent versus verbal consent among lower versus higher income respondents, 45% of individuals in the lowest educational stratum still preferred verbal consent. Moreover, respondents of all races preferred verbal consent. These differences further bolster the argument in favor of context-sensitive prospective involvement. Such approaches provide greater transparency, a benefit that may be especially important for communities who are less trustful of research. Additionally, recognition of the fact that certain groups may have concerns about consent alternatives reinforces the importance of good communication, including explaining the rationale for the consent process and the nature of the study after enrollment has occurred.

Another interesting finding was the distinction between respondents' "recommendations" as a member of the ethics review committee and their personal preference. Respondents chose written consent over the alternative more frequently when asked to make a recommendation as a committee member. The distinction between making a recommendation for others and stating personal preferences has been observed in other contexts, including emergency research conducted under the exception from informed consent.^{29–31} While some individuals "crossed over" in both directions, these data demonstrate a tendency to recommend more extensive consent processes when making decisions for others in the IRB role. This tendency is understandable and well-intentioned. In fact, some may argue- due to a combination of ethical and liability concerns- that IRBs *should* be more conservative and err on the side of formality and completeness in order to avoid less than fully informed consent. However, it must be recognized that attempts to make consent processes more patient-centered could be impeded if IRB members default to requiring more lengthy written consent processes in circumstances where they do not personally think it is meaningful.

One novel aspect of this study was the experimental assessment of the impact of providing information about cost. Cost is an important reason to conduct pragmatic trials of standard

medical practice and was one driver of the HEAT-PPCI trial on which this study was based. However, given prevalent concerns about cost as a basis for medical decisions, we hypothesized that transparency about this issue might drive greater demand for in-depth consent or reduce willingness to enroll. In this study, cost did not have a substantial effect on consent preferences or attitudes toward the study. These data suggest some potential for heterogeneity in the meaning of cost information for different socioeconomic and demographic groups, which may provide some support for transparency about cost in trials.²² Whether individuals feel such transparency is important, and how it affects decisions, warrants further study with a greater focus on cost and more involved and explicit cost disclosure.

Limitations

Several limitations merit acknowledgement. First, this study involved the general public and not patients. However, these results generally cohere with available data on views of patients and trial enrollees in favoring prospective involvement in enrollment decisions and de-emphasis on consent forms. Future work evaluating alternative strategies within ongoing trials is essential. Second, this study examined consent preferences regarding a single pragmatic trial in an acute context. While prior data suggest a general preference for consent across various types of trials in MI, future work examining the impact of study features on specific consent preferences would be useful.¹⁵ Third, the response rate limits generalizability to some extent, but respondents were similar demographically to the general population. The experimental design also adds internal validity. Fourth, findings related to cost disclosure, as well as sub-group analyses, should be considered preliminary and hypothesis-generating. Finally, surveys are vulnerable to framing effects, but the scripts were designed to communicate advantages and disadvantages of approaches to consent and avoided overstating benefits or minimizing risks of the trial. The content was also well-understood in pre-testing.

Conclusions

In a time of ongoing regulatory change and evolving paradigms for clinical research, pragmatic trials in acute conditions such as STEMI pose important practical and ethical challenges. These data suggest that respect for research participants in these settings may be advanced by prospective involvement. However, they suggest it may be most appropriate to plot a course between the two most commonly mentioned choices. Both in-depth written consent processes and waiver of consent appear to have important shortcomings. Our findings provide support for development and evaluation of approaches that provide transparency and key information in a way that is sensitive to the acute care context.

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Appendix 1- Survey Instrument

We are trying to learn what people think about medical research in emergency rooms and the way that patients are asked to participate in this research. It is important that you read the description of the research carefully.

Comparing treatments against each other

In many cases, there is more than one FDA-approved, commonly used treatment for a medical problem. Sometimes doctors don't know whether one treatment is better than another unless they do a research study comparing these treatments head-to-head. In head-to-head studies, some patients are treated with one medicine, while others are treated with the other medicine. The results in the two groups are compared to see which medicine is better. This information can then be used to make sure all patients get the best treatment. In this survey, we will ask you about a research study that compares two common, FDA-approved treatments for heart attack.

Heart attacks and blood thinner medicines

A heart attack happens when blood vessels in the heart get suddenly blocked by a clot. Heart attacks must be treated very quickly. One part of treatment is giving patients a blood thinner. Two common, FDA-approved blood thinners are HEP and BIV. These medicines are started within 10 or 15 minutes of arrival to the emergency room. Most patients then go for a procedure to open the blood vessel.

What you need to know about these two medicines

- Both HEP and BIV are FDA-approved for heart attack, are considered effective, and have been used for years.
- The most common side effect of both medicines is bleeding. Bleeding is usually minor, but it can be life-threatening and may require a blood transfusion.
- One medicine or the other might be better in helping more people survive, reducing heart damage, preventing blockages after the vessel is opened up, or preventing bleeding.
- Because HEP and BIV have not been compared enough in head-to-head studies, it is not known which one is better.

[RANDOMIZE THE FOLLOWING STATEMENT- ½ of Group A and ½ of Group B receive it]

- [BIV costs a lot more than HEP, but doctors would use BIV if it were clearly shown to be better than HEP in a head-to-head study.]

Head-to-head study of BIV and HEP

All patients in the emergency room with a heart attack will be considered for the head-to-head study. For patients in the study, a computer program (not the individual doctor) will

randomly decide whether the patient receives HEP or BIV. No other part of their heart attack treatment will be affected by being in the study. Patients who receive HEP will be compared to patients who receive BIV to see which medicine is better.

[RANDOMIZE HERE]

Group A (SKIP TO GROUP B FOR RESPONDENTS ASSIGNED TO GROUP B)

The ethics review board and written informed consent

Usually, patients are asked to read and sign an informed consent form if they want to be in a research study. This is called a written consent form. These forms describe:

- the purpose of the study,
- risks and benefits of the study,
- a statement that patients can choose not to be in the study and receive standard care instead,
- any alternative treatments,
- how patient privacy will be maintained, and
- contact information for the study team in case patients have questions.

The hospital ethics review board makes sure that research studies are safe as possible and protect patients' rights and well-being. They are discussing whether written consent should be required for this study.

Some members of the ethics review board think that written consent is not appropriate for this study. They argue it is inappropriate for four main reasons:

- Patients may be having chest pain and difficulty breathing. They may be too frightened and stressed to understand the study very well and to make a decision about whether to be in it.
- Decisions have to be made quickly so that treatment can begin. Reading the consent form carefully would take too much time. Patients might sign the form but are unlikely to read it.
- Both medicines are FDA-approved, commonly used, and known to be effective, so there is little additional risk to patients from being in the research study.
- Doctors do not normally ask patients which of these medicines they want.

Other members think that written consent should be required in order to make sure patients are making an informed decision about whether they want to be in the study. They think that:

- People are used to being asked to read and sign forms for medical care and research.
- Using written consent forms is the standard way to make sure that patients are informed about a study and agree to be a part of it.

Notification after enrollment

The members of the review board who don't think written consent is appropriate propose that doctors should not ask heart attack patients for permission before enrolling them in this study. Instead, they think doctors should decide for patients whether to be in the study because heart attack is too much of an emergency and too stressful. Under "notification after enrollment," doctors would not ask for consent initially but would notify patients after the patients have been treated that they were included in the head-to-head study. These board members also recommend that the hospital put up descriptions of emergency research around the hospital and in the emergency department as a way of notifying patients and families. However, they understand that not all patients will see this information.

Questions

- 1a.** If you were a member of the ethics review board for this study, would you recommend written consent before enrollment or notification after enrollment?

Written Consent before enrollment		Notification after enrollment	
Definitely	Probably	Probably	Definitely
1	2	3	4

- 2a.** If you were a patient having a heart attack and being treated in this health system's emergency room, would you personally prefer written consent before enrollment or notification after enrollment?

Written Consent before enrollment		Notification after enrollment	
Definitely	Probably	Probably	Definitely
1	2	3	4

SKIP TO Q3

Group B

The ethics review board and written informed consent—Usually, patients are asked to read and sign an informed consent form if they want to be in a research study. This is called a written consent form. These forms describe:

- the purpose of the study,
- risks and benefits of the study,
- a statement that patients can choose not to be in the study and receive standard care instead,
- any alternative treatments,
- how patient privacy will be maintained, and
- contact information for the study team in case patients have questions.

The hospital ethics review board makes sure that research studies are safe as possible and protect patients' rights and well-being. They are discussing whether written consent should be required for this study.

Some members of the ethics review board think that written consent is not appropriate for this study. They argue it is inappropriate for four main reasons:

- Patients may be having chest pain and difficulty breathing. They may be too frightened and stressed to understand detailed information about the study and to make a decision about whether to be in it.
- Decisions have to be made quickly so that treatment can begin. Reading the consent form carefully would take too much time. Patients might sign the form but are unlikely to read it.
- Both medicines are FDA-approved, commonly used, and known to be effective, so there is little additional risk to patients from being in the research study.
- Doctors do not normally ask patients which of these medicines they want.

Other members think that written consent should be required in order to make sure patients are making an informed decision about whether they want to be in the study. They think that:

- People are used to being asked to read and sign forms for medical care and research.
- Using written consent forms is the standard way to make sure that patients are informed about a study and agree to be a part of it.

Verbal consent—The members of the ethics board who don't think written consent is appropriate propose that the doctors have a very short conversation at the time of treatment where they describe the study very briefly and ask patients permission (verbal consent) to be enrolled. There would be no form to sign, and the information would be less detailed than a written consent form. The doctor would describe that:

- Both medicines are approved, are known to be effective, and have similar side effects.
- Doctors do not know which one is better overall.
- Which medicine patients receive will be chosen at random by a computer.
- Patients who choose not to be in the study will receive the medicine the doctor would normally use.

Questions

- 1b.** If you were a member of the ethics review board, would you recommend written consent or verbal consent?

Written Consent	Verbal Consent
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Definitely	Probably	Probably	Definitely
1	2	3	4

- 2b.** If you were a patient having a heart attack and being treated in this health system's emergency room, would you personally prefer written consent or verbal consent?

Written Consent		Verbal Consent	
Definitely	Probably	Probably	Definitely
1	2	3	4

ALL RESPONDENTS

We would like your opinions on a few other questions about this head-to-head study of BIV and HEP. Please rate the following statements on a scale of 1 to 7 with 1 meaning strongly disagree and 7 meaning strongly agree.

- 3.** It is valuable to do this study directly comparing BIV and HEP to see which one is better for treating heart attacks.

1 – Strongly Disagree			4 – Neutral			7 – Strongly Agree
1	2	3	4	5	6	7

- 4.** Patients who participate in the head-to-head study face greater risks than patients who receive usual care (a medication chosen by the doctor treating them).

1 – Strongly Disagree			4 – Neutral			7 – Strongly Agree
1	2	3	4	5	6	7

- 5.** Patients who participate in the head-to-head study are more likely to get better treatment for their heart attack than are patients who receive usual care (a medication chosen by the doctor treating them).

1 – Strongly Disagree			4 – Neutral			7 – Strongly Agree
1	2	3	4	5	6	7

- 6.** Imagine you were a patient having a heart attack and were asked to be a part of this study. How would you rate the following statement?

I would give doctors permission to include me in the head-to-head study comparing HEP and BIV.

1 – Strongly Disagree			4 – Neutral			7 – Strongly Agree
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1	2	3	4	5	6	7
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7. Have you ever had a heart attack or been in an emergency room with a friend or family member when they were having a heart attack?

☐ Yes, I have personally had a heart attack

☐ Yes, I have been in an emergency room with a friend or family member having a heart attack

☐ No

Appendix 2 –

Characteristics of respondents by group assignment (unweighted)

	Overall (n = 2027), N (%)	Group A – Written consent v. Notification after enrollment (n=1013)	Group B – Written consent v. Verbal consent (n=1014)
		Overall Group A (n = 1013), %	Overall Group B (n = 1013), %
		No Cost Information (n = 506), %	No Cost Information (n = 506), %
		Cost Information (n = 507), %	Cost Information (n = 508), %
Characteristics			
Age			
18–29 years	362 (17.9)	19.4	17.0
30–44 years	571 (28.2)	26.3	27.7
45–59 years	548 (27.0)	27.1	26.7
60+ years	546 (26.9)	27.3	28.3
Gender			
Female	944 (46.6)	45.3	46.1
Male	1083 (53.4)	54.7	54.0
Race			
White, Non-Hispanic	1526 (75.3)	78.3	75.2
Black, Non-Hispanic	159 (7.8)	6.3	7.7
Other/Two or more races, Non-Hispanic	150 (7.4)	7.1	7.3
Hispanic	192 (9.5)	8.3	9.9
Education			
Less than high school	149 (7.4)	7.5	7.1
High school	521 (25.7)	24.9	27.8
Some college	560 (27.6)	28.7	29.0
Bachelors	443 (21.9)	19.6	21.9
Postgraduate	354 (17.5)	19.4	14.2
Income			
Less than \$25,000	239 (11.8)	10.7	11.6
\$25,000 - <\$50,000	392 (19.3)	20.2	18.9

	Overall (n = 2027), N (%)	Group A – Written consent v. Notification after enrollment (n=1013)	Group B – Written consent v. Verbal consent (n=1014)
		Overall Group A (n = 1013), %	Overall Group B (n = 1013), %
		No Cost Information (n = 506), %	No Cost Information (n = 506), %
		Cost Information (n = 507), %	Cost Information (n = 508), %
\$50,000 - <\$75,000	373 (18.4)	18.7	18.2
\$75,000 or more	1023 (50.5)	50.0	51.0
Employment			
Employed	1309 (64.6)	65.6	63.6
Retired	410 (20.2)	19.6	20.9
Disabled	78 (3.9)	3.2	4.5
Unemployed or other	230 (11.4)	11.8	11.0
Marital Status			
Married	1233 (60.8)	61.4	60.3
Widowed	71 (3.5)	3.7	3.4
Divorced	180 (8.9)	8.7	9.1
Separated	23 (1.1)	0.7	1.6
Never married	410 (20.2)	19.2	21.3
Living with partner	110 (5.4)	6.4	4.4
Region			
Northeast	396 (19.5)	19.6	19.5
Midwest	494 (24.4)	24.5	24.3
South	669 (33)	33.2	32.8
West	468 (23.1)	22.8	23.4
Experience with MI			
No	1757 (86.7)	85.7	87.7
Yes (personal or with friends/family)	224 (11.1)	11.9	10.2
Did not answer	46 (2.3)	2.4	2.2

* Does not include the 'Did not answer' category for Group A or Group B

Appendix 3 –

Attitudes Toward the Trial by Respondent Characteristics (unweighted)

Characteristic	Overall, N (%)	Q3-It is valuable to do this study directly comparing BIV and HEP to see which one is better for treating heart attacks. % Agree	Q4- Patients who participate in the head- to-head study face greater risks than patients who receive usual care (a medication chosen by the doctor treating them). % Agree	Q5- Patients who participate in the head- to-head study are more likely to get better treatment for their heart attack than are patients who receive usual care (a medication chosen by the doctor treating them). % Agree	Q6- I would give doctors permission to include me in the head-to-head study comparing HEP and BIV % Agree
Overall (weighted)	2027 (100)	56.7	25.3	24.0	46.7
Age					
18-29 years	362 (17.9)	55.3	28.5	25.1	40.6
30-44 years	571 (28.2)	55.0	22.9	24.0	47.8
45-59 years	548 (27.0)	63.5	23.0	22.6	48.9
60+ years	546 (26.9)	62.8	24.7	20.3	58.1
Gender					
Female	944 (46.6)	59.4	24.9	24.9	49.2
Male	1083 (53.4)	59.5	24.0	21.1	50.0
Race					
White, Non-Hispanic	1526 (75.3)	61.9	23.7	21.2	52.5
Black, Non-Hispanic	159 (7.8)	53.5	28.9	26.4	38.4
Other/Two or more races, Non-Hispanic	150 (7.4)	50.7	21.3	27.3	44.0
Hispanic	192 (9.5)	52.1	28.7	29.7	40.1
Education					
Less than high school	149 (7.4)	42.3	26.2	28.9	33.6
High school	521 (25.7)	50.3	22.5	23.0	43.4
Some college	560 (27.6)	61.4	28.8	25.2	48.6
Bachelors	443 (21.9)	66.8	22.8	20.1	55.8
Postgraduate	354 (17.5)	67.8	21.8	19.8	59.3

	Overall, N (%)	Q3-It is valuable to do this study directly comparing BIV and HEP to see which one is better for treating heart attacks. % Agree	Q4- Patients who participate in the head- to-head study face greater risks than patients who receive usual care (a medication chosen by the doctor treating them). % Agree	Q5- Patients who participate in the head- to-head study are more likely to get better treatment for their heart attack than are patients who receive usual care (a medication chosen by the doctor treating them). % Agree	Q6- I would give doctors permission to include me in the head-to-head study comparing HEP and BIV % Agree
Income					
Less than \$25,000	239 (11.8)	42.3	22.6	26.8	36.0
\$25,000 - <\$50,000	392 (19.3)	56.6	24.5	23.7	46.2
\$75,000 or more	1023 (50.5)	64.4	23.9	21.1	54.5
Employment					
Employed	1309 (64.6)	60.8	23.8	22.8	50.0
Retired	410 (20.2)	62.7	25.4	21.2	54.9
Disabled	78 (3.9)	52.6	30.8	28.2	43.6
Unemployed or Other	230 (11.4)	48.3	24.4	23.9	39.6
Marital Status					
Married	1233 (60.8)	60.1	24.4	21.3	51.5
Widowed	71 (3.5)	57.8	16.9	16.9	57.8
Divorced	180 (8.9)	66.1	21.7	27.2	53.3
Separated	23 (1.1)	52.2	13.0	26.1	30.4
Never married	410 (20.2)	55.4	27.6	27.3	42.9
Living with partner	110 (5.4)	59.1	24.6	19.1	45.5
Region					
Northeast	396 (19.5)	57.3	25.8	22.5	50.3
Midwest	494 (24.4)	57.9	22.3	25.1	46.8
South	669 (33)	60.5	26.2	21.4	50.2
West	468 (23.1)	61.3	23.1	22.9	51.1
Personal Experience with MI					
No	1757 (86.7)	59.8	24.6	22.7	49.4
Yes (personal or with friends/family)	224 (11.1)	65.6	27.7	27.7	58.0

Overall, N (%)	Q3-It is valuable to do this study directly comparing BIV and HEP to see which one is better for treating heart attacks. % Agree	Q4- Patients who participate in the head- to-head study face greater risks than patients who receive usual care (a medication chosen by the doctor treating them). % Agree	Q5- Patients who participate in the head- to-head study are more likely to get better treatment for their heart attack than are patients who receive usual care (a medication chosen by the doctor treating them). % Agree	Q6- I would give doctors permission to include me in the head-to-head study comparing HEP and BIV % Agree
46 (2.3)	17.4	2.2	4.4	17.4
Did not answer				

Appendix 4 –

Alignment of Recommendation (board member) and Personal Preference

Group A - Written consent v. Notification after enrollment (n=1013)			N(%)
Concordant	Recommended Written consent (board member)		420 (41.46)
	Preferred Written consent (personal)		
	Recommended Notification after enrollment (board member)		326 (32.18)
	Preferred Notification after enrollment (personal)		
Discordant	Recommended Written consent (board member)		145 (14.31)
	Preferred Notification after enrollment (personal)		
	Recommended Notification after enrollment (board member)		87 (8.59)
	Preferred Written consent (personal)		
Did not answer	Did not answer	1 question	35 (3.46)
Group B - Written consent v. Verbal consent (n=1014)			
Concordant	Recommended Written consent (board member)		215 (21.20)
	Preferred Written consent (personal)		
	Recommended Verbal Consent (board member)		338 (33.33)
	Preferred Verbal Consent (personal)		
Discordant	Recommended Written consent (board member)		255 (25.15)
	Preferred Verbal Consent (personal)		
	Recommended Verbal Consent (board member)		129 (12.72)
	Preferred Written consent (personal)		
Did not answer	Did not answer	1 question	77 (7.59)

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Figure 1–. Study flow diagram

Figure 2-- Consent Preferences

Table 1.
Respondent characteristics and consent preferences of respondents, Unweighted (N = 2027)

Characteristic	2016 US Census Data, %	Overall, N (%)	Group A – Personal Preference for Written consent v. Notification after enrollment (n=1013) ^a	Written Consent, %	Notification after Enrollment, %	Group B – Personal Preference for Written consent v. Verbal consent (n=1014) ^a	Written Consent, %	Verbal Consent, %
Age								
18-29 years	21.4	362 (17.9)	50.0	45.1	33.7	61.8		
30-44 years	25.2	571 (28.2)	51.5	43.8	29.8	66.2		
45-59 years	26.5	548 (27.0)	51.5	47.3	40.2	56.3		
60+ years	26.8	546 (26.9)	48.1	50.0	34.2	64.4		
Gender								
Female	51.7	944 (46.6)	49.6	47.9	35.2	61.2		
Male	48.3	1083 (53.4)	51.0	45.4	34.1	63.0		
Race								
White, Non-Hispanic	64.9	1526 (75.3)	49.3	48.0	34.6	62.9		
Black, Non-Hispanic	11.7	159 (7.8)	59.2	36.6	37.5	59.1		
Other/Two or more races, Non-Hispanic	7.9	150 (7.4)	46.6	50.7	35.1	59.7		
Hispanic	15.5	192 (9.5)	55.4	39.1	32.0	61.0		
Education								
Less than high school	12.2	149 (7.4)	60.8	32.4	49.3	45.3		
High school	29.6	521 (25.7)	46.8	50.2	41.3	53.2		
Some college	28.4	560 (27.6)	52.7	46.2	32.5	64.9		
Bachelors		443 (21.9)	50.0	46.2	29.2	68.7		
Postgraduate	29.8	354 (17.5)	47.7	48.2	29.4	69.0		
Income								
Less than \$25,000	17.4	239 (11.8)	61.1	33.6	37.3	55.6		
\$25,000 - <\$50,000	21.3	392 (19.3)	53.7	43.4	38.5	59.4		

Characteristic	2016 US Census Data, %	Overall, N (%)	Group A – Personal Preference for Written consent v. Notification after enrollment (n=1013) ^a	Group B – Personal Preference for Written consent v. Verbal consent (n=1014) ^a
			Written Consent, %	Written Consent, %
			Notification after Enrollment, %	Verbal Consent, %
\$50,000 - <\$75,000	17.8	373 (18.4)	50.3	32.6
\$75,000 or more	43.6	1023 (50.5)	46.6	33.3
Employment				
Employed		1309 (64.6)	51.2	34.0
Retired		410 (20.2)	52.1	39.6
Disabled		78 (3.9)	48.5	34.4
Unemployed or Other		230 (11.4)	37.5	32.6
Marital Status				
Married		1233 (60.8)	48.6	34.9
Widowed		71 (3.5)	46.0	44.1
Divorced		180 (8.9)	53.4	39.1
Separated		23 (1.1)	71.4	25.0
Never married		410 (20.2)	52.6	30.6
Living with partner		110 (5.4)	56.9	37.8
Region				
Northeast	18.1	396 (19.5)	53.0	33.3
Midwest	21.3	494 (24.4)	47.2	35.8
South	37.2	669 (33)	48.5	32.7
West	23.4	468 (23.1)	54.1	37.1
Experience with MI				
No		1757 (86.7)	51.5	35.4
Yes (personal or with friends/family)		224 (11.1)	47.9	30.1
Did not answer^b		46 (2.3)	20.8	22.7

^aDoes not include the 'Did not answer' response to consent preference questions for Group A or Group B

^bThis question was specifically asked in the survey. All other demographic data were available for respondents and provided by Gfk.

Table 2.

Respondent characteristics and preferences for consent and likelihood of enrollment

		OR (95% CI)	OR p-value	Type 3 p-value
Group A - Personal Preference for Written consent v. Notification after Enrollment (n = 975)				
Income	1. <\$25,000	-	-	0.091
	2. \$25,000 - \$49,999	0.76 (0.47–1.22)	0.260	
	3. \$50,000 - \$74,999	0.70 (0.42–1.17)	0.173	
	4. \$75,000+	0.55 (0.34–0.90)	0.017	
Education	1. Less than high school	-	-	0.063
	2. High school	0.49 (0.30–0.80)	0.005	
	3. Some college	0.58 (0.35–0.97)	0.039	
	4. Bachelor’s degree	0.63 (0.35–1.13)	0.120	
	5. Postgraduate	0.69 (0.37–1.27)	0.234	
Employment	1. Employed	-	-	0.067
	2. Retired	0.82 (0.53–1.27)	0.366	
	3. Disabled	0.38 (0.18–0.80)	0.011	
	4. Unemployed or other	0.79 (0.52–1.21)	0.283	
Group B - Personal Preference for Written consent v. Verbal consent (n = 974)				
Region	1. Northeast	-	-	0.186
	2. Midwest	1.13 (0.72–1.75)	0.595	
	3. South	1.13 (0.76–1.68)	0.546	
	4. West	1.57 (1.01–2.43)	0.044	
Education	1. Less than high school	-	-	0.001
	2. High school	0.87 (0.55–1.38)	0.559	
	3. Some college	0.50 (0.30–0.82)	0.006	
	4. Bachelor’s degree	0.45 (0.26–0.79)	0.006	
	5. Postgraduate	0.42 (0.23–0.77)	0.005	
Employment	1. Employed	-	-	0.152
	2. Retired	0.90 (0.58–1.41)	0.657	
	3. Disabled	0.80 (0.42–1.52)	0.498	
	4. Unemployed or other	1.55 (1.01–2.37)	0.045	
Likelihood of Enrollment (n = 1954)				
Race	1. White	-	-	0.006
	2. Black	0.83 (0.63–1.08)	0.168	
	3. Other	0.58 (0.43–0.80)	0.001	
	4. Hispanic	0.87 (0.68–1.12)	0.284	
Education	1. Less than high school	-	-	0.009
	2. High school	1.27 (0.95–1.70)	0.106	
	3. Some college	1.32 (0.98–1.78)	0.071	
	4. Bachelor’s degree	1.65 (1.17–2.32)	0.004	

	OR (95% CI)	OR p-value	Type 3 p-value
5. Postgraduate	1.84 (1.28–2.65)	0.001	
Personal experience with MI	1.47 (1.14–1.90)	0.003	-

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Table 3.

Relationship between likelihood of enrollment and personal consent preference

Likelihood of enrollment	Group A - Personal preference for written v. Notification after enrollment (n=1013) ^a		Group B - Personal preference for written v. verbal consent (n=1014) ^a	
	Overall (n = 2027), %	Written Consent, %	Notification after enrollment, %	Written Consent, %
Unlikely	15.1	77.5	20.9	47.4
Neutral	34.8	54.1	43.9	41.0
Likely	46.7	43.1	56.7	29.0
Did not answer	3.5	21.8	9.8	13.0
				10.1

^aDoes not include the 'Did not answer' category for Group A or Group B

Table 4.

Relationship between provision of cost information and consent preference and likelihood of enrollment

	Cost information, %	No cost information, %
Group A – Personal Preference for Written consent v. Notification after enrollment (n=1013)		
Preference for written consent	50.7	51.5
Preference for notification after enrollment	45.9	45.7
Did not answer	3.4	2.9
Group B – Personal Preference for Written consent v. Verbal consent (n = 1014)		
Preference for written consent	36.8	34.3
Preference for verbal consent	59.1	61.0
Did not answer	4.1	4.7
Likelihood of enrollment (n = 2027)		
Unlikely	14.7	15.5
Neutral	33.1	36.5
Likely	48.4	45.0
Did not answer	3.9	3.0