What gives them the right? Legal privilege and waivers of consent for research

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Abstract
Waivers of informed consent for research participation are permitted in the United States under the Common Rule, the Health Insurance Portability and Accountability Act regulations, and the US Food and Drug Administration's Exception from Informed Consent rule for emergency research. We assess the novel question regarding what legal right researchers have to carry out research procedures on or about another person, be it experimental medical intervention, psychological or social manipulation, or invasion of privacy, without the permission of their subjects. Our analysis frames waivers of consent as a species of presumed consent, and we address the underlying empirical question of whether it is reasonable to believe that subjects from whom no consent is sought would in fact agree, if asked. A scoping review of what is known about participation and refusal rates in United States-based research suggests that a large minority, on average, do not agree to take part in research. Refusal rates vary widely. This suggests that, while researchers may assert the social utility of their studies are high enough to justify waivers, there is reason to suspect that many who would be enrolled under a waiver of consent would not want to be enrolled. We conclude that waivers should be rare and that institutional review boards and researchers must explicitly address study acceptability in the community at large and the target population of their proposed research.

Keywords
Waiver, informed consent, presumed consent, delayed consent, privilege, legal privilege

Background
Research without consent is permitted in the United States for certain minimal risk research under the Common Rule,1 regulations issued under the Health Insurance Portability and Accountability Act (HIPAA),2 and for emergency research under the US Food and Drug Administration's (FDA) Exception from Informed Consent (EFIC) rule.3,4 Until recently, waivers and exceptions from informed consent have predominantly been granted for studies in which securing prospective consent is impossible or impracticable. However, there appears to be increasing use of waivers for other types of trials, particularly comparative effectiveness (CE) or pragmatic trials (also referred to as research on medical practices). For example, a recent randomized trial in which deceased kidney donors bodies were cooled down prior to kidney excision involved no consent from donors (because they were deceased) nor their families, and more problematically, waived consent of the living recipients of those organs because the study posed no more than minimal risk to subjects and only clinical follow-up data were accessed to assess graft function.5

In this article, we use the legal doctrine of privilege to assess the legitimacy of waivers of consent for research. We begin by assessing legal requirements to secure consent from human subjects for research, as well as the legal bases on which research may be carried out without consent. Our review of the literature suggests that this analysis is unique and long overdue, as it addresses the fundamental question of what legal right researchers have to carry out research procedures on another person, be it experimental medical intervention, psychological or social manipulation, or...
invasion of privacy, without the permission of the subjects of their research. Our analysis frames waiver of consent as a species of presumed consent, in which we address the underlying empirical question of whether it is reasonable to believe that subjects from whom no consent is sought would in fact agree, if asked.

Privilege and consent for research

The law of privilege grants an exceptional dispensation from a legal norm to certain people or classes of people to enable them to perform an important societal function.6 For example, witnesses in legal proceedings may typically be compelled to testify about what they know or have observed. The testimonial privilege recognizes that certain individuals such as priests, physicians, lawyers, and spouses may not be compelled to testify regarding confidential communications without the permission of the person to whom they owe an obligation of secrecy, in order to promote those confidential relationships.6 We are focused here on privilege in tort law, where privilege arises from either consent or is recognized in law irrespective of consent. Privilege provides an affirmative defense to a prima facie tort such as battery, assault, or trespass. If a defendant can show that either she had the plaintiff’s consent or she was acting in furtherance of a goal of sufficient social importance, then privilege will insulate her from liability for the plaintiff’s damages (assuming she was otherwise observing the appropriate standard of care). Importantly, the nature and scope of the privilege is proportional to the social value of the interest at stake.9

The well-established emergency privilege permits healthcare providers to administer emergency treatment to incapacitated patients at risk of death or serious bodily harm without their explicit consent.8 Normally, treating patients without their consent would be a battery. Indeed, the right to consent to or refuse medical interventions is firmly established in US law.9 But in emergency situations, individuals may be unable to consent. It would violate public policy to allow these patients to die or sustain a serious disability simply because they are unable to consent and no surrogate is available to consent on their behalf. It is also reasonable to believe that most people in an emergent condition, such as immediately after being in a serious car accident, would agree to medical care for their injuries. This presumption is a necessary but not sufficient condition for the privilege to be exercised. There also must be no evidence that the individual patient would not have wanted to be treated under the circumstances.10 Thus, the privilege is a form of presumed or implied consent.11 As commentary in the Restatement of Torts puts it:

The emergency doctrine reflects a narrow set of circumstances in which the actor reasonably believes that plaintiff would have consented, if he or she had the opportunity to do so ... (emphasis in original)9

The FDA’s EFIC rule is predicated upon the same balancing of interests as the emergency privilege to treat. Emergency research serves the valuable social function of testing the safety and efficacy of new emergency interventions where current therapies are “unproven or unsatisfactory.”12 This primarily benefits future emergency patients, although treatments tested under the EFIC provisions must offer a reasonable prospect of direct therapeutic benefit, so enrollment could potentially help the subjects themselves. While it is reasonable to believe that accident victims would agree to be treated if asked, it is much less clear that accident victims would agree to be in research, even with all the procedural safeguards required by the EFIC rule.

We posit that the ethical and legal legitimacy of the privilege to provide standard of care treatment or to waive consent for research is predicated upon the reasonable belief that potential subjects would agree if they were asked and capable of consent. As the FDA stated in its comments to the final EFIC rule,

The agency would not consider writing a rule that would permit the waiver of informed consent in a situation where if consent were requested, it would be refused. Such an action would violate ethical principles.13

This is based on the legal and moral rights of people to consent to or refuse participation in research.14 The right to consent extends beyond trials run in emergency settings to other interventional or experimental studies. As a general matter, state laws uniformly require consent to any physical invasion of the body, especially for medical care. Moreover, state laws generally require consent from subjects in research. Numerous states have statutorily recognized the rights of people to consent or refuse to take part in research, either in their informed consent statutes or Patient Bill of Rights statutes.15–21 Moreover, a recent review yielded eighteen state and federal court cases in which a common-law duty to secure informed consent from biomedical research subjects has been recognized, and there have been no cases holding otherwise.22

The picture is less clear regarding the need for consent to access data for research purposes. Federal HIPAA regulations generally require consent for disclosures for research, but permit waivers for retrospective studies using medical records, and these regulations preempt state laws except to the extent state laws provide greater protections for patients’ privacy.23 Thus, while
HIPAA has largely standardized the law for research use of medical records, the legal protections for other types of data collected on people are much less certain. Whether state courts would recognize a duty of researchers to secure consent from subjects whose nonmedical record data is accessed for research is unknown.

While the federal rules create a legal basis for waiving consent in limited circumstances, neither the Common Rule nor the EFIC rule preempts state laws. Notably, some states have modified their laws to recognize the privilege to waive consent created by the EFIC rule and in some cases the Common Rule, but by no means have all states done so. It is critical that under the Common Rule, a waiver of consent must not “adversely affect the rights … of the subjects.” HIPAA similarly requires that a waiver not “adversely affect the privacy rights” of subjects. To the extent individuals have a right to decide whether to take part in research or to have their private records disclosed to researchers, then the adverse effects from infringing these rights increase with the likelihood that people would refuse to take part or permit the disclosures, if asked.

This leads us to ask about people’s willingness to participate in research. Various CE trials that involved waivers at least for some subjects raise the concern that people are not particularly willing to take part in research, undermining the validity of the presumption that people would consent if asked. In the Acute Respiratory Distress Syndrome Network (ARDS-Net) ARMA trial, which involved random assignment of subjects requiring mechanical ventilation to one of two tidal volumes, one of the 10 sites permitted waiver if subject or surrogate consent could not be secured. Overall, the trial had a refusal rate of 28.0%; correcting for enrollment at the single site for 16 subjects for whom waiver was granted increases the refusal rate to 28.5% (H Silverman, personal communication, 2017).

The Normoglycemia in Intensive Care Evaluation - Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, run in Canada, Australia, and New Zealand, involved tight versus loose control of blood glucose levels in intensive care patients and was stopped early due to high mortality in the former arm. Consent was required in Canada, while a form of waiver—delayed consent—was permitted in Australia and New Zealand. The refusal or failure to affirm enrollment in the latter countries was 9%, while the refusal rate by capable patients or surrogates in Canada was 41% (S Finfer, personal communication, 2012). The high rates of refusal in these trials raise an ethical flag, insofar as the rights of substantial minorities—roughly a third—of subjects to not be enrolled in research against what their wishes presumptively would be were permanently infringed.

What do we know about participation and refusal rates?

While these examples suggest that large numbers of solicited people will not take part in research, we performed a broader, systematic search to get a more robust answer to our question. In September–October 2016, we performed an initial literature search of PubMed, Google Scholar, and Web of Science for articles reviewing participation and refusal rates in real studies, and rounded out this preliminary review by examining relevant references. Our intent was to perform a scoping study to assess the extent to which available literature lends insight into research participation and refusal rates in the United States. We included any paper that reviewed participation and refusal rates in other studies. While most reviews were of published studies, we also included several reviews of consortium trials. These data were presented by one of us in a number of seminars (detailed in the ‘Acknowledgements’ section) in the spring and summer of 2017 and early 2018 to vet the thesis of this article. In September 2017, we expanded our sample by performing a systematic search of Medline and PsychInfo, identifying English-language review articles involving combinations of the following terms and their roots: (consent or refuse or participation or recruitment) and (rate or barrier or bias or “informed consent”) and research, for all dates available. We did not include any reviews or data of purely hypothetical or mock studies except for those of EFIC trials, where there is no data possible on actual refusal rates. We also excluded reviews focused on response rates to mailed surveys, which are notoriously low. We attempted to limit the search to reviews of studies run in the United States, but this was not always possible, as most papers captured studies based on where they were published, not where they were performed. All searching, screening, and coding was performed by Jon Merz, and the preliminary sample was checked by Francis Baker. An overview of the search strategy is shown in the PRISMA (preferred reporting items for systematic reviews and meta-analyses) flowchart in Figure 1.

Our tabled findings are presented in the Supplementary material (see supplementary material). Research articles included in the reviews varied widely in the documentation of subject participation or refusal, with many authors noting uniformly poor compliance with the Consolidated Standards of Reporting Trials (CONSORT) reporting requirements in reviewed publications. The Supplementary material includes the number of studies encompassed by the review, the number of subjects included in those studies, whether the review fulfilled PRISMA requirements, and the mean or median participation rate or, when reported,
the mean or median refusal rate, as well as the ranges on these rates (or the interquartile range when that was reported in lieu of actual data). In total, 33 reviews presented detailed data on included studies and 2 authors provided raw data, allowing reanalysis of participation and refusal rates. In general, rates of participation and refusal are derived for eligible subjects; when papers were explicit about the population described (i.e., solicited, responded, screened, and eligible), this is noted. Participation rates and refusal rates are only loosely related, in that refusal is but one reason for nonparticipation. In nine cases, we contacted authors to seek clarification of their reports, seven of whom provided more information (including two who provided their complete data sets).

In an attempt to detect any patterns of refusal or participation, we present the studies loosely grouped by methods or target populations involved. We believe no formal quantitative analysis is feasible, given the observed heterogeneity of these data. Drawing comparisons across studies and types of studies is difficult or impossible because of unreported differences in approaches to screening, assessment of inclusion and exclusion criteria, solicitation, consent, and withdrawal. Indeed, one review author admitted by email that he was unable to discern precisely what was going on across the trials included in his review. Nonetheless, this review shows that participation rates in research vary widely, but on average do not demonstrate a high general willingness to participate by potential subjects. Moreover, refusal rates are likewise highly variable, but on average support our anecdotal observation that many people—an average rate roughly on the order of 30%—do not take part in research when asked.

Discussion

These data raise a fundamental question about the moral and legal significance of high refusal rates by potential subjects in research. In emergency research,
various writers have wrestled with the troubling implications of low community acceptance of planned trials. As Neal Dickert and colleagues summarize, "No consensus exists about what levels of disagreement are problematic." Emily Largent and colleagues suggested that specified conditions may be posited to permit an ethical consent "substitute," one of which is that there are no conflicting preferences, which they define to be compelling reasons to believe that participation conflicts with subjects' values or interests. The data compiled here arguably meets that test. For nonemergency research, presumptively high refusal rates simply weigh against the ethical and legal legitimacy of the privilege to waive consent. Even in noninterventional research, such as research using existing medical records or biosamples, where the primary interests of subjects involve violations of privacy but not bodily integrity, refusal rates appear to be high enough to raise ethical concerns. Bob Veatch, writing about the ethics of medical record research, suggested that researchers should survey a subsample of their targeted research population, concluding:

There is no standard level of approval, but a level of 95 percent of the sample might suffice. This approval rate could justify the belief that the subjects who are actually drafted into the study would have agreed with the idea that consent was unnecessary.

Our review suggests this standard would be largely unattainable. Thus, we believe there needs to be much more discussion and explicit consideration about what level of agreement by potential subjects is necessary to justify waivers of consent. Several commentators before us have identified an ethical obligation for researchers who wish to waive or modify consent to explore whether potential subjects in their proposed research would agree to take part if asked. At least one country, Australia, has incorporated this requirement in their national guidelines for waiver of consent. Analogously, an ethics committee for the US Department of Health and Human Services Organ Procurement and Transplantation Network concluded that presumed consent would not be ethical for organ donation in the United States, in large part because "a significant portion of the public is opposed to donation."

There are several limitations in this analysis. First, some might argue that our data show that the reasonable person generally would agree to take part in research and that a simple majority or super majority of 2/3 is legally and ethically sufficient. We agree that a simple majority might be adequate for the least intrusive research, but not necessarily. For example, the secondary analysis of blood samples collected for "study of the causes of biobehavioral/medical disorders" examined, among other topics, the migratory history of the Havasupai tribe. The analysis was fundamentally "contrary to the tribe's origin story." Presuming consent of even a majority was unjustified, and the dignity harm to the population from performing and publishing the analysis suggests that a much higher threshold, along with express concurrence by Tribal leaders, would be ethically required. In our view, a simple majority would not be appropriate for all secondary uses of data, depending on the questions asked and the population involved. Second, others may argue that informed consent is notoriously difficult and ineffectual and that refusals are un- or ill-informed and should not be accorded much weight. Hopefully, it need not be stated that people may refuse for any reason, or no reason at all, and they need not make a decision in a manner or according to rules satisfactory to the researcher (or the ethicists). Third, there are two potential limitations on the review data presented. We contacted authors of 9 of 75 papers (12%) seeking clarification of their reports. Since we did not systematically do this with all relevant but incomplete papers, we may have unwittingly biased the sample presented here. Given that all nine papers were included, and we did not seek data from any authors of relevant papers that were not included (as detailed in Figure 1), we believe our contacting some authors did not impute any bias. In addition, we have not attempted to control for overlap of reviewed studies, leaving the possibility that multiple reviews included overlapping sets of studies. We believe the effect of overlap is minimal because the papers span several decades and hundreds of thousands of potential subjects, with a few exceptions have disparate sampling frames, and we are not quantitatively combining studies in any formal manner.

For research that poses greater physical or psychological risks, or poses more of a threat to cultural values and mores, we believe there must be good evidence that the overwhelming majority of individuals who would be enrolled would agree, if asked. Moreover, if researchers and institutional review boards (IRBs) are going to infringe upon the rights of individuals to choose to be subjects, the value of the research and what is hoped to be learned must be worth the sacrifice, as judged by the community at large and the target populations of the research. This suggests that the potential benefits of proposed research must be substantial enough to justify the privilege to forego consent. We also believe that the infringement on the right to consent must be minimized. As a practical matter, we believe that the acceptability of a waiver in a target population for study must be inversely related to the gravity of the interests implicated by participation. For example, these interests may range from minor dignitary insults from deceptive research practices, to more serious violations of privacy from retrospective uses of sensitive identifiable data or biosamples, to informational harms that could
stigmatize research populations or violate cultural values, to matters of bodily integrity directly affected by interventional clinical trials.

This conclusion will not sit well with those who seek to expand the use of waivers in order to facilitate research. Indeed, the researchers who performed the highly maligned SUPPORT trial, in which extremely low birth weight babies were randomly assigned to one of two target pulse oxygen saturation ranges, argued that the difficulty, expense, and imputed bias from securing consent was justification enough for using waiver. Despite an extremely aggressive enrollment approach that included a median of 2 and up to 11 attempts to secure consent (which process was not described in the protocol), more than 45% of parents refused to take part. In our view, waiver should never be used to override the expected preferences of the target population or known preferences of specific individuals.

While our concern about waivers is in part motivated by the potential for expanded use in CE trials, none of the reviews we found focused on such trials. To the extent it may be presumed that people would be more willing to take part in such trials because of lower risk, comparison of “accepted” treatments, and minimal burden of trial participation, our findings here may be construed as being inapposite to CE trials. Our anecdotal observations of CE trials made above, with refusal rates in ARMA of 28%, NICE SUGAR of 41%, and SUPPORT of 45%, show participation rates well within the ranges for randomized controlled trials (RCTs) reviewed. Moreover, a number of studies have asked people about the acceptability of waivers in CE trials, and a consistent majority favor consent in some form to outright waivers. Thus, it should be incumbent upon those seeking waivers for those trials to show that they indeed would be acceptable to an appropriate majority.

The baseline rate of refusal explored above poses an ethical and legal quandary. Our analysis suggests that waivers should be rare and based on much more explicit input about study acceptability among the target population (or populations). This is a call for more input about study acceptability among the target populations. This is a call for more input about the methods of biomedical science and development, because we cannot be sure that education addresses the underlying reasons—such as lack of trust or suspicion of being a “guinea pig”—for peoples’ unwillingness to participate in research. We also believe that the suggestions for an “integrated” consent that masks research behind the facade of clinical informed consent, or for abbreviated consent or “informed refusal,” fail to avoid the problem we’ve outlined here. Opt-outs, which have been implemented by various sites and IRBs in EFIC research, address the problem in part, by enabling the most aggressively self-protective to exclude themselves. Of course, opt-outs are only effective if community consultation and public notices provide actual notice to potential subjects, which is not always the case.

Methods of soliciting insights and feedback from populations from which individuals may be potentially drafted into research, such as deliberative democracy, fail to address the problem that individuals’ preferences for their own participation in research may vary significantly from group considerations about the desirability and value of research participation in the abstract. Similarly, various writers have suggested that CE trials optimally would be embedded in learning healthcare systems in which patients and other stakeholders could play large roles in setting priorities, thereby providing oversight as well as allowing broader perspectives to be considered when framing proposed research. Of course, even when broader perspectives are expressly addressed, some individuals’ preferences would still be overridden.

The unwillingness of a plurality of people to participate in research must be addressed head-on; it is real, and it poses a problem that cannot be avoided by ethical work-arounds merely for the expediency of research. Nor can it be avoided by circumscribing the right to refuse participation in research, as several states have done, by creating a state law privilege for research conducted under the federal rules. This review shows that the default presumption that most people would concur with waiver of consent in emergency settings for treatment cannot be extended to research, even in emergency settings. Thus, IRBs and researchers must explicitly address the question about study acceptability in the target population, and it should be incumbent upon researchers to establish by clear, sound evidence that proposed studies would be acceptable in the target populations.

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In the last 3 years, J.F.M. has been employed as an expert witness in two wrongful death civil lawsuits, both of which alleged IRB negligence (1 plaintiff, 1 defense), has continuing service on several Data and Safety Monitoring Boards, and serves on a Pharmacogenomics Ethics advisory board for Merck. J.F.M. has been the moderator of the IRBForum (http://www.irbforum.org/) since 2003, ownership of which was transferred to Public Responsibility in Medicine and Research in 2012, which has since then supported J.F.M.’s role with a grant to the University of Pennsylvania for partial salary support.

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