Rethinking Informed Consent Requirements for Pragmatic Comparative Effectiveness Trials

by
Danielle Whicher

A dissertation submitted to Johns Hopkins University in conformity with the requirements for the degree of Doctor of Philosophy

Baltimore, Maryland
January, 2014

© 2014 Danielle M. Whicher
All Rights Reserved
Abstract

Recently, there has been an increasing demand for more and higher quality evidence of the comparative effectiveness of different health technologies. Much of the comparative effectiveness research (CER) designed to address this demand will compare widely-used technologies and will be closely integrated with clinical care. These design features raise the question of whether current standards of informed consent should always be required for CER studies. Considering the acceptability of alternatives to informed consent is important as alternatives may improve the efficiency and quality of this research.

This dissertation considers whether alternatives to informed consent are morally and socially acceptable by addressing three aims, each of which is explored in a separate paper. Aim one explores which alternatives to informed consent are acceptable to key stakeholders for low-risk CER trials of widely-used therapies. To address this aim, interviews were conducted with institutional review board members and researchers and focus groups were conducted with patients at two health systems. The results demonstrate that many participants felt that although it was important for eligible individuals to be informed about CER trials, it was acceptable to streamline the amount of information disclosed and to ask individuals to opt-out if they would prefer not to participate.

Aim two considers which alternatives to prospective informed consent are morally permissible for CER studies. Addressing this aim, paper two is a moral analysis that argues that when enrolling individuals in these activities, it is sometimes acceptable to limit individual choice in situations where the decision to participate is unlikely to engage important self-determination interests that individuals have. Based on this
argument, several recommendations regarding the moral permissibility of altering consent requirements for CER are provided.

Aim three develops preliminary policy recommendations for reforming the informed consent regulations. Building on aims one and two, paper three suggests that it may be appropriate to streamline disclosure statements for low-risk CER trials and that it may also be appropriate to ask participants to opt-out instead of opt-in. However, in order for policy change to occur, it is necessary to continue to build the case for the importance of conducting CER studies.

Primary Readers: Nancy Kass, ScD (Advisor)

Jodi Segal, MD, MPH (Chair)

Ruth Faden, PhD, MPH

Maria Merritt, PhD

Alternate Readers: Albert Wu, MD

Darcy Phelan, DrPH
Acknowledgments

Conducting the multi-site qualitative research project and the moral analysis described in this dissertation required the mentorship and assistance of many different individuals – without whom I would never have been able to complete this work. I am so thankful for all the help and advice I have been provided with during these past few years.

I would first like to thank my advisor, Dr. Nancy Kass, who has been the best mentor I ever could have hoped for. Nancy has always challenged me to further refine my research and writing and to reach out and work with other colleagues at the School of Public Health as well as at other institutions. She has also provided constant and thoughtful feedback throughout my time in the PhD program at the Johns Hopkins Bloomberg School of Public Health. Her support and her dedication to her students is one of the primary reasons I have had such a wonderful experience at Hopkins and I am certainly going to miss our bi-weekly meetings to discuss my dissertation work.

I would also like to thank Dr. Ruth Faden, who, along with Nancy, was instrumental in helping me develop my dissertation proposal and whose advice regarding my dissertation work has been invaluable. In addition to providing me with mentorship through the course of my dissertation, both Nancy and Ruth allowed me to work on a number of different projects with them. The experience of being able to work with two such thoughtful and intelligent women in the fields of public health and bioethics has and will continue to have an influential role in shaping my career in those fields.
Other members of my dissertation committee have also provided me with a huge amount of useful advice and support throughout my dissertation work. I very much enjoyed my conversations with Dr. Maria Merritt. Maria’s thoughtful comments on my moral analysis helped shape that work and also helped to further my own knowledge of the field of moral philosophy. Additionally, I want to acknowledge the support of Drs. Jodi Segal and Albert Wu. Jodi and Albert provided valuable advice on my research plan and project materials.

I would also like to thank several other individuals who acted as members of either my dissertation proposal or defense committees including Drs. Holly Taylor, Marie Nolan, and Darcy Phelan as well as Dr. Hilary Bok who graciously agreed to review a draft of my moral analysis and provide me with feedback.

In addition to members of my exam and advisory committees, it would not have been possible to complete this dissertation without the assistance of individuals from both the Johns Hopkins Community Physicians network and the Geisinger Health System. In particular, I would like to thank Dr. Gary Noronha, Wendy Greenberg, and Rebecca Mead for their help with the recruitment of patients from the Johns Hopkins Community Physicians network as well as Dr. Walter Stewart, Dr. Stephen Steinhubl, and Rebecca Search for their help with recruitment of participants from Geisinger Health System. I would also like to thank Dr. Stewart for his assistance in developing the idea for the qualitative research project as well as for his guidance on creating the case studies that were used for that project.

I feel that it is also important to thank all of those individuals who participated in interviews and focus groups as part of my qualitative research project. The insights and
ideas the participants shared with me were so insightful and I had a great time speaking with everyone them.

In addition to the research communities and participants, I relied heavily on the support of my family and friends throughout this process. I would especially like to thank my mother, my brother Jon, and Amir. My mother has always been there to give me advice, review drafts, and generally provide me with all her love and support. Amir has patiently listened to numerous practice presentations, has always been willing to listen to my ideas and review materials, and has always been there to encourage me when I needed encouragement and to make me laugh when I needed to laugh.

Last but certainly not least I would like to acknowledge the Agency for Healthcare Research and Quality who provided me with a dissertation grant award to support my dissertation work. This dissertation was supported by grant number R36HS021064. However, the content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.
# Table of Contents

Introduction ........................................................................................................................................... 1

Paper 1: Stakeholders’ Views of Alternatives to Prospective Informed Consent for Low-Risk Pragmatic Comparative Effectiveness Trials ................................................................. 7

  Background and Introduction .................................................................................................................. 8

  Methods ............................................................................................................................................... 11

  Results from Interviews with Research and Institutional Review Board Members .......................... 18

  Results from Focus Groups with Migraine and Hypertension Patients ........................................... 27

  Discussion .......................................................................................................................................... 36

  Conclusion ......................................................................................................................................... 42

  Tables and Figures .............................................................................................................................. 44

  References ......................................................................................................................................... 49

Paper 2: Rethinking the Balance of Self-Determination Interests with Interests in Achieving High Quality Health Care ............................................................................................. 53

  Background and Introduction .............................................................................................................. 54

  Demonstrating Respect for the Moral Status of Individuals Enrolled in QI and CER Activities ....... 57

  Features of QI and CER Activities that are Relevant to the Acceptability of Waiving or Altering Informed Consent Requirements ............................................................................. 59
B. Johns Hopkins/Geisinger Institutional Review Board Members ..................140
C. Johns Hopkins/Geisinger Patients with Hypertension ............................143
D. Johns Hopkins/Geisinger Patients with Migraines ...............................147

Appendix 6: In-depth Interview Guide and In-depth Focus Group Guide ..........151
   A. In-Depth Interview Guide ........................................................................151
   B. Focus Group Guide ..............................................................................155

Appendix 7: Case Studies .............................................................................161
   A. Hypertension Case Study Description ....................................................161
   B. Migraine Case Study Description ............................................................164

Appendix 8: Description of the Models of Consent, Disclosure, and Authorization...167

Appendix 9: Participant Surveys ....................................................................172
   A. Survey for Researchers and Institutional Review Board Chairs/Longstanding
      Members ..................................................................................................172
   B. Survey for Institutional Review Board Community Members ...............175
   C. Survey for Patients with Hypertension or Migraines .............................178

Appendix 10: Interview and Focus Group Coding Scheme .............................182

Curriculum Vita .............................................................................................185
List of Tables

1.1: Description of Hypothetical Case Studies and Models of Disclosure and Authorization .......................................................... 44
1.2: Demographic Characteristics of Interview Participants .................................................. 45
1.3: Selected Participant Comments Related to the Theme of Respect for Autonomy or Components of Respect for Autonomy ........................................... 46
1.4: Demographic Characteristics of Focus Group Participants ........................................... 48
A.1: Focus Group Composition ......................................................................................... 123
A.2: Description of Four Models of Disclosure and Authorization ..................................... 132
List of Figures

1.1: Comments Related to the Amount of Information that Should Be Provided to Individuals if Model 3 is Used........................................................................................................................................49
Introduction

Over the last several decades, there have been increasing calls for more and higher quality evidence of clinical effectiveness. This has included increased demand for knowing how technologies or other health care innovations impact health outcomes and clinical care in the real world (Committee on Comparative Effectiveness Research Prioritization, 2009, 1; Olsen et al, 2007; Tunis et al, 2003). Determining the effectiveness of drugs and technologies in clinical practice requires the development of a research paradigm that draws “clinical research closer to the experience of clinical practice, including the development of new study methodologies adapted to the practice environment” (Olsen et al, 2007, 5). This shifting clinical research paradigm in which research is more closely integrated within clinical care raises a number of unique and important ethical issues that must be addressed to ensure that this type of research is conducted in socially and morally appropriate ways.

Much of the research ethics literature to date has focused on ethical issues in traditional clinical trials, while newer literature has begun to address issues related to the use of data from electronic medical records for research purposes, including how to manage privacy and confidentiality and whether informed consent is required from patients. However, relatively little has been written about the ethical issues that emerge when comparative effectiveness studies are conducted in ongoing clinical practice settings, including whether current standards of prospective informed consent should always be required for pragmatic clinical trials (PCTs). PCTs are randomized controlled trials designed to demonstrate how effective health technologies are in routine clinical settings (Mullins et al, 2010). These trials are generally designed to be more closely...
integrated with clinical practice and generally impose few, if any, additional burdens on participants (Thorpe et al, 2009; Olsen et al, 2007, 9). Moreover, given their frequent use of widely-prescribed, non-experimental therapies, PCTs often have a lower risk and uncertainty profile than traditional Phase 3 trials, and certainly lower than Phase 1 and 2 safety studies. Because of these differences, researchers’ duties regarding respect and consent may fall somewhere in between the fairly modest and more informal consent norms of clinical practice (Braddock et al, 1997; Braddock et al, 1999) and the far stricter consent norms of clinical research. Therefore, consistent with the arguments that some scholars have made (Truog et al, 1999), it may be appropriate to implement alternatives to prospective informed consent for at least some randomized comparative effectiveness trials of widely-used, non-experimental therapies. When waiving or altering informed consent requirements is morally permissible, doing so may be preferable because current consent requirements are time consuming, resource intensive, difficult to integrate into clinical care, and can result in selection bias.

This dissertation addresses the question of whether there are morally permissible and socially acceptable alternatives to prospective informed consent for low-risk PCTs comparing two or more widely-used, non-experimental medical interventions.

To address this question, this dissertation has three aims:

(1) to explore which of several different models consent, disclosure, and authorization are acceptable to patients, institutional review board (IRB) members, and comparative effectiveness researchers for PCTs comparing evidence-based and widely-used therapies for migraine and hypertension, and
which factors affect stakeholders’ perceptions of the acceptability of these models;

(2) to conduct a moral analysis outlining which models of consent, disclosure, and authorization are morally permissible for quality improvement and comparative effectiveness activities, including PCTs; and

(3) to provide preliminary policy recommendations for reforming the informed consent regulations in morally and socially acceptable ways as well as guidance on how to further refine those recommendations and move toward implementation.

Each of these aims is addressed in a separate paper included in this dissertation. Aim 1 is addressed in the first paper which describes a qualitative study that engaged three different types of stakeholders – patients, IRB members, and comparative effectiveness researchers – from Johns Hopkins Health System and Geisinger Health System in discussions about waiving or altering informed consent requirements for low-risk PCTs comparing widely-used, non-experimental interventions. Specifically, eight focus groups were conducted with migraine or hypertension patients and eighteen interviews were conducted with IRB members and comparative effectiveness researchers. The results of this study demonstrate that many participants felt that although it was important for eligible individuals to be informed about low-risk PCTs, it was also acceptable for the amount of information disclosed to be simplified. Additionally, many participants felt that it was acceptable to use an opt-out model as long as opting-out was relatively easy.
Aim 2 is addressed in the second paper. This moral analysis argues that when enrolling individuals in quality improvement or comparative effectiveness activities, it is sometimes acceptable to limit the autonomous choice of those individuals in situations where there is a strong justification for doing so and where the decision to participate is unlikely to engage important self-determination interests that an individual has. This analysis also describes specific features of quality improvement and comparative effectiveness activities that impact the likelihood that the decision to participate in those activities will engage important self-determination interests. Based on this analysis, a number of recommendations regarding the moral permissibility of waiving or altering informed consent requirements for these types of activities are provided.

Finally, aim 3 builds on the results of aims 1 and 2 and is addressed in the third paper. This paper considers the policy implications of this work as well as appropriate next steps that should be undertaken in order to move towards both morally and socially appropriate policy changes to the current informed consent regulations in the United States. Specifically, based on the results of aims 1 and 2, the third paper recommends that study-specific disclosure statements for low-risk PCTs be simplified such that the information provided about widely-used, non-experimental interventions is similar to the amount of information provided about those interventions as part of appropriate standard clinical care practices. This paper also recommends that patients be asked to opt-out of these activities if they would prefer not to participate. Nevertheless, in order for policy change to occur, this third paper suggests that it is necessary to continue to build the case for the importance of conducting pragmatic comparative effectiveness trials.
This body of work contributes to the growing research ethics literature by providing data, as well as a normative analysis, concerning the acceptability of waiving or altering prospective informed consent requirements for pragmatic comparative effectiveness trials of widely-used interventions. However, more work of this sort is needed to help identify what constitutes appropriate public policy in this context. For instance, there is a need for additional discussion regarding what appropriate clinical standards for disclosure of information about medical interventions are. There is also a need for more work that considers if and how a community’s level of trust in a medical institution should factor into moral and policy analyses about the appropriateness of different alternatives to prospective informed consent. Moreover, although the results of the qualitative study presented in the first paper provide useful information on the views of important stakeholders, because this was a relatively small study, it is necessary to engage even more stakeholders from additional institutions in discussions about the appropriateness of waiving or altering informed consent requirements for pragmatic comparative effectiveness trials. Finally, there is a need to ensure that there are efficient and effective mechanisms for implementing the results from these types of trials back into clinical care so that they have a positive impact on the quality of health care delivered to patients.

References


Paper 1: Stakeholders’ Views of Alternatives to Prospective Informed Consent for Low-Risk Pragmatic Comparative Effectiveness Trials

Abstract

As interest in conducting comparative effectiveness research continues to build, questions have emerged regarding whether it is ever acceptable to waive or alter prospective informed consent requirements for research when individual patients are randomly assigned to different evidence-based and widely-used therapies. This paper reports on a qualitative research project that aims to understand the views of Institutional Review Board (IRB) members, researchers, and patients regarding the acceptability of four different models of disclosure and authorization for low-risk pragmatic comparative effectiveness trials of widely-used therapies. Participants were recruited from two institutions: the Geisinger Health System in Danville, PA and the Johns Hopkins Health Care System in Baltimore, MD. A total of 18 interviews were conducted with IRB members and researchers and a total of 8 focus groups were conducted with Geisinger and Johns Hopkins patients between July, 2012 and June, 2013. During the interviews and focus groups, participants discussed the acceptability of the four different models of disclosure and authorization in relation to either a hypertension or migraine treatment case study developed for this project. Each case study described a pragmatic trial comparing widely-used therapies for the condition in question. The results suggest that participants value autonomous choice and therefore, most did not find models that they viewed as significantly infringing on autonomous choice to be acceptable. However, many participants also believed that it was acceptable to simplify the amount of information disclosed to individuals eligible for the hypothetical studies and that it was
acceptable to ask eligible individuals to opt-out if they would prefer not to participate (as opposed to opting-in). Participants from Geisinger were more likely than participants from Johns Hopkins, and patients and researchers were more likely than IRB members, to state that alternatives to prospective informed consent were acceptable. This work provides some preliminary evidence that important stakeholders find alternatives to prospective informed consent acceptable for low-risk pragmatic comparative effectiveness trials of widely-used therapies as long as a sufficient amount of patient control is preserved.

Background and Introduction:

Although technological innovation has led to important advancements in medical care, patients continue to receive many health services for which the evidence regarding whether the service is effective is incomplete or unavailable (Tunis et al. 2010). Recognizing the need for robust evidence to support clinical and health policy decision making, increasing attention has focused on the importance of conducting comparative effectiveness research (CER) (Committee on Comparative Effectiveness Research Prioritization 2009). To support such efforts and to underscore the public’s interest in having such evidence, the Federal Government has recently devoted substantial resources to support CER both through the American Recovery and Reinvestment Act of 2009 and the Patient Protection and Affordable Care Act of 2010, which also established the Patient Centered Outcomes Research Institute to coordinate and fund CER activities.

CER has been defined as “the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and
monitor health conditions in “real world” settings” (Federal Coordinating Council for Comparative Effectiveness Research 2009). Understanding how different widely-used, evidence-based interventions work in the “real world” generally requires that CER studies be closely integrated with clinical practice. Further, although some CER questions can be answered with observational studies, generating robust evidence of comparative effectiveness will, at times, require randomized controlled trials (RCTs). Pragmatic clinical trials (PCTs) are a type of RCT design that is meant to be closely integrated with clinical care while maintaining the benefits in terms of improved study validity that result from randomly assigning individuals to treatment arms (Mullins et al. 2010). So that they reflect the effectiveness of interventions in the “real world”, PCTs generally have minimal exclusion criteria, include a wide range of clinical settings, collect data on patient-relevant outcomes, and are designed to have only a minimal impact on the clinical care experienced by participants (Luce et al. 2009; Tunis et al. 2003). Given these features, PCTs will be an important strategy by which to address many CER questions (Mullins et al. 2010).

Since PCTs are often designed to understand the effectiveness of widely-used, evidence-based interventions, these trials will differ in ways that are significant, morally, from more traditional clinical research measuring efficacy and safety. Unlike PCTs, efficacy and safety studies generally compare experimental interventions, impose greater burdens on participants, and are conducted in carefully selected patients and settings. Given these differences, PCTs often have different risk, benefit, and burden profiles than traditional clinical research and as such, as CER becomes a more widely-used and promoted research methodology, several scholars have questioned whether informed
consent strategies required for traditional RCTs should always be required for PCTs (Kass et al. 2012; Faden et al. 2013).

The moral justification for informed consent is the need to respect the autonomy of potential research participants as well as the desire to protect individuals from risks that they did not agree to accept (Emanuel et al. 2003; Faden and Beauchamp 1986, 294). Obtaining informed consent is required, with few exceptions, by U.S. federal regulations, in part, because research is assumed to carry both increased risk of harm and uncertainty of effectiveness and/or safety. While current regulations do allow, in certain circumstances, some low-risk studies to obtain a waiver of informed consent (45CFR46.116), it is extremely rare for trials that randomize individuals to clinical interventions to qualify for such waivers. This may be because the paradigm for clinical research that emerged over the last several decades was that RCTs were used to study therapies of uncertain efficacy and as a result were thought to routinely carry higher risks. However, as discussed above, these assumptions often do not apply to PCTs and as such, researchers’ duties regarding consent may fall somewhere in between the more informal consent norms of much of clinical practice (Braddock et al. 1997; Braddock et al. 1999) and the far stricter consent norms of clinical research.

Unfortunately, there is very little information about stakeholders’ views regarding the acceptability of implementing alternative approaches to prospective informed consent for low-risk PCTs comparing widely-used, evidence-based interventions (Rogers et al.

1 Also relevant is that the US Food and Drug Administration (FDA) guidelines hardly ever allow informed consent requirements to be waived (21 CFR 50.23). This is perhaps because of the assumption that studies being submitted to the FDA are for approval of experimental drugs or for approval of new indications for previously approved drugs (off-label), and are therefore more risky. However, there are cases where this assumption does not hold such as in situations where investigators would like to compare evidence-based therapies to each other and may ultimately submit the results to the FDA for additional labeling, even for their indicated use.
1998). Understanding stakeholders’ views is important because informed consent, as currently solicited and documented, is logistically burdensome, time consuming, resource intensive, and introduces selection bias. If alternative models were both morally permissible and acceptable to relevant stakeholders, regulatory changes could be made that might facilitate the more efficient implementation of these trials and potentially the increased participation of more diverse populations and practices. We conducted a qualitative study designed to understand Institutional Review Board (IRB) members’, researchers’, and patients’ views of the appropriateness of several different models of disclosure and authorization for enrolling patients in PCTs comparing widely-used, evidence-based interventions.

Methods

To explore stakeholders’ views, this study conducted a series of 18 semi-structured interviews with IRB members and researchers and 8 semi-structured focus groups with patients between July, 2012 and June, 2013. Qualitative methods were used because they are appropriate when little information exists about a given topic as well as when a research project aims to understand people’s perspectives and the reasons behind them (Taylor et al. 2010, 193-195). This study was approved by the Johns Hopkins Bloomberg School of Public Health IRB and the Geisinger Health System IRB.

I. Study Setting and Sample

Interviews and focus groups were conducted within two health care systems: Johns Hopkins Health System (JHS) and Geisinger Health System (GHS). These two
sites were selected because they differ in ways that may impact individuals’ views on the appropriateness of implementing alternatives to prospective informed consent. GHS is a private, non-academic institution located in rural Pennsylvania that serves a predominantly Caucasian patient population and which has been “developing and refining an innovation infrastructure that can adapt to new evidence efficiently, and rapidly translate that evidence into care delivery” (Paulus et al. 2008). JHS is a large academic medical institution located mainly in an urban setting- Baltimore, Maryland that serves a racially diverse patient population. Although there is significant ongoing research within this institution, explicit policies and commitments for adapting and translating research findings similar to GHS do not exist in the same way at JHS.

a. **IRB Member and Research Interviews**

IRB members were eligible to participate if they were either an IRB chair or had been an IRB member for one year or longer. IRB community members were also included given their considerable IRB experience as well as their perspectives as non-scientists. Researchers were eligible if they were known to have, or were identified by colleagues as having, experience conducting CER. A purposefully chosen sub-sample of eligible individuals at each institution was sent an invitation email explaining the study as well as how to opt-out. Specifically, IRB chairs were invited to participate first as were researchers who had a greater amount of experience conducting CER studies. If invited individuals did not respond or opt-out within a week, they were contacted by telephone to seek their willingness to participate. Additional individuals were recruited using this same method until data saturation was reached.
b. **Patient Focus Groups**

As described below, during the interviews and focus groups, participants discussed one of two hypothetical case studies; one case described a PCT comparing migraine drugs and the other described a PCT comparing hypertension drugs (table 1.1). Since individuals who have been diagnosed with a given health condition are more knowledgeable about that condition and it was thought that this knowledge made the topics discussed during the focus groups more relevant, only individuals who had been diagnosed with either migraines or hypertension were eligible to participate. Four of the eight focus groups (two at each site) were attended by individuals who had been diagnosed with migraines and 4 (two at each site) were attended by individuals who had been diagnosed with hypertension. Eligible individuals also had to be over the age of 18 and had to have been receiving their health care at the health care system where the focus group was taking place for at least one year to ensure some familiarity with that system.

At GHS, a random sample of patients who met the eligibility criteria and who lived within a short distance of the health care facility in Danville, PA were identified through Geisinger’s electronic medical record system and were mailed an invitation letter. The letter informed individuals about how to opt-out of the study and informed them that if they did not opt-out, they may receive a follow-up telephone call. A GHS representative called individuals who did not opt-out until a sufficient number of individuals had been recruited to the focus groups. At JHS, recruitment posters were hung in waiting rooms and exam rooms of two sites within the Johns Hopkins Community Physicians (JHCP) network. Those interested in participating were instructed
to contact the study investigator who screened individuals to verify that they met eligibility criteria.

II. **Interview and Focus Group Structure**

At the beginning of each interview and focus group, oral informed consent was obtained from participants. All interviews and focus groups were conducted by the same study investigator (DW). Interviews with professionals from GHS were conducted by telephone while most interviews with professionals from JHS and all focus groups were conducted in-person.

a. **Introductory Questions**

Participants were first asked several introductory questions. IRB members and researchers were asked about their professional experience and their perceptions of current informed consent regulations. Patient participants were asked to discuss whether they had ever been asked to participate in medical research, what they believed the term ‘medical research’ meant, and whether they thought it was important to conduct more research about treatments for migraines or hypertension.

b. **Discussion of a Hypothetical Case Study**

Participants were then given a brief description of CER and were read one of two hypothetical case studies developed for this project. The purpose of reviewing these case studies was to provide a more concrete example to which study participants could react. Both case studies describe a PCT designed to compare two US Food and Drug
Administration (FDA) approved and widely-used drugs that are both taken orally and that are similar in terms of their side effect profiles. Also, in both cases, some additional burden was imposed on individuals enrolled in the PCT (table 1.1). The case study described why doing the hypothetical PCT was important, what participation in the PCT would entail, and how being enrolled in the PCT was different from receiving clinical care outside of the trial. One of the hypothetical case studies described a PCT comparing anti-hypertension drugs and the other described a PCT comparing drugs prescribed to relieve migraines. These two disease areas were selected because both are important areas for future CER. However, they also differ in ways that may affect individuals’ perceptions about the disease and treatments and subsequently their views about participation in a PCT as well as appropriate models of disclosure or authorization. Specifically, while migraines are a symptomatic condition, hypertension is a silent disease and while migraines are an acute, episodic condition, hypertension is a chronic condition.

After reviewing the hypothetical case, participants were asked to discuss any risks of harm they thought existed for patients enrolled in the case study, any benefits to enrolled patients, and any social benefits resulting from the case study being conducted. IRB members and researchers only were also asked whether they were aware of any trials like the one described in the case study.

c. Discussion of Four Different Models of Disclosure and Authorization

Next, participants were told about four different models of disclosure and authorization (table 1.1) including what some people may view as the pros and cons of
each. Most interviewees and all focus group participants were also told that a major difference between models 2 and 3 versus model 4 is the amount of information provided to eligible individuals. All 3 models inform patients about the PCT but with models 2 and 3, the amount of information provided about the drugs being studied is similar to the amount of information provided in standard care, meaning patients are told about the main risks and are given additional information when they pick up the drug at the pharmacy. With model 4, the amount of information provided is typical of a standard informed consent form meaning patients are told about all the risks associated with the drugs.

Participants were asked the following about each model:

1. Please discuss whether or not you think this is an acceptable way of telling people about the medical research study we just discussed.

2. Please discuss what you think the benefits of using this approach are.

3. Please discuss any concerns you have about this approach.

Participants were then asked to discuss which model they felt was most appropriate to use when enrolling patients in the PCT described in the case. During the focus groups, the study investigator (DW) specifically asked each participant in the group to state which model they preferred.

Last, participants were asked to complete surveys with some demographic questions. The IRB member and researcher survey also had questions about participants’ experience conducting human subjects research and their past experience participating in research. The patient surveys had questions about participants’ past experience participating in research, their perceptions of the importance of research, how they prefer
medical decisions to be made, and their trust in medical researchers. The materials used during the interviews and focus groups were very similar except that patients were provided with more information on key concepts such as medical research, CER, randomization, and selection bias. Prior to beginning the study, all project materials were pilot tested.

III. Data Management and Analysis

All interviews and focus groups were audio recorded and transcribed. Data analysis progressed in an iterative fashion. Transcripts were reviewed for accuracy and personal information was redacted. During this review, significant quotes and themes were noted. Transcripts were then read more carefully and a coding scheme was developed. Once the coding scheme was finalized, all transcripts were read again and coded. Additionally, a second coder used the coding scheme to independently code three transcripts and a study investigator (DW) checked the coded transcripts for consistency. Because there was a high level of consistency among the way the codes were applied by the two coders, only minor changes were made to the organization of the coding scheme. The coded transcripts were then reviewed a final time and summary documents that described the main themes from each interview and focus group were developed. The study investigator (DW) also noted how many interviewees discussed each specific code. For the focus group data, the investigator noted how many focus groups discussed a certain theme, since recording numbers of participants would suggest false precision. Finally, major patterns were identified in the data. Quantitative data from the surveys
were entered into excel, double checked to ensure accurate data entry, and analyzed to understand background characteristics of participants.

This manuscript reports on data related to participants’ perceptions of the different models of disclosure and authorization. Data on patients’ perceptions of the importance of research, how patients prefer medical decisions to be made, and whether there is any relationship between these variables and the model of disclosure and authorization an individual prefers is reported elsewhere.

Results from Interviews with Researchers and Institutional Review Board Members

Interviews lasted between an hour and an hour and a half. One of the interviews was dropped from the analysis because the participant did not speak English very well and it was not clear that she understood the materials. The demographic characteristics of GHS participants were similar to those of JHS participants except that GHS participants were, on average, slightly younger (table 1.2). Additionally, interviewees from JHS had been employed by the institution for a longer period of time compared to interviewees from GHS and more JHS interviewees saw patients clinically (table 1.2). At each institution, one of the researchers interviewed was also an IRB member. Finally, the two African American interviewees from JHS were IRB community members.

Three current or recent IRB community members from GHS were invited to be part of this study but none were able to participate.
I. Perceptions of the Case Studies

Most researchers and IRB members commented that there are problems with current informed consent requirements (n=14) including that consent forms are too long and complex (n=9) and that the process is ineffective (n=1) or overly protective (n=2). When asked if they were familiar with research like the PCT described in the hypothetical case, although many participants did provide an example or two (n=11) or mentioned that they thought that trials like this were going on (n=3), their comments suggest that they did not believe that these kinds of trials were common. When asked about risks of the case study trial, most participants commented that there were either no or minimal risks (n=8) or that the risks were the same as standard care (n=6). Other risks mentioned included the potential for a breach of confidentiality (n=8), the potential for conflicts of interests if the doctor treating a patient is also an investigator in the research (n=2), and the toxic side effects associated with the drugs (n=5). However, of those individuals who mentioned the risks associated with the drugs, over half commented that these are no different than the risks associated with standard care (n=3).

Regarding benefits, many participants mentioned that patients in the case studies would receive closer monitoring (n=11), while others mentioned that the benefits to patients in the case studies are not greater than those associated with standard care (n=4). A large majority of participants also believed the results from the study would be socially beneficial:

There’s benefit for society at large in advancing the field and knowledge…We’re going to learn something. We’re going to either learn that one of the drugs is better than the other, or they’re essentially equivalent and that’s helpful information for clinicians. (JHUIRB2)
Since there were no significant differences in the themes discussed by interviewees who reviewed the hypertension case study and interviewees who reviewed the migraine case study, the results from all interviews will be described together.

II. Perceptions of Model 1: Disclosure of Institutional Policy

A majority of participants felt that model 1 was unacceptable. Only three participants, all from GHS (2 researchers and 1 IRB member also involved in CER), believed that model 1 was acceptable and of these, only one participant felt that this was the best approach to use for enrolling patients in the hypothetical case study. Also, over half of the GHS respondents mentioned that the institution uses a similar model as a way of broadly informing patients that the institution does research using de-identified medical information and that they may be contacted to participate in research; patients can opt-out of either (n=5).

a. Views Expressed by Participants who found Model 1 Acceptable

The three GHS participants who found this model acceptable justified their views by describing the benefits this model would have in enhancing study validity (n=3) and improving the efficiency of the research (n=1). Additionally, all three emphasized that the study compares similar and widely-used drugs (n=3), one commented that doctors have the ability to switch a patient’s drug at any time (n=1), and another commented that the risk of harm to participants is minimal (n=1). One participant also mentioned that he believes that patients in a health care system should be helping to advance knowledge:

My view is that if you're part of the health care system... you should be part of advancing knowledge... [by] participating in research. I think that's like real fair and reasonable to say right up front. (GHSCER2)
However, because they recognized that model 1 infringes on the autonomous choice of individuals, one participant commented that patients should be able to broadly opt-out of participating in this type of research and two said there would need to be strict criteria regarding what types of activities qualify for this model:

There will have to be really, really strict guidelines about what sets of drugs, and the relations between those drugs, in terms of evidence of superiority, inferiority, and risks are allowed to be called comparable and fall under this type of category. (GHSIRB1)

b. **Views Expressed by Participants who found Model 1 Unacceptable**

Although many participants recognized the benefits of model 1 for the case study, a majority of those who found it unacceptable justified their view with comments related to the theme of respect for autonomy (table 1.3) (Beauchamp and Childress 2009, 118-135). Some participants mentioned that model 1 infringes on autonomous choice (n=6), many were concerned that information about the hypothetical study is not disclosed to participants (n=10) and many also felt that this model infringes on the ability of patients to make voluntary decisions (n=9). In order to justify their views further, most participants discussed aspects of the hypothetical case study design or the study setting including that the study imposes burdens on participants (n=9), may impose additional financial risks (n=2), alters clinical care (n=5) by limiting treatment options (n=1) or by randomly assigning patients to different treatments (n=3), and involves drugs which are inherently risky interventions (n=3). Additionally, several participants from JHS mentioned that there is a significant amount of distrust in the surrounding community and therefore, this is a particularly bad model to implement at JHS (n=3). Indeed, a few participants, most of whom were from JHS and a couple of whom also commented on the
lack of trust in the community, felt that implementing this model could result in people feeling wronged or angered and could decrease trust in the institution (n=4):

[I would be] more concerned about the issue of people participating in research and not being aware of it, and the downstream bad effects of that in terms of undermining trust. (JHUIRB2)

A couple participants also worried that if this model were used, studies would get done under this model that really required individual informed consent (n=2).

III. Perceptions of the Acceptability of Model 2: Study Specific Disclosure with No Routine Option to Opt-Out

Most participants also felt that model 2 was unacceptable. Only two participants, both of whom were from GHS and also found model 1 acceptable (1 researcher and 1 IRB member also involved in CER), felt that model 2 was acceptable and only one of those felt that this model was the best model to use.

a. Views Expressed by Participants who found Model 2 Acceptable

The two GHS participants who found model 2 acceptable commented that compared to model 1, this model is more respectful of patient autonomy because patients are informed about the study (n=2). However, these interviewees did worry that because model 2 does not inform patients of the option to opt-out, it limits voluntary choice. Both individuals further commented that model 2 retains many of the benefits in terms of efficiency and enhanced internal and external validity. One individual commented that the reason he felt that model 2 was acceptable was because the hypothetical case study is comparing widely-used drugs and because patients can switch drugs at any time.
b. Views Expressed by Participants who found Model 2 Unacceptable

Similar to model 1, the reasons participants provided to justify why they felt model 2 was unacceptable mainly related to respect for autonomy (table 1.3). A few participants simply stated that model 2 is disrespectful or paternalistic (n=2), most expressed concern that this model limits voluntary choice (n=10), and many expressed concern that model 2 does not inform individuals of their options regarding participation (n=7), which one participant described as deceptive. Related, several participants worried that patients would not understand their options (n=2) or would not understand that they are being enrolled in research (n=2). To further justify their view, several participants again discussed the same aspects of study design and setting that were discussed in reference to model 1, including that the study imposes additional burden (n=1), involves drugs (n=1), and alters care by limiting treatment options (n=2) or randomly assigning patients (n=2). Three participants also mentioned the level of distrust in the surrounding community:

One of the other things that would have to be dealt with, and it might be very specific to Hopkins, is trust, and we’re in a community which … often does not trust what we do. So to have studies conducted without consent opt-in…would just reinforce many people’s opinions. (JHUCER3)

Several participants from JHS were also concerned that model 2 could result in people feeling wronged or angered or could increase distrust (n=5) and two participants worried that if this model were used, patients would just not do the extra things requested of them, which included completing surveys as well as going to the doctor’s office for two extra blood pressure reads or completing a migraine diary. One participant also commented that model 2 is not that much more efficient than model 3.
IV. **Perceptions of the Acceptability of Model 3: Study Specific Disclosure with an Explicit Option to Opt-Out**

A majority of interviewees believed that model 3 was acceptable, including seven interviewees from JHS and five from GHS, and five felt that this was the best model for the case studies. Importantly, most interviewees who felt this model was preferable were researchers (n=4). Five interviewees felt that this model was unacceptable and most of these were IRB members (n=4). Two IRB members from JHS commented that prospective informed consent (model 4) is the model they have spent a good deal of time enforcing. As a result, it was difficult for them to think about departing from it.

a. **Views Expressed by Participants who found Model 3 Acceptable**

Most interviewees who found this model acceptable justified their view by discussing themes related to respect for autonomy (table 1.3). A few participants just stated that model 3 is more respectful (n=3), others stated that they believed it gives patients a sufficient amount of control over their participation (n=8), and one participant said he felt that it was appropriate to require people to expend some energy to resist participating in the hypothetical case studies (table 1.3). To further justify why they felt that model 3 was appropriate, several participants discussed study design features including that patients can switch medication (n=2), that the study involves widely-used drugs (n=2), and the minimal risk nature of the research (n=3). Additionally, several researchers stated that model 3 is more efficient than model 4: prospective informed consent (n=2) and would likely result in improved study validity (n=1):
I think this is probably in my mind, the only model that really makes sense because it protects the doctor/patient relationship. It preserves autonomy, at the same time, facilitates research in a far greater capacity than the current system of an informed consent for [studies comparing] FDA-approved medications. (JHUCER4)

However, a few participants felt that model 3 was only acceptable if it was relatively easy for patients to opt-out (n=3) and about half of the interviewees, including six who felt model 3 was acceptable and two who ultimately decided it was unacceptable, commented that the acceptability of model 3 depended on exactly what information was provided to eligible individuals (figure 1). Yet, a few participants also stated that it was appropriate for the amount of information provided about the drugs to be less than is generally provided in research prospective informed consent forms and/or more similar to the amount of information provided in standard care (n=3).

b. Views Expressed by Participants who found Model 3 Unacceptable

Many of the individuals who thought that model 3 was unacceptable had concerns related to respect for autonomy. One participant commented that he felt that having more information is always better, a few were concerned that individuals would not understand the full implications of being in the research study (n=3), and one was concerned that the decision to participate “may not reflect an authentic choice on the part of patients” (JHUIRB2). Several also commented on the same aspects of the study design that led them to find models 1 and 2 unacceptable including that the study involves drugs (n=3), alters clinical care (n=2) by randomly assigning patients or limiting treatment options, and imposes burdens (n=1). Lastly, one participant from JHS was concerned that this model could negatively impact patient trust and that researchers would try to use it for research that imposes greater risk and burdens.
V. Perceptions of the Acceptability of Model 4: Prospective Informed Consent

All participants except for two researchers (one from each institution) felt that model 4 was acceptable. Ten participants (three researchers and seven IRB members) said they thought it was preferred. Of these, eight were from JHS.

a. Views Expressed by Participants who found Model 4 Acceptable

A majority of those individuals who felt that model 4 was acceptable again emphasized themes related to respect for autonomy (n=11) (table 1.3) including that patients are most informed under this model (n=6), that patients have the greatest understanding of what study participation involves (n=3), and that the decision to participate is completely voluntary (n=7). About half of those who preferred model 4 discussed aspects of the study design including the fact that the study involves drugs (n=2) and alters clinical care (n=2). Several participants also felt patients enrolling under model 4 would be willing participants, more likely to do the extra things asked of them, resulting in increased internal validity (n=4). Further, several participants felt that this model would result in increased trust (n=3) and improve the public perception of research (n=4).

However, several participants, including about half of those who preferred model 4, thought that the information provided to patients could be simplified (n=5):

I think the key for this type of research is to have the information regarding risk to be akin to clinical practice…sort of Option 3 is more like that where you kind of say, “Look, I’m going to give you this medicine, anyway. Here’s some things I want you to watch out for in terms of side effects. If they occur, give us a call.” (JHUCER3)
b. Views Expressed by Participants who felt that Model 4 was Unacceptable

Of those participants who felt that model 4 was unacceptable or unnecessary, several commented that using model 4 would have a negative impact on the ability to efficiently (n=2) do valid research (n=4) because only a select group of people will participate:

I think it’s not as optimal for… the purpose that the trial is trying to accomplish which is to get a large, unbiased sample of people to generate information in a timely way. (GHSCER1)

As a result, one participant believed that using model 4 would result in “learning a lot less.” (GHSCER2) Additionally, two participants commented that the amount of information provided when model 4 is used could scare or overwhelm patients. To further justify their views, several participants also discussed study design features including that the study compares widely-used drugs (n=3) and is minimal risk (n=3):

If your goal is to test a new agent for which the risk/benefit is poorly defined, then fine… But it’s not your goal here. What you’re saying is, “Look, we know the risk and benefit of each treatment, and experts acting independently have determined these are both appropriate.” (JHUCER4)

Results from Focus Groups with Migraine and Hypertension Patients

Each of the eight focus groups had between three and eight participants and lasted between two and a half and three hours. A total of 38 patients participated in these focus groups. Demographic characteristics of participants are reported in table 1.4. A majority of the participants were female, especially in the migraine focus groups, and, on average, migraine participants were slightly younger than participants with hypertension. Both trends were expected given that a majority of migraine sufferers are females and given the differences in the average age of individuals impacted by these conditions (Migraine Research Foundation; Centers for Disease Control and Prevention 2011). Additionally, as
anticipated, racial differences existed between participants from JHS and GHS (table 1.4). Numbers reported in parenthesis in this section refer to the number of focus groups in which a certain theme was discussed, rather than the number of individuals who discussed a specific theme.

I. Perceptions of the Hypothetical Case Studies

When asked about risks of the case study trial, participants from five different focus groups mentioned that they believed that there were no or minimal risks or that the risks were the same as the risks associated with standard care. However, many participants from six different groups also commented that there are always risks associated with taking a newly prescribed medication. Additionally, one participant discussed the risk of a breach of confidentiality and one mentioned that there was a risk associated with narrowing treatment options available to patients. Regarding benefits, several participants mentioned that patients in the case studies would receive closer monitoring (n=5 groups), several mentioned that patients in the studies would be treated for their condition and/or that they might find a drug that works well for them (n=6 groups), and a few indicated that patients in the studies can feel good about helping others (n=3 groups). Participants from all focus groups felt that the hypothetical case studies would provide useful information and/or would help to determine which drugs are best for which types of people:

The more information they collect, then doctors will become more aware of which ones are helping and [in] which circumstances.
(GHSMIG3 P4)

One participant also commented on discussions she had had with her doctor regarding the amount of uncertainty that exists about which treatments are best:
Many times I say to my doctor, which one is best...And he says, flip a coin, we don’t know...there’s really no answer there right now.

(GHSHTN1 F3)

II. Perceptions of Model 1: Disclosure of Institutional Policy

Most focus group participants from JHS and about half of the focus group participants from GHS felt that model 1 was unacceptable; stated differently, at least some individuals from seven of the eight focus groups stated that this model was unacceptable. Of the few JHS participants who believed model 1 was acceptable, only two participants from the same focus group felt it was the best model to use. At GHS, close to half of the individuals who believed model 1 was acceptable stated that it was the best model to use (n=2 groups). Interestingly, all GHS participants who stated that model 1 was preferable were individuals with hypertension.

a. Views Expressed by Participants who found Model 1 Acceptable

Many participants who found model 1 acceptable justified their view by discussing different features of the study design. This included that the case studies compare widely-used drugs (n=3 groups), that patients who are eligible for the case studies are treatment naïve and need to be prescribed a drug anyway (n=2 groups), and that patients can switch treatments if needed (n=2 groups):

To me, doesn’t seem that big of a deal, because, okay, I’m newly diagnosed, just like what I was 13 years ago. [The doctor says] “We’re going to start you on this med.” Great. Okay. So this med happens to be part of this trial. Doesn’t really bother me, probably going to start me on that med anyway, and if it doesn’t work, he’s going to switch me from it anyhow. If it does work, great, we don’t need to mess with it.”

(GHSHTN1 F4)
A few participants from two different focus groups mentioned that their health care institution is a teaching/research hospital and that they expect that research is going on all the time:

I was assuming that’s what was going on all the time anyway [studies like the ones described in the case]…it’s a teaching hospital. I think every hospital needs to do something like this. (GHSHTN2 F12)

Additionally, several participants mentioned the benefits model 1 would have in terms of improving the efficiency of trial enrollment, decreasing costs, and allowing the research to be completed quickly (n=3 groups).

However, like interviewees, several focus group participants felt that model 1 was only acceptable under certain conditions. A few participants from one focus group felt that model 1 was only acceptable if no additional costs would be imposed on patients. A couple of participants from a different focus group thought that there needed to be some way to demarcate those activities that patients were being asked to do that were not part of standard care. Additionally, several participants felt that patients should be able to broadly opt-out (n=3 groups) and a few mentioned that it was important to frequently remind patients about the institutional policy (n=3 groups).

b. Views Expressed by Participants who found Model 1 Unacceptable

Although participants generally recognized the benefits of model 1, many participants who stated that this model was unacceptable justified their view with comments related to respect for autonomy (n=7 groups) (table 1.3). Many participants expressed concern that patients are not informed about the study (n=6 groups) and/or that model 1 infringes on voluntary choice (n=5 groups). Additionally, many participants felt that model 1 was unacceptable because the case studies impose additional burdens (n=6
groups), one participant mentioned that the case alters clinical care and relies on personal health information, and one JHS participant mentioned the lack of trust in the community.

Many participants from five different focus groups, including all four JHS focus groups, also felt that model 1 could result in people feeling angered or upset or losing trust. Additionally, several participants felt that patients would not be willing to do the extra things asked of them (n=3 groups):

If you’re asked … to write stuff down, you may just think that’s no big deal, but if you knew you’re writing this down as part of a study and that your opinion counted, you’d be a lot more committed to actually following through. (GHSMIG2 F9)

Finally, one participant was concerned that if model 1 were allowed for some kinds of research, it would end up being used in situations where it is inappropriate.

III. Perceptions of the Acceptability of Model 2: Study Specific Disclosure with No routine Option to Opt-Out

A vast majority of participants from each of the eight focus groups felt that model 2 was unacceptable. Only one JHS participant and only a few GHS participants from three different focus groups felt that this model was acceptable. Of those, only one GHS participant stated that this was the best model to use.

a. Views Expressed by Participants who found Model 2 Acceptable

The few participants who felt that model 2 was acceptable discussed features of the study design including that the case study allows switching (n=1 group) and compares widely-used drugs (n=1 group):
So it’s not like it’s a brand [new drug] …at least it’s been out there in the market and people are not walking and hitting the floor, you know what I mean?.. I really just don’t see any difference. If I got to take something new, I don’t know anyway what’s going to happen to me, till you take it. (JHUHTN2 F2)

A couple participants in the same focus group also highlighted the benefits of this model in terms of allowing research to be completed faster and at a lower cost and one participant said that she is fine with model 2 because she trusts her doctor and knows he would not enroll her in anything harmful.

b. Views Expressed by Participants who found Model 2 Unacceptable

A majority of participants who found model 2 unacceptable again had concerns broadly related to respect for autonomy (n=8 groups) (table 1.3). Many participants mentioned that model 2 is deceptive and/or that patients should be told about the option to opt-out (n=8 groups). Others commented that this model pressures people to participate (n=7 groups) and a few worried that participants would not understand their options or that they are in a research study (n=2 groups).

Features of the study design or study setting were not widely discussed with the exception of participants from one focus group mentioning that the case study imposes additional burdens. However, some participants felt that if model 2 were implemented, patients would be less likely to do the extra things asked of them (n=3 groups) and/or that this model would result in patients feeling upset or angered or losing trust in their doctor or health care institution (n=6 groups):

You know, you’re supposed to be able to trust your doctor, and…that’s sort of not being very trustworthy…he’s not tell you everything. In fact, that’s making me mad right now just thinking about it. (GHSMIG2 F6)
Finally, a couple participants commented that this model is not that much more efficient than model 3 (n=1 group).

IV.  **Perceptions of the Acceptability of Model 3: Study Specific Disclosure with an Explicit Option to Opt-Out**

An overwhelming majority of participants believed that model 3 was acceptable and of those who believed it was acceptable, almost half felt that this was the best model to use. Multiple participants from each of the eight focus groups stated that they believed this was an acceptable model. Although individuals from both institutions believed this model was acceptable, a far greater number of participants from GHS stated that this is the model they felt was the best model to use.

a.  **Views Expressed by Participants who found Model 3 Acceptable**

A majority of those participants who found model 3 acceptable justified their view by discussing themes related to respect for autonomy (n=8 groups) (table 1.3). Several commented that this model is more respectful (n=2 groups), a number of participants liked that patients are informed about the study as well as their ability to opt-out (n=7 groups), and several liked that patients have more control over their participation (n=5 groups). Related, a couple participants did not think it was overly burdensome for patients to have to opt-out (n=3 groups).

A few participants also felt that, compared to model 4, the amount of information disclosed would be less likely to scare or overwhelm patients (n=3 groups):

This...actually seems like a really nice balance between getting people to acknowledge and understand what they’re getting into versus the overwhelming amount of information. (JHUMIG2 M1)
Moreover, several participants discussed the benefits model 3 could have in terms of not betraying trust or making people feel upset or angered (n=1 group) as well as in terms of selecting patients that are more willing to participate (n=3 groups). Most participants did not discuss features of the study design when justifying their views, although a couple did highlight that the study involves widely-used drugs (n=2 groups).

However, a number of participants did express some concerns about model 3. Several mentioned that model 3 may result in lower participation rates (n=6 groups) and/or that it is less efficient and more costly compared with models 1 and 2 (n=3 groups). For these reasons, some participants who felt that model 3 was acceptable felt that model 1 was preferable, while other participants felt that because model 3 is more respectful of autonomy, it was still preferable to models 1 or 2.

b. Views Expressed by Participants who found Model 3 Unacceptable

Only two participants, one from each institution, stated that they felt that model 3 was unacceptable. One JHS participant stated that she did not believe it was appropriate for patients to “have to go through the trouble to opt-out” (JHUMIG1 F4) if they did not want to participate, while one GHS participant emphasized the low-risk nature of the research as well as its social value and felt that giving patients the ability to opt-out really compromised the ability to do this type of research.

V. Perceptions of the Acceptability of Model 4: Prospective Informed Consent

A majority of participants also felt that model 4 was acceptable, including individuals from seven of the eight focus groups, and of those, just under half stated that
it was preferable. A far greater number of participants from JHS felt that model 4 was both acceptable and preferable when compared to participants from GHS, who found it acceptable but were more likely to find other models preferable. Just under half of the participants from GHS from three different focus groups felt that model 4 was unacceptable.

a. Views Expressed by Participants who found Model 4 Acceptable

A majority of participants who stated that they felt that model 4 was acceptable justified their view by discussing themes related to respect for autonomy (table 1.3). A few participants felt that model 4 was the most respectful of patients (n=2 groups) and several commented that patients are the most informed and/or that the decision to participate is completely voluntary under this model (n=6 groups). However, one participant who felt that this model was preferable also felt that it was unnecessary to give patients information on all the potential risks associated with the drugs:

What I need to know is that this is a study, and we’re comparing two drugs… these are the main side effects of the one, and this is the main side effects of the other … if you choose to participate, you’re going to be randomly assigned to one of them, and we’re going to see how it goes, and we want you to do these things.” (JHUMIG1 F4)

Additionally, a few participants felt that if model 4 were used, patients would be more willing to do the extra study-related activities (n=2 groups) and a couple patients from JHS felt that using model 4 could help improve trust (n=2 groups).

b. Views Expressed by Participants who found Model 4 was Unacceptable

Many participants who stated that model 4 was unacceptable felt that the amount of information provided to patients as part of model 4 would scare or overwhelm those
individuals (n=3 groups). This concern was also raised by several participants who felt that this model was acceptable but not preferred (n=2 groups):

I think it’s information overload… I don’t think it would benefit the person because they’re listing everything … [the patient would] just walk out of there going, huh? (GHSMIG1 F1)

Additionally, several participants commented that if model 4 were used, it is likely that fewer patients would participate (n=4 groups) and/or that this model is more time consuming and more costly than the other models (n=4 groups). Finally, a few participants commented that they felt that model 4 was unnecessary because the case studies compare widely-used drugs (n=2 groups):

What comes to my mind is … that you’re using drugs that are already readily used in the treatment of people with blood pressure and they’re being evaluated by their doctor ahead of time… So, to do this [model 4]… I think is overkill… but to draw from my experience, I'm taking a drug that's not available in the marketplace that's reached a certain level of human testing so that I'm very comfortable with [it]… So that's where you use something like this [model 4] whereas the scenario we're talking about does not require this extreme control. (GHSHTN2 M13)

**Discussion**

The goal of this study was to understand what patients, IRB members, and comparative effectiveness researchers thought were acceptable approaches for disclosure and authorization of low-risk PCTs. Participants were asked to discuss the acceptability of four different disclosure and authorization models for PCTs comparing widely-used blood pressure or migraine medicines. Although participants generally agreed that doing this type of research was socially beneficial, of potential benefit to enrolled patients, and that there were no or minimal risks, participants differed in their views about the acceptability of the different models of disclosure and authorization.
One thing that most participants did agree on was the importance of preserving autonomous choice. Both interview and focus group respondents spoke of the importance of information disclosure and voluntary choice in reference to all 4 models, and the theme of respect for autonomy emerged more than any other broad theme in this study. Many participants felt that respect for autonomy was particularly important because the PCTs described in the case studies imposed additional burdens on participants and because not allowing patients to make a voluntary choice could result in patients feeling wronged or angered or losing trust in their physician or health care institution. Since many participants felt that models 1 and 2 infringed on components of autonomous choice, most participants felt that these models were unacceptable. Participants generally viewed models 3 and 4 to be more respectful of autonomy since both models explicitly inform patients about the research as well as about the voluntariness of participation. Likely because of this, most participants believed that both of these models were acceptable.

Nevertheless, although most participants felt that both models 3 and 4 were acceptable, their views were mixed in terms of which model they felt was preferable. About one-third of interviewees, most of whom were researchers, and about half of patient participants preferred model 3. These respondents described it as best balancing concerns about respect for autonomy with concerns about being able to efficiently do high quality PCTs. However, some participants who favored model 3 emphasized the importance of ensuring that it was relatively easy for patients to opt-out. Also, several participants explicitly mentioned that the reason that they felt that model 3 was acceptable was because the hypothetical case studies were low-risk, compared widely-
used drugs that had similar side effects, and allowed switching, indicating that they felt that it was appropriate to have different disclosure and authorization requirements for different types of research.

Just over half of the interview respondents, a majority of whom were IRB members, and just over a quarter of patient participants stated that they preferred model 4. These participants felt that model 4 was most respectful of autonomy and because of this, some felt it would result in the greatest cooperation with study activities and the greatest amount of trust. Given this, although many recognized that model 4 would increase the risk of selection bias and that it was more time consuming and costly than the other models, they felt that the benefits described above outweighed these drawbacks.

Still, several participants who preferred model 4 –like those who preferred model 3-- also felt that the information disclosed to patients could be simplified. This finding is supported in the literature where, for more than 20 years, scholars have discussed the need to simplify the information disclosed in informed consent documents (Davis et al. 1998; Dresden and Levitt 2001; Rogers et al. 1998; Strunkel et al. 2010) and more recently, several scholars have specifically argued that it is appropriate to simplify disclosure for low-risk RCTs comparing widely-used therapies (Van Staa et al. 2012; Wendler and Grady 2008).

Unfortunately, since opt-out approaches are rarely allowed under the current human subjects research regulations for enrollment of patients in low-risk trials of widely-used interventions, there is little direct evidence related to the impact opt-out compared to opt-in models of enrollment have on patients’ willingness to do extra activities as part of medical research studies and we are not aware of any direct evidence
of how opt-out models impact trust in health care professionals or institutions. The one study of which we are aware that looked at the impact of opt-out approaches for enrollment suggests that the use of opt-out approaches does not have a negative impact on the willingness of participants to do extra activities (Roger et al. 1998). Additionally, there is some evidence that when opt-out approaches are used for recruitment of individuals to an observational study, participants are still willing to do the extra research-related activities asked of them (Junghans et al. 2005). Although the small amount of available evidence suggests that individuals are willing to participate in additional study-related activities when opt-out approaches are used, future research should verify this and there is also a need for additional research to understand if opt-out models like model 3 have any impact on patients’ trust in health care professionals or institutions.

Another important finding is that the respondents who preferred model 4 were much more likely to be from JHS than from GHS. Similarly, IRB members were more likely to prefer model 4 than were researchers and patients. Perhaps related, many respondents from JHS spoke of distrust in the community surrounding JHS. Likely as a result of this, participants from JHS referred to the impact that they believed explicit consent might have on participants’ trust in research and believed it to be important for this reason. The literature also has examples of individuals who have less trust in their health care institution or the group doing the research tending to prefer models of consent that give them more control over their participation (Damschroder et al. 2007). Additionally, as mentioned by several IRB members and researchers from GHS, GHS already has some experience implementing a policy similar to model 1, although not for
research that involves random assignment of participants to different therapies.

Importantly, however, no patient participants mentioned that GHS has this policy, which could suggest that patients are not aware or do not remember that this policy is in place. A possible reason that IRB members were less likely than researchers and patients to prefer alternatives to model 4 is that, as mentioned by two interviewees, IRB members have spent a significant amount of time trying to enforce the current standard of prospective informed consent and therefore, they may be more tied to this model than other stakeholders. Patients may also have been more likely to prefer model 3 at least in part because of a view expressed by many patients, but only 2 interviewees, that the amount of information disclosed when model 4 is used could scare or overwhelm eligible individuals.

It is also important to highlight that although there was a significant amount of support for the use of model 3 and although many participants agreed that the amount of information disclosed could be simplified, several IRB members and researchers noted that the acceptability of this model depends on exactly what information is provided to patients. Therefore, future research should be conducted to address the question of what information needs to be provided as part of a more streamlined study-specific disclosure. Also interesting is that only a few interviewees and just one patient participant discussed random assignment as relevant to their views regarding the acceptability of the different models. This could be because participants did not feel that random assignment increased risk of harm to individuals and therefore it was not an important consideration or because they recognized that when there is a lack of evidence regarding the comparative effectiveness of different interventions, there is already “an element of chance in the way
treatment choices are made in ordinary clinical practice” (Kass et al. 2012). However, in the case of patients, it is not possible to say whether this is because patients did not believe this was a relevant consideration or if it was because at least some proportion of patients did not understand the concept of randomization, even though the process of and rationale for random assignment was discussed in detail during each focus group.

Other limitations of this study are that both institutions from which participants were recruited are engaged in a significant amount of research and it may be that individuals from institutions that do not regularly engage in research would have a different perspective on the acceptability of the different models. Further, the four models of disclosure and authorization were presented in the same order during each interview and focus group and it may be that the order in which the models are presented could affect participants’ perceptions of those models. Additionally, individuals who participated in the focus groups may have different perspectives compared with individuals who were unwilling or uninterested in participating in this study. Finally, no IRB community members from GHS participated in this study and therefore, there is no information on the views of this stakeholder group.

In general, because this was the first study of this kind that we are aware of, it is necessary to perform additional research on this topic to gather more information regarding the views of different stakeholders of the acceptability of alternative processes to prospective informed consent. Currently, there is an ongoing effort to gather additional evidence of the acceptability of several of these alternative processes for enrolling patients in both observational and randomized CER studies where no additional burden is imposed on participants (PCORI 2013). This and future studies should further clarify
which factors are most important to patients and other stakeholders as they consider which approaches to disclosure and authorization are most important to them for different types of studies.

Conclusions

The results of this qualitative study provide some preliminary evidence that stakeholders favor simplifying the amount of information provided to participants about PCTs comparing widely-used drugs. The results also suggest that participants generally found opt-out approaches acceptable for this type of research as long as patients were informed that they could opt-out and doing so was relatively easy. Nevertheless, many participants still preferred traditional prospective informed consent. Since, as was suggested by the comments provided by IRB members and researchers, studies like those described in the hypothetical cases are not widely done at this time, the additional time, cost, and risks to the validity of PCTs when prospective informed consent is used may not seem to present an important problem to these respondents and they may not think it is reasonable to allow alternatives to prospective informed consent to be used for such a small body of research. Nevertheless, given the interest in being able to more routinely generate evidence of comparative effectiveness as well as interests in transforming the U.S. health care system into a learning health care system (Olsen et al. 2007), it is likely that PCTs will become more prevalent. As they do, it may be that stakeholders’ perceptions of the acceptability of these alternative models to prospective informed consent will change as well. For now, it is important to consider the moral permissibility of alternatives to prospective informed consent (Faden et al. 2013; Whicher 2013), to
continue to collect additional information regarding stakeholders’ perceptions, and to continue to discuss the purpose of such research with health care consumers. That way, future policy alternatives can be supported by evidence about which options are both morally and socially acceptable.
**Table 1.1: Description of Hypothetical Case Studies and Models of Disclosure and Authorization**

<table>
<thead>
<tr>
<th>Summary Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>• This PCT is designed to compare two widely-used, evidence-based drugs that are similar in terms of their route of administration and side-effect profiles</td>
</tr>
<tr>
<td>• To be eligible to participate, patients must be treatment naive and their doctor must confirm that either of the drugs in the PCT are reasonable options for the patient</td>
</tr>
<tr>
<td>• Enrolled patients are randomly assigned to one of the drugs being compared in the PCT</td>
</tr>
<tr>
<td>• A physician is allowed to switch his/her patient to a different drug or prescribe add-on therapies if the drug is not working or if the patient is not satisfied with the drug</td>
</tr>
<tr>
<td>• Care remains unchanged except:</td>
</tr>
<tr>
<td>• Participants complete short surveys with questions about their use of and satisfaction with the prescribed drug</td>
</tr>
<tr>
<td>• Participants in the migraine PCT complete a migraine diary for the next 3 migraines they experience</td>
</tr>
<tr>
<td>• Participants in the hypertension PCT return to the clinic for 2 additional blood pressure checks not usually required as part of standard care</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 1: Disclosure of institutional policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Individuals in a health care system are informed broadly that the system engages in CER of widely-used interventions and that sometimes patients are enrolled in these studies if they already need that general type of medicine.</td>
</tr>
<tr>
<td>• Patients who might have been given either of the drugs in the study anyways might automatically be enrolled in these studies if they are eligible.</td>
</tr>
<tr>
<td>• Patients are also informed how rights and interests are protected.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 2: Study specific disclosure with no routine option to opt out</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients are told that their health care system does a lot of medical research studies to compare widely-used drugs to each other to figure out which drugs work best.</td>
</tr>
<tr>
<td>• If a patient is eligible for one of these studies, that patient is told about the study and then enrolled.</td>
</tr>
<tr>
<td>• Patients can opt-out of the study, although they are not told this explicitly.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 3: Study specific disclosure with an explicit option to opt out</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients are told that their health care system does a lot of medical research studies to compare widely-used drugs to each other to figure out which drugs work best.</td>
</tr>
<tr>
<td>• If a patient is eligible for one of these studies, that patient is told about the study and is also told that if he or she does not want to be part of the study, he or she can opt-out.</td>
</tr>
<tr>
<td>• If a patient does not opt-out, he or she is enrolled in the study.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 4: Prospective informed consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients are told that their health care system does a lot of medical research studies to compare widely-used drugs to each other to figure out which drugs work best.</td>
</tr>
<tr>
<td>• If a patient is eligible for one of these studies, that patient is told about the study and then asked if they would like to be a part of the study before being enrolled.</td>
</tr>
</tbody>
</table>
Table 1.2: Demographic Characteristics of Interview Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Johns Hopkins Health System (n=10)</th>
<th>Geisinger Health System (n=7)**</th>
<th>Total (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>8</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>African American</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other*</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 39</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>40-59</td>
<td>8</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>≥ 60</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Length of Time Employed at Institution (n=14)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10 years</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td><strong>Sees Patients Clinically (n=14)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td><strong>Current Professional Effort Spent Conducting Medical Research (n=14)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 39%</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>40%-59%</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>≥ 60%</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td><strong>Previous Experience Participating in Research as a Patient or Healthy Volunteer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

*Other includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander

**No IRB community members participated from Geisinger Health System

*This question was not asked of IRB community members because it was not relevant to this stakeholder group. Therefore, the total number of participants who answered this question was 14.
<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respect/Respect for Autonomy</strong></td>
<td><strong>Yeah, that just takes away all autonomy.</strong> (GHSIRB3)</td>
<td><strong>I’d feel like the option 2 I don’t get no respect. Option 3 is I get some respect.</strong> (JHUHTN1 M1)</td>
<td><strong>“It’s the most formalized way to respect people’s autonomy and their willingness to participate.” (JHUIRB1)</strong></td>
</tr>
<tr>
<td><strong>Information Disclosure/Understanding</strong></td>
<td><strong>Not informing people that they have the option to opt-out is the major issue here if in fact some people would have that option and it’s just a question of saying, “If you don’t want to do this you don’t have to.”” (JHUIRB1)</strong></td>
<td><strong>It seems reasonable because they are informed of this particular study, and then they’re also told that they can opt-out.” (GHSCER2)</strong></td>
<td><strong>“On the information scale there appears to be more information…So I think that gives patients more of a sense … of being able to control this process.” (JHUIRB 3)</strong></td>
</tr>
<tr>
<td><strong>Voluntary Choice</strong></td>
<td><strong>I don’t really care for that one…My husband … would go and not question his doctor at all, whatever the doctor would tell him, that’s what he would do…He would not understand any of that stuff …if you gave him the option [to opt-out] I think he would understand it more.” (GHSHTN1 F8)</strong></td>
<td><strong>That’s more informative than the other one. The person does have the option to opt-out…the doctor does tell the patient right up front.” (GHSMIG2 F5)</strong></td>
<td><strong>“I think the subjects have the opportunity to understand that they’re part of research and understand what that means for this particular study.” (JHUCER2)</strong></td>
</tr>
<tr>
<td><strong>Voluntary Choice</strong></td>
<td><strong>It sort of takes that [voluntariness] off the table. I mean … you could argue that they’re volunteering because they’ve been told that this is going on and you have the option to go to another system. But not everybody has that option of mobility. So people who are</strong></td>
<td><strong>You feel better when you have more information about something…It makes you more empowered.” (JHUHTN1 F2)</strong></td>
<td><strong>“Well, I think it has the best chance of maximizing the patient’s voluntary informed choice. So I think there are a lot of barriers to getting an authentic voluntary consent, even with this approach, but without this approach, I think that’s even harder to achieve.” (JHUIRB2)</strong></td>
</tr>
<tr>
<td><strong>Voluntary Choice</strong></td>
<td><strong>“I think in some ways, we have to – you could argue we almost have to bend over backwards to allow people to opt-out as opposed to making it harder for them to opt-out in terms of the issue of voluntariness.” (JHUIRB2)</strong></td>
<td><strong>“I think that it is important… that they don't have to expend too much energy if [they want to opt-out]… But I’m in favor of making them expend some energy to get out of trial as opposed to just making it a pure choice between yes or no … given the low risk of this study and the possible benefit,</strong></td>
<td><strong>“I think in some ways, we have to – you could argue we almost have to bend over backwards to allow people to opt-out as opposed to making it harder for them to opt-out in terms of the issue of voluntariness.” (JHUIRB2)</strong></td>
</tr>
</tbody>
</table>

Table 1.3: Selected Participant Comments Related to the Theme of Respect for Autonomy or Components of Respect for Autonomy
sort of captive in this particular system … [so] I don’t really think there’s the same level of voluntariness there.” (JHUIRB2)

“I think if they want to do a study, they need your permission at all times…They’re basically saying they [patients] don’t have a choice.” (JHUMIG1 F3)

they’re railroaded. The doctor said I have to be in this, so then they would just – they wouldn’t know they had a choice. [The patient might] feel betrayed, sort of, that they’re thrown into a study.” (GHSHTN1 F3)

it's okay to assume a default position that's efficient.” (GHSCER1)

“The other two [models 1 and 2], the patients are generally saying, “Oh, okay.” But this you’re starting to get the patient to be more directly involved in that decision.” (GHSHTN2 M13)

“It’s like opt-in versus opt-out, I always want to opt-in…it shouldn’t be harder for patients to get out of it.” (JHUMIG1 F4)
<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Johns Hopkins Health System (n=16)</th>
<th>Geisinger Health System (n=22)</th>
<th>Total (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>11</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian</td>
<td>6</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>African American</td>
<td>10</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Other*</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Hispanic</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Age</td>
<td>≤ 39</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>40-59</td>
<td>12</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>≥ 60</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Education Level</td>
<td>Less than High School</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>High School Diploma/GED</td>
<td>4</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Some College</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>College Degree</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Graduate Level Degree</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Previous Experience Participating in Research as a Patient or Healthy Volunteer</td>
<td>Yes</td>
<td>11</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5</td>
<td>17</td>
<td>22</td>
</tr>
</tbody>
</table>

*Other includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander
Figure 1.1: Comments Related to the Amount of Information that Should Be Provided to Individuals if Model 3 is Used

- “So I think it has to be very thoughtfully planned out how, you know, the time sequence – how this is even going to work. But assuming that could be done thoughtfully, my opinion is this is probably the best way to do things, to clearly explain the risk and the benefit and the reasons why there's no particular risk that is known, anyway, because of the unknowns about these two drugs. But to say that it would, you know, “It would be really helpful possibly for you, possibly for other people if you would be in this but we're not going to force you to take the drug that's randomly chosen. So if you're not comfortable, you can decline and then just, you know, make your choice of treatment the normal way.”” (GHSCER1)

- “I mean if you were to arguably say, “We’re giving you two medicines that we think are very similar. We honestly don’t know if one is better than the other. In a generic way we think that the side effects are similar and we’re not trying to do this.” You could be very broad I think in that information and provided it’s true enough if really the side effect are similar that kind of thing. I mean the truth of the matter is when we prescribe things to people clinically we don’t get informed consent. We don’t tell them typically every side effect. We sort of may hit on some of the big ticket items.” (JHUIRB1)

- “I think the first thing the patient needs to know what are the other options out there. I mean other than what are these two drugs first, or not – or something else. It would be important to know what are those “something else out there.” Are there any particular risks associated with these medications that’s above and beyond taking something else? What are the side effects? They get that information, but not in the same way when you’re in a research study… The participant would want to know, “Are you doing anything extra? Anything different that falls outside the standard of care?” because there’s a cost burden – there may be a cost associated with that, more than just time.” (GHSIRB2)

References


United States Food and Drug Administration, Department of Health and Human Services, Code of Federal Regulations, Title 21, Part 50.23.


Paper 2: Rethinking the Balance of Self-Determination Interests with Interests in Achieving High Quality Health Care

Abstract

As the number of quality improvement and comparative effectiveness activities continues to increase, questions have emerged regarding whether it is always necessary to obtain prospective written informed consent from individuals participating in these activities. Determining whether consent is necessary requires balancing interests individuals likely have in being able to decide whether or not to participate with other interests individuals and societies likely have in being able to access high quality health care. This paper aims to further clarify when it is morally permissible to waive or alter informed consent requirements for quality improvement and comparative effectiveness activities by employing Madison Powers and Ruth Faden’s theory of well-being and its relationship to self-determination interests. This paper argues that in order to justify waiving or altering consent requirements, it is important that quality improvement or comparative effectiveness research activities address issues of relevance to the setting or settings in which they are conducted and that those settings have a plan in place to implement the results from those activities. This paper further argues that there are certain features of these types of activities that impact the likelihood that the decision to participate will engage important self-determination interests that individuals have. These features include the health benefits and risks of harm to individuals enrolled, the burden imposed on participants, and whether the activity limits the ability of individuals to participate in health care decisions that engage meaningful preferences that they have. Because the ultimate goal of these activities is to further interests individuals have in
having access to high quality medical care, when it is likely that the results from the activity will be used to improve care and it is unlikely that an activity will impact important self-determination interests that individuals have, individuals likely do not have overriding interests in the decision to participate in those activities and as a result, waiving or altering informed consent requirements is morally permissible. Drawing on this analysis, this paper delineates a number of recommendations regarding morally permissible alternatives to prospective informed consent for quality improvement and comparative effectiveness activities.

**Background and Introduction**

Increasingly, there is a growing recognition of the lack of high quality evidence to support many clinical and health care policy decisions. In response, there have been efforts to systematically gather evidence from ordinary or slightly modified clinical encounters to better learn what does or does not work in ongoing clinical practice (Institute of Medicine 2007; Selby and Krumholz 2013). Two areas that embody this learning from standard or slightly modified clinical practice, and that will serve as the focus of this analysis, are quality improvement (QI) and comparative effectiveness research (CER). QI has been defined as “systematic, data-guided activities designed to bring about immediate improvements in health care delivery in particular settings” (Lynn et al. 2007) while CER has been defined as “the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in “real world” settings” (Federal Coordinating Council for Comparative Effectiveness Research 2009). As these
definitions suggest, many QI and CER activities\(^2\) are distinct from earlier phase clinical research in that they are designed to systematically implement or compare different, widely-used, non-experimental therapies, diagnostics, or processes of delivering care in order to determine which is most beneficial.

Scholars generally agree that engaging in QI and CER is valuable as it furthers interests that societies and individuals have in high quality health care and therefore, it is important to ensure that these sorts of activities are conducted. Some scholars have also recognized that informed consent requirements can sometimes create practical barriers to the efficient implementation of these activities (Van Staa et al. 2012). This is because informed consent requirements are resource intensive, time consuming, and sometimes impractical (Dubler et al. 2007; Manson and O’Neill 2007, 116; Lynn et al. 2007; Lo and Groman 2003; Peddicord 2010). In addition, engaging in informed consent may result in selection bias, thereby threatening the validity and thus the social value of certain activities (Miller 2008; Largent, Joffe, and Miller 2011; Tu et al. 2004). As a result of these considerations and because many QI and CER activities require large sample sizes to detect small but clinically meaningful differences in clinical outcomes, several scholars have argued that traditional informed consent procedures are ill suited and not morally required for at least some subset of QI and CER activities (Baily et al. 2006; Dubler et al 2007; Faden et al. 2013b; Miller and Emanuel 2008; Largent, Joffe, and Miller 2011; Lo and Groman 2003; Lynn et al. 2007; Peddicord 2010; Sabin et al. 2008; Selker et al.

\(^2\) The word “activity” will be used throughout this paper instead of “research” or “practice.” This is because there is some discussion regarding whether the labels of “research” and “practice” are really that useful for making decisions regarding the necessity of oversight and informed consent (Faden et al. 2013a) as well as some discussion regarding if and when quality improvement efforts should be considered research (Casarett, Karlawish, and Sugarman 2000; Harrington 2007; Lynn et al. 2007). Attempting to address these issues is beyond the scope of this paper and the term ‘activities’ was chosen to avoid these controversies.
2011). To justify this view, many of these scholars also point out that most QI and CER activities are designed to generate information on widely-used, non-experimental interventions and generally do not significantly alter patients’ medical care. Nevertheless, scholars also recognize that it is important to demonstrate respect for the moral status of individuals participating in these activities.

How to balance these different considerations is a matter of some debate. This paper aims to further clarify when it is morally permissible to waive or alter informed consent requirements for QI and CER activities. To accomplish this aim, this paper will employ Madison Powers and Ruth Faden’s theory of well-being and its relationship to self-determination to further claims made in the literature about the moral permissibility of waiving or altering informed consent requirements for at least some subset of QI or CER activities. This paper will also incorporate current thinking from a recently developed framework for learning health care systems (Faden et al. 2013a).

Although it has not previously been applied in this context, Power and Faden’s theory is helpful in justifying why all liberty interests are not deserving of equivalent levels of policy protection as well as why it is that certain features of an activity and of the health care system in which that activity is being implemented are important to consider when making decisions about the moral permissibility of limiting, in some way, the ability of an individual to make a choice regarding his or her participation in that QI or CER activity. After describing the relevance of Powers and Faden’s theory, this paper will review those features of an activity and the health care system in which it is implemented that are important to consider when making decisions about the moral permissibility of waivers of or alternatives to prospective informed consent. Although the
moral significance of these features is not unique to QI and CER activities, this paper will explore their relevance within these contexts. Based on this analysis, this paper will discuss when it is permissible to waive or alter informed consent requirements for QI and CER activities.

Demonstrating Respect for the Moral Status of Individuals Enrolled in QI and CER Activities

It is often asserted that informing individuals about research activities that they may be enrolled in, and engaging them in decisions about participating in those activities, is important because these actions demonstrate respect for the moral status or moral standing of those individuals. Although there is some disagreement regarding what exactly confers this special moral status on persons, it is generally recognized that there is something unique about humans that makes it such that their interests matter morally in this way (Dillon 2010; Jaworska and Tannenbaum 2013). Furthermore, it is generally accepted that the centrally important demonstration of respect for moral status in research with human subjects is respect for the autonomy of competent individuals.

Nevertheless, although informing individuals about a research activity or activities, ensuring that they understand that information, and allowing them to voluntarily decide whether to participate are often discussed together, these are distinct components of demonstrating respect for autonomy. Additionally, it is important to recognize that respect for autonomy is a component of respect more broadly. In the

---

3 I have elected to use the terms “moral status” or “moral standing”, which I am using as synonyms, in part to avoid controversies that accompany terms such as “moral worth” or “human dignity”. Attempting to defend or resolve controversies about exactly what is unique about human beings that confers this special moral status on them is beyond the scope of this paper.
context of QI or CER, other components of respect could include engaging individuals impacted by QI and CER activities in other decisions related to those activities, informing individuals who receive their care at an institution about that institution’s commitment to regularly engaging in QI and CER activities to improve health care quality, and informing individuals about institutional policies as they relate to the rights and protection of individuals who may be enrolled in those activities (Baily et al. 2007; Faden et al. 2013b; Largent, Joffe, and Miller 2011; Lo and Groman 2003). Finally, respect can also be demonstrated by ensuring that there is adequate oversight of QI and CER activities so that individuals are protected from disproportionate risks of harm. All of these components can, in certain situations, play an important role in demonstrating respect for individuals who are eligible to participate in QI and CER activities. However, what this paper aims to demonstrate is that not all of these components of respect are morally required in all situations. Specifically, this paper will argue that treating people with respect does not always require that those individuals be given a robust way to affect the course of events with regard to their participation in QI and CER activities. Yet, in situations where the ability of individuals to control their participation in QI and CER activities is limited, implementing policies related to the other components of respect discussed above becomes even more critical.

---

4 For instance, individuals can be engaged in policy discussions about the acceptability of waivers of or alternatives to prospective informed consent, in priority setting discussions for QI and CER activities, or in discussions surrounding the design and implementation of these activities.

5 In addition to being required by the principle of beneficence, protecting individuals can arguably also be considered to be a form of demonstrating respect for potential research participants. In its explication of what is required to fulfill the principle of respect for persons, the Belmont Report asserts that “persons with diminished autonomy are entitled to protection” (National Commission 1978). However, even for competent individuals, requiring that QI and CER activities receive ethical oversight is still arguably partly required out of respect for persons as it would be disrespectful of the moral status of those individuals to allow them to enroll in research that is associated with unreasonable risks or burdens.
As will be further described in the next section, whether it is necessary to give people the ability to control their participation in a QI or CER activity and the amount of control people ought to have depends on the features of that activity and features of the institution or health care system in which the activity is implemented. Since individuals seeking care at a health care institution are all interdependent members of a health care community, it is permissible at times to place limits on the choices available to those individuals in order to further interests that those individuals and others within their health care system have in being able to access high quality health care (Dickert 2009). The following section employs a theory developed by Madison Powers and Ruth Faden to demonstrate why it may be morally permissible to limit the ability of individuals to make autonomous choices regarding their inclusion in certain QI and CER activities.

Features of QI and CER Activities that are Relevant to the Acceptability of Waiving or Altering Informed Consent Requirements

The starting point for this discussion is an understanding of the moral importance of interests that individuals have. Specifically, although it is generally important to respect the interests of competent individuals, not all individual interests are of equal moral significance. Rejecting this view would require one to adopt the position that all interests that individuals have are worthy of the same level of respect from others, which is inconsistent with many moral theories as well as many current public policies. Justifying why it is that not all individual interests or aims are of equal moral significance, TM Scanlon explains that “[m]any rationale aims are quite specific and limited, such as the aim of solving a certain puzzle, or getting to the top of a mountain, or
helping a friend out of some difficulty. Other aims take the form of what Joseph Raz has called “comprehensive goals” – plans or intentions that shape a large part of one’s life. Success in these more comprehensive goals has a larger effect on a person’s life than success in more limited aims, and consequently…. make a greater contribution to well-being” (1998, 121-122).

More recently, Madison Powers and Ruth Faden, focusing specifically on public policies and liberty interests, further described why it is that not all liberty interests that individuals have deserve of equal policy protections. Since the theory proposed by Powers and Faden is best suited for questions about appropriate public policy options, this paper will apply this theory to develop arguments regarding the moral permissibility of waiving or altering consent requirements for QI and CER activities. Similar to TM Scanlon, Powers and Faden argue that one reason why respecting the autonomous choice of competent individuals is often considered to be an important component of respecting the moral status of those individuals is because being able to exercise self-determination is a critical element of well-being. These scholars assert that “[w]hat matters is that our lives be shaped at least in part by our choices, informed by our own values and interests” (Powers and Faden 2006, 28). Given this, individuals place a high value on making decisions that may impact important interests that they have and the ability to make these decisions plays a central role in an individual’s well-being (Miller and Wertheimer 2010, 83; Powers and Faden 2006, 26-29). Since the experiences people have participating in certain QI and CER activities can, at times, affect these interests, in those situations it is

---

6 Autonomy and self-determination are related but distinct terms. Autonomy refers to the ability of a competent individual to self-govern. Individuals can and do exercise autonomy in many situations. Some of those situations have an important impact on an individual’s self-determination, meaning her ability to shape her life in ways that are important to her, whereas other situations in which an individual might exercise autonomy are very unlikely to impact that individual’s self-determination in important ways.
important to allow “competent individuals to decide whether participation in research is consistent with their interests” (Wendler and Grady 2008).

However, not all decisions regarding participation in QI and CER activities impact these interests that individuals have in important or significant ways. Recognizing that not all choices individuals make are of equal moral significance, Powers, Faden, and Saghai further claim, using John Stuart Mill’s theory as the basis of their moral argument, that “it is a mistake to suppose that all liberties of all sorts are on a moral par. They are not appropriately viewed as being on a moral par in the sense that not all stand in an equally privileged position at the front end of a balancing process when liberties conflict with other competing interests” (2012). Instead, it is most important to “protect the kinds of choices that structure the contours of one’s life in their most fundamentally defining ways” (2012). Not all interests that individuals have are of equal moral worth and therefore, “they do not all merit the same level of protection in public policy” (Faden and Powers 2011). Since participating in some QI or CER activities will have only a very limited impact on an individual’s interests or rational aims, participation in those activities is unlikely to have a significant impact on an individual’s well-being.

Nevertheless, Powers, Faden, and Saghai also argue that “[l]iberty interests matter in any case as concerns that trigger the need for justification, even if they do not loom so large as ones that figure centrally in the value of a self-determining life” (2012). Essentially what these scholars are arguing is that those choices that engage interests individuals have in the course of their lives or their health – interests that Faden and colleagues have called “autonomy interests” in the passage referenced below and that will be referred to throughout this paper as “self-determination interests”– deserve stronger
policy protections than those choices that do not engage individual interests in this way. However, all liberties are of some moral importance and should not be infringed upon without sufficient justification.

In a more recent article, Faden and colleagues make a similar argument. Specifically, these scholars state:

Respecting autonomy is primarily about allowing persons to shape the basic course of their lives in line with their values and independent of the control of others. Not all health care decisions are likely to be attached to a significant autonomy interest of individual patients, and deference of the wrong sort can constitute a moral failure to take adequate care of patients rather than an instance of showing respect.

In interpreting the obligation to respect autonomy in learning health care contexts, we should assess both whether a learning activity unduly limits the choices of patients and the value of those choices to patients. Many decisions in health care—such as how often simple laboratory tests should be repeated during a hospitalization or whether medications should be dispensed by one qualified professional or another—are not likely to engage values of central importance to the patient. Learning activities that relate to such decisions can be undertaken by health professionals and institutional officials without a violation of obligations to respect the rights or dignity of patients (Faden et al. 2013a).

Arguments made by other scholars in favor of waiving or altering consent requirements for some QI and CER activities and even the current regulations governing informed consent in human research are consistent with the view that interests in controlling participation are more important to protect in some types of activities than in others, especially when balanced against other interests health care consumers have in receiving high quality medical care (45CFR46.116(d); Baily et al. 2006; Dubler et al. 2007; Faden et al. 2013b; Miller and Emanuel 2008; Largent, Joffe, and Miller 2011; Lo and Groman 2003; Lynn et al. 2007; Peddicord 2010; Sabin et al. 2008; Selker et al. 2011). The importance of protecting these liberties depends on certain features of QI and

---

7 This paper discusses the relevance of whether the QI or CER activity is conducted in the context of a learning health care system below.
CER activities including the potential benefits of the QI or CER activity to the participant, the risk that a participant will experience harm as a result of participating in an activity, the level of burden imposed on participants, and whether the decision to participate in the activity engages meaningful preferences that an individual has.\(^8\)

This paper will discuss each of these features, including relevant arguments made by other scholars, and will demonstrate that what these features have in common is the impact they have on the likelihood that the decision to participate in a QI or CER activity engages important self-determination interests an individual has.\(^9\) As a result of the influence these features have on these individual self-determination interests, these features also impact the moral importance of participants being able to control their participation in certain QI and CER activities. However, as was discussed by Powers and Faden, in addition to understanding the impact of choice on self-determination and ultimately well-being, it is also important to ensure that there is a sufficient justification for limiting choice. This paper will argue that an important piece of the justification for waiving or altering informed consent requirements relates to the value of a particular QI or CER activity to the health care system or systems in which it is implemented and the likelihood that the information generated will be used to improve clinical care. Given the important role these later features have in the justification for waiving or altering consent requirements, they will be discussed first, followed by the features of QI and CER

\(^8\) Although the regulations governing the practice of informed consent for human subjects do allow for waivers of informed consent when risks of harm to individuals are minimal and it is not practical or possible to do the research if informed consent is required, this paper asserts that there are additional features of the study design and study setting that are important to consider when making decisions about the moral permissibility of waiving consent requirements. Because the current regulations do not account for these additional features, they may not appropriately balance interests individuals have in controlling their participation with other interests in having access to high quality medical care.

\(^9\) It is important to note that none of these features on its own can be used to determine the moral permissibility of waiving or alternating informed consent requirements. Rather, it is necessary to examine each of these features when making this determination.
activities that impact the likelihood that the decision to participate engages important self-determination interests.

*Ability of the Health Care System to Use the Results from a QI or CER Activity to Improve Care*

As mentioned earlier, QI and CER activities are intended to further interests patients have in being able to access a health care system that is designed to deliver high quality medical care. To achieve such a goal, there must be a high likelihood that the results from QI and CER activities will actually succeed in improving health care quality. The likelihood that QI and CER activities will advance health care quality is furthered when these activities are designed to address issues of significance in the setting or settings in which they are conducted and when those settings are able to routinely translate the findings into practice. Therefore, these features are an important component of the justification for waiving or altering informed consent requirements. Further, it is important to note that both of these features are critical. Although ensuring that QI and CER activities address issues of particular importance in the setting or settings in which they are conducted increases the likelihood that the information generated will be relevant in that particular setting, generating the information is not sufficient to change medical practice and, in turn, to deliver on the goal of achieving optimal clinical outcomes.

In order for the information generated to have a positive impact on medical care, there must be a plan in place that describes how that information will be used in clinical practice. Having a plan in place to routinely and efficiently implement the results
demonstrates to patients that the QI and CER activities in which they are involved will likely be helpful in promoting important interests that those patients have in their health and demonstrates a commitment on the part of the institution or system to improving the quality of care provided to patients. Unfortunately, it is often the case that it takes many years for the results of clinical research to change practice, if it happens at all. When the results from activities are not efficiently implemented, it becomes more difficult to justify limiting the ability of patients to make a voluntary decision regarding their participation in those activities especially in cases where participating in the activity may result in a setback in other interests that participants have. This is because part of the justification for limiting individual choice regarding participation is to allow activities to be conducted efficiently so that the results are available and used to improve medical care sooner and this justification is only relevant in situations where there is some actionable and efficient plan for using the results of the activity to improve care.  

Additionally, when there are plans or policies in place for implementing the findings, it is important to inform patients both about them as well as about how information generated from other QI and CER activities has led to advancements in medical care within the health care system so that patients are aware of how these activities promote their interests. As mentioned earlier, providing information about these sorts of policies is important to demonstrating respect for the moral status of individuals being enrolled in these activities.

---

10 An actionable plan to implement findings would entail more than just a plan to disseminate results. Developing a plan might entail speaking to leadership at the institution(s) in which the activity is being conducted to understand whether it will be possible to change systems level policies based on the results of the activity or considering whether it would be possible to integrate the findings from the activity into electronic health record systems so that it is available to medical staff. If the activity is just a first step toward addressing a larger problem, the plan should indicate next steps and how the results from the combination of activities will be implemented to improve clinical care.
Since QI and CER activities are generally concerned with the comparative benefits and harms of widely-used and/or evidence-based interventions, it is reasonable to expect the results of these activities will be more readily integrated into clinical care than the results from early phase clinical research, which generally requires further development, testing, and approval before the outcome will have an impact on clinical care. Several scholars have argued that a defining feature of QI activities is the high likelihood that the results from these sorts of activities will impact clinical practice in a particular setting within a short amount of time because QI projects are designed to address problems relevant to a particular setting and often incorporate features of that setting in to the design (Baily et al. 2006; Dubler et al. 2007; Lynn et al. 2007). However, it is important to recognize that these design features are not necessarily unique to the field of QI. CER activities can incorporate these design features as well and different health care settings are developing plans and policies for implementing the results of these types of activities. For instance, some health care settings have the capability to change physician “best of care” order sets, which are a component of care provider order entry systems, based on current evidence (Ozidas et al. 2006). This means that if evidence generated through CER activities demonstrate that one intervention is more effective than another for patients or certain subgroups of patients, this information can be translated in to these physician order sets. Additionally, there have been increasing calls for health care systems in the United States to become learning health care systems, where the defining features of a learning health care system are that there are the continuous efforts to learn from usual or slightly modified medical care and that there are ongoing efforts to translate the findings to improve the medical care delivered to patients
(Institute of Medicine 2007). Since a critical component of achieving a learning health care system is the ability to use findings from activities to improve clinical practice, it is reasonable to expect that efforts will be made to identify additional mechanisms by which to routinely and efficiently implement the results from these activities into clinical care.

Impact on the Likelihood that Patients will Experience Optimal Clinical Outcomes

It is widely recognized in the research ethics literature and in the federal regulations that it is important to consider the potential health benefits to participants in research or learning activities (Emanuel, Wendler, and Grady 2000; National Commission 1978). Understanding whether individuals enrolled in a QI or CER activity are likely to experience a health benefit as a result of their enrollment is important because being healthy is often critical to achieving other goals an individual has set for him or herself. Therefore, if being in a QI or CER activity is likely to further interests individuals have in their own health or, at the very least, is unlikely to have a negative impact on individual health outcomes when compared with standard clinical care, then waiving or altering consent in those situations is more likely to be morally permissible than it is in situations where there is less certainty regarding how being in the activity will impact health outcomes for patients.

Again, because QI and CER activities are generally designed to compare or systematically implement widely-used, non-experimental practices or interventions, the health outcomes experienced by individuals in these activities will often not differ from those experienced by patients as part of standard clinical care. Bernard Lo and Michelle Groman further assert that some QI activities will likely improve health outcomes for
those enrolled. These scholars provide an example of a QI project designed to improve the “use of aspirin, β-blockers, and statins after myocardial infarction,” all of which have previously been shown to improve outcomes for patients but are still currently underutilized (2003). As part of the activity, physicians of patients who experienced a myocardial infarction but who were not given these drugs will be sent a letter to remind them to provide these drugs to the patient if appropriate. Lo and Groman argue that there is a high likelihood that patients of physicians involved in this activity will experience improved health outcomes as a result of this activity being implemented (2003).

Nevertheless, it is often the case that how likely it is that an activity of this sort will improve outcomes for participants depends on the quality of the evidence upon which the existing knowledge or guidelines are based and the degree to which monitoring or other aspects of care delivery are modified as is discussed in greater detail below.

QI and CER activities that are unlikely to impact the health benefits experienced by patients include observational QI or CER activities since these activities have no impact on the medical care that a patient receives (Faden et al. 2013b; Miller 2008). While arguably more controversial, some QI and CER activities that involve the manipulation of medical care, such as, but not limited to, the random assignment of patients to different treatment arms, may also have no impact on patients’ health benefits since it is not always the case that manipulating medical care results in increased uncertainty regarding health outcomes (Faden et al. 2013b). Instead, if an activity is comparing two or more widely-used, non-experimental interventions where there is no evidence that one of the interventions will result in better clinical outcomes and where there are no other interventions that the individual could have been offered outside of the
activity that would likely have resulted in better outcomes, there is no reason to believe that patients enrolled in that activity will have worse outcomes than patients receiving care outside of that activity.

However, there are cases where QI or CER activities are designed to systematically implement or compare interventions that are not based on existing evidence. For instance, a CER activity may compare a widely-used intervention that is consistent with standard care to an intervention that is being used “off-label” and in such a way that is not widely practiced in standard care. In this situation, although the intervention being used “off-label” may work well for another clinical indication, the evidence demonstrating that the intervention is effective for the indication for which it is being used in the CER activity is limited. In these situations, the impact that the activity will have on health outcomes experienced by patients is more uncertain; consequently, there is a greater likelihood compared to other types of QI and CER activities that individuals will experience a worse clinical outcome than they would have experienced in standard clinical care. As a result, the decision to participate in QI and CER activities of this sort likely engages important self-determination interests that people have and therefore, in these situations, it is critical to ensure that liberty interests are preserved.

*Risks of Personal Harm, Risks to Privacy, and Risks of Group Harm*

In addition to benefits, there is also general agreement in the literature and in current regulations that the risk of harm to participants is an important criterion to consider when evaluating a QI or CER activity in general as well as when making decisions about the permissibility of waiving or altering informed consent requirements.
According to Tom Beauchamp and James Childress, the term risk of harm “refers to a possible future harm, where harm is defined as a setback of interests, particularly in life, health, and welfare” (2009, 221). This definition is very broad and, as is discussed in further detail below, as written encompasses burdens as well, which are conceptually distinct from harms. However, this definition is beneficial in demonstrating the relationship between risks of harm, burdens, and individual self-determination interests. Beauchamp and Childress further add that when adjectives such as “minimal” or “high” are used before “risk”, they are generally referring to the probability that harm will occur although sometimes they are also used to refer to the severity or magnitude of the harm.11

Risks of harm in research include physical risks of bodily harm, psychological risks related to stress or depression, social risks if the activity’s findings or participation in the activity could result in social stigma or employment or insurance discrimination, as well as economic risks if individuals have to bear any of the financial costs associated with participation (Levine 1978, 2-5).12 Although all risks of harm are morally significant, not all risks are of equal moral importance. When making decisions about the permissibility of waiving or altering informed consent requirements, it is necessary to consider the different sources, types, and risks of harm that exist as well as whether it is likely that those harms will engage important individual self-determination interests.

---

12 For some activities, the additional costs to the participants are knowable at the time that an individual is enrolled in the study. For instance, if an activity is comparing two different interventions and one costs the patient more than the other, than individuals who receive the more expensive intervention will have to pay more than individuals who receive the less expensive intervention. In other activities, there may be some uncertainty regarding whether patients will experience additional costs. For instance, an activity may implement a systems level intervention designed to increase monitoring of patients experiencing a certain health condition. If, as part of the additional monitoring, patients have to return to the hospital for additional office visits, there may be costs associated with these visits, such as finding child care services, that are not recognized by those implementing the activity. This paper considers both of these to be a form of financial risk to participants.
Considering different sources and types of additional risk of harm in QI and CER activities: Some risks of harm that individuals experience as part of QI or CER activities are no different from the risks those individuals would have experienced as part of standard clinical care, while others are specific to a particular activity. When evaluating the significance of the risks imposed on individuals, some scholars suggest first differentiating risks associated with standard clinical care for a person with a certain health condition from those risks that are not. This is because, according to Charles Weijer, risks associated with standard clinical care are “justified by their potential to benefit the subject” (Weijer 2000). Since most individuals have an interest in promoting their own health, individuals will generally accept the risks associated with standard clinical care because these risks should be offset by the prospect of direct health benefits. Additionally, there are already accepted mechanisms for consent to treatment within the context of standard clinical care and as part of these processes, patients already agree to the risks associated with treatment. Risks of harm not associated with standard clinical care are often not offset by direct health benefits to the individual. Instead, participants accept these risks to further other interests that they have in ensuring that they, along with other patients, receive high quality medical care in the future. While important, interests in obtaining high quality health care in the future may not carry the same weight for an individual as interests in avoiding risks of harm that are not.

\[\text{Footnotes:}\]

13 Nevertheless, it is important to acknowledge that standard clinical care is not risk free. There are many practices that are part of standard clinical care that are not based on high quality evidence or that are overutilized such that the risks associated with those practices may not be offset by direct health benefits to patients (Kass, Faden, Goodman et al. 2013).

14 It is also important to note that different types of consent are used in the clinical context depending on features of the medical treatment and that there are some parts of clinical care, such as when a patient is undergoing surgery, when medical practitioners do seek consent more formally.

15 This is similar to an idea raised by Charles Weijer who argues that the risks are justified by their potential to generate knowledge (Weijer 2000).
offset by more immediate health benefits. As a result, these risks of harm are of greater importance when making decisions about the moral permissibility of waiving or altering prospective informed consent requirements.

In QI and CER activities, risks of harm beyond those associated with standard clinical care can occur (1) when sensitive and personal information about an individual is being used in ways that are not consistent with standard clinical care, (2) when participation in a study increases the likelihood that a certain group will experience social stigma compared to standard clinical care (Faden et al. 2013b), (3) when participants are provided with less than standard clinical care (Dubler et al. 2007; Lo and Groman 2003) or when interventions that are not evidence-based and/or consistent with standard clinical practice are used (Miller and Emanuel 2008; Lo and Groman 2003; Sabin et al. 2008; Selker et al. 2011), (4) when one of the interventions being compared is associated with greater risks of harm than other standard of care interventions (Morris and Nelson 2007; Largent, Joffe, and Miller 2011; Truog et al. 1999), or (5) when participants are asked to do extra things that are not consistent with standard clinical practice and that may cause them harm (Morris and Nelson 2007). The final three potential sources of additional risks occur when a QI or CER activity involves some form of manipulation of medical care or when an activity imposes additional burden on participants. It is important to note that some activities may involve several different sources of additional non-clinical risks. In those situations, the combined risk of harm of the different components needs to be considered when making determinations about the level of risk (Weijer 2000; Weijer and Miller 2004; Wendler and Miller 2006) and how those risks may impact important individual interests.
The nature of the risks of harm imposed on participants: Although each of the potential sources and types of additional risks of harm are important to consider, not all risks will impact an individual’s health or his or her ability to accomplish other life goals in significant ways. This is either because it is very unlikely that the harm will occur or because the harm itself is relatively benign. Recognizing that not all risks are of equal moral importance, there is general agreement in the literature and in the federal regulations that waivers of prospective informed consent are more acceptable when an activity involves only minimal risk to individual participants (45CFR46.116(d); Baily et al. 2006; Dubler et al. 2007; Lynn et al. 2007; Miller and Emanuel 2008; Lo and Groman 2003; Selker et al. 2011) as well as only minimal risk of group harms (Faden et al. 2013b). According to the federal regulations, minimal risk “means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests” (45CFR46.102). Unfortunately, this definition has resulted in considerable disagreement regarding what counts as minimal risk in part because the terms used in the definition lack clarity. Part of the confusion comes from difficulties with defining what constitutes ordinary daily life and whether that should differ for different sets of individuals based on the setting in which they live, their age, or their health status (Kopelman 2000; Resnik 2005).16

As a result of this ambiguity and confusion, although there is general agreement that it is important to distinguish minimal risk from greater than minimal risk activities,

---

16 David Resnik suggests that the definition of minimal risk should be shortened to the following: minimal risks are “the risks associated with routine physical or psychological exams.” (2005) However, this does not completely resolve the confusion in part because standards of clinical care are always changing and, more importantly, because what is routine for a person with a certain health condition may not be routine for an individual with a different health condition.
people differ in exactly where they believe that line should be drawn. Unfortunately, attempting to address this ambiguity is beyond the scope of this paper. Instead, for the reasons described previously, this paper adopts the view that the risks of harm that are most important to consider are those that are not associated with the routine clinical care for an individual with a certain health condition and that these risks should be considered to be minimal risk only when they will not significantly impact other interests individuals have in their overall health and general life course. In order for it to be morally permissible to waive or alter informed consent requirements, the QI or CER activity must be under the minimal risk threshold, in terms of the risks involved that are beyond those posed by standard clinical care. However, this does not mean that waivers or alternatives are permissible for all activities that present only minimal additional risks to participants. Instead, the permissibility of waiving or altering informed consent also depends on the other characteristics of the activity and the institution in which the activity is being conducted.

Based on this analysis, a few additional points can be made. The first point is that for observational QI or CER activities that do not impose additional burdens on participants, as long as there are adequate confidentiality protection measures in place and severe repercussions for any breaches of confidentiality, the risks of harm to participants will generally fall below the minimal risk threshold. Therefore, in these situations, it is unlikely that the decision to participate will engage important self-

---

17 Even if readers disagree with this definition of minimal risk, they may still agree with the general points described below.

18 The exception to this is if the information is particularly sensitive and/or could result in group harms.
determination interests.\footnote{Franklin Miller further adds that in cases where an activity relies exclusively on personal health information and involves no interventions, as long as confidentiality is adequately protected, there is “no interference with [an individual’s] freedom or the course of their lives.” As a result, being afforded the liberty to decide whether to participate in these sorts of activities is less important than being afforded the liberty to decide whether to participate in other sorts of activities “especially when balanced against the public interest in research with the potential to improve medical care or promote public health.” (Miller 2008)} The second point is that not all activities that involve some sort of manipulation of medical care, such as but not limited to the random assignment of individuals to different interventions, impose more than minimal additional risks of harm beyond those associated with standard clinical care. Morris and Nelson argue that activities that involve random assignment do not increase or only minimally increase risks of harm to participants when the following five criteria are met: “1) genuine clinical equipoise exists; 2) all of the treatment options included in the research study fall within the current standard of care; 3) there is no currently available treatment with a more favorable risk-benefit profile than the treatments included in the research study; 4) the nontherapeutic components of the research are safely under the minimal risk threshold; and 5) the research protocol provides sufficient latitude for treating physicians to individualize care when appropriate” (2007). Expanding on Morris and Nelson’s fourth criteria, Faden and colleagues argue that activities that meet these criteria and that impose some additional burden on participants can still be considered to be minimal risk activities as long as the additional burden imposes no or only minor additional risks of harm to participants (Faden et al. 2013b). In situations where activities meet these criteria, there is a lower likelihood that the activity will have a significant impact on important self-determination interests that an individual has related to his or her health or general course of life and therefore, it is not as important to ensure that individuals are given the opportunity to decide whether to participate. Since many QI and CER activities
that do involve manipulating medical care only involve widely-used and/or evidence-based interventions, it is reasonable to expect that many will fall under this minimal risk threshold.

*Burden to Individuals Participating in the Activity*

A burden can be defined here as anything extra that an individual is asked to do for the sake of the activity beyond what that individual would have been asked to do as part of standard clinical practice. As previously mentioned, it is important to recognize that burdens are conceptually distinct from risks of harm and that not all burdens placed on participants will increase the risk that those individuals will experience a physical, psychological, social, or economic harm. For instance, asking participants to complete additional questionnaires will not increase risk of harm as long as the questionnaires are not about a subject that is upsetting to participants and include no personal sensitive information (Faden et al. 2013b). Moreover, if as part of an activity, participants are asked to return to their doctors’ offices for extra visits, as long as those visits do not involve additional procedures that impose risk and that are not consistent with standard clinical care and as long as individuals are compensated for the direct and indirect costs associated with those visits, they do not impose additional risks of harm on that individual. Nevertheless, these extra tasks may result in setbacks to important interests that participants have, to a greater or lesser extent, and therefore, it is necessary to consider whether an activity imposes additional burdens on individuals regardless of whether or not those burdens also involve additional risks of harm.
It is also important to recognize the huge variation that exists in the types of burdens that QI and CER activities might impose on participants and that different burdens will have more or less of an impact on an individual’s self-determination interests. Returning to the types of burdens described above, filling out a questionnaire, especially if it is during an already scheduled appointment, is very unlikely to impact other interests an individual has in his or her health or general life course. Alternatively, if the questionnaire was administered more frequently and not during already scheduled appointments, as would be the case if a QI or CER activity included a monthly phone questionnaire to collect additional data on patient reported outcomes, then the impact that additional burden may have on individual interests starts to increase. Nevertheless, this additional burden is still unlikely to have a significant impact on important interests that individuals have since individuals can simply choose to not take the call or complete the questionnaire (assuming that they appreciate that they have this option). However, other burdens such as returning to a clinic for extra blood pressure measurements, keeping a daily diary, for instance of foods consumed or of migraine symptoms, or wearing a twenty-four hour blood pressure monitor may have a more significant impact on self-determination interests. As a result, in these situations, it becomes more important to ensure that individuals recognize that these additional tasks are for the purposes of a QI or CER activity.

Although many scholars writing about QI and CER activities agree that it is important to consider the additional burdens imposed on participants when making decisions about the necessity of informed consent, scholars differ in terms of whether they believe that waivers or alternatives to consent are only acceptable for activities
where patients experience no additional burden beyond what they would have experienced as part of routine clinical care, as is the case with QI or CER activities relying exclusively on routinely collected health information, or whether they believe that some minor additional burdens can be acceptable. For instance, Dubler and colleagues argue that waivers of informed consent should only be allowable for QI activities that do not impose any additional burden on participants (2007) whereas Ruth Faden and colleagues as well as Emily Largent and colleagues assert that waivers may also be acceptable in situations where activities impose only minor additional burdens compared to standard clinical care (Faden et al. 2013b; Largent, Joffe, and Miller 2011). What is interesting is that both of the latter sets of scholars believe that health care should be delivered within the context of a learning health care system where these QI and CER activities are routinely conducted such that there is a demonstrable commitment on the part of the institution to improving clinical care and where there are mechanisms by which to translate the results from an activity. Further, both sets of scholars assert that patients should be broadly informed of an institution’s policies regarding QI and CER activities, which, as discussed earlier, can be an important component of demonstrating respect for the moral standing of individuals. In these situations, these scholars presumably feel that demonstrating respect in these ways is sufficient given the limited impact minor additional burdens have on individuals and given the commitment on the part of the institution to implement the results of the activity.

This paper argues that when no additional burdens are imposed on individuals, waivers of or alternatives to prospective informed consent are more likely to be morally permissible. Further, as suggested by Faden and colleagues and Largent and colleagues,
when a QI or CER activity imposes only minor additional burdens that are unlikely to impact important self-determination interests that individuals have, waiving or altering informed consent requirements can still be permissible. In order for waiving consent to be permissible, there must be a plan in place to efficiently implement the results from the activity such that it is likely that the activity will promote other interests individuals have in receiving high quality health care and patients must be informed about their institution’s policies regarding QI and CER activities so that they understand how their interests are protected. Examples of minor additional burdens include completing an extra questionnaire at an already scheduled appointment, completing health related quality of life surveys administered over the phone, or having one’s blood pressure taken both at the beginning and at the end of a physical exam instead of just at the beginning. However, in cases where QI or CER activities impose minor burdens of this sort but where there is no plan in place for efficiently implementing the results, it is important that individuals be informed about those burdens and also that doing these additional tasks is voluntary. The reason for this is that although these additional burdens are unlikely to impact important self-determination interests, they may still be an inconvenience and in cases where there is no plan to implement the results, it is uncertain whether those inconveniences will be offset by furthering other interests individuals have in having access to high quality care. Nevertheless, in instances where it is relatively easy for individuals to simply not complete the extra tasks asked of them, such as completing additional questionnaires or surveys, while those in charge of the activity should inform individuals about these minor, additional tasks, they should not be morally required to get written authorization from individuals completing them.
Finally, in cases where QI or CER activities impose greater than minor additional burdens, since these additional burdens may impact important self-determination interests that a person has, it is important that it is disclosed to a patient that these additional tasks are for the purposes of a QI or CER activity and that completing them is voluntary regardless of whether the institution has a plan in place for implementing the results. Examples of this type of burden would include additional office visits that are not part of standard clinical care or other tasks that may interfere with an individual’s life like wearing a 24 hour blood pressure monitor for the purposes of the activity or recording certain information on a daily basis, such as in a food diary, that are not normally requested as part of standard clinical care.  

Likelihood that the Activity Impacts Medical Decisions that Engage Meaningful Preferences

In addition to benefits, risks of harms, and burdens, it is important to consider whether a QI or CER activity limits the ability of patients and physicians to make medical decisions that engage meaningful preferences that patients have. Although individuals may have preferences about whether to participate in QI or CER activities in general, this section is focused on preferences individuals have with regard to their medical treatment. QI and CER activities can only impact these sorts of preferences when these activities manipulate medical care in some way. However, just because an activity involves the manipulation of medical care, it does not follow that that activity necessarily

20 Several scholars have noted that individuals may be more willing to do the extra tasks for the purposes of a QI or CER activity if those individuals are informed about the activity and the rationale for asking them to complete the additional tasks (Lo and Groman 2003). For instance, in the case of a food diary, if people understand the importance of the activity, they may keep more accurate records than they otherwise might have if they did not realize that the information was being collected as part of a QI or CER activity.
limits patient preferences regarding medical treatment in meaningful ways. One reason for this is that there are certain decisions regarding the way patients are treated that institutions, rather than individual patients and doctors, routinely make and, arguably, are in the best position to make. Additionally, even in cases where patients and their doctors are in the best position to make an individual-level treatment decision, not all QI and CER activities that involve the manipulation of medical care infringe on these decisions in significant ways.

**Activities that Involve Health Systems-Level Interventions:** Some QI and CER activities are designed to determine the effect of a health systems or practice-level intervention, such as policy changes or changes to the process of delivering care, on patient outcomes. Patients may have reasoned preferences about the implementation of these interventions within their health care setting and these interventions may impact important interests individuals have in their health. However, according to Julius Sim and Angus Dawson, one factor that distinguishes health systems or practice-level interventions from patient-level interventions is that during the course of receiving medical care, individual patients are not normally consulted before these types of interventions are implemented and this “reflects an acceptance that such measures are legitimately decided at a higher level and that the same degree of consent is not expected for community-level interventions as it is for individual treatment decisions” (2012). For instance, a health care institution would not ask patients for permission prior to changing from paper-based medical records to electronic medical records. Health care institutions
also would not ask patients for permission prior to implementing a new set of hand washing guidelines designed to decrease the risk of nosocomial infections.

There are several potential reasons why this has become an accepted norm in clinical practice. One reason is that asking individual patients for their permission prior to implementing different health systems-level interventions would be inefficient and costly. Additionally, because systems-level interventions apply to a large population of patients, allowing individual patients to make decisions about these interventions is often impractical. However, arguably the most important justification for this practice is that when making decisions about the implementation of such interventions, the institution must make trade-offs among a number of different considerations including, for instance, what is in the best interest of the patient population, the evidence supporting the intervention, cost concerns, and the feasibility of implementing the intervention. Because it would be extremely difficult or impossible to inform all patients about these different considerations, it structurally has never been the practice to allow individual patients to have a say in making these decisions. As a result, since institutions are in the best position to weigh these different considerations, patients must entrust institutions with the authority to make decisions regarding the implementation of systems-level interventions. For these reasons, if a QI or CER activity involves the systematic implementation or comparison of different health systems-level interventions or practices, it is not as important, morally speaking, that the patient be involved in decisions regarding the implementation of those interventions or practices. Therefore, it is not as important, morally speaking, to allow individuals to decide whether or not to participate in that activity. However, in situations where an activity poses greater than minimal risks or
burdens or may negatively impact the ability of a patient to experience an optimal clinical outcome, it is important to have strong institutional ethical oversight of that activity. Additionally, in situations where the activity imposes greater than minor additional burden on individuals for the purposes of collecting additional information for the activity, it is still important that patients be informed about those burdens and that completing them is voluntary.

**Activities that Involve Patient-Level Interventions:** Unlike health systems or practice-level interventions, patients and their physicians are generally in the best position to decide which considerations are most important and to weigh those different considerations when making patient-level treatment decisions. Even when there is uncertainty regarding which of several patient-level interventions is likely to result in the best clinical outcome for patients, individuals still may have other reasons for preferring one of the interventions over others, some of which are more meaningful than others. QI or CER activities that limit the ability of patients and clinicians to make treatment decisions based on patient preferences include activities where:

1. individuals or groups of individuals are randomly assigned to different patient-level interventions (Miller 2010, 388; Lo and Groman 2003),
2. individuals are asked to stop taking a medication that they are familiar with and switch to a different medication, or
3. the activity limits the number of treatment options patients have, compared with standard clinical care.

---

21 Whether the activity involves randomization at the level of a cluster or at the individual level is irrelevant in determining whether and how that activity limits choices that engage meaningful personal preferences.
The difficulty is that although not all preferences individuals have are of equal moral significance, it is generally not possible to distinguish preferences that are meaningful for an individual from those that are not. While it is clear that preferences based on superficial characteristics such as name or color of a specific treatment do not have any impact on important self-determination interests and that other preferences such as those based on risks or burdens clearly do, there are many instances where the choice between two interventions may engage preferences that are meaningful for some individuals but not others. For instance, consider a study comparing taking a medication in the morning to taking that same medication at night (NIH Collaboratory 2013). Many patients will not have a strong preference regarding when they take their medication while others might prefer to take the medication in the morning because that is when those individuals take other medications and they may be concerned that they will forget to take their medication in the evening. Although a preference for taking one’s medication in the morning is not as important as a preference for surgery instead of chemotherapy, it is arguably still important for individuals to know if they are being asked to take the medication at a certain time for the purposes of a QI or CER activity instead of for purely medical reasons. Because individuals form preferences for a variety of reasons, many of which may not be known to the investigators conducting a QI or CER activity, some individuals may reasonably have meaningful preferences about treatment decisions that other patients see as trivial. Since individual patients and doctors are in the best position to understand individual patient preferences, when a QI or CER

---

22 Truog and colleagues suggest that the “reasonable person” standard should be used to differentiate ethically relevant preferences from those that are less important. However, these scholars also admit that “validity of the reasonable-person standard depends in large part on how it is implemented” (Truog et al. 1999).
activity limits patient-level treatment decisions in some way, it is important for patients to understand how their options are being limited and why. Furthermore, it is important for patients to have an opportunity to select another treatment option with their clinicians from the range of options that would have been available to them if there is a reason for the patient to prefer an alternative treatment.

However, some activities that involve manipulation of individual treatment decisions only infringe on preferences in a very limited way. For instance, when it is easy for the patient and clinician to override the random choice and select another treatment from the choices that would otherwise have been available to the patient, the impact randomization has on patient preferences regarding medical treatment is minimal.23 Demonstrating this point, Sabin and colleagues provide a hypothetical example of a cluster randomized study where patients diagnosed with a certain condition at one health plan are prescribed one medication (Drug A) and patients with the same medical condition at a different health plan are prescribed a different medication (Drug B). Both medications are approved by the United States Food and Drug Administration and widely-used and physicians are free to override the cluster randomization if they feel that one of the medications is better for a particular patient or if the patient has a reason to prefer another medication. Based on a literature review and interview data, Sabin and colleagues reason that because physicians in the trial are only asked to prescribe the favored therapy unless the physician or the patient has a reason to prefer the alternative, “[t]here is nothing in this chain of steps that is inherently different from ordinary practice.

With regard to the prescribing of A or B, there is no “experiment” being done and

23 Of course, allowing patients and physicians to relatively easily override the random assignment will impact the internal validity of the study. However, this issue is not the focus of this paper and therefore, although this is an important consideration, it will not be further discussed here.
nothing requiring informed consent beyond what is ordinarily required in clinical practice” (2008).

Presumably, there is nothing inherently different because both of the medications are commonly used and because doctors are free to override the random assignment if there is a reason for the patient to prefer a different medication. Since it is extremely easy to override the random assignment, enrollment in that activity would not significantly infringe on meaningful preferences, assuming that patients are given enough information about other treatment options to understand how medication selection may impact meaningful preferences that they might have. Therefore, in these situations, it is not as important to allow the individual to decide whether or not to participate in the activity.

Discussion: Recommendations Regarding the Moral Permissibility of Limiting an Individual’s Ability to Decide Whether to Participate in a QI or CER Activity

The ability of QI and CER activities to provide needed information on the relative benefits and harms of interventions and practices in order to improve the quality of health care delivered to patients is furthered when there is near universal participation in these activities (Faden et al. 2013a; Lynn et al. 2007). This is because generating robust evidence of effectiveness, and especially comparative effectiveness, often requires large sample sizes in order to detect small but clinically meaningful differences in outcomes and because high participation rates allow the research to be completed faster. Additionally, near universal participation decreases the risk of selection bias and improves the generalizability of the results. Being able to achieve near universal

---

24 Arguably, this information should also be provided as part of standard clinical care. However, an in-depth discussion of this is beyond the scope of this paper.
participation and to implement these activities as efficiently as possible has led to an interest in the availability of waivers of or alternatives to prospective informed consent, at least in some circumstances. These reasons combined with the fact that QI or CER activities often do not involve manipulating medical care and when they do, they often involve widely-used and/or evidence-based interventions or practices raises the question of whether it may be morally permissible to implement alternatives to current informed consent requirements for at least some subset of QI and CER activities.

The goal of this paper was to demonstrate that the moral importance of allowing individuals to decide whether or not to participate in a QI or CER activity, and thus the importance of engaging in full prospective informed consent, depends on a number of features of that activity as well as of the health care system in which it is being implemented. These include the ability of the health care system to implement the findings from the activity, the health benefits and risks of harm to individuals enrolled, the burden imposed on participants, and whether the activity limits the ability of individuals to participate in individual-level treatment decisions that may engage meaningful preferences. The first feature is an important component of the justification for waiving or altering informed consent requirements. The remaining features are important because each influences the likelihood that the decision to participate in the activity engages important self-determination interests that individuals have. If, after considering these features, it is clear that the decision to participate does not engage important interests and preferences that individuals have in their health or general life course and if the system or institution in which the activity is implemented has a plan to efficiently implement the findings from the activity to improve clinical care,
implementing waivers of or alternatives to prospective informed consent in order to improve the ability of those activities to efficiently generate evidence to improve clinical care is morally permissible. Alternatively, if the decision to participate does engage important interests and preferences, it is necessary to ensure that individuals are able to decide whether participating is consistent with the interests and preferences that they have. The reason for this is that infringing on the autonomy of individuals by not allowing them to make informed choices about participation in these activities can have a negative impact on the overall well-being of those individuals.

Based on this line of reasoning, it is possible to draw the following conclusions about the moral permissibility of waiving or altering prospective informed consent requirements for certain kinds of QI and CER activities.

1. *Prospective informed consent should always be required for QI and CER activities that involve the manipulation of individual-level treatment decisions and that impose greater than minimal risks of harm or burdens beyond those associated with standard care or that involve interventions that are associated with significant uncertainty regarding the health benefits to participants.*

When a QI or CER activity involves manipulating individual-level treatment decisions, the activity may limit the ability of patients and physicians to make choices based on meaningful preferences that patients have. Because of this, individuals should be given some authority to resist participation if they feel that participation is not aligned with their interests and preferences. If the activity also imposes greater than minimal additional risk of harm beyond those associated with standard clinical care (as would be
the case when experimental interventions are being tested) or if there is significant uncertainty regarding the impact participation will have on patient health outcomes, prospective informed consent should be obtained from individuals prior to enrolling them. It is also necessary to obtain prospective informed consent when a QI or CER activity imposes greater than minor additional burdens on participants. In these situations infringing on the autonomy of individuals is likely to have a negative impact on the well-being of those individuals since decisions regarding participation are likely to impact important self-determination interests that they have.

2. For QI or CER activities that involve manipulating individual-level treatment decisions and that impose only minimal additional risks or minor additional burdens compared to standard clinical care and involve only interventions that are widely-used and/or evidence-based, it is sometimes permissible to alter informed consent requirements by setting up defaults to encourage patient participation:

   Even if a QI or CER activity that involves the manipulation of individuals-level treatment decisions only involves widely-used and/or evidence-based interventions, is unlikely to negatively impact health outcomes experienced by patients, and does not involve greater than minimal additional risks or burdens, it is still important that individuals be given some authority to resist participating. In these situations, it is necessary to allow patients, in consultation with their clinicians, to consider the different treatment options available to them and to decide whether they are willing to allow their
treatment options to be limited in order to help generate evidence of the effectiveness of those interventions.

Nevertheless, there are some design features of these sorts of activities that can decrease the likelihood that treatment decisions will be constrained in ways that may engage meaningful preferences. First, since the decision to switch treatments once a patient has found a treatment plan with which he or she is satisfied will often engage meaningful preferences, activities that only enroll individuals who are treatment naïve are less likely to infringe on meaningful preferences than activities that enroll individuals who currently have treatment plans in place. Additionally, for activities that involve random assignment of individuals or groups of individuals to different treatments, if, as part of an activity, clinicians are given the authority to override the random assignment at any time if their patient has a reason to prefer a different treatment, if the patient requires a different dose of the treatment, or if the patient and physician believe that the patient would benefit from an add-on therapy, then the activity only limits the ability of patients and clinicians to make decisions that might engage meaningful preferences in a very limited way. However, even in these situations, it is important that patients be informed about the potential treatment options that would have been available to them as part of standard clinical care as well as the main risks of harm associated with those different options because this information is necessary in order for patients to understand if and how the choice among treatments might engage meaningful preferences that they have.²⁵

As part of this disclosure, patients should also be aware of how the activity limits their

²⁵ However, it is not the case that patients need to be informed of every potential risk associated with each treatment option. Instead, Wendler and Grady argue that it is appropriate for those conducting the activity to rely on existing and appropriate clinical standards to determine what information should be disclosed to patients about the risks of widely-used, evidence-based therapies being studied in minimal risk activities that randomly assign patients to different treatment arms (2008).
treatment options. Further, even in situations where QI or CER activities incorporate the
design features described in this paragraph, patients should have some authority to resist
participating in those activities.

However, this does not necessarily mean that patients should be asked for their
authorization prior to being enrolled. Instead, for activities where (1) all interventions are
widely-used and/or evidence-based, (2) none of the interventions involves a
significantly greater risk of harm or is significantly more burdensome than other
interventions available as part of standard clinical care, and (3) the design features
described in the previous paragraph are incorporated into the activity, it is morally
permissible to set up defaults to encourage patient participation, as long as there is a plan
in place to efficiently implement the findings from those activities. The reason for this is
again because the decision to participate in activities that meet these criteria is unlikely to
engage important self-determination interests. Given this, instead of engaging in
prospective informed consent, it is morally permissible to ask individuals to opt out of the
activity if they would prefer not to participate. When opt out models are used, the
 presumption is that individuals should participate and that if individuals do not want to
participate, it is acceptable for them to have to exert some effort to remove themselves
from the activity. The moral permissibility of opt out models hinges on how easy it is for
an individual to resist participating (Blumenthal-Barby and Burroughs 2012). Building on
the concept of resistibility developed by Ruth Faden and Tom Beauchamp (1986,
260,341-343, and 367-368), Yashar Saghai asserts that “resistibility is a criterion for
testing the degree to which an influence is controlling.” Saghai further explains that an
influence is easily resistible if an individual can relatively effortlessly oppose that
influence (Saghai 2012, 48-49). In situations where opt out approaches are used, it is important to ensure that it is not excessively difficult for individuals to refuse to participate.

3. **Waivers or alternatives to informed consent are generally morally permissible when QI or CER activities involve manipulating medical care through the implementation of a health care system or practice-level intervention.** However, individuals should be informed about greater than minor additional burdens and ethical oversight is needed if the activity imposes greater than minimal additional risks of harms or burdens or if it could negatively impact the ability of patients to experience optimal clinical outcomes:

Since institutions, rather than individual patients and physicians, are generally given the authority to make decisions regarding the implementation or manipulation of health systems-level interventions, individuals have no choice but to entrust the institution with the authority to weigh the possible risks, benefits, and burdens of these types of interventions and to make appropriate choices regarding their use. Therefore, when a QI or CER activity involves a systems-level intervention, not informing patients about the activity and allowing them to make a voluntary decision regarding participation is morally permissible unless the activity imposes greater than minor additional burdens on individuals for the purposes of activity-related data collection.\(^{26}\) When a QI or CER

\(^{26}\) It is also important to note that in cases where an activity involves retrospective analysis of existing data or where the activity involves the implementation of a health systems-level intervention, it is often more difficult to obtain prospective informed consent from participants. This feasibility concern also serves to help justify waiving informed consent requirements. However, although feasibility concerns can help to justify waiving or altering informed consent requirements, it is not the case that feasibility concerns are always a necessary part of the justification.
activity involving systems-level interventions does impose greater than minor additional burdens for the purposes of additional data collection, individuals should be informed about those burdens and should be given the opportunity to make a voluntary decision about completing them. If a QI or CER activity relies on routinely collected information, it is necessary to ensure that proper confidentiality protections are in place and that there are severe repercussions if confidentiality is breached. Also, in situations where the activity may negatively impact health outcomes for patients or poses greater than minimal risk, it is important that that activity receives additional ethical oversight beyond the oversight associated with standard clinical care.

Moreover, to justify conducting QI and CER activities of this sort without patient informed consent there should be a plan in place for efficiently implementing the results of the activity, especially if minor additional burdens are imposed on participants. Additionally, to demonstrate respect for individuals, it is important that institutions regularly inform patients that these sorts of activities are conducted without consent. As part of this process of informing patients, institutions should describe why these activities are being done, how patients’ interests and preferences are protected, and how the results from these activities will be used to improve clinical practice.²⁷

On a related note, it is important to point out that it is generally already widely accepted that consent should not be required for many QI activities. One of the predominant arguments in favor of this practice is that these activities should be considered “a normal part of health care operations” whereas other activities, including CER activities, are outside of normal health care operations (Baily et al. 2006; Dubler et

²⁷ As mentioned earlier, institutions could also considering engaging individuals impacted by QI and CER activities in other decisions related to those activities.
al. 2007; Lynn et al. 2007). This criterion relates to the justification for waiving or altering informed consent requirements. Specifically, QI activities are often designed to address important issues in the health care system in which they are conducted and there are often mechanisms in place for using the information generated from these activities to improve medical care or, stated differently, to further interests patients have in being able to access high quality medical care (Kass et al. 2013). However, also relevant is that QI activities often involve health systems or practice-level interventions instead of individual-level treatment decisions, often impose only minimal additional risks and burden on those enrolled, and often are unlikely to negatively impact the health outcomes of patients. It is for these reasons that it is generally morally permissible to waive informed consent requirements for QI activities.

4. **Waivers or alternatives to informed consent are generally morally permissible when QI or CER activities have no impact on the medical care patients receive and impose no or only minimal risks of harm and no or only minor additional burdens:**

In these situations, interests individuals have in high quality of health care are more important, morally speaking, than the ability to make a decision regarding participation and therefore, infringing on the autonomy of individuals is justified. As a result, in these situations it is morally permissible to limit the ability of individuals to decide whether or not to participate. The kinds of QI or CER activities that fit this description are observational activities that either rely exclusively on routinely collected information or that only require patients to assume minor additional burdens such as
completing a short survey while in the waiting room for a regularly scheduled appointment. In order to be considered minimal risk, those in charge of the activity need to ensure that there are confidentiality protections in place and that there are severe repercussions if confidentiality is breached. Also, if, in order to conduct an activity, there is a need to access particularly sensitive information, such that breaches of confidentiality will result in severe harms to individuals, then informing individuals about the activity and asking them for their authorization prior to enrolling them should be required. Nevertheless, it is still important that the institution has mechanisms in place for translating the results of these activities into clinical practice and that patients are informed of the institution’s policies regarding these types of activities as described above. It is also important that institutions ensure that these activities receive ethical oversight.

Conclusions and Next Steps

This paper makes several recommendations about when it is morally permissible to waive or alter prospective informed consent requirements based on an analysis of when the decision to participate in QI and CER activities engages important self-determination interests. Nevertheless, there is still some additional normative and empirical work that should be done to build on this initial set of recommendations. For instance, one issue that was not discussed in this paper as it is beyond the paper’s scope is whether and how the level of trust a community has in health care institutions or in clinical research should factor into decisions about the moral permissibility of waiving or altering prospective informed consent (Truog et al. 1999). Given the critical role that trust
plays in the proper functioning of the medical and research enterprises, future work should consider whether obtaining prospective informed consent is more significant, morally, in situations where there is already a lack of trust. Additionally, since it has been argued that choice has intrinsic value regardless of whether it leads to better outcomes or impacts well-being (Scanlon 1986, 189), one issue that deserves further attention is whether allowing waivers of or alternatives to prospective informed consent to be used in these additional situations would cause individuals to feel wronged. This paper adopts the view that if waivers or alternatives are only used in situations in which decisions regarding participation are unlikely to impact individual self-determination interests, it is reasonable to expect that individuals will not feel as wronged as they may feel if their ability to decide whether to participate in other types of research were restricted. This paper also suggests that when consent requirements are waived or altered, it is important to demonstrate respect for individuals in other ways. While this is not meant to suggest that demonstrating respect in these other ways can replace the importance of choice, doing so may still help to alleviate feelings of being wronged. However, additional empirical work on this topic is needed in order to support this normative claim.

Future work should also focus on delineating what non-clinical risks of harm should reasonably fall under the minimal risk threshold as well as which burdens are so minor that they are unlikely to impact interests individuals have with regard to their health or general life course. It would be useful to engage in a closer examination of the different risks and burdens associated with previously implemented QI and CER activities to determine whether there are specific criteria that could be developed that would assist with this classification. There is also a need for more evidence to understand
if using opt out approaches is more efficient than traditional informed consent and results in higher participation in QI and CER activities since both considerations are important parts of the justification in favor of adopting these approaches. Finally, although it is already generally accepted that many QI activities do not require prospective informed consent, future work is needed to understand the social and political feasibility of implementing the morally permissible alternatives to informed consent described in this paper for CER activities (Faden et al. 2013b; Whicher 2013).

Despite these outstanding issues, this paper builds on the small but growing body of literature devoted to understanding if the current regulations governing the practice of informed consent in the United States appropriately balance concerns about respect for the self-determination interests of individuals with interests in improving the quality of health care delivered to patients. The arguments in this paper suggest that there are additional situations in which it is morally permissible to waive or alter prospective informed consent requirements for QI and CER activities. Ensuring that the regulations appropriately balance these different considerations is critical as imposing overly protective consent requirements can prevent or delay the development of evidence necessary for improving health care quality.

References


Scanlon TM. What We Owe to Each Other. Cambridge, MA: First Harvard University Press 1998.


Paper 3: Simplified Disclosure Statements and Opt-Out Approaches as Policy Alternatives to Prospective Informed Consent for Low-Risk CER Trials

Introduction

There is a growing body of literature arguing for the importance of conducting randomized comparative effectiveness research (CER) trials of widely-used interventions in order to improve health care quality (Mullins et al. 2010; Tunis et al. 2003). Related, there has been increasing federal support for CER efforts, and, as such, the number of CER trials is likely to increase going forward (Patient Protection and Affordable Care Act 2010; Selby et al. 2012). Moreover, for the first time in forty years, there have been efforts to reform the U.S. federal human subjects research regulations (45CFR46). One piece of the proposed changes aims to further ensure that the level of protection required for research projects is commensurate with the level of risk to individuals participating in those projects (Department of Health and Human Services 2011; Emanuel and Menikoff 2011). While the proposed changes do not explicitly discuss streamlined oversight and consent options for CER, scholars have suggested that it may sometimes be appropriate to waive or alter consent requirements for this type of research (Kass et al. 2012).

Related, it has been suggested elsewhere that under certain conditions, randomized trials pose no more than minimal risk to participants (Morris and Nelson 2007). Indeed, several scholars have questioned the appropriateness of always requiring that prospective informed consent be obtained from individuals eligible for randomized trials comparing widely-used, clinically indicated interventions (Faden et al. 2013; Selker et al. 2011; Truog et al. 1999).
As CER trials are deliberately and increasingly integrated into ongoing clinical care, current consent requirements become challenging because of their length and complexity (Van Staa et al. 2012). Also, consent requirements are resource intensive, introduce selection bias, and can result in lower participation rates, while CER trials generally require large sample sizes to detect small but clinically meaningful differences between interventions. Such features of informed consent, of course, are relevant to all research and are not themselves sufficient for altering consent requirements, which are intended to provide protection to those who enter research and to demonstrate respect for autonomy. Instead, these considerations must be weighed against the importance of this protection and of exercising autonomy in different types of situations (Whicher 2013a).

Constructing Viable Alternatives to Prospective Informed Consent

Current regulations already allow waivers of consent for certain types of research studies, including observational studies relying on existing data. This reflects a view that when autonomy interests and the need for protection are thought to be more limited, it may be acceptable to allow commitments to improving clinical care to take precedence. However, there are several notable differences between observational studies and randomized CER trials that make supporting waivers for the latter more challenging. First, observational research does not alter patient care in any way. Second, obtaining consent may be more difficult in observational research than in randomized CER trials, since observational research is often retrospective while randomized trials are conducted prospectively. Given these differences, individuals may be more likely to feel wronged --
that is, more likely to feel violated or treated unfairly-- if they are enrolled in randomized
trials without their consent (Lo and Groman 2003).

Nevertheless, not all randomized trials are the same. Different features of a trial’s
design or setting may affect whether the decision to participate engages significant
autonomy interests and, as a result, how wronged individuals might feel if consent
requirements are altered. Specifically, it has been suggested that individuals may feel less
wronged if it is easy for physicians to over-ride the randomization, if all of the
interventions being compared are widely-used and evidence-based and none of the
interventions is significantly riskier than the others, and if the evidence generated is likely
to be used to improve care (Whicher 2013a). Moreover, and importantly, there are
several options that one might consider for disclosure and authorization of clinical
research besides completely waiving consent requirements or engaging in full prospective
informed consent. These other options may more appropriately balance the ability to
generate robust comparative effectiveness evidence with the desire to respect individuals’
interests and preferences. Alternatives can differ from prospective informed consent in
the amount of information disclosed, the amount of control afforded to individuals over
the decision to participate, and the format in which information is delivered and decisions
documented.

Notably, scholars have questioned the current requirement to disclose more
information in CER trials about clinically indicated interventions than would be provided
as part of standard clinical care (Van Staa et al. 2012). Instead, scholars have asserted that
while patients should be informed about the research, it is appropriate to rely on “existing
(appropriate) clinical standards to determine how much information to disclose regarding
clinically indicated procedures” (Wendler and Grady 2008). Additionally, our own preliminary qualitative research suggests that many patients, comparative effectiveness researchers, and institutional review board members would support such an approach (Whicher 2013b). Several patients in our study also commented that disclosing information that is not routinely provided in clinical care could scare or overwhelm individuals.

Another option for low-risk CER trials is the use of “opt-out” rather than “opt-in” approaches. Again, in our own work, many participants felt that opt-out approaches were acceptable if individuals were informed about both the trial and the opt-out option and opting-out was relatively easy. Under these conditions, the opt-out alternative arguably gives patients a sufficient amount of control over their participation while signaling the low-risk nature of the research as well as its importance. There is also some limited evidence from within clinical research (Berry et al. 2012; Rogers et al. 1998) and even stronger evidence from outside that context that opt-out approaches result in higher recruitment and participation rates (Jayaraman et al. 2003; Johnson and Goldstein 2004; Madrian and Shea 2001). Moreover, there is evidence that opt-out procedures can be readily integrated in standard care (Haukoos et al. 2010).

Moving Towards Policy Change

Either disclosing the same level and types of risk/benefit information as is given in standard care or using opt-out mechanisms could be considered as a possible alternative to full, prospective consent for low-risk CER trials of widely-used, clinically indicated interventions. However, applying these two approaches in tandem would likely
be more effective than either one alone at increasing the efficiency of conducting these trials and integrating them into clinical practice. Furthermore, because some degree of choice is preserved, these alternatives are less likely to result in individuals feeling wronged compared to complete waivers of consent. However, implementing these alternatives requires regulatory change. To work towards such change, several key next steps must occur.

First, to justify these changes, it is necessary to continue to build the case for the importance of CER by demonstrating its utility in improving health care quality. This will require ensuring that evidence generated from CER trials will be efficiently implemented in clinical care. Second, additional discussions are needed to determine what information should be disclosed to eligible individuals, including further defining appropriate clinical standards for disclosure. These discussions should also focus on determining effective mechanisms for disclosing information and documenting decisions. Third, it is necessary to gather additional information regarding stakeholders’ perceptions of the acceptability of using opt-out approaches (PCORI 2013). Fourth, additional work is needed to further define what kinds of research should qualify for these alternatives. Finally, it is important to conduct demonstration projects examining whether these approaches result in patients feeling sufficiently respected, actually improve efficiency, and are easier to integrate into clinical care to ensure that making policy changes to the informed consent regulations would have the desired positive effects.

Given the recent focus on improving care quality through research, and also on reforming the U.S. human subjects research regulations, it is an important time to re-evaluate current consent policies to ensure that they are achieving the socially and
morally desirable outcomes that they were designed to achieve. Respecting autonomy interests and protecting individuals is important. Simplified disclosure statements and opt-out approaches may satisfy what is required in fulfilling these commitments in the context of low-risk CER trials of widely-used interventions, and may more appropriately balance these concerns with the need to generate robust evidence to improve health care quality.

References


Patient Protection and Affordable Care Act, Pub L No. 111-148, 124 Stat 727, §6301.


Appendix 1: Johns Hopkins Bloomberg School of Public Health IRB Approval Notice

**INSTITUTIONAL REVIEW BOARD OFFICE**

615 North Wolfe Street / Suite E3100
Baltimore, Maryland 21205
Office Phone: (410) 955-3195
Toll Free: 1-800-262-0342
Fax Number: (410) 952-9584
Email Address: irb@jhsph.edu
Website: [www.jhsph.edu](http://www.jhsph.edu)

**Date:** March 30, 2012

**To:** Nancy Kass, ScD, PhD
(Danielle Whicher)
Department of Health, Policy and Management

**From:** Elizabeth A. Skinner, MSW
Chair, IRB-X

**Re:** Study Title: “Rethinking Informed Consent for Pragmatic Comparative Effectiveness Trials”
IRB No: 0004044

The JHSPH IRB-X voted to approve the above referenced application at its meeting on December 15, 2011. The Board made the following determinations:

<table>
<thead>
<tr>
<th>Expedited</th>
<th>Convened</th>
<th>DHHS 46.110</th>
<th>DHHS 56.110</th>
<th>FDA</th>
<th>FDA 56.110</th>
<th>FDA</th>
<th>Category: 6 &amp; 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>GWAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Vulnerable Populations:**

- Children
- Foster Care Children
- DHHS 46.404
- 46.405
- 46.406
- FDA 50.51
- 50.52
- 50.53

**Consent/Parental Permission Required From:**

- Adult Participant
- LAR
- One Parent
- Two Parents
- Legal Guardian (Foster Care Children)

**Form of Consent/Permission:**

- Written Consent
- Waiver of Signature
- Waiver of Informed Consent
- HIPAA Authorization
- HIPAA Waiver

**Assent Required From:**

- No children (waived)
- Children aged:

**Form of Assent:**

- Written
- Oral
- Assent Statement in Parent Permission

**Pregnant Women/Fetuses:**

- Neonates 46.205
- 46.305
- 46.306

**Prisoners:**

- Epidemiological Research

**Sample Sizes:**

- Screened plus enrolled
- Pilot=10
- FGD=64
- ID=26
- Total=100

**Secondary Data Analysis:**

- (8 samples/participants)

Approval of the research is for the period of December 15, 2011 to December 14, 2012. A Progress Report for continuing review must be submitted to the IRB Office no later than six weeks prior to the approval lapse date of December 14, 2012.
This approval is inclusive of the following documentation:

Research Plan (Version #2, 12-22-11)

Oral Conset Script for In-Depth Interviews (Version #1, 12-15-11)

Oral Conset Script JHMI Comparative Effectiveness Reserachers (Version #1, 12-15-11)

Oral Conset Script JHMI-Geisinger Health System Comparative Effectiveness Researchers (Version #1, 12-15-11)

Oral Conset Script JHMI-Geisinger-Patients with Hypertension (Version #1, 12-15-11)

Oral Conset Script JHMI-Geisinger Institutional Review Board Members (Version #1, 12-15-11)

Oral Consent Script for System Patients with Migraines (Version #1, 12-15-11)

Oral Consent Script for JH Patients with Hypertension (Version #1, 12-15-11)

Oral Consent Script-JHMI Institutional Review Board Members (Version #1, 12-15-11)

Oral Consent Form for Focus Groups-JH Patients with Migraines (Version #1, 12-15-11)

Oral Consent Script for Pilot Test Interviews-JHMI Comparative Effectiveness Researchers (Version #1, 12-15-11)

Oral Consent Script-JH Patients with Hypertension (Version #1, 12-15-11)

Oral Consent Script-JHMI Institutional Review Board Members (Version #1, 12-15-11)

Oral Consent Script-JH Patients with Migranes (Version #1, 12-15-11)

Attachment 1: PCP Email Notification (Version #1, 1-11-12)

Attachment 2: Phone Script-hypertension (Version #1, 12-22-11)

Attachment 4: Geisinger Recruitment Phone Script: Patients with Hyertension (Version #2, 1-18-12)

Attachment 5: Geisinger Recruitment Phose Script: Patients with Migraine (Version #2, 1-18-12)

Attachment 6: Email to IRB/CER Researcher (Version #1, 1-11-12)

Attachment 11: Email for IRB Staff Dir. (Version #1, 12-22-11)
As principal investigator of the research, you are responsible for fulfilling the following requirements of approval:

1) The co-investigators listed on the application should be kept informed of the status of the research.

2) Submit an Amendment Request Form for any changes in research. These changes in research are required to be reviewed and approved prior to the activation of the changes, with the following exceptions:
   a) changes made to eliminate an apparent immediate hazard to the research participant may be instituted immediately and the JHSPH IRB should be informed of such changes promptly; and
   b) changes to IRB Approved questionnaires, interview or focus group guides, other data collection or recruitment materials – limited to rewording to clarify meaning, correcting grammatical or typographical errors, or removing items that will not be used in the research.

3) Unanticipated problems involving risk of harm to participants or others that are related to the study procedures must be reported to the JHSPH IRB within 10 days of the time that the PI learns of such problems. A Problem Event Report Form must be submitted to the IRB immediately.

4) Only consent forms with a valid JHSPH IRB approval stamp or logo, with the correct IRB Approved version number and approval date may be presented to participants. All consent forms signed by subjects enrolled in the study should be retained on file. The Office of Graduate Education and Research conducts periodic compliance monitoring of study records, and consent documentation is part of such monitoring.

5) Federal regulations require review of approved research not less than once a year, unless a shorter period is determined by the IRB. Therefore, a Progress Report for continuing review must be submitted to the IRB Office no later than six weeks prior to the approval lapse date. This will allow sufficient time for review of the application to be completed prior to the approval lapse date. Failure to submit a Progress Report prior to the approval lapse date will result in termination of the study, at which point new participants may not be enrolled and currently enrolled participants must discontinue participation in the study. All ongoing research activities must stop immediately, including data analysis.

6) If your research involves international travel, please don’t forget to register with the International Travel Registry https://apps4.jhsph.edu/ITR/Default.aspx so that the School may locate you in the event of an emergency.

EAS/ero
Appendix 2: Geisinger Health System IRB Approval Notice

Institutional Review Board
M.C. 30-69
100 North Academy Avenue
Danville, PA 17822
570 271 8663 Tel
570 271 6701 FAX

Geisinger
Health System

Approval Notice
Initial Review - Expedited Review

March 6, 2012

Walter F. Stewart, Ph.D.
Center for Health Research
100 North Academy Avenue
M.C. 44-00
Danville, PA 17822-4400
Phone: (570) 214-9391

RE: Research Protocol # 2012-0152
“Rethinking Informed consent for Pragmatic Comparative Effectiveness Trials”

Dear Walter F. Stewart, Ph.D.:

Members of Institutional Review Board (IRB) reviewed and approved your research protocol under expedited review procedures [45 CFR 46.110(b)(1) and/or 21 CFR 56.110(b)(1)] on March 1, 2012. You may now begin your research.

Your research was found to have met the following specific category:

7 Research on individual or group characteristics or behavior (including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

(NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Please note the following information about your approved research protocol:

<table>
<thead>
<tr>
<th>Protocol Approval period:</th>
<th>March 1, 2012 - February 28, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent:</td>
<td>Oral informed consent</td>
</tr>
<tr>
<td>HIPAA Research Authorization:</td>
<td>Waiver granted</td>
</tr>
<tr>
<td>Recruiting Material(s):</td>
<td>Records (e.g. Medical, Employment, School), Information Letter/Pamphlets, other - email</td>
</tr>
</tbody>
</table>
Approved Subject Enrollment #: 250

Performance Sites: Geisinger Health System

Approved PHI:
Names, Geographic subdivisions smaller than a state, Dates, Telephone numbers, Email addresses

Please remember to:

**Please note: No recruitment can begin or letters sent until sites have been determined and Physician Attestation forms have been submitted and accepted by the IRB**

→ Use your research protocol number (2012-0152) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements of the, "Investigator Responsibilities, Protection of Human Research Subjects"

Please note that the Geisinger IRB has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

If you have any questions or need further help, please contact the Human Research Protection Program (HRPP) staff at 570-271-8663. Please send any correspondence about this protocol to the Human Research Protection Program (HRPP) at 30-69.

Sincerely,

W. Andy Faucett, MS
IRB Member
Institutional Review Board

Enclosure(s): (1) Investigator Responsibilities, Protection of Human Research Subjects (2) Attachments:
- PCP Email notification (Attachment 1)- Version 1 dated 1/11/12
- CE researcher consent form (Attachment 9)- Version 2 dated 1/11/12
- Email to IRB (Attachment 6)- Version 2 dated 2/29/12
- Geisinger Phone Script- high blood pressure (Attachment 4)- Version 2 dated 1/18/12
- Geisinger Phone Script- migraine (Attachment 5)- Version 2 dated 1/18/12
- Geisinger Recruitment letter- high blood pressure (Attachment 2)- Version 1 dated 1/11/12
- Geisinger Recruitment letter- migraine (Attachment 3)- Version 1 dated

IRCREXPAPP: 1/6/12
1/11/12

- Hypertension consent form (Attachment 7)- Version 1 dated 1/11/12
- IRB member consent form (Attachment 10)- Version 1 dated 1/11/12
- Migraine consent form (Attachment 8)- Version 1 dated 1/11/12
- Email for IRB staffing director (Attachment 11)- Version 1 dated 12/22/11

(3) Forms:
- Hypertension Case Study (patients) (Form I-1)- Version 1 dated 12/22/11
- Hypertension Case Study (IRB + res) (Form I-2)- Version 1 dated 12/22/11
- Recruitment letters for Comparative Effectiveness Researcher and IRB members (Form H)- Version 1 dated 12/22/11
- Migraine Case Study (patients)- (Form J-1)- Version 1 dated 12/22/11
- Migraine Case Study (IRB + res) (Form J-2)- Version 1 dated 12/22/11
- Focus Group Guide (Form K)- Version 1 dated 12/22/11
- Models descriptions (Form L)- Version 1 dated 12/22/11
- Participant Survey (Form M)- Version 1 dated 12/22/11
- In-Depth Interview Guide IRB Members (Form N)- Version 1 dated 12/22/11
- In-Depth Interview Guide CE researchers (Form O)- Version 1 dated 12/22/11
- Survey for Comparative Effectiveness Researcher Geisinger (Form P)- Version 1 dated 12/22/11
- IRB Community Member Survey (Form Q-1)- Version 1 dated 12/22/11
- IRB Member Survey: Geisinger (Form Q-2)- Version 1 dated 12/22/11
- Participant information document for hypertension case (Form R)- Version 1 dated 12/22/11
- Participant Information document for migraine case (Form S)- Version 1 dated 12/22/11
- Participant fact sheet models (Form T)- Version 1 dated 12/22/11

cc: Rebecca A. Search (44-00)
Investigator Responsibilities
Protection of Human Research Subjects

Version 1.1 – February 20, 2004

The Institutional Review Board (IRB) recently reviewed and approved your research. The IRB reviews research to ensure that the federal regulations for protecting human research subjects outlined in Geisinger’s policy, the Department of Health and Human Services (DHHS) regulations (45 CFR 46) and the Food and Drug Administration (FDA) regulations (21 CFR Parts 50 & 56) as well as other requirements are met. Geisinger’s Federalwide Assurance (FWA) (FWA# 00000063) awarded by the Office for Human Research Protections (OHRP) at DHHS, is a written pledge to follow federal guidelines for protecting human research subjects in accordance with the principles of the Belmont Report. All investigators must read both the Belmont Report and the FWA to understand their responsibilities in conducting human subject research. Both documents are available on the Clinical Research website at and in hard copy. Some of the responsibilities investigators have when conducting research involving human subjects are listed below:

1. Conducting the Research. You are responsible for making sure that the research is conducted according to the IRB approved research protocol. You are also responsible for the actions of all your co-investigators and research staff involved with this research.

2. Subject Enrollment. You may not recruit or enroll subjects prior to the IRB approval date or after the expiration date of IRB approval. All recruitment materials for any form of media must be approved by the IRB prior to their use. If you need to recruit more subjects than was noted in your IRB approval letter, you must submit an amendment requesting an increase in the number of subjects.

3. Informed Consent. You are responsible for obtaining and documenting effective informed consent using only the IRB-approved consent documents, and for ensuring that no human subjects are involved in research prior to obtaining their consent. Please give all subjects copies of the signed consent documents. Keep the originals in your secured research files for at least six (6) years. When appropriate, you should place a copy of the consent document in the subject’s medical record.

4. Continuing Review. The IRB must review and approve all IRB-approved research protocols at intervals appropriate to the degree of risk but not less than once per year. There is no grace period. Prior to the date on which the IRB approval of the research expires, the Human Research Protection Program (HRPP) will send you a reminder to submit a Continuing Review Application.

5. Although the Human Research Protection Program (HRPP) sends reminders, it is ultimately your responsibility to submit the continuing review report in a timely fashion to ensure a lapse in IRB approval does not occur. If IRB approval of your research lapses, you must stop new subject enrollment, and contact the Human Research Protection Program (HRPP) immediately.

6. Amendments and Changes. If you wish to amend or change any aspect of your research (such as research design, interventions or procedures, number of subjects, subject population, consent...
document, instruments, surveys or recruiting material), you must submit the amendment to the IRB for review using the Amendment/Modification Form. You **may not initiate** any amendments or changes to your research without first obtaining written IRB review and approval. The **only exception** is when it is necessary to eliminate apparent immediate hazards to subjects and the IRB should be immediately informed of this necessity.

7. **Adverse or Unanticipated Events.** Any serious adverse events, subject complaints, and all unanticipated problems that involve risks to subjects or others, as well as any research related injuries, occurring at Geisinger or at other performance sites must be reported to the IRB within **five** (5) days of discovery of the incident. You must also report any instances of serious or continuing problems, or non-compliance with the IRB’s requirements for protecting human research subjects. The only exception to this policy is that the death of a Geisinger research subject must be reported within 24-48 hours of discovery. All reportable events should be submitted to the IRB using the Adverse Event Problem Report Form available on the Geisinger website.

8. **Research Record Keeping.** You must keep the following research related records, at a minimum, in a secure location for a minimum of six years: the IRB approved research protocol and all amendments; all consent documents; recruiting materials; continuing review reports; adverse or unanticipated events; and all correspondence to and from the IRB.

9. **Reports to FDA and Sponsor.** When you submit the required annual report to the FDA or you submit required reports to your sponsor, you **must** provide a copy of that report to the Human Research Protection Program (HRPP) for the IRB. You may submit the report at the time of continuing IRB review.

10. **Provision of Emergency Medical Care.** When a physician provides emergency medical care to a subject without prior IRB review and approval, to the extent permitted by law, such activities will not be recognized as research nor the data used in support of research.

11. **Final reports.** When you have completed (no further subject enrollment, interactions, interventions or data analysis) or stopped work on your research, you must submit a Final Report to the IRB.

12. **On-Site Evaluations, FDA Inspections, or Audits.** If you are notified that your research will be reviewed or audited by the FDA, the sponsor, any other external agency or any internal group, you **must** inform the Human Research Protection Program (HRPP) immediately of the impending audit/evaluation.

If you have any questions or need assistance, please contact the Human Research Protection Program (HRPP) staff at (570) 271-8663.
Appendix 3: Johns Hopkins Community Physicians Research and Projects Committee Approval

July 20, 2012

Nancy Kass, ScD
Johns Hopkins University
School of Public Health
Professor
1809 Ashland Ave
Baltimore, MD 21205

Re: “Explaining Randomization”

Dear Dr. Kass,

The Johns Hopkins Community Physicians (JHCP) Research Committee has approved the first phase of this two phase protocol to distribute post flyers/posters, recruit patients, conduct focus groups, and request meeting space at JHCP’s EBMIC and Wyman Park practices for the time period of 7/20/12 – 1/31/13. Please be advised that the committee will need to review the second phase of this protocol once it is developed and approved by the IRB. This letter is your authorization for you to approach the Office Medical Directors (OMDs) and Practice Administrators (PAs) of the planned recruitment sites to determine whether they wish to have their practices participate in this study. Please include this letter with your correspondence to the sites. Attached is a listing of the JHCP sites with the contact information for the OMDs and PAs.

In keeping with JHCP policy, all flyers/posters will have the IRB number and/or approval/expiration date printed on them. The project staff is responsible for ensuring that the flyers/posters are removed at the end of the approval period. Maintaining an aesthetically pleasing workspace is a high priority and we greatly appreciate your attention to this detail. We would like to work with you as the trial develops to identify ways to maximize recruitment under these circumstances.

Please recall that your IRB certification currently expires on May 9th 2013 and an annual renewal is required. Send a copy of this as soon as it is available. Please provide us an annual update on your project and also let us know the results of your analysis. The JHCP RC must be informed of any adverse events as they occur, and any changes in protocol or recruitment strategies. In order to help us keep track of the progress of trials please send us your final IRB termination letter as soon as it is available. Finally, JHCP is interested in fostering the translation of clinical research into practice; please send us copies of publications stemming from your work so we can share them with our clinicians.

We will look forward to hearing from you and wish you success with your project.

Sincerely,

Norman Poulsen, MD
Regional Medical Director

RC-292
Appendix 4: Extended Methods Section for Aim 1 Qualitative Study Exploring Stakeholders’ Views of the Acceptability of Different Models of Consent, Disclosure, and Authorization

This study explored stakeholders’ views on the acceptability of implementing alternatives to prospective informed consent for pragmatic randomized controlled trials (PCTs) comparing drugs that are widely-used in clinical practice and similar in terms of their route of administration as well as their side effect profiles. To do so, this study conducted a series of 8 focus groups with patients and 18 semi-structured interviews with Institutional Review Board (IRB) members and researchers between July, 2012 and June, 2013. Qualitative methods were used because qualitative approaches are appropriate when little information exists about a given topic as well as when a research project aims to understand people’s perspectives or attitudes and the reasons for these views (Sugarman and Sulmasy, 2010, 193-195). Focus groups were used to explore patient perspectives because informed consent is not a topic that many patients are familiar with and therefore, having other people with whom to discuss this topic could help to spur discussion. IRB members and researchers, on the other hand, have more experience discussing human subjects research and informed consent and may be more comfortable expressing their thoughts without their colleagues present. This study was approved by the Johns Hopkins Bloomberg School of Public Health IRB as well as the Geisinger Health System IRB.

IV. Development of Materials for the Interviews and Focus Groups

Materials used for the interviews and focus groups included the following: recruitment materials, consent forms, in-depth interview and focus group guides,
descriptions of the migraine and hypertension case studies (described in greater detail below), descriptions of four different models of consent, disclosure, and authorization (also described in greater detail below), and participant surveys. The in-depth interview and focus group guides contained the following: a set of introductory questions, background information on comparative effectiveness research (CER) and the case studies, a set of discussion questions about the case studies, and a set of questions designed to elicit participants’ perceptions of the different models of consent, disclosure, and authorization. Each of these domains is described in greater detail below. All of the materials were developed by the student investigator (DW) and were reviewed and revised by a second member of the study team (NK).

Prior to beginning the study, all project materials were pilot tested. To pilot test the focus group materials, a student investigator (DW) conducted 3 pilot interviews with hypertension patients and 2 pilot interviews with migraine patients from the Johns Hopkins Community Physicians (JHCP) network who met the eligibility criteria for this study, as described below. To pilot test the interview materials, the student investigator conducted 2 pilot interviews with researchers from Johns Hopkins Health System (JHS) and 3 individuals who previously served on an IRB at JHS. All but one of the pilot interviews was conducted in person; the other was conducted by phone. Pilot interviews were recorded but not transcribed. The student investigator took structured notes during the interview and directly following the interview. All project materials were updated based on feedback provided by pilot participants. Changes that were made included:
(1) changing the description of the process of randomization in the case study information provided to patients from “flipping a coin” to “a computer selects” because patients felt that the “flipping a coin” language seemed unprofessional;

(2) adding details to the description of the case studies because IRB members felt that it was distracting that additional information was provided when the case study was being verbally described by the student investigator (DW) that was not available in the case study information sheet; and

(3) creating a PowerPoint presentation for the focus groups because one pilot participant suggested that it would be useful to have a visual to accompany the focus group discussion. The PowerPoint described the main points of the background information provided and listed the various discussion questions that participants were asked to talk about.

Additionally, minor changes were made to the language in the descriptions of the case studies, the descriptions of the different models of consent, disclosure, and authorization, and the in-depth interview and focus group guides to further clarify the information provided. Revised materials were submitted to the IRB and approved prior to the start of the study.

V. Study Sites and Study Sample

Focus groups and interviews were conducted at two locations: Johns Hopkins Health System (JHS) and Geisinger Health System (GHS). These two sites were selected because they differ in ways that may impact individual views on the appropriateness of implementing alternatives to prospective informed consent. GHS is a private, non-
academic institution located in rural Pennsylvania that serves a predominantly Caucasian patient population. Additionally, GHS has a strong commitment to “developing and refining an innovation infrastructure that can adapt to new evidence efficiently, and rapidly translate that evidence into care delivery, and focus on patient benefit in a setting where many (or most) patients would be excluded from randomized trials because of age, comorbidities, and other limiting factors” (Paulus et al, 2008). JHS is situated within a large academic medical center located largely in an urban setting- Baltimore, Maryland and serves a racially diverse patient population. Although there is significant ongoing research within this institution, JHS arguably does not have internal and direct feedback loops for researchers’ findings to be integrated into the health system’s clinical guidelines and formularies.

a. Patient Focus Groups

As described in greater detail below, during the focus groups and interviews, two hypothetical case studies developed for this project were presented. The first case study described a PCT comparing widely-used drugs used to treat migraines and the second case described a PCT comparing widely-used drugs used to treat hypertension. Since individuals who have been diagnosed with a given health condition generally have more knowledge of that condition and the treatments for that condition and it was thought that knowledge made the topics discussed during the focus group more relevant, only individuals who had been diagnosed with either migraines or hypertension were eligible to participate in the focus groups. Specifically, 4 of the 8 focus groups (2 at each site) were attended by individuals who had been diagnosed with migraines and the other 4 (2
at each site) were attended by individuals who had been diagnosed with hypertension (table A.1). To be eligible, individuals also had to be over the age of 18 and had to have been receiving their health care within the health care system where the focus group was taking place for at least 1 year to ensure that they had some familiarity with the system.

<table>
<thead>
<tr>
<th>Focus Group</th>
<th>Institution</th>
<th>Composition</th>
<th>Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Geisinger</td>
<td>Adults diagnosed with hypertension</td>
<td>Hypertension study</td>
</tr>
<tr>
<td>B</td>
<td>Geisinger</td>
<td>Adults diagnosed with hypertension</td>
<td>Hypertension study</td>
</tr>
<tr>
<td>C</td>
<td>Geisinger</td>
<td>Adults diagnosed with migraine</td>
<td>Migraine study</td>
</tr>
<tr>
<td>D</td>
<td>Geisinger</td>
<td>Adults diagnosed with migraine</td>
<td>Migraine study</td>
</tr>
<tr>
<td>E</td>
<td>Johns Hopkins</td>
<td>Adults diagnosed with hypertension</td>
<td>Hypertension study</td>
</tr>
<tr>
<td>F</td>
<td>Johns Hopkins</td>
<td>Adults diagnosed with hypertension</td>
<td>Hypertension study</td>
</tr>
<tr>
<td>G</td>
<td>Johns Hopkins</td>
<td>Adults diagnosed with migraine</td>
<td>Migraine study</td>
</tr>
<tr>
<td>H</td>
<td>Johns Hopkins</td>
<td>Adults diagnosed with migraine</td>
<td>Migraine study</td>
</tr>
</tbody>
</table>

At GHS, a random sample of 100 migraine patients and 100 hypertension patients who met the eligibility criteria and who lived within a short distance of the health care facility in Danville, PA were identified through Geisinger’s electronic medical record system. This sample of patients was then mailed an invitation letter from the staff at GHS after approval from the patient’s primary care physician had been obtained. The letter informed individuals about how to opt out of the study and also informed them that if they did not opt out, they would receive a follow-up telephone call to inquire about their interest in participating in the study. The phone survey unit at GHS then called individuals who did not opt out until a sufficient number of individuals had been recruited to the focus groups. Of the 200 eligible individuals who were mailed an invitation letter about this study, 21 individuals opted out (6 migraine patients and 21 hypertension patients) and 156 were called by the calling center in order to identify a sufficient number of individuals for the focus groups (71 migraine patients and 85
hypertension patients). Of those, 34 individuals (16 migraine patients and 18 hypertension patients) signed up to participate in one of the four focus groups and a total of 22 individuals ended up actually participating.

Due to a combination of resource constraints and JHS not having the built-in infrastructure for research recruitment that GHS has, it was not possible to use this same method to recruit participants from JHS. Instead, to identify individuals who were willing and eligible to participate at JHS, recruitment posters were hung in exam rooms and waiting rooms at two clinics within the JHCP network. JHCP is a network of health care clinics located throughout the state of Maryland. Individuals were recruited from either the Wyman Park clinic or the Canton Crossing clinic, which are both located in Baltimore, MD, in order to ensure that it was a short distance for individuals to attend the focus groups. The recruitment posters contained information on the purpose of the study, the eligibility criteria, the amount of compensation given to participants, and contact information. Patients who were interested in participating and who believed they were eligible were asked to contact the student investigator by phone or email. The student investigator then described the research study in more detail to those who called and screened individuals to verify that they met the eligibility criteria. A total of 21 individuals from JHCP (10 migraine patients and 11 hypertension patients) called the recruitment phone number after seeing the recruitment flyer posted in their clinic. Of those, 16 ended up participating in one of the four focus groups (8 migraine patients and 8 hypertension patients). The others did not participate because they were ineligible, unavailable, or did not attend the focus group after confirming that they would attend.
All focus group participants with given a $60.00 VISA gift card to compensate them for their time.

b. IRB Member and Research Interviews

IRB members from both institutions were eligible if they were either an IRB chair or if they had been an IRB member for 1 year or longer. This was to ensure that participants had experience dealing with issues of research oversight and informed consent for different types of research. IRB community members were also eligible to participate as these individuals provide both considerable IRB experience as well as the perspective of a non-scientist. Researchers were eligible to participate if they had experience conducting a CER project and/or if they were identified by their colleagues as having expertise in the field of CER. The investigators determined if individuals had experience conducting an RCT by reviewing their peer reviewed publications as well as their biographical sketches, if available.

At GHS, once eligible individuals were identified by the study investigators, a purposefully-selected sub-sample of those individuals was sent an introductory email by an investigator from GHS. Specifically, IRB chairs were invited to participate first as well as researchers who had more experience conducting CER studies. This email provided a brief explanation of the study, mentioned that an investigator from Johns Hopkins would contact them by email and provide additional details, and provided instructions regarding how to opt out of the study. A week later, an invitation email was sent from the student investigator (DW) at Johns Hopkins to all individuals who did not opt out. This email provided information about the study and indicated that the student
investigator would follow-up regarding scheduling an interview. The email also provided clear instructions on how to opt out of the study. If invited individuals did not respond or opt out within a week, they were contacted by telephone to seek their willingness to schedule an interview. Additional individuals were recruited from the list of eligible IRB chairs and longstanding members and researchers using this same recruitment method until data saturation were reached. A total of 7 researchers were invited to participate and of those, 5 were interviewed. Additionally, 5 IRB chairs or longstanding members and 3 IRB community members were invited to participate and of those, 3 chairs or longstanding members agreed to participate and were interviewed. No IRB community members agreed to be part of this study. Also, one of the researcher interviews was later dropped from the data analysis because the participant did not speak English very well and it was not clear that she understood the concepts or materials. This participant did not present any new themes or information that was not already discussed in other interviews.

A similar process was followed to recruit participants from JHS. Again, a purposefully-chosen sub-sample of individuals was selected from the list of eligible individuals. Again, IRB chairs were invited to participate first as well as researchers who had more experience conducting CER studies. Researchers were sent an invitation letter that explained the study and indicated that the investigator would follow-up regarding scheduling an interview. The email also provided clear instructions on how to opt out of the study. The email was sent by a student investigator at JHS (DW) and was co-signed by an academic comparative effectiveness researcher from JHS as it was felt that researchers may be more responsive if they were aware that one of their colleagues supported this study. If invited individuals did not respond or opt out within a week, they
were contacted by telephone to see if they were willing to schedule an interview. Eligible IRB members were sent an introductory email from the director of human subjects research operations. This email provided a brief explanation of the study and mentioned that the student investigator (DW) would be following up with additional details. Shortly after, an invitation email, which provided a more detailed explanation of the study and also provided information about how to opt out, was sent from the student investigator (DW). If individuals did not respond within a week, they received a follow-up telephone call. Participants were recruited using this same recruitment method until data saturation was reached. A total of 7 researchers were sent invitation emails inquiring about their willingness to participate in this study. Of those, 4 were interviewed. Additionally, a total of 8 IRB chairs or longstanding members and 6 IRB community members were invited to participate and of those, 3 chairs and 3 community members were interviewed.

VI. Focus Group and Interview Structure

At the beginning of each focus group and interview, oral informed consent was obtained from participants. All focus groups were conducted in-person by the student investigator from Johns Hopkins (DW). A note-taker was also present at each of the focus groups. Each of the interviews was conducted by the same student investigator (DW). Interviews with professionals from GHS were conducted by phone. A majority of the interviews with professionals from JHS were conducted in-person with the exception of one, which was conducted by phone. All focus group and interview discussions were recorded and later transcribed. The interviews and focus groups all followed the same structure. The only minor difference was that a PowerPoint presentation was developed.
to supplement the information that was provided to focus group participants. No PowerPoint presentation was used during the interviews.

a. Introductory Questions

At the beginning of each focus group and interview, participants were asked several introductory questions. Patient participants were asked to introduce themselves, and to discuss how long they had had either migraines or hypertension, whether they had ever been asked to participate in a medical research study, what they believe the term ‘medical research’ meant, and whether they thought it was important to conduct more research about treatments for migraines or hypertension. IRB members and researchers were asked a series of close-ended questions about their professional experience and their perceptions of the current regulations governing the practice of informed consent. The purpose of the introductory questions was to get the participants comfortable talking about medical research and informed consent and to obtain some background information.

b. Discussion of a Hypothetical Case Study

Following these introductory questions, participants were given a brief description of CER and were then read one of two hypothetical case studies developed for this project. Both case studies described a PCT designed to compare two FDA approved and widely-used drugs that are both taken orally and that are similar in terms of their side effect profiles. Participants were told why doing the hypothetical trial was important and what participation in that hypothetical trial would entail, including who would be eligible
for the study, that individuals enrolled in the study would receive one of the drugs through a process of random assignment, and that there would be some minimal additional burdens imposed on individuals enrolled in the hypothetical trial. Focus group and interview participants were also told how being enrolled in the study was different from receiving clinical care outside of the study.

One of the hypothetical case studies described a trial comparing anti-hypertension drugs to each other, and the other described a trial comparing drugs taken by patients to relieve migraine pain. Patients in focus groups reviewed the case study that related to the health condition that they had (either migraines or hypertension) whereas researchers and IRB members were assigned to one of the two cases such that about half of the interviewees reviewed the migraine case and the other half reviewed the hypertension case. These two disease areas were selected for several reasons. First, both conditions are highly prevalent in the United States and therefore pose a significant public health burden. In addition, for both conditions, there are a diverse set of therapies (both generic and brand name) that are prescribed to patients and there is a lack of information regarding the comparative effectiveness of these different therapies. There are also significant variations in the costs of the therapies. However, these conditions are also of interest because they differ from one another in notable ways. While migraines are a symptomatic condition, hypertension is a silent disease. In addition, while migraines are an acute, episodic condition, hypertension is a chronic condition. Therefore, although these conditions are amenable to the implementation of a PCT, they differ in ways that may affect individuals’ perceptions about the disease and treatments. As a result, these
differences may also affect their views about participation in a randomized trial and, in turn, about appropriate models of consent, disclosure, or authorization.

The two case studies were the same except for slight differences in the additional burdens imposed on study participants. In both of the case studies, participants in the hypothetical study would be asked to complete short surveys after they saw their doctor. The surveys would ask questions about patients’ use of and level of satisfaction with the drug they were prescribed. In addition, in the hypertension case, participants would be asked to return to the clinic two additional times beyond what is usually done as part of standard clinical care to have their blood pressure checked by a nurse. In the migraine case, participants would be asked to write down information about the next three migraines they experienced after being prescribed a drug. The information requested includes the time when the individual first felt migraine pain and how bad that pain was, the time when the individual took the medication he or she was prescribed, how bad the migraine pain was 15 minutes, 30 minutes, 1 hour, and 2 hours after taking the drug, and whether the migraine returned within 24 hours of it going away. The purpose of reviewing these two case studies was to facilitate discussion and to provide a more concrete example to which study participants could react.

After reviewing the hypothetical case studies with participants, the student investigator (DW) asked several discussion questions about the case. Specifically, focus group and interview participants were asked to discuss any risks of harm to patients who might enroll in the hypothetical case study trial and any benefits to patients who might enroll. Focus group and interview participants were also asked about any social benefits that could result from the hypothetical case study trial being conducted. Additionally,
interview participants only (IRB members and researchers) were asked whether they were aware of any trials like the one described in the case study. These questions were asked because of a view that respondents' perceptions of the risks and benefits as well as their perceptions of the number of trials like the ones described in the case study might relate to their views on the acceptability of the different models of consent, disclosure, and authorization for these particular case studies.

c. Discussion of Four Different Models of Consent, Disclosure, and Authorization

After the discussion of the hypothetical case study, participants were told about four different models of consent, disclosure, and authorization (table A.2) and were asked to consider the acceptability of each model as a way of enrolling individuals in the hypothetical case studies. Specifically, participants were read a description of each model and were told what some people may view as the pros and cons of it. The reason for providing some information on what people may see as the pros and cons of each model was so participants had some knowledge of the trade-offs involved in choosing between the different models. After being read each description, participants were asked their initial reactions to the model as well as if they had any questions about the model. Most interviewees and all focus group participants were also told that a major difference between models 2 and 3 versus model 4 is the amount of information provided to eligible individuals. With models 2 and 3, patients who are eligible for one of the hypothetical case studies are told about the study and what study participation entails. The amount of information provided about the drugs is similar to the amount of information provided as
part of standard clinical care, meaning patients are told about the main risks and are given additional information when they pick up the drug at the pharmacy. With model 4, patients are also provided with information on the study and what study participation entails. However, when this model is used, the amount of information provided is typical of a standard informed consent form meaning individuals are told about all of the risks associated with a drug as well as what the alternatives to study participation are.

<table>
<thead>
<tr>
<th>Table A.2: Description of Four Models of Disclosure and Authorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
</tr>
<tr>
<td>Model 1: Disclosure of institutional policy</td>
</tr>
<tr>
<td>• Individuals in a health care system are informed broadly that the system engages in CER of widely-used interventions and that sometimes patients are enrolled in these studies if they already need that general type of medicine.</td>
</tr>
<tr>
<td>• Patients who might have been given either of the drugs in the study anyways might automatically be enrolled in these studies if they are eligible.</td>
</tr>
<tr>
<td>• Patients are also informed how rights and interests are protected.</td>
</tr>
<tr>
<td>Model 2: Study specific disclosure with no routine option to opt out</td>
</tr>
<tr>
<td>• Patients are told that their health care system does a lot of medical research studies to compare widely-used drugs to each other to figure out which drugs work best.</td>
</tr>
<tr>
<td>• If a patient is eligible for one of these studies, that patient is told about the study and then enrolled.</td>
</tr>
<tr>
<td>• Patients can opt-out of the study, although they are not told this explicitly.</td>
</tr>
<tr>
<td>Model 3: Study specific disclosure with an explicit option to opt out</td>
</tr>
<tr>
<td>• Patients are told that their health care system does a lot of medical research studies to compare widely-used drugs to each other to figure out which drugs work best.</td>
</tr>
<tr>
<td>• If a patient is eligible for one of these studies, that patient is told about the study and is also told that if he or she does not want to be part of the study, he or she can opt-out.</td>
</tr>
<tr>
<td>• If a patient does not opt-out, he or she is enrolled in the study.</td>
</tr>
<tr>
<td>Model 4: Prospective informed consent</td>
</tr>
<tr>
<td>• Patients are told that their health care system does a lot of medical research studies to compare widely-used drugs to each other to figure out which drugs work best.</td>
</tr>
<tr>
<td>• If a patient is eligible for one of these studies, that patient is told about the study and then asked if they would like to be a part of the study before being enrolled.</td>
</tr>
</tbody>
</table>

After being told about all four models and providing their initial reactions, participants were asked a series of discussion questions about each of the models. Specifically, for each model, participants were asked the following:
(1) Please discuss whether or not you think this is an acceptable way of telling people about the medical research study we just discussed.

(2) Please discuss what you think the benefits of using this approach are, if any.

(3) Please discuss any concerns you have about this approach, if any.

Patients were also asked to discuss how they would feel if their health care system used the different models to tell them about the hypothetical medical research study described in the case. Following this discussion, participants were asked to discuss which model they felt was the best way of telling patients about the medical research study described in the case.

At the very end of the focus groups and interviews, participants were asked to complete short surveys. The patient surveys contained demographic questions as well as questions about several topics including past experience participating in research and perceptions of the importance of research. The survey also contained the 4 item “Trust in Medical Researchers” scale, which was validated in a national survey (Hall et al, 2006). The IRB member and research surveys also contained some demographic questions as well as questions about the participant’s experience conducting human subjects research and his or her past experience participating in research.

The materials used during the interviews and focus groups were very similar. The only difference was that patients were provided with more information on key concepts such as medical research, CER, randomization, and selection bias. Additionally, at the end of the interviews, IRB members and researchers were asked four additional “variation questions”. Specifically, these individuals were asked if and how their
perceptions of the acceptability of the models would change in response to several variations on the case study:

1. The case study trial compared drugs that are administered differently
2. The case study trial compared drugs that had very different side effect profiles
3. The case study trial compared drugs that differently in terms of costs, even if patient in the trial would not be expected to pay for the drugs
4. The case study trial placed an even greater burden on participants

VII. Data Management and Analysis

Following each focus group or interview, the student investigator typed up her notes from the interview. She also noted key themes, any issues that arose, and ways to improve future focus groups or interviews. Additionally, the audio recording was sent out for transcription. When transcripts were received, all identifiable information was redacted from those transcripts. Transcripts were then checked against the audio recording and any mistakes were corrected. During this review, important or significant quotes were highlighted and additional themes were noted. Then, focus groups and interview transcripts were read more carefully and a coding scheme was developed. Once the coding scheme was finalized, all transcripts were read again and coded. Following this, a second coder used the coding scheme to independently code three transcripts (1 focus group transcript, 1 interview transcript from an interview with a researcher, and 1 interview transcript from an interview with an IRB member). The student investigator (DW) then checked the coded transcripts for consistency. Because there was a high level of consistency among the way the codes were applied by the two coders, only minor
changes were made to the organization of the coding scheme. The coded transcripts were then reviewed a final time and summary documents that described the main themes from each of the focus groups and interviews were developed. The student investigator (DW) also noted how many interviewees discussed each specific code. For the focus group data, the student investigator noted how many focus groups discussed a certain theme, since recording numbers of participants would suggest false precision. Finally, major patterns were identified in the data.

Quantitative data from the surveys participants were asked to complete at the end of the interviews and focus groups were entered into excel, double checked to ensure accurate data entry, and analyzed to understand background characteristics of participants as well as some of their views on research.

Data reported in this dissertation relate to parts of this project that have to do with participants’ perceptions of the different models of consent, disclosure, and authorization for the hypothetical case studies. Data on patients’ perceptions of the importance of research, how patients prefer medical decisions to be made, and whether there is any relationship between these variables and the model of consent, disclosure, and authorization an individual prefers will be reported in a subsequent paper. Additionally, data on how interviewees’ opinions changed in response to the variations on the hypothetical case studies is not reported on in this dissertation but it will be described in a subsequent paper.
References


Appendix 5a: Participant Consent Form: Johns Hopkins/Geisinger Comparative Effectiveness Researchers

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH AND GEISINGER HEALTH SYSTEM

ORAL CONSENT SCRIPT FOR IN-DEPTH INTERVIEWS

[Johns Hopkins OR Geisinger] Health System Comparative Effectiveness Researchers

Study Title: Rethinking Informed Consent for Pragmatic Comparative Effectiveness Trials
Principal Investigator: Dr. Nancy Kass (Johns Hopkins)
Dr. Steven Steinhubl (Geisinger)

What you should know about this study

- You are being asked to join a research study.
- This consent form explains the research study and your part in the study.
- Please review it carefully and take as much time as you need.
- You are a volunteer. You can choose not to take part and if you join, you may quit at any time. There will be no penalty if you decide to quit the study.

Purpose of research project

This research project is being done to learn what people think are acceptable strategies for informed consent, disclosure, and authorization for randomized comparative effectiveness trials.

If you join this project, I will ask you to participate in an approximately one hour and a half long interview. During the interview, we will talk about one or two examples of medical research studies. Both of these are examples of what is often called "comparative effectiveness research". That is, in each example, the research we talk about will be comparing two different drugs to see which drug works better. One example will be about migraine medications and the other example will be about hypertension medications. The goal of our interview will be to talk through different approaches to informed consent, disclosure, and authorization that could be used for these hypothetical medical research studies.

We want to know what you think of the different approaches to informed consent, disclosure, and authorization that could be used for the medical research study described in the examples.
Why you are being asked to participate

You are being asked to participate because as a comparative effectiveness researcher, you have a lot of experience with speaking to people about medical research studies and asking them to participate.

Procedures

If you join this research study, you will be asked to participate in an interview. The interview will last approximately one hour and a half. At the beginning of the interview, you will be asked a couple of questions about your professional experience. You will also be asked a couple of questions about your opinions of the current regulations governing the practice of informed consent. Then you will be asked to talk about one or two examples of medical research studies. One of the medical research studies is designed to understand which of two drugs is best for patients with hypertension. The other medical research study is designed to understand which of two drugs is best for patients with migraines. Last, you will be asked questions about your opinions of a number of different models of informed consent, disclosure, and authorization that could be used for the example medical research studies. During the final 5 minutes of the interview, you will be asked to complete a short survey about your professional experience.

I would like to record this interview so that I can capture all that you say without having to take a lot of notes during the interview. All recordings will be erased as soon as they have been transcribed.

Risks/discomforts

This is a very low risk project. You do not have to answer any questions you would prefer not to answer. In this project, we are not asking you questions directly about yourself but rather we seek your professional opinion about how to explain comparative effectiveness research trials to patients.

Benefits

There is no direct benefit to you from being in this study. However, we do hope that the results will help improve the way medical researchers tell people about medical research studies and ask them to participate.

Protecting data confidentiality

All research projects carry some risk that information about you may become known to people outside of a study. There is a risk that someone may find out that you participated in this project. We will do everything we can to prevent that from happening.

We will not include any identifying information, such as your name, in any notes or transcripts from the interview. You will not be named in any reports that are written
based on this research project. The recording and transcript of the interview will be stored on a password-protected computer. Only the members of the research team will have access to this information, and they will not be allowed to share it with anyone else.

**Who do I call if I have questions or problems?**

- Call the principal investigator, Nancy Kass, at (410) 614-5579 if you have questions or complaints related to this study.

- Call or contact
  
  - For Johns Hopkins: the Johns Hopkins Bloomberg School of Public Health IRB Office if you have questions about your rights as a study participant. Contact the IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:

    Address: Johns Hopkins Bloomberg School of Public Health  
    615 Wolfe Street, Suite E1100  
    Baltimore, MD 21205

    Telephone: 1-410-955-3193  
    Toll Free: 1-888-262-3242  
    Fax: 410-502-0584  
    E-mail: irboffice@jhsph.edu

  - For Geisinger: the Human Research Protection Program staff of the Geisinger Institutional Review Board (which is a group of people who review the research to protect your rights) at (570) 271-8663.

**What does your voluntary permission mean?**

Your oral permission means:

- You have been informed about this study’s purpose, procedures, possible benefits and risks.
- You have been given the chance to ask questions.
- You have voluntarily agreed to be in this study.

**PERMISSION TO PROCEED**

Is it okay to proceed with the interview?
Appendix 5b: Participant Consent Form: Johns Hopkins/Geisinger Institutional Review Board Member

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH AND GEISINGER HEALTH SYSTEM

ORAL CONSENT SCRIPT FOR IN-DEPTH INTERVIEWS

[Johns Hopkins OR Geisinger] Health System Institutional Review Board Members

Study Title: Rethinking Informed Consent for Pragmatic Comparative Effectiveness Trials
Principal Investigator: Dr. Nancy Kass (Johns Hopkins)
Dr. Steven Steinhubl (Geisinger)

What you should know about this study

- You are being asked to join a research study.
- This consent form explains the research study and your part in the study.
- Please review it carefully and take as much time as you need.
- You are a volunteer. You can choose not to take part and if you join, you may quit at any time. There will be no penalty if you decide to quit the study.

Purpose of research project

This research project is being done to learn what people think are acceptable strategies for informed consent, disclosure, and authorization for randomized comparative effectiveness trials.

If you join this project, I will ask you to participate in an approximately one hour and a half long interview. During the interview, we will talk about one or two examples of medical research studies. Both of these are examples of what is often called "comparative effectiveness research". That is, in each example, the research we talk about will be comparing two different drugs to see which drug works better. One example will be about migraine medications and the other example will be about hypertension medications. The goal of our interview will be to talk through different approaches to informed consent, disclosure, and authorization that could be used for these hypothetical medical research studies.

We want to know what you think of the different approaches to informed consent, disclosure, and authorization that could be used for the medical research study described in the examples.
Why you are being asked to participate

You are being asked to participate because as an Institutional Review Board member, you have a lot of experience thinking about how to protect and respect individuals who are asked to participate in medical research studies.

Procedures

If you join this research study, you will be asked you to participate in an interview. The interview will last approximately one and a half hours. At the beginning of the interview, you will be asked a couple of questions about your professional experience. You will also be asked a couple of questions about your opinions of the current regulations governing the practice of informed consent. Then you will be asked to talk about one or two examples of medical research studies. One of the medical research studies is designed to understand which of two drugs is best for patients with hypertension. The other medical research study is designed to understand which of two drugs is best for patients with migraines. Last, you will be asked questions about your opinions of a number of different models of informed consent, disclosure, and authorization that could be used for the example medical research studies. During the final 5 minutes of the interview, you will be asked to complete a short survey about your professional experience.

I would like to record this interview so that I can capture all that you say without having to take a lot of notes during the interview. All recordings will be erased as soon as they have been transcribed.

Risks/discomforts

This is a very low risk project. You do not have to answer any questions you would prefer not to answer. In this project, we are not asking you questions directly about yourself but rather we seek your professional opinion about how to explain comparative effectiveness research trials to patients.

Benefits

There is no direct benefit to you from being in this study. However, we do hope that the results will help improve the way medical researchers tell people about medical research studies and ask them to participate.

Protecting data confidentiality

All research projects carry some risk that information about you may become known to people outside of a study. There is a risk that someone may find out that you participated in this project. We will do everything we can to prevent that from happening.

We will not include any identifying information, such as your name, in any notes or transcripts from the interview. You will not be named in any reports that are written
based on this research project. The recording and transcript of the interview will be stored on a password-protected computer. Only the members of the research team will have access to this information, and they will not be allowed to share it with anyone else.

**Who do I call if I have questions or problems?**

- Call the principal investigator, Nancy Kass, at (410) 614-5579 if you have questions or complaints related to this study.

- Call or contact

  - For Johns Hopkins: the Johns Hopkins Bloomberg School of Public Health IRB Office if you have questions about your rights as a study participant. Contact the IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:

    Address: Johns Hopkins Bloomberg School of Public Health
    616 Wolfe Street, Suite E1100
    Baltimore, MD 21205

    Telephone: 1-410-955-3193
    Toll Free: 1-888-262-3242
    Fax: 410-502-0584
    E-mail: irboffice@jhsph.edu

  - For Geisinger: the Human Research Protection Program staff of the Geisinger Institutional Review Board (which is a group of people who review the research to protect your rights) at (570) 271-8663.

**What does your voluntary permission mean?**

Your oral permission means:

- You have been informed about this study’s purpose, procedures, possible benefits and risks.
- You have been given the chance to ask questions.
- You have voluntarily agreed to be in this study.

**PERMISSION TO PROCEED**

Is it okay to proceed with the interview?
Appendix 5c: Participant Consent Form: Johns Hopkins/Geisinger Patients with Hypertension

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH
AND GEISINGER HEALTH SYSTEM

ORAL CONSENT SCRIPT FOR FOCUS GROUPS

[Johns Hopkins OR Geisinger Health System] Patients with Hypertension

Study Title: Rethinking Informed Consent for Pragmatic Comparative Effectiveness Trials
Principal Investigator: Dr. Nancy Kass (Johns Hopkins)
Dr. Steven Steinhubl (Geisinger)

What you should know about this study

- You are being asked to join a research study.
- This consent form explains the research study and your part in the study.
- Please read it carefully and take as much time as you need.
- You are a volunteer. You can choose not to take part and if you join, you may quit at any time. There will be no penalty if you decide to quit the study.

Purpose of research project

This research project is being done to figure out the best ways to tell people about medical research studies.

Today, we are asking you to be part of a 2-3 hour focus group. During the focus group, we will talk about an example of a medical research study. The goal of the medical research study example will be to figure out which of two drugs works better for people with high blood pressure. What we want to talk to you about today is different options for telling people about the high blood pressure study.

We want to know what you think of the different ways of telling people about the medical research study described in the example.

Why you are being asked to participate

Since the example is about a research study related to high blood pressure, we think the best people to give us advice on how to talk to patients about it are also people with high blood pressure. So we only want people to be part of this group today who have been receiving medical care at [Johns Hopkins OR Geisinger] Health System for high blood pressure. There will be between 6 to 8 people in each focus group.
Procedures

If you join this research study today, you will be asked to be part of a focus group. The focus group will last 2-3 hours. During the focus group, you will be asked to talk about an example of a medical research study that is designed to understand which of two drugs is best for patients with high blood pressure. The group will then discuss a number of different ways to tell people with high blood pressure about the medical research study example described.

At the end of the focus group, you will be asked to complete a short survey with some questions about yourself. The survey will also ask you what you think about medical research.

You should also know that this focus group discussion will be recorded so that we can keep track of the comments you make without having to take too many notes today. All recordings will be erased as soon as they have been transcribed.

Risks/discomforts

This is a very low risk project. You do not have to answer any questions you would prefer not to answer.

Benefits

There is no direct benefit to you from being in this study. However, we do hope that the results will help improve the way medical researchers tell people about medical research studies.

Payment

You will be given a $60 gift card for being part of the group today. This money is meant to cover your travel costs and the 2-3 hours you will spend in the focus group discussion. You will be paid at the end of the focus group. If you have to leave early, your payment will be given to you at the time you leave the focus group.

Protecting data confidentiality

All research projects carry some risk that information about you may become known to people outside of a study. There is a risk that someone may find out that you are in this project and that you have high blood pressure. We will do everything we can to prevent that from happening.

We will not include any identifying information, such as your name, in any notes or transcripts from the focus group. You will not be named in any reports that are written from this project. The recording and transcript of the focus group will be stored on a
password-protected computer. Only the members of the research team will have access to this information, and they will not be allowed to share it with anyone else.

The other members of the focus group will be asked not to discuss who else was part of the focus group.

**Protecting subject privacy during data collection**

To help protect everyone's privacy, only two people from the research team will be in the room during the focus group.

**What happens if you leave the focus group early?**

If you leave the focus group early, there will be no negative consequences to you. You will be given your payment for participation at the time you leave the focus group.

**Who do I call if I have questions or problems?**

- Call the principal investigator, Nancy Kass, at (410) 614-5579 if you have questions or complaints related to this study.

- Call or contact
  - For Johns Hopkins: the Johns Hopkins Bloomberg School of Public Health IRB Office if you have questions about your rights as a study participant. Contact the IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:
    - Address: Johns Hopkins Bloomberg School of Public Health
      617 Wolfe Street, Suite E1100
      Baltimore, MD 21205
    - Telephone: 1-410-955-3193
    - Toll Free: 1-888-262-3242
    - Fax: 410-502-0584
    - E-mail: irboffice@jhsph.edu
  - For Geisinger: the Human Research Protection Program staff of the Geisinger Institutional Review Board (which is a group of people who review the research to protect your rights) at (570) 271-8663.

**What does your voluntary permission mean?**

Your oral permission means:

- You have been informed about this study’s purpose, procedures, possible benefits and risks.
• You have been given the chance to ask questions.
• You have voluntarily agreed to be in this study.

PERMISSION TO PROCEED
Is it okay to proceed with the focus group?
Appendix 5d: Participant Consent Form: Johns Hopkins/Geisinger Patients with Migraines

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH
AND GEISINGER HEALTH SYSTEM

ORAL CONSENT SCRIPT FOR FOCUS GROUPS

[Johns Hopkins OR Geisinger] Health System Patients with Migraines

Study Title:  Rethinking Informed Consent for Pragmatic Comparative Effectiveness Trials
Principal Investigator:  Dr. Nancy Kass (Johns Hopkins)
                Dr. Steven Steinhubl (Geisinger)

What you should know about this study

• You are being asked to join a research study.
• This consent form explains the research study and your part in the study.
• Please read it carefully and take as much time as you need.
• You are a volunteer. You can choose not to take part and if you join, you may quit at any time. There will be no penalty if you decide to quit the study.

Purpose of research project

This research project is being done to figure out the best ways to tell people about medical research studies.

Today, we are asking you to be part of a 2-3 hour focus group. During the focus group, we will talk about an example of a medical research study. The goal of the medical research study example will be to figure out which of two drugs works better for people with migraines. What we want to talk to you about today is different options for telling people about the migraine study.

We want to know what you think of the different ways of telling people about the medical research study described in the example.

Why you are being asked to participate

Since the example is about a research study related to migraines, we think the best people to give us advice on how to talk to patients about it are also people with migraines. So we only want people to be part of this group today who have been receiving medical care at [Johns Hopkins OR Geisinger] Health System for migraines. There will be between 6 to 8 people in each focus group.
Procedures

If you join this study today, you will be asked to be part of a focus group. The focus group will last 2-3 hours. During the focus group, you will be asked to talk about an example of a medical research study that is designed to understand which of two drugs is best for patients with migraines. The group will then discuss a number of different ways to tell people with migraines about the medical research study example described.

At the end of the focus group, you will be asked to complete a short survey with some questions about yourself. The survey will also ask you what you think about medical research.

You should also know that this focus group discussion will be recorded so that we can keep track of the comments you make without having to take too many notes today. All recordings will be erased as soon as they have been transcribed.

Risks/discomforts

This is a very low risk project. You do not have to answer any questions you would prefer not to answer.

Benefits

There is no direct benefit to you from being in this study. However, we do hope that the results will help improve the way medical researchers tell people about medical research studies.

Payment

You will be given a $60 gift card for being part of the group today. This money is meant to cover your travel costs and the 2-3 hours you will spend in the focus group discussion. You will be paid at the end of the focus group. If you have to leave early, your payment will be given to you at the time you leave the focus group.
Protecting data confidentiality

All research projects carry some risk that information about you may become known to people outside of a study. There is a risk that someone may find out that you are in this project and that you have migraines. We will do everything we can to prevent that from happening.

We will not include any identifying information, such as your name, in any notes or transcripts from the focus group. You will not be named in any reports that are written from this project. The recording and transcript of the focus group will be stored on a password-protected computer. Only the members of the research team will have access to this information, and they will not be allowed to share it with anyone else.

The other members of the focus group will be asked not to discuss who else was part of the focus group.

Protecting subject privacy during data collection

To help protect everyone's privacy, only two people from the research team will be in the room during the focus group.

What happens if you leave the focus group early?

If you leave the focus group early, there will be no negative consequences to you. You will be given your payment for participation at the time you leave the focus group.

Who do I call if I have questions or problems?

- Call the principal investigator, Nancy Kass, at (410) 614-5579 if you have questions or complaints related to this study.

- Call or contact
  - For Johns Hopkins: the Johns Hopkins Bloomberg School of Public Health IRB Office if you have questions about your rights as a study participant. Contact the IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:

    Address: Johns Hopkins Bloomberg School of Public Health
              618 Wolfe Street, Suite E1100
              Baltimore, MD 21205

    Telephone: 1-410-955-3193
    Toll Free: 1-888-262-3242
    Fax: 410-502-0584
    E-mail: irboffice@jhsph.edu
For Geisinger: the Human Research Protection Program staff of the Geisinger Institutional Review Board (which is a group of people who review the research to protect your rights) at (570) 271-8663.

What does your voluntary permission mean?

Your oral permission means:
- You have been informed about this study’s purpose, procedures, possible benefits and risks.
- You have been given the chance to ask questions.
- You have voluntarily agreed to be in this study.

PERMISSION TO PROCEED
Is it okay to proceed with the focus group?
Appendix 6a: In-Depth Interview Guide: Comparative Effectiveness Researchers and Institutional Review Board Members

- Thank you for volunteering to help with this project. I appreciate your willingness to share your time and ideas.

- The goal of this project is to understand the best methods for describing to patients and asking patients to participate in comparative effectiveness trials comparing widely available drugs in order to understand which drugs work best.

- Just as a reminder, what you say here is confidential – your name will not be used in any of our write-ups

- So before we begin, is it alright with you if I record this discussion?

- Do you have any questions before we begin?

Close Ended Questions

- I would like to begin by asking a number of closed ended questions about your professional experience. [Not all questions were asked of all interviewees. Relevant questions were asked based on the expertise of the interviewee.]

1. How long have you been employed at [Johns Hopkins or Geisinger]?

2. How long have you been a member of the IRB?

3. Are you currently involved in the conduct of a prospective randomized control trial?

4. Have you ever been involved in the conduct of a prospective randomized control trial?

5. Do you have experience seeking informed consent for randomized control trials?
   a. Probe: What did you or do you think of the process?

6. Can you think of any recent IRB applications where the IRB had a difficult time deciding whether the application qualified for a waiver or alteration of informed consent or where the IRB wanted to implement a waiver and the regulatory people wouldn’t allow them to?
   a. Probe: Why did the IRB have a difficult time deciding?

7. How well do you think the current informed consent regulations do at protecting and respecting research subjects?
a. Probe: What changes, if any, do you think should be made to improve the current regulations?

**Explanation of the First Case Study**

- Today I would like to discuss a certain subset of comparative effectiveness trials
- That is ones that are:
  - conducted in routine clinical settings
  - compare two or more FDA approved and widely used drugs,
    - where there is considerable disagreement about which of the drugs work best, and
    - where there are not significant differences in how the drugs are administered or the side effects associated with the drugs.
  - And ones where patients are randomly assigned to treatment arms
- So that we have a more concrete example to discuss, I would like to go through a specific case study that describes a trial that meets this description
- Please turn to the first handout and feel free to take notes as we review it together.

1. Do you have questions before I start reading the case study?

[Read through one of the two case studies]

**Case Study Discussion Questions**

1. Are you aware of any trials like the one described in the case study meaning a trial that compares similar and widely used therapies to one another in a routine clinical setting that are currently ongoing? *Note: the study doesn’t have to be about blood pressure or migraine drugs

2. Can you describe what you believe are the risks of harm to people who participate in the kind of clinical trial described in the case study?

3. Can you describe what you believe are the benefits to patients who participate in the kind of clinical trial as well as the benefits to patients more broadly?

**Explanation of consent, disclosure, and authorization models**

- I would now like to discuss a number of different ways that patients could be informed about the trial described in the case study.

- As you are aware, prospective informed consent is generally required for all clinical trials involving individual randomization of patients.

- However, what I am interested in getting your perspective on is whether there are alternative, less burdensome models of consent, disclosure, or authorization (and I will describe what I mean by these terms shortly) that are acceptable to use in trials
comparing similar and widely used drugs to each other in the context of routine clinical care such as the trial described in the case.

- Again, you have a document that describes the different models as well as what some people view as the pros and cons of those different models that I would like to go through together

- Feel free to take notes and I will pause after each section for feedback

1. Do you have any questions or comments before we begin?

[Read second handout]

**Perceptions of the Different Models**

- I would now like to ask you some questions to understand what you think of the different models. For the sake of this project I would like to know what you think is acceptable and not what the current human subjects regulations require.

We will first start by discussing the first model: broad authorization [review models briefly].

1. Thinking about the case, please describe whether or not you think this is an acceptable method.
   a. Probe participants on why they think this is acceptable or not
      i. Can you tell me about why you think this is acceptable?
      ii. Can you tell me about why you don’t think is acceptable?
   b. If participants are discussing randomization, probe on why randomization is relevant.
   c. If participants point out other aspects of the study as being problematic, probe on why they think that part of the case study is problematic.

2. Describe what you think the benefits of using this approach are

3. Describe any concerns you have about this method
   a. Probe: Tell me about how important these concerns are to you

Now let’s turn to the second model: disclosure with no option to opt out.

1. Again, thinking about the trial described in the case, please describe whether or not you think this is an acceptable method.
   a. Probe participants on why they think this is acceptable or not
      i. Can you tell me about why you think this is acceptable?
      ii. Can you tell me about why you don’t think is acceptable?
   b. If participants are discussing randomization, probe on why randomization is relevant.
c. If participants point out other aspects of the study as being problematic, probe on why they think that part of the case study is problematic

2. Describe what you think the benefits of using this approach are

3. Describe any concerns you have about this method
   a. Probe: Tell me about how important these concerns are to you

Great – now let’s discuss the third way of telling patients. The only difference between this models and the way we just discussed is that if this model were used, patients would be able to tell a nurse that they would not like to be part of the trial.

1. Given this, please discuss how your opinions change if patients were able to tell someone involved in the trial that they would not like to be part of the study.

Finally, we will discuss informed consent.

1. Thinking about the case, please describe what you think are the benefits of using this approach

2. Discuss whether you think this approach is better or worse than the other approaches we described

Okay great. So…

1. Given our discussion today, please discuss what you think is the best way of telling patients about the example medical research study comparing drugs used to treat [migraine or hypertension].

Just a couple more questions.

- Can you describe how your opinions regarding the acceptability of the models would change if the case study trial were comparing 2 different drugs that are administered differently?
- Can you describe how your opinions would change if the therapies being compared had very different side effect profiles?
- Can you describe how your opinions would change if one of the therapies was much more costly than the other therapy even if patients in the trial would not be expected to pay for the therapies?
- Can you describe how your opinion would change if patients were required to attend even more follow up visits?
Appendix 6b: Focus Group Guide: Patients with Hypertension or Migraines

- Thank you for volunteering to help with this project. I appreciate your willingness to share your time and ideas.

- The goal of this project is to understand what the best ways are for telling patients about medical research studies. During this group discussion, I’m going to tell you about a particular type of medical research. I’m then going to ask your advice on how to explain this research to people, and how much explaining is needed.

- The focus group will last 3 hours. During this time, I’m hoping we can have a real discussion, meaning that I hope you’ll talk to each other at least as much as you talk to me. Feel free to disagree with what others have said or give another opinion: the more different ideas I hear, the more information I will have to work with. But also please be respectful of other members of the group.

- I will let you know when we are near the end of our time. If you have to go to the bathroom, just slip out quietly and come back as quickly as you can.

- At the very end of the discussion, I will ask you to complete a short survey where you will be asked to answer several questions about yourself and where you will be asked to provide any final thoughts you have based on today’s discussion. Once you have handed in your survey, you will receive a $60 visa gift card to show our appreciation for your participation in this focus group.

- Just as a reminder, what you say here is confidential – your name will not be used in any of our write-ups

- I also want to ask that none of you states your last name during the focus group discussion. You may even choose to not to use your real name during the focus group if you wish. If you prefer not to use your real name, feel free to make up another name that you would like people to use during the focus group.

- Also, once we leave the focus group, I would like to ask that you do not repeat what anyone else said during the focus group or tell other people who was part of this focus group with you.

- If you have any questions about this focus group or the project after we leave, you can me at 978-407-7265 or write me an email at dwhicher@jhsph.edu.

- So before we begin, is it alright with you if I record this discussion?

- Do you have any other questions before we begin the focus group?
Introductory Questions
I would now like to ask you a couple of introductory questions.

1. Please introduce yourself and tell us your first name. If you would prefer not to use your real name, feel free to make up another name that you would like people to use.

2. Can each of you please share how long you have had [high blood pressure or migraines] for?

3. Has anyone ever talked with you about being part of a medical research study – either related to your [high blood pressure or migraines] or to something else?

4. Please describe what the term ‘medical research’ means to you.

5. Please discuss whether you think more research about treatments for [migraine or high blood pressure] is important?

Explanation of the Case Example

- Today I want to talk to you about a particular type of research study for [high blood pressure or migraine] that might be done.

- Some research studies test brand new drugs to see if they work at all and might include a placebo. But the kind of study I want to talk to you about is different. Today we will be talking about medical research studies that compare drugs that doctors use all the time to treat patients with [high blood pressure or migraines] because they know that these drugs work. However, the reason they want to do a medical research study is because they do not know which one works the best.

- So we are talking about medical research studies where people in the study get 1 of 2 drugs that are given to patients with [high blood pressure or migraines] all the time by doctors. This means that none of the patients in the study will get a placebo.

- To begin the discussion, I am going to read you an example of a medical research study that fits this description that medical researchers might do to figure out what the best drug is to treat [high blood pressure or migraine]. Please note, this is a hypothetical research study – [Johns Hopkins or Geisinger] is not actually doing this.

- You have received a handout that describes the important points about this medical research study. Feel free to take notes on that sheet of paper while I read through the case with you and feel free to stop me at any point if you have questions. I will start by describing why this study might be done. I will then describe what would happen to patients who are in the study and finally, how being in the study is different from just getting ordinary clinical care without being in a study.

2. Does anyone have questions before I start reading about the example medical research study?
Case Example Discussion Questions

1. Please describe whether you think that the results from this medical research study will be useful for patients like you and your doctor.

2. Can you tell me about whether there are any risks of harm or bad things that could happen to patients if they are a part of the medical research study?

3. Can you tell me about whether there are any benefits or good things that could happen to patients if they are a part of the medical research study?

4. Can you tell me about whether there are any benefits or good things that could happen for other patients with [migraine or high blood pressure] at [Johns Hopkins or Geisinger] as a result of this medical research study being done?

Explanation of consent, disclosure, and authorization models

- Now that we have gone through the case study, I want to talk to you about a few different ways that doctors or medical researchers could tell patients about medical research studies going on in their clinics or hospitals.

- Today we will talk about 4 different ways that patients might be told about medical research studies like the one in the case example we just talked about.

- After we go through all 4, I will ask you what you think about these different ways of telling patients about the medical research study described in the case example.

- The next document in your folder describes the different ways patients might be told. Let’s go through this document together.

1. Are there any questions before we begin?

[Read through hand out on models of consent, disclosure, and authorization]

1. Are there any questions on any of the information we have discussed so far?

- Now I just want to quickly talk about how these models relate to the case study we talked about and what normally happens when patients go to see their doctor.

- When you go to your doctor’s office for an appointment, you are not generally asked for your permission for everything your doctor does. Instead, by going to your
doctor’s office, it is assumed that you are agreeing to allow the doctor to give you a check-up and to give you basic medical care if needed.

- Remember, the example medical research study we discussed is like what happens when you go to your doctor’s office because many patients who receive a drug to treat their [migraines or high blood pressure] are given one of the two drugs that patients who are part of the medical research study get.

- However, it is different from what happens when you go to your doctor’s office because patients in this medical research project are assigned one drug or the other based on a random assignment, meaning their treatment is chosen by a computer. Also, information about how well the drugs work at [relieving pain or reducing blood pressure] will be collected by medical researchers from patients who are part of the medical research study to help them figure out which drug is best.

Perceptions of the Different Models
Okay, now, given all the information we talked about today, I would like to understand your opinions about each of the 4 different ways patients might be told about medical research studies.

We will first start by discussing the first way of telling patients about medical research studies that is listed on your handout called “Broad Authorization” where patients are told that [Johns Hopkins or Geisinger] does a lot of studies like the one we discussed and patients are not told about every one.

4. Please discuss whether or not you think this is an acceptable way of telling people about the medical research study we just discussed.
   a. Probe participants on why they think this is acceptable or not
   b. If participant is discussing randomization, probe on why randomization is so problematic.
   c. If participants point out other aspects of the study as being problematic, probe on why they think that part of the case study is problematic.
   d. If participants describe changing the way care is delivered as being problematic, ask what are the kinds of changes that a doctor can make that you would not need to be told about?

5. Please discuss how you would feel if [Johns Hopkins or Geisinger] used this way of telling you about the medical research study we discussed earlier.

6. Please discuss what you think the benefits of using this approach are

7. Please discuss any concerns you have about this method
   a. Probe: Tell me about how important these concerns are to you

8. There are some medical research studies where nothing happens to patients. Instead, all that happens is that medical researchers look at your medical records.
Please discuss if you think this is an acceptable way of telling patients about medical research studies where researchers were only looking at information in people’s medical records.

Now let’s turn to the second model which involves telling patients about a specific medical research study, such as the one we discussed, without giving them a way to choose not to be part of the medical research study. Remember the key points about this way of telling people are on your handout.

4. Please discuss whether or not you think this is an acceptable way of telling people about the medical research study we just discussed.
   a. Probe participants on why they think this is acceptable or not
   b. If participants are discussing randomization, probe on why randomization is so problematic.
   c. If participants point out other aspects of the study as being problematic, probe on why they think that part of the case study is problematic

5. Please discuss how you would feel if [Johns Hopkins or Geisinger] used this way of telling you about the medical research study we discussed earlier.

6. Please discuss what you think the benefits of using this approach are

7. Please discuss any concerns you have about this method
   a. Probe: Tell me about how important these concerns are to you

Great – now let’s discuss the third way of telling patients. The only difference between this way of telling patients and the way we just discussed is that if this way of telling patients were used, patients would be able to tell a nurse that they would not like to be part of the medical research study.

8. Given this, please discuss how your opinions would change if patients were able to tell someone involved in the medical research study that they would not like to be part of the study.

Finally, we will discuss the last way of telling people about medical research studies that is listed on your handout. This where patients are told about the medical research study and are allowed to choose whether or not to participate.

3. Describe what you think are the benefits of using this way of telling people about and asking them to be part of the medical research study we just discussed.

4. Please discuss how you would feel if [Johns Hopkins or Geisinger] used this way of telling you about the medical research study we discussed earlier

5. Discuss whether or not you think this way of telling people is better or worse than the other ways we discussed
Okay great. I just have one final question.

1. Given our discussion today, please discuss what you think is the best way of telling patients about the example medical research study comparing drugs used to treat [migraine or hypertension].

We have come to the end of our discussion. I have reserved the last 15 minutes to allow you time to complete a short survey. Please select the answer to these questions that you feel best describes your feelings about these topics – there is no right or wrong answer – I am most interested in your own opinions. At the end of the survey you will be given the opportunity to provide any final thoughts you have based on today’s discussion. Please remember that you do not have to answer any questions that make you uncomfortable.

Thank you for participating - your opinions and ideas are very valuable. Once we leave the focus group, I would like to ask that you do not repeat any of the focus group discussion to others and please do not discuss who else participated in this focus group with you.
Appendix 7a: Case Studies: Hypertension Case Study Description

*This was the version of the case study provided to patients. The version provided to researchers and IRB members had less explanation of key concepts such as randomization.

The High Blood Pressure Medical Research Study: Case Study Information

Introduction

- Right now, there are many different drugs that are used to lower blood pressure for patients who have high blood pressure if diet and lifestyle changes are not enough. Some doctors start their patients on one of these drugs and some doctors start their patients on another.

- Even though all the drugs lower blood pressure and all of them are safe, doctors are not sure which one works the best at lowering blood pressure and reducing the chance that a patient will have a heart attack or a stroke. This is because not a lot of research has been done that compares these drugs to one another.

- Medical research studies that compare these drugs to each other can help us figure out which drug is the best at lowering blood pressure and reducing the chance that a person will have a heart attack or stroke. Therefore, [Johns Hopkins or Geisinger] would like to do a study to compare two drugs that are often used to lower blood pressure.

How would the medical research study work?

- Patients at [Johns Hopkins or Geisinger] with high blood pressure who need to start taking a drug to lower their blood pressure will be prescribed one of the two most commonly used drugs based on a random assignment.

- This means that a computer program will select one of the two drugs in the study and the patient’s doctor will prescribe that drug to the patient. Therefore, patients in the study have an equal chance of being prescribed either of the two drugs.

- The two drugs that are being studied are ones that patients would likely have been prescribed even if they were not in the medical research study. This means that patients in the medical research study are getting the same drugs as many patients who are not in the medical research study.
• Also, a patient can only be in the medical research study if that patient’s doctor determines that both drugs in the study are appropriate for treating the patient’s high blood pressure.

• Once patients are prescribed one of the drugs, they will see their doctor one week after they have started to take the drug, one month after they have started to take the drug, six months after, and 1 year after. This is the same number of times that patients would normally see their doctor even if they were not in the study.

• During these doctors’ appointments, the patient’s doctor will take the patient’s blood pressure. The doctor will also ask the patient how he or she is doing and if there have been any side effects. If the drug is not working or if the patient does not like the drug, the patient’s doctor can switch the patient to a different drug or can change the amount of the drug the patient takes.

• Patients will also be asked to complete a short survey after they see their doctor. Patients not in the study are not asked to complete this survey. The survey will ask:
  o what the patient likes or does not like about the drug
  o how often the patient took the drug
  o what time of day the patient usually took the drug, and
  o when the last time the patient took the drug was

• In addition, for the purposes of this medical research study, patients will be asked to return to the clinic 2 extra times to have their blood pressure read by a nurse.

• A copy of the extra blood pressure measurements and the patient’s survey responses will be given to the patient’s doctor so that the doctor can use this information to help figure out how well the drug is working for the patient.

• Medical researchers will compare the blood pressure measurements and survey results of patients in the medical research study who are taking one drug to the blood pressure measurements and survey results of patients taking the other drug. Medical researchers will also look at patients' medical records to see if any patients had a heart attack or stroke within 3 years of getting the drug.

How is that different from what would have happened to patients as part of ordinary clinical care?

• Patients in the medical research study are given a drug based on a random assignment. If a patient just went to his doctor, the patient’s doctor would select the drug for the patient that that doctor likes best.

• It is important to remember that even if a patient were not in the medical research study, it is very likely that his or her doctor would select one of the drugs given to
patients in the medical research study to treat the patient’s high blood pressure because each is a very safe drug that is used a lot to treat high blood pressure.

- Patients in the medical research study will see their doctor just as often as patients not in the medical research study. In addition, patients in the medical research study will be asked to go to the clinic 2 extra times to have their blood pressure read by a nurse.

- Patients in the medical research study will be treated the same way as other patients when they see their doctor. The only difference is that doctors of patients in the medical research study will have more information to help them figure out how well the drug is working because patients in the medical research study will be asked to complete a survey and will have their blood pressure read 2 additional times.

- After they see their doctor, patients in the medical research study will be asked to complete a short survey. Patients are not asked to complete surveys as part of ordinary clinical care.

- Medical researchers will look at the medical records of patients in the medical research study, which does not happen as part of ordinary clinical care.

- Patients who are part of the medical research study will be helping to figure out which drug is best for patients with high blood pressure. Understanding which drug is best is important for improving medical care for patients with high blood pressure.
Appendix 7b: Case Studies: Migraine Case Study Description

*This was the version of the case study provided to patients. The version provided to researchers and IRB members had less explanation of key concepts such as randomization.

The Migraine Medical Research Study:  
Case Study Information

Introduction

- Right now, there are many different drugs that are used to treat migraines. Some doctors start their patients on one of these drugs and some doctors start their patients on another.

- Even though they all relieve migraines and all of them are safe, doctors are not sure which one works the best. This is because not a lot of research has been done that compares these drugs to one another.

- Medical research studies that compare one of the drugs to another can help us figure out which drug is the best for treating migraines. Therefore, [Johns Hopkins or Geisinger] would like to do a study to compare two drugs that are often used to treat migraines.

How would the medical research study work?

- Patients at [Johns Hopkins or Geisinger] with migraines who need to start taking a drug to treat their migraines will be prescribed one of the two most commonly used drugs based on a random assignment.

- This means that a computer program will select one of the two drugs in the study and the patient’s doctor will prescribe that drug to the patient. Therefore, patients in the study have an equal chance of being prescribed either of the two drugs.

- The two drugs that are being studied are ones that patients would likely have been prescribed even if they were not in the medical research study. This means that patients in the medical research study are getting the same drugs as many patients who are not in the medical research study.

- Also, a patient can only be in the medical research study if that patient’s doctor determines that both drugs in the study are appropriate for treating the patient’s migraines.

- Once patients get a drug, they will be asked to write down the following information for the next three migraines they experience:
The time they first felt migraine pain and how bad the migraine pain was
The time when they took the drug they were prescribed
How bad the migraine pain was 15 minutes, 30 minutes, 1 hour, and 2 hours after taking the drug
If the migraine pain returned within 24 hours of it going away

- Patients will give this information to their doctor at their next appointment.

- During the next doctor’s appointment, the patient’s doctor will review this information with the patient and will ask the patient if he or she has had any side effects. The doctor will then provide the patient with information on how well the drug seems to be working compared to how well it can be expected to work. If the drug is not working or if the patient does not like the drug, the patient’s doctor can switch the patient to a different drug or change the amount of the drug the patient takes.

- Patients will be asked to complete a short survey after they see their doctor. Patients not in the study are not asked to complete this survey. The survey will ask:
  - What the patient likes or does not like about the drug
  - How many times the patient has taken the drug since it was prescribed
  - If the patient takes the drug every time they experience migraine pain

A copy of the patient’s survey responses will be given to the patient’s doctor so the doctor can use the information to help figure out how well the drug is working.

- Medical researchers will compare the survey responses and information written down by patients who are taking one drug in the medical research study to the survey responses and information written down by patients taking the other drug. Medical researchers will also look at patients' medical records to see if the patients had any side effects or switched drugs.

How is that different from what would have happened to patients as part of ordinary clinical care?

- Patients in the medical research study are given a drug based on a random assignment. If a patient just went to his doctor, the patient’s doctor would select the drug for the patient that he or she likes best.

- It is important to remember that even if a patient were not in the medical research study, it is very likely that his or her doctor would select one of the drugs given to patients in the medical research study to treat the patient’s migraines because each is a very safe drug that is used a lot to treat migraines.

- Patients in the medical research study are asked to write down information about how fast the drug relieved their migraine pain. Patients are not asked to write down this information as part of ordinary clinical care.
• Patients in the medical research study are treated the same way as other patients when they see their doctor. The only difference is that doctors of patients in the medical research study will have more information to help them figure out how well the drug is working because patients in the medical research study will be asked to write down information about each migraine they experience and to complete a survey.

• After they see their doctor, patients in the medical research study will be asked to complete a short survey. Patients are not asked to complete surveys as part of ordinary clinical care.

• Medical researchers will look at the medical records of patients in the medical research study as well as the information they recorded in the survey and at home, which does not happen as part of ordinary clinical care.

• Patients who are part of the medical research study will be helping to figure out which drug is best for patients with migraines. Understanding which drug is best is important for improving medical care for patients with migraines.
Appendix 8: Description of the Models of Consent, Disclosure, and Authorization

Ways of Telling Patients about Medical Research Studies:
Information Sheet

1. **Broad Authorization:** Patients are told that [Johns Hopkins or Geisinger] does a lot of medical research studies to compare widely used drugs to each other to figure out which drugs work best. Patients who might have been given either of the drugs in the study anyway might automatically be enrolled in these studies if they are eligible.

How it would work.
- When this way of telling patients is used, patients are told that medical research studies like the study described in the case example that compare safe and widely used drugs to each other are done all the time at [Johns Hopkins or Geisinger] and patients are sometimes included in studies when they need that general type of medicine.

- This means that patients are not told every time a study comparing safe and widely used drugs is done.

- This is so that [Johns Hopkins or Geisinger] can quickly do these medical research studies and use the information to improve the care they provide to patients.

- If patients want to find out more about medical research studies that [Johns Hopkins or Geisinger] is doing, they can call a research office to get more information.

Why some people like this.
- This way of telling patients takes the least amount of time, which means that more busy doctors and nurses will participate. If more doctors and nurses participate, more of their patients will also be part of the study meaning the study can potentially be completed in a shorter amount of time.

- This also means that there will likely be many different kinds of patients who are part of the medical research study which would allow researchers to see which drug works best for all different types of patients. This is important because sometimes one drug can be the best for a patient with certain traits while another drug can be best for a patient with different traits.

- This way of telling patients costs the least amount of money.

Why some people DO NOT like this.
- Patients will not know every time they are part of a medical research study.

- Patients will not always be able to say whether or not they want to be part of a medical research study.
• Patients may be asked to do extra things like [write down information about their migraines or go see their doctor two extra times] that they would not normally have to do even though they were not asked if they wanted to be part of the medical research study.

2. Disclosure with No Routine Option to Opt Out: Patients are told that [Johns Hopkins or Geisinger] does a lot of medical research studies to compare widely used drugs to each other to figure out which drugs work best. Patients who might have been given either of the drugs in the study anyway are also told about each study they are eligible for. Patients might then automatically be enrolled in these studies if they are eligible.

How it would work.
• Patients at [Johns Hopkins or Geisinger] are told that sometimes medical research studies comparing safe and widely used drugs to each other are done to figure out which drug is best.

• Patients are also given more information about each medical research study they could be a part of. Patients are told that everyone who is part of the medical research study will get the same kind of medical treatments as patients not in the study.

• After patients are told about the medical research study, they are told that in order to help [Johns Hopkins or Geisinger] figure out which drug is best, they will be enrolled in the study.

• If, after being told about the study, a patient says that he or she does not want to be a part of it, that patient will not be included in the study.

Why some people like this.
• Patients will be told about each medical research study that [Johns Hopkins or Geisinger] is doing that they could be included in.

• This way of telling patients takes less time than the other two ways described next, which means that more busy doctors and nurses will participate. If more doctors and nurses participate, more of their patients will also be part of the study meaning the study can potentially be completed in a shorter amount of time.

• This also means that there will likely be many different kinds of patients who are part of the medical research study which would allow researchers to see which drug works best for all different types of patients. This is important because sometimes one drug can be the best for a patient with certain traits while another drug can be best for a patient with different traits.

• This way of telling patients still does not cost very much.
Why some people DO NOT like this.
- Patients will not be told that they do not have to be in the study.

- Patients may be asked to do extra things like [write down information about their migraines or go see their doctor two extra times] that they would not normally have to do even though they were not asked if they wanted to be part of the medical research study.

3. **Disclosure with an Option to Opt Out**: Patients are told that [Johns Hopkins or Geisinger] does a lot of medical research studies to compare widely used drugs to each other to figure out which drugs work best. Patients who might have been given either of the drugs in the study anyway are also told about each study they are eligible for. Patients might then be enrolled in these studies but are told that if they do not want to be part of the medical research study, they don’t have to.

**How it would work.**
- Patients at [Johns Hopkins or Geisinger] are told that sometimes medical research studies comparing safe and widely used drugs to each other are done to figure out which drug is best.

- Patients are also given more information about each medical research study they could be a part of. Patients are told that everyone who is part of the medical research study will get the same kind of medical treatments as patients not in the study.

- After patients are told about the medical research study, they are told that in order to help [Johns Hopkins or Geisinger] figure out which drug is best, they will be enrolled in the study.

- Patients are also told that if they do not want to be part of the medical research study, they can talk to a study nurse at the front desk or talk to their own doctor and they will not be included in the medical research study.

Why some people like this.
- Patients will be told about each medical research study that [Johns Hopkins or Geisinger] is doing that they could be a part of.

- Patients are able to choose whether or not to be in the medical research study.

- This way of telling patients takes less time and costs less money than the way of telling patients described next.

Why some people DO NOT like this.
- Patients have to tell someone if they do not want to be part of the medical research study instead of being asked if they would like to be a part of it.

- Some patients may choose not to be part of the medical research study even though those patients benefit from other people being part of medical research studies.
• Some patients may choose not to be part of the medical research study even though it is very likely that nothing bad will happen to them if they are in the study.

• If some patients choose not to be part of the medical research study, there will not be any information about which drug is best for those patients and it may also take longer to figure out which drug is best overall.

4. **Prospective Informed Consent**: Patients are told that [Johns Hopkins or Geisinger] does a lot of medical research studies to compare widely used drugs to each other to figure out which drugs work best. Patients are also told about each study they are eligible for. Patients who might have been given either of the drugs in the study anyway are then asked if they would like to be a part of the study before they are enrolled.

**How it would work.**

• Patients at [Johns Hopkins or Geisinger] are told that sometimes medical research studies comparing safe and widely used drugs to each other are done to figure out which drug is best.

• Patients are also given more information about each medical research study they could be a part of. Patients are told that everyone who is part of the medical research study will get the same kind of medical treatment as patients not in the study.

• Patients are asked whether or not they would like to be part of the medical research study.

• If patients would like to be a part of the medical research study, they are enrolled in it.

**Why some people like this.**

• Patients will be told about each medical research study that [Johns Hopkins or Geisinger] is doing that they could be a part of.

• Patients are asked whether or not they would like to be part of the medical research study.

**Why some people DO NOT like this.**

• This way of telling people takes the most time and costs the most money.

• Many patients may choose not to be part of the medical research study even though those patients benefit from other people being part of medical research studies.
• Some patients may choose not to be part of the medical research study even though it is very likely that nothing bad will happen to them if they are in the medical research study.

• If some patients choose not to be part of the medical research study, there will not be any information about which drug is best for those patients and it will take longer to figure out which drug is best.
Appendix 9a: Survey for Researchers and Institutional Review Board Chairs/Longstanding Members

Please answer the following questions.

1. What is your gender?
   □ Male
   □ Female

2. What is your age?
   □ Under 30
   □ 30-39
   □ 40-49
   □ 50-59
   □ 60-69
   □ 70-79
   □ 80 or over

3. What is your ethnicity?
   □ Hispanic
   □ Non-Hispanic

4. What is your race? (You may select more than one)
   □ American Indian or Alaska Native
   □ Asian
   □ Black or African American
   □ Native Hawaiian or Other Pacific Islander
   □ White or Caucasian
   □ Other

5. How long have you been employed at [Johns Hopkins or Geisinger]?
   □ Less than 1 year
   □ 1-3 years
   □ 4-6 years
   □ 7-10 years
   □ Greater than 10 years

6. [Only asked on IRB member survey] How long have you been a member of the [Johns Hopkins or Geisinger] IRB?
   □ 1-3 years
   □ 4-6 years
   □ 7-10 years
   □ Greater than 10 years
7. Do you currently see patients clinically?
   □ Yes
   □ No

8. If you answered “yes” to the last question, please check the box next to the position you hold.
   □ Doctor
   □ Nurse
   □ Other ________________________________________

9. Have you ever been involved with the conduct of a medical research study as a principal investigator or a co-investigator?
   □ Yes
   □ No

10. Are you currently involved in the conduct of a medical research study as a principal investigator or a co-investigator?
    □ Yes
    □ No

11. If you answered “yes” to the last question, approximately what proportion of your professional time is spent conducting medical research studies?
    □ 0-19%
    □ 20-39%
    □ 40-59%
    □ 60-79%
    □ 80-100%

12. How many prospective randomized control trials enrolling over 100 patients have you been involved with designing and/or conducting?
    □ 0
    □ 1
    □ 2
    □ 3 or more

13. Have you ever been asked to participate in a medical research study as a patient or as a healthy volunteer?
    □ Yes
    □ No

14. Have you ever participated in a medical research study as a patient or as a healthy volunteer?
    □ Yes
    □ No
15. Would you be willing to be a patient participant in the medical research study or studies we discussed?
☐ Yes
☐ No
☐ Don’t know

16. Thinking about the medical research study we discussed today, please place a check mark next to the different ways that you think it is acceptable for doctors or medical researchers to tell people about the medical research study. You may select more than one answer.

☐ 1. Patients are told that [Johns Hopkins or Geisinger] does a lot of medical research studies to compare widely used drugs to each other to figure out which drugs work best. Patients who might have been given either of the drugs in the study anyway might automatically be enrolled in these studies if they are eligible.

☐ 2. Patients who might have been given either of the drugs in the study anyway are told about each study they are eligible for. Patients then might be automatically enrolled in these studies if they are eligible.

☐ 3. Patients who might have been given either of the drugs in the study anyway are told about each study they are eligible for. Patients are then enrolled in these studies if they are eligible but are told that if they do not want to be part of the medical research study, they don’t have to.

☐ 4. Patients are told about each study they are eligible for. Patients who might have been given either of the drugs in the study anyway are then asked if they would like to be a part of the study before they are enrolled.

17. Thinking about our discussion today and your own feelings, please state why you think the models you selected are appropriate and why the models you did not select are not appropriate in the space below. If you need more room, you can write on the back of this survey.
Appendix 9b: Survey for Institutional Review Board Community Members

Please answer the following questions.

1. What is your gender?
   - Male
   - Female

2. What is your age?
   - Under 30
   - 30-39
   - 40-49
   - 50-59
   - 60-69
   - 70-79
   - 80 or over

3. What is your ethnicity?
   - Hispanic
   - Non-Hispanic

4. What is your race? (You may select more than one)
   - American Indian or Alaska Native
   - Asian
   - Black or African American
   - Native Hawaiian or Other Pacific Islander
   - White or Caucasian
   - Other

5. How long have you been a member of the [Johns Hopkins or Geisinger] IRB?
   - 1-3 years
   - 4-6 years
   - 7-10 years
   - Greater than 10 years

6. Please select the statement that best describes how you would like you and your doctor to make decisions about how to treat your medical condition.
   - I prefer to make the decision about which treatment I will receive
   - I prefer to make the final decision about my treatment after seriously considering my doctor’s opinion
   - I prefer that my doctor and I share responsibility for deciding which treatment is best for me
   - I prefer that my doctor makes the final decision about which treatment will be used but seriously considers my opinion
   - I prefer to leave all decisions regarding treatment to my doctor.
7. Have you ever been asked to participate in a medical research study as a patient or as a healthy volunteer?
   □ Yes
   □ No

8. Have you ever participated in a medical research study as a patient or as a healthy volunteer?
   □ Yes
   □ No

9. Would you be willing to be a patient participant in the medical research study or studies we discussed?
   □ Yes
   □ No
   □ Don’t know

10. How important do you think it is to do more medical research to see how well drugs for [high blood pressure or migraine] work for patients?
    □ Very important
    □ Important
    □ Somewhat important
    □ Not important
    □ Don’t know

11. How important do you think it is for people to participate in medical research studies?
    □ Very important
    □ Important
    □ Somewhat important
    □ Not important
    □ Don’t know

**For the following four items, please check the box next to the response that best reflects your view.**

12. How much do you trust doctors to always provide the best medical care available?
    □ A great deal
    □ Some
    □ Very little
    □ Not at all

13. Doctors who do medical research tell their patients everything that patients need to know about being in a research study.
    □ Strongly agree
    □ Agree
    □ Neutral
    □ Disagree
14. Medical researchers treat people like “guinea pigs”.
   - Strongly disagree
   - Strongly agree
   - Agree
   - Neutral
   - Disagree
   - Strongly disagree

15. I trust doctors who do medical research.
   - Strongly agree
   - Agree
   - Neutral
   - Disagree
   - Strongly disagree

16. Thinking about the medical research study we discussed today, please place a check mark next to the different ways that you think it is acceptable for doctors or medical researchers to tell people about the medical research study. You may select more than one answer.
   - 1. Patients are told that [Johns Hopkins or Geisinger] does a lot of medical research studies to compare widely used drugs to each other to figure out which drugs work best. Patients who might have been given either of the drugs in the study anyway might automatically be enrolled in these studies if they are eligible.
   - 2. Patients who might have been given either of the drugs in the study anyway are told about each study they are eligible for. Patients then might be automatically enrolled in these studies if they are eligible.
   - 3. Patients who might have been given either of the drugs in the study anyway are told about each study they are eligible for. Patients are then enrolled in these studies if they are eligible but are told that if they do not want to be part of the medical research study, they don’t have to.
   - 4. Patients are told about each study they are eligible for. Patients who might have been given either of the drugs in the study anyway are then asked if they would like to be a part of the study before they are enrolled.

17. Thinking about our discussion today and your own feelings, please state why you think the models you selected are appropriate and why the models you did not select are not appropriate in the space below. If you need more room, you can write on the back of this survey.
Appendix 9c: Survey for Patients with Hypertension or Migraines

Please answer the following questions.

1. What is your gender?
   - Male
   - Female

2. What is your age?
   - Under 30
   - 30-39
   - 40-49
   - 50-59
   - 60-69
   - 70-79
   - 80 or over

3. What is the highest level of education you have completed?
   - Less than high school
   - High school diploma or GED
   - Some college
   - College degree
   - Graduate level degree
   - Other ______________________

4. What is your ethnicity?
   - Hispanic
   - Non-Hispanic

5. What is your race? (You may select more than one)
   - American Indian or Alaska Native
   - Asian
   - Black or African American
   - Native Hawaiian or Other Pacific Islander
   - White or Caucasian
   - Other

6. In general, how would you rate your health?
   - Excellent
   - Very good
   - Good
   - Fair
   - Poor
7. Please select the statement that best describes how you would like you and your doctor to make decisions about how to treat your medical condition.
  □ I prefer to make the decision about which treatment I will receive
  □ I prefer to make the final decision about my treatment after seriously considering my doctor’s opinion
  □ I prefer that my doctor and I share responsibility for deciding which treatment is best for me
  □ I prefer that my doctor makes the final decision about which treatment will be used but seriously considers my opinion
  □ I prefer to leave all decisions regarding treatment to my doctor.

8. Have you ever been asked to participate in a medical research study as a patient or as a healthy volunteer?
  □ Yes
  □ No

9. Have you ever participated in a medical research study as a patient or as a healthy volunteer?
  □ Yes
  □ No

10. Would you be willing to participate in the medical research study we discussed today?
    □ Yes
    □ No
    □ Don’t know

11. How important do you think it is to do more medical research to see how well drugs for [migraines or high blood pressure] work for patients?
    □ Very important
    □ Important
    □ Somewhat important
    □ Not important
    □ Don’t know

12. How important do you think it is for people to participate in medical research studies?
    □ Very important
    □ Important
    □ Somewhat important
    □ Not important
    □ Don’t know
For the following four items, please check the box next to the response that best reflects your view.

13. How much do you trust doctors to always provide the best medical care available?
   □ A great deal
   □ Some
   □ Very little
   □ Not at all

14. Doctors who do medical research tell their patients everything that patients need to know about being in a research study.
   □ Strongly agree
   □ Agree
   □ Neutral
   □ Disagree
   □ Strongly disagree

15. Medical researchers treat people like “guinea pigs”.
   □ Strongly agree
   □ Agree
   □ Neutral
   □ Disagree
   □ Strongly disagree

16. I trust doctors who do medical research.
   □ Strongly agree
   □ Agree
   □ Neutral
   □ Disagree
   □ Strongly disagree
17. Thinking about the medical research study we discussed today, please place a check mark next to the different ways that you think it is acceptable for doctors or medical researchers to tell people about the medical research study. You may select more than one answer.

☐ 1. Patients are told that [Johns Hopkins or Geisinger] does a lot of medical research studies to compare widely used drugs to each other to figure out which drugs work best. Patients who might have been given either of the drugs in the study anyway might automatically be enrolled in these studies if they are eligible.

☐ 2. Patients who might have been given either of the drugs in the study anyway are told about each study they are eligible for. Patients then might be automatically enrolled in these studies if they are eligible.

☐ 3. Patients who might have been given either of the drugs in the study anyway are told about each study they are eligible for. Patients are then enrolled in these studies if they are eligible but are told that if they do not want to be part of the medical research study, they don’t have to.

☐ 4. Patients are told about each study they are eligible for. Patients who might have been given either of the drugs in the study anyway are then asked if they would like to be a part of the study before they are enrolled.

18. Thinking about our discussion today and your own feelings, please state why you think the models you selected are appropriate and why the models you did not select are not appropriate in the space below. If you need more room, you can write on the back of this survey.
Appendix 10: Interview and Focus Group Coding Scheme

- Codes related to policy implications [policy]
  - Few trials will compare interventions that are so similar so it doesn’t make sense to have different consent standards [few trials like this]
  - Slippery slope
  - Hard enough enforcing one standard
  - Litigation against institution [litigation]
    - Documentation

- Codes related to the study setting [study setting]
  - Autonomy interests (autonomy is highly regarded in setting in which the research is conducted)
  - Trust of community/importance of considering community context [community trust]
    - Need for community input if alternative models are to be used [community input]
  - Recognition that institution is a teaching hospital [teaching hospital]

- Codes related to the study design [study]
  - Risk
    - Financial risk
    - Involves drugs which are powerful agents which could adversely impact patients [trial involves drugs]
  - Alters clinical care
    - Limits treatment options
    - Randomization
      - Impacts clinical/therapeutic decision making (including discussions of impact on the patient/provider relationship)
      - Impacts the ability patients to participate in health care decisions (this code is also in model characteristics section so need to see if participant is talking about the study or the model)
  - Characteristics of the drugs being compared
    - Drugs being compared in the trial are similar [similar drugs]
    - Involves non-experimental/FDA approved/widely used drugs [widely used drugs]
  - Allows doctors to switch drugs [switching allowed]
  - Imposes a burden on participants (including discussions of collecting data that is not routinely collected) [imposes burdens]
  - Impacts the ability of or the likelihood that patients will experience optimal clinical outcomes [optimal clinical outcome]
  - Relies on personal health information (PHI)/medical records [PHI]

- Codes related to characteristics of the model
  Ethical concerns about the model [model]
○ Respect for autonomy/paternalistic
  ✷ Respect (participants just mentions respect without discussing autonomy)
  ✷ Patient used as a means to an end/guinea pig [means to an end]
  ✷ Information/disclosure
    ○ Patients should know what is happening with their bodies
    ○ Informed about the study
    ○ The amount or type of information provided (use this code if the participant is saying that the model doesn’t provide enough information, provides too much information, or if they are talking about the type of information that should be disclosed to participants)
      ○ Amount of information will scare or overwhelm people or lead to the hypochondriac effect
      ○ Deception/being explicit/being transparent
  ✷ Understanding
    ○ May not understand why they are being asked to do extra things
    ○ May not understand their options
  ✷ Voluntariness/intentional action
    ○ Rights of participants to control participation/ability to control participation [ability to control participation]
      ○ Forced participation
      ○ Pressured to participate
        ○ Only assertive people will refuse to participate
        ○ Coercion
      ○ Resistibility (how easy or burdensome it is to get out of participating in a study)
    ○ Treating participants as partners (makes participant feel important and that their opinions matter)
    ○ Model limits the ability of patients to participate in healthcare decisions (this code is also in study characteristics section so need to see if participant is talking about the study or the model) [limiting participation in HC dec]
  ○ Fairness/discrimination/equity
  ○ Protecting patients

Ethical concerns about the impact the model will have on participants or on the study [model impact]

○ Impact on trust
  ✷ Patient trust of doctors or the health care system [patient trust]
    ○ Impact of patient/provider dynamics
  ✷ Community trust
○ Impact on the likelihood that patients will feel wronged or betrayed or angered/would switch docs or HC systems [patients may feel wronged]
○ Impact on the number of people who will participate
○ Impact on the ability to complete the research
○ Impact on internal validity
  ▪ Impact on patient behavior (patient may change behavior if they know they are in the study)
  ▪ Adherence (also included in this category is discussions of participants being committed to the study or providing accurate information)
  ▪ Selection bias
○ Impact on external validity/generalizable knowledge
○ Impact on the efficiency of the research
  ▪ Burden on clinicians or researchers [because takes more time to explain]
  ▪ Burden on patient [because takes more time to explain]
  ▪ Time to enroll patients
  ▪ Time to do the research
  ▪ Cost
○ Impact on altruistic motivation

• Other (potential) codes [Other]
  ○ Balancing comments
  ○ Informed consent lite (ask people but just discuss main side effects)
  ○ Distinction between opting in and opting out
  ○ Distinction between model 2 and 3 doesn’t exist in the real world
    ▪ Any good doctor would tell patients they can opt out
  ○ Amount of information provided as part of normal clinical practice
  ○ Percent of people who generally agree to participate in studies
  ○ Many patients just defer to doctors judgments/trust that doctors wouldn’t do anything harmful
  ○ Different people will prefer different models because of
    • Age
    • Health condition
    • Length of time with health condition
    • Rapport with doctor
Curriculum Vita

Danielle Marie Whicher was born on October 3, 1984 in Melrose, Massachusetts. She received her Bachelor of Arts from Colgate University in 2007. She then received a Masters of Health Science from the Johns Hopkins Bloomberg School of Public Health in the Department of Health Policy and Management in 2009. Before returning to the Johns Hopkins Bloomberg School of Public Health for the Doctor of Philosophy program, Dr. Whicher worked at the Center for Medical Technology Policy (CMTP) in Baltimore, MD as a Project Manager. CMTP is a non-profit organization that focuses on the design and implementation of comparative effectiveness research to produce information that helps patients, clinicians, and payers make informed treatment and policy decisions. While she was enrolled in the Doctor of Philosophy Program, Dr. Whicher received an Agency for Healthcare Research and Quality Dissertation Award to support her dissertation project. She also worked as a contractor for the World Health Organization to develop a paper summarizing the literature on ethics and patient safety research and for Drs. Nancy Kass and Ruth Faden as a research assistant and then a research coordinator on several projects that were designed to study ethical issues that arise in comparative effectiveness research and quality improvement activities. Following the completion of her dissertation, Dr. Whicher will continue to work in the field of comparative effectiveness research as a Program Officer at the Patient Centered Outcomes Research Institute (PCORI) in Washington, DC.