

Informed Consent

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Informed consent describes a process for enabling individuals to make voluntary decisions about participating in research with an understanding of the purpose, procedures, risks, and benefits of the investigation, as well as alternatives to participating. As described below, the basis for informed consent—including the requirement to obtain consent, situations in which that requirement might be modified or waived, and the content of the information provided—is grounded both in ethical principles and government regulations.

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Ethical Foundation of Informed Consent

U.S. federal regulations for the protection of human research participants are founded upon a 1979 report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Known as the [Belmont Report](#), this landmark document defines three fundamental ethical principles for research involving human participants:

Respect for Persons – that competent individuals should be treated as autonomous (self-determining) agents, and that persons with diminished autonomy are entitled to protection;

Beneficence – that persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being; and

Justice – that the benefits and burdens of research be distributed fairly.

Based on these principles, the Belmont Report identifies three key parts to informed consent:

Information

Prospective participants must be given the information needed to make an informed decision about whether or not to take part in research. This includes information about the purpose of the research and any procedures that are part of it; possible harms and benefits; alternatives to participating; and the right to stop participating at any time and for any reason. The Report suggests a “reasonable volunteer” standard, meaning that the extent and nature of information provided should be based on what a reasonable person would want to know, given that “...the procedure is neither necessary for their care nor perhaps fully understood.”

Comprehension

According to the Report, “The manner and context in which information is conveyed is as important as the information itself.” Prospective participants must be provided information about the research in a language they can understand and must be given enough time to absorb the information, ask questions about it, and make an informed choice. The Report emphasizes that investigators are responsible for determining that participants adequately comprehend the information—an obligation that increases along with the seriousness of the risks.

Voluntariness

The Report notes that “An agreement to participate in research constitutes a valid consent only if voluntarily given.” This means that obtaining informed consent requires conditions that are free from coercion (i.e., threatening the prospective participant with harm or negative consequences) or undue influence (such as offering an excessive amount of money or other inappropriate reward in return for participation, or allowing an authority figure or even a family member to pressure a person into taking part in the study).

Influential Documents in Human Research Ethics

The [Nuremberg Code](#)

The World Medical Association’s Helsinki Declaration

The Council for International Organizations of Medical Sciences’
International Ethical Guidelines for Biomedical Research Involving Human
Subjects

Regulatory Foundations of Informed Consent

In the United States, federal policy for the protection of human participants (also referred to as *human subjects*) in much health-related research can be found in [Title 45 of the Code of Federal Regulations Part 46 \(45 CFR 46\)](#). Although these regulations apply specifically to research that is conducted or supported by the federal government, many academic institutions sign an assurance pledging to apply these regulations to all research in which they are [engaged](#), regardless of funding source. The regulations concerning informed consent are found in Subpart A, which is known as the [Common Rule](#) because it has been incorporated into separate regulations by 15 federal departments and agencies.

The U.S. Food and Drug Administration (FDA) is not a signatory to the Common Rule but has its own regulations for human research protections. These regulations, which apply to clinical investigations that support applications for permits for products regulated by the FDA, can be found in [Title 21 of the Code of Federal Regulations Part 50](#). FDA requirements for [informed consent](#) are largely similar to those of the Common Rule, with a few important exceptions: for example, FDA regulations do not permit waiving of the requirement to obtain informed consent except in emergency situations. (Click [here](#) to see a table summarizing all of the differences.)

In general, however, informed consent is required for research that involves human subjects, unless the research is exempt or meets the criteria for a waiver of the requirement to obtain consent. More information about these concepts and how these determinations are made is available through the federal Office for Human Research Protections (OHRP), which provides a series of [Human Subject Regulations Decision Charts](#).

When informed consent is required, federal regulations set forth the [elements of information](#) that must be provided to prospective participants, including a set of required items as well as some “additional” elements. These regulations contain more flexibility than many realize. For example, even among the required elements, several include the modifier “if any”—in other words, some elements may be required only if they are applicable to a given study and helpful to a prospective participant’s decision about whether to take part. The [Secretary’s Advisory Committee on Human Research Protections \(SACHRP\)](#) approved a [helpful document](#) clarifying what federal regulations do and do not require with regard to consent information. OHRP provides other [guidance documents](#), including a variety of materials on [informed consent](#), to assist the research community in conducting ethical research that complies with U.S. Department of Health and Human Services (HHS) regulations.

In summary, federal regulations and associated guidances provide an important foundation for informed consent. Within the context of adhering to these regulations, it is crucial that the content of consent forms and the process for obtaining consent be tailored to the individual study and remain focused on the ethical goal of enabling informed, comprehending, and voluntary research participation.

Waiving Informed Consent Requirements

Although the basic ethical principles underlying informed consent apply to all research, they may be applied in different ways depending on the nature of the risk and the goals of the research [1]. Regulatory requirements for informed consent apply primarily to research that exposes human participants to non-trivial risk, and perhaps most readily to clinical research involving an experimental intervention, such as a drug or medical device. However, because the Common Rule covers both biomedical and social science research whether experimental or observational, flexibility is required to optimize protections while minimizing burden. Thus, the regulations provide for the possibility of waiving or altering the requirement to obtain informed consent. These provisions require that four criteria be met (45 CFR §46.116(d)):

1. **The research involves no more than minimal risk to the subjects.** According to the Common Rule definition ([45 CFR §46.102\(i\)](#)), “minimal risk” means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. In 2007, SACHRP provided a series of [illustrative cases](#) to aid in understanding minimal risk.
2. **The waiver or alteration will not adversely affect the rights and welfare of the subjects.** For this criterion, SACHRP [recommended](#) that IRBs consider whether there are other federal, state, or local laws that require informed consent, as well as whether the participant population in general would object to a waiver or feel that a waiver could have adverse consequences for their well-being.
3. **The research could not practicably be carried out without the waiver or alteration.** “Not practicably” is often taken to mean impossible to carry out—a narrow interpretation that can lead to requiring consent in circumstances where it is less than meaningful [2]. Assessments of practicability should not be based solely on convenience, cost, or speed, but SACHRP [suggested](#) several other considerations, such as whether scientific validity would be compromised or ethical concerns raised if consent was required, and whether there is a scientifically and ethically justifiable rationale why the research could not be conducted with a population from whom consent can be obtained.
4. **Whenever appropriate, the subjects will be provided with additional pertinent information after participation.** This criterion is rooted in studies involving deception and, as indicated by the phrase “as appropriate,” will not apply to all research.

Despite available guidance, Institutional Review Boards (IRBs) and researchers often struggle to interpret whether and how these criteria should be applied. Noting that nuances in the language have deterred IRBs from exercising the flexibility that the regulations were intended to provide, SACHRP recently recommended [modification](#) of the regulations to empower IRBs to waive selected elements of consent when appropriate and to clarify the circumstances in which an IRB may grant a complete waiver of informed consent.

For studies that do not meet the criteria for a complete waiver, the Common Rule provides for the waiver of documentation of consent (45 CFR §46.117(c)). This requires that the IRB find either:

1. That the only record linking the participant and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality; or
2. That the research presents no more than minimal risk of harm and involves no procedures for which written consent is normally required outside of the research context.

Even when the requirement for documentation is waived, the IRB may require investigators to provide participants with written information about the research.

Obtaining Informed Consent

As the principles of the Belmont Report make clear, promoting and confirming comprehension of the information provided to prospective participants is vital to ensuring that their decision to participate in research is in fact informed and voluntary. Unfortunately, significant and persistent problems with consent comprehension have been documented across many types of studies [3-9].

The Informed Consent Process

Although much attention is understandably focused on the consent form, it is nevertheless only one part of a larger informed consent *process*. Thus, the process by which consent is obtained as well as the consent form itself both merit careful attention, as the National Bioethics Advisory Commission emphasizes [2]:

From an ethics perspective, the informed consent process is the critical communication link between the prospective participant and the investigator, beginning with the initial approach of the investigator to the participant and continuing until the end of the project. It should be an active process of sharing information by both parties throughout which the participant at any time is able to freely decide whether to withdraw or continue participating in the research (p.100).

Resources for Creating Informed Consent Materials

Resources to Improve Readability:

Group Health Research Institute: [Program for Readability In Science & Medicine \(PRISM\)](#) - readability toolkit and online training

The National Cancer Institute (NCI): [Clear & Simple: Developing Effective Print Materials for Low-Literate Readers](#)

Model Templates and Guides:

Agency for Healthcare Research & Quality (AHRQ): [Informed Consent and Authorization Toolkit for Minimal Risk Research](#)

NCI: [Simplification of Informed Consent Documents](#)

However, the consent process has been shown to fall short in a number of crucial ways. For example, in a survey of approximately 1600 people who had recently completed a clinical trial [10], nearly one in seven reported that no one reviewed the consent form with them, and a similar proportion said they signed the form without reading it. Seventy percent indicated they didn't know what questions to ask, and 1 in 10 said they were too afraid to ask questions. Only 17 percent said that they sought input from others (such as a family member, friend, or personal physician) as part of their decision to participate.

Additional problems have been identified with consent being obtained by persons lacking sufficient background to adequately explain study requirements and answer questions; with special consent procedures, such as when the next of kin or a legal guardian signs the consent form; and with inappropriate timing, such as study candidates being given multiple consent forms to read and sign just before an invasive clinical procedure is done [11].

The Common Rule provides relatively little detail about the consent process, stating only:

An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence” (§46.116).

However, the Association of Clinical Research Professionals recently published a [white paper](#) that offers guidance on how to structure the informed consent process, including considerations related to environment, assessment of capacity to consent, presentation of the elements of consent, use of a delayed consent procedure, assessment of comprehension, documentation of consent, and ongoing consent.

Consent Forms

A written consent document is one important way that information is communicated to prospective participants. It can provide a helpful “script” during the process of obtaining consent, and serves as a resource that participants can take home and refer to throughout the study. However, numerous studies show that consent forms are often too long and complex [12-24] and contain an overwhelming level of detail that may undermine the basic goals of informed consent:

(Consent forms are) “becoming ever more intimidating, and perhaps inhibiting rather than enhancing participants’ understanding. Participants may not even read them, much less understand them.”

—Hastings Center Report, 2008

To help reverse this trend, it is essential that consent forms be “participant-centric”—meaning that they are easy to read, accurately tailored to the individual study, and designed to clearly highlight the information that a reasonable volunteer would find most important to making an informed decision.

Special Situations and Settings

Although the same basic principles and regulations apply to all research involving human subjects, some situations and settings involve particular challenges.

Cluster-Randomized Trials

In [cluster-randomized trials](#) (CRTs), the unit of the study that is randomly assigned to a treatment or intervention is a group (the “cluster”)—such as a clinic, hospital, or even a geographical region—rather than an individual. Groups often comprise many layers (e.g., healthcare clinic—physicians—patients) and the intervention under study can be targeted and assessed at multiple levels. For example, in a study of online versus in-person training for providers, randomization could occur at the clinic level, the intervention could be applied at the provider level, and assessments of the outcome measured at both the provider and patient levels. These characteristics present challenging issues for informed consent [25-28]:

- **Identifying research participants.** Who meets the definition of a “human subject” from whom we should consider obtaining consent?
- **Obtaining informed consent.** When is consent required, and when can it be waived?
- **Gatekeepers.** Can a gatekeeper give proxy consent on behalf of the group?

The complexity of these issues can be compounded by specific features of the study design. For instance, unlike in a traditional clinical trial, randomization in a CRT may occur before there is an opportunity to obtain consent. Also, the rationale for using a cluster design may be to avoid contamination between study arms, whereby individuals allocated to the control arm are exposed to the intervention through interaction with individuals in the treatment arm. This leads to questions about which aspects of the study should be disclosed during the informed consent process. As Edwards and colleagues note [29]: “Informing controls fully about the experimental arm(s) is likely to produce the very effect that randomising by cluster was designed to avoid—that is, prompting controls to adopt the treatment(s) under investigation (p.1409).”

Finally, CRTs are often used to assess interventions considered to be standard of care, for which specific informed consent would not typically be required in a clinical setting. This raises questions about research exceptionalism, as well as potential gaps in patient education about the risks and uncertainties involved in usual care.

Genomic Research and Biobanking

Much basic, clinical, and translational research involves a genetic component, and research involving genetics often includes banking of biospecimens and data for future research:

The vision of ‘personalized medicine’ is to improve the standard of medical care by including an individual’s genetic and molecular information in the clinical decision-making process....Human biospecimens are the fuel that drives the basic and translational research needed to achieve this vision [30].

—J. Vaught et al, 2011

Resources for Informed Consent in Genomic Research

Best practice guidelines and recommendations:

National Bioethics Advisory Commission (1999): [Research Involving Human Biological Materials: Ethical Issues and Policy Guidance](#) (PDF)

RAND (2003): [Best Practices for a Biospecimen Resource for the Genomic and Proteomic Era](#) (PDF)

Organization for Economic Cooperation and Development (2010): [OECD Guidelines on Human Biobanks and Genetic Research Databases](#)

NCI (2011): [Best Practices for Biospecimen Resources](#) (PDF)

Reviewarticles and resources:

McGuire & Beskow (2010): [Informed consent in genomics and genetic research](#)

NHGRI’s [Informed Consent for Genomics Research](#) *Model templates and related materials:*

Beskow et al. [Simplified consent form for biobanking](#)

Cancer Human Biobank (caHUB): [Consent template and supplement](#)

NHGRI: [Consent form examples and model language](#)

NCI’s Cooperative Group Banks: Consent template, IRB information sheet, and patient [brochure](#)

P3G: [Model consent form and information pamphlet](#)

Data suggest that the public is generally supportive of such research; for example, in a large survey (n=4659) that explored the prospect of a national cohort study investigating genes, environment, and lifestyle, 84% of respondents supported the idea and 60% said they would participate [31]. Similar results have been found in other studies of attitudes toward the research use of specimens originally collected under a variety of circumstances [32-37].

Even so, biobanking and genomic research raise questions about when consent must be obtained and present challenges in communicating complicated information.

When Is Informed Consent Required?

With limited exceptions, informed consent is required for research that involves human subjects. Federal regulations define a “human subject” as *a living individual about whom an investigator obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information* ([45 CFR §46.102\(f\)](#)). Collecting biospecimens constitutes an “intervention or interaction with the individual”; thus, consent must be obtained when biospecimens are collected for research use.

When research involves only the study of biospecimens and data that were collected for purposes other than the currently proposed project, the second component of the regulatory definition — “identifiable private information”—becomes pivotal. Samples used in genomic research are often coded, meaning that direct patient identifiers are removed and replaced with a code that is linked to identifying information through a key.

In 2008, OHRP issued a [guidance](#) stating that when coded materials were not collected for the currently proposed project and the investigators involved in the research cannot readily ascertain the identities of the individuals, the research could be determined not to involve human subjects and thus would not require informed consent. Investigators involved in the research would be unable to readily ascertain individuals’ identities when, for example, the key linking the code to identifying information is destroyed before the research begins, or when the key holder is prohibited from releasing it to the investigators (such as through an agreement with the researchers, a repository’s IRB-approved written policies and procedures, or other legal requirements).

Thus, much genomic research using banked specimens and data takes place without the specific consent of the individuals from whom they were obtained. In general, this approach is not inconsistent with studies of public attitudes and preferences, which suggest the following:

People want to be asked. People typically want to be asked whether their biospecimens can be used for research. For example, in a survey (n=751) about a proposed biobank at a major academic medical center, 67% of respondents preferred an opt-in approach over opt-out or no consent at all [38]. Similar results have been found in other studies asking about biospecimens collected for research and about biospecimens originally collected for clinical purposes [36,39,40].

Many accept broad consent for future research use. Beyond being asked for initial consent, people often do not want significant control over how their biospecimens are used. In the survey noted above, broad consent was preferred over categorical and study-specific consent models. Again, similar results have been found in other studies with regard to both research and clinical biospecimens [36,37,40-43].

Context matters. Different kinds of biospecimens can be procured for different purposes from people in different situations within different geographical, social, and historical contexts. For example, a one-time general consent may be inappropriate when the research involves a defined community that is vulnerable to group harm or stigmatization [44].

Informed Consent Disclosures

Despite the lack of a “one-size-fits-all” approach, it is safe to assume that when consent is required for biospecimen research, prospective participants want concise, understandable information—“to spend as much time as necessary, but not more, obtaining information and making a decision about taking part in research” [45].

In addition to the elements of information required by federal regulations, best practice guidelines recommend that additional elements be communicated to prospective participants in genomic and biobanking research, such as explanations of large-scale data sharing (e.g., [dbGaP](#)); the possibility of re-contact (to obtain updated information, to collect a new biospecimen, or for recruitment into additional research); confidentiality protections (including the [Genetic Information Non-Discrimination Act](#)); the possibility that the research could result in commercial products; and whether and what kinds of individual, incidental, and aggregate results will be offered to participants.

Although some of this information is complex and even controversial, it remains essential that it be conveyed in a way that is concise, easy to read, and that highlights details most important to informed decision-making.

Vulnerable Populations

The Common Rule calls for unspecified safeguards to protect the rights and welfare of vulnerable participants “...such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons” (§46.111(b)). Moreover, other subparts of the federal regulations *require* additional protections when certain groups are involved in research, including [pregnant women, fetuses, and neonates](#); [prisoners](#); and [children](#).

In general, concerns about informed consent in vulnerable populations are related to diminished capacity to provide consent, as well as the potential for undue influence or coercion. Even so, well-intended efforts to protect vulnerable individuals and communities from harm may actually generate new harms, such as reinforcing stigma, producing unfairness, hindering research unnecessarily, ignoring systemic problems, and restricting individuals’ right to exercise their autonomy [46]. DuBois and colleagues recently offered a series of recommendations intended to restore balance between the imperatives of protecting participants and fostering genuine respect for them, including thinking first about the risks posed by the study design and developing safeguards based on best available evidence as well as dialog with relevant communities.

Emerging Issues & Controversies

Proposed Changes to the Common Rule

In July 2011, the federal government announced proposed changes to the Common Rule—regulations that, although amended over the years, were adopted more than 2 decades ago. These changes were described in an Advance Notice of Proposed Rulemaking ([ANPRM](#)), titled *Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing*

Burden, Delay, and Ambiguity for Investigators. According to the [Federal Register Notice](#), the proposed changes were motivated by concern that the regulations

...have not kept pace with the evolving human research enterprise, the proliferation of multi-site clinical trials and observational studies, the expansion of health services research, research in the social and behavioral sciences, and research involving databases, the Internet, and biological specimen repositories, and the use of advanced technologies, such as genomics (p.44512).

–Federal Register, September 1, 2011

The ANPRM requested [public comment](#), including input on more than 70 specific questions, on how current regulations protecting human research participants might be modernized and revised to be more effective. With regard to informed consent, the ANPRM highlighted problems with consent form length and complexity, as well as confusion and inflexibility surrounding requirements governing waivers of consent. Changes related to informed consent were proposed in three broad categories (p.44522-4):

1. **Improving consent forms.** Modifications to current regulations could include: (a) prescribing with greater specificity the appropriate content that must be included; (b) restricting content that would be inappropriate to include; (c) limiting the acceptable length of various sections; (d) prescribing how information should be presented; (e) reducing institutional “boilerplate”; and (f) making available standardized consent form templates.
2. **Waiver of informed consent in primary data collection.** In addition to requesting comments on how to better clarify current waiver criteria, the ANPRM noted that studies that only involve surveys, focus groups, and interviews with competent adults would generally qualify for a new “Excused” category of research, with only oral consent required.
3. **Strengthening consent protections related to existing data and biospecimens.** The proposed changes would require written consent for research use of biospecimens collected for clinical purposes. The ANPRM suggests that such consent could be obtained via a brief standard consent form, which could be broad enough to cover any data or biospecimens to be collected at any time by the institution. Thus, “the general rule would be that a person needs to give consent, in writing, for research use of their biospecimens, though that consent need not be study-specific, and could cover open-ended future research” (p.44515).

Given the sweeping nature of these and other proposed changes, it is not surprising that the ANPRM has sparked controversy. For example, Lo and Barnes [47] note that although the goal of enhancing protections while eliminating unreasonable burdens is admirable, some proposed changes may allow serious risks. With regard to informed consent, they urged the identification of studies that should be exceptions to any presumption in favor of templated consent forms. They also expressed concern about participants whose ability to give free and informed consent is compromised, and suggested the use of a checklist to assess whether significantly vulnerable participants are targeted in research protocols that would otherwise qualify for the “Excused” category. Allyse and colleagues [48] decried the ANPRM’s focus on informational rather than

participatory risk, questioning the use and effectiveness of blanket consent that would permit unlimited use of biospecimens and data. In contrast, Dresser [49] noted that new requirements for simplified consent forms could promote more informed choices about research participation. She also commented favorably on a prospect raised by one of the questions posed in the ANPRM; namely, whether regulations should require that investigators assess potential participants' comprehension before they are allowed to sign the consent form for at least some types of studies (Q38, p.44523).

Notice of Proposed Rulemaking (NPRM) Released

The interval for public comment on the ANPRM officially closed on October 26th, 2011. On September 2, 2015, DHHS [announced](#) the release of the Notice of Proposed Rulemaking (NPRM) [50], which incorporates feedback gathered during the public-comment period.

The [full NPRM document](#), which is over 130 pages in length, was made publicly available at the Federal Register website on September 8, 2015. A link on the page to regulation.gov allows readers to submit formal comments.

Key changes proposed in the NPRM, as summarized in the [HHS announcement](#), are reproduced below:

- *Strengthened informed consent provisions to ensure that individuals have a clearer understanding of the study's scope, including its risks and benefits, as well as alternatives to participating in the study.*
- *Requirements for administrative or IRB review that would align better with the risks of the proposed research, thus increasing efficiency.*
- *New data security and information protection standards that would reduce the potential for violations of privacy and confidentiality.*
- *Requirements for written consent for use of an individual's biological samples, for example, blood or urine, for research with the option to consent to their future use for unspecified studies.*
- *Requirement, in most cases, to use a single institutional review board for multisite research studies.*
- *The proposed rule would apply to all clinical trials, regardless of funding source, if they are conducted in a U.S. institution that receives funding for research involving human participants from a Common Rule agency.*

Public feedback on the NPRM will be collected for 90 days from the date of posting.

Additional Resources Regarding the ANPRM/NPRM

[Free full-text summary](#) of key aspects of the ANPRM

[Frequently Asked Questions](#) regarding the ANPRM

[A table](#) comparing existing regulation with changes in the ANPRM

[Full text of the NPRM](#) from the Federal Register

The SUPPORT Study Controversy

Background

In 2005, researchers at the University of Alabama–Birmingham (UAB) began a clinical research study in premature infants delivered at 24–28 weeks of gestation. Sponsored by the [Eunice Kennedy Shriver National Institute of Child Health and Human Development](#) (one of the National Institutes of Health) and conducted through the [Neonatal Research Network](#), The Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT; ClinicalTrials.gov #[NCT00233324](#)) was designed to evaluate optimal amounts of oxygen therapy for preventing retinopathy in premature babies.

[Retinopathy of prematurity \(ROP\)](#) is a common cause of vision problems, including permanent blindness, in premature infants. ROP can result from high levels of [oxygen saturation](#), such as those typically targeted by physicians treating premature infants; however, insufficient levels of oxygen saturation in premature infants can result in a variety of negative outcomes. The best possible balance between higher and lower levels of oxygen [has yet to be established](#) [51]. Following review and approval by the individual IRBs at each participating research site, SUPPORT investigators enrolled 1316 premature infants into the trial after obtaining the informed consent of the infants’ parents. Patients were randomly assigned to groups that were targeted for either a lower level (85%-89%) of oxygen saturation or a higher level (91%-95%). Both oxygen saturation ranges were within values considered to represent an acceptable standard of care by the [American Academy of Pediatrics](#).

The [results of the SUPPORT study](#) [52] were published in the *New England Journal of Medicine* in 2010. A total of 130 out of 654 (19.9%) infants in the lower-range group died before hospital discharge, compared with 107 out of 662 (16.2%) in the higher-range group. A total of 41 out of 475 (8.6%) infants in the lower-range group developed severe ROP, compared with 91 out of 509 (17.9%) in the higher-range group. In both cases, the differences were statistically significant. In short, infants enrolled in SUPPORT who received the lower range of oxygen saturation were less likely to suffer ROP, but were at a greater risk of dying.

Issues Surrounding Informed Consent in the SUPPORT Study

In March of 2013, OHRP issued a [letter](#) addressed to university administrators at UAB, identifying deficiencies in the sample consent form approved by the UAB IRB for use in the SUPPORT trial. In particular, it noted three problems with the section that described the “Possible Risks” of participation:

The paragraph does not include any information about the prior research and analyses that had been done looking at the relationship between oxygen and ROP, and what that work indicates about how changing the oxygen range might affect whether an infant develops ROP.

The paragraph does not include any information about the prior research and analyses that had been done looking at the relationship between oxygen and mortality and other forms of morbidity (apart from developing ROP).

The paragraph does not identify any specific risk relating to randomizing infants to a high or low range of oxygen.

OHRP determined that the consent form violated the standards mandated in the Common Rule that prospective participants be provided with “a description of any reasonably foreseeable risks or discomforts” ([45 CFR §46.116\(a\)\(2\)](#)).

Public and Professional Reaction

Following publication of the letter from OHRP, the SUPPORT trial began to receive renewed scrutiny. The advocacy group [Public Citizen](#) drew attention to OHRP’s findings and published an [open letter](#) (PDF) addressed to the Secretary of DHHS that demanded the public release of data from other studies in premature infants being performed by the Neonatal Research Network. In the letter, Public Citizen Director Sydney M. Wolfe and Deputy Director Michael A. Carome described the SUPPORT study as “highly unethical” and the consent form deficiencies as “egregious.” The *New York Times* published an [article](#) and a [news analysis](#) describing the study and the issues raised in OHRP’s letter. Shortly after these articles were published, the [Birmingham Business Journal](#) announced that a class-action lawsuit had been filed against the UAB’s IRB on behalf of the parents of infants enrolled in SUPPORT.

The principal investigators of the SUPPORT study published a [letter](#) [53] defending the trial in the *New England Journal of Medicine*. They noted that the increased risk of death for infants receiving the lower range of oxygen saturation was an unexpected finding and described the consent form used in the study as having been “...conscientiously drafted according to the Code of Federal Regulations and...based on the best available evidence.”

A number of physicians, scientists, and bioethicists have defended the SUPPORT study as appropriate, ethical, and well-conducted. An [editorial](#) [54] published in the *New England Journal* argued that the consent form fairly conveyed prevailing knowledge and provided the information parents needed to make informed decisions about study participation. An accompanying [perspective article](#) [55] noted that

“With regard to SUPPORT, the OHRP is asking that research be described as riskier than it really is and is suggesting that the parents were duped into enrolling their frail infants in dangerous research. Not only is that not true, but it also poses substantial risk to the conduct of valuable comparative effectiveness research both for premature infants and for the general public who continue to face too many treatments where uncertainty prevails about what is best.”

The *New England Journal* also published a [perspective from the NIH](#) [56] in which NIH Deputy Director Kathy Hudson, NICHD Director Alan Guttmacher, and NIH Director Francis Collins disagreed with OHRP's conclusions. They noted that the consent form captured the state of clinical equipoise at the time of the study—but also welcomed the opportunity for substantive national dialogue “...on how best to respect and protect participants in research studies conducted within the standard of care and how to define ‘reasonably foreseeable risks’ in this setting.” In the same issue of the Journal, a [letter](#) [57] from a group of over 40 medical ethicists and pediatricians similarly argued that although “The consent process for clinical research can no doubt be improved,” OHRP's conclusion with regard to the SUPPORT study consent form was “...without substantive merit and overreaches.”

Others, however, have continued to question the SUPPORT study and its consent process. Another [letter](#) [58], also co-signed by more than 40 physicians, scholars, and researchers and published in the *New England Journal*, countered:

“The SUPPORT study itself was complicated. However, the question of whether the consent forms were adequate is not... Although the consent forms varied in content among the institutions at which the study was conducted, none specifically mentioned death as a possible risk... The forms also lacked adequate descriptions of alternative courses of treatment... The oxygen interventions in the study differed from usual clinical care, and that information should have been included...”

An [editorial](#) [59] published in the journal *Nature* also expressed skepticism:

The goals of SUPPORT were laudable and addressed a need for better information for physicians... But in an age in which it is more important than ever that transparency and respect for research subjects must be beyond reproach, the SUPPORT consent forms simply do not pass muster. And although it is true that, collectively, the infants enrolled in the study may have been at no greater risk of a negative outcome than infants who were not enrolled, it is not collectives who sign informed consent documents. It is individuals.

In another [letter](#) (PDF) to UAB in June 2013, OHRP acknowledged the extensive scientific and public discussions since their original determination and their obligation to provide clear guidance with regard to disclosure of risks in randomized studies of treatments that fall within the range of standard of care. Compliance actions against UAB were put on hold, and OHRP [announced](#) a public meeting to gather input from all interested parties. A [transcript of remarks](#) from this meeting (“Matters Related to Protection of Human Subjects and Research Considering Standard of Care Interventions”) is available on the OHRP website; [video of all presentations](#) (YouTube) is also available.

On January 31, 2014, SUPPORT Trial Principal Investigator Wally Carlo, MD, provided an overview of the study as part of the joint NIH Collaboratory/PCORnet Grand Rounds series *Rethinking Clinical Research*. Full video of the presentation together with audio of subsequent discussion is available [here](#); a set of **slides** (PDF) from the presentation are also available.

On August 13, 2015, a U.S. District Court [dismissed the class-action lawsuit](#) filed by parents who alleged their babies had suffered serious injuries as a result of participation in SUPPORT [60]. The judge determined that the infants were already at very high risk of developing complications due to their severe prematurity, and there was insufficient proof to show that the study was the cause. [Editorials in the *New England Journal of Medicine*](#) heralded the ruling as “[vindication for SUPPORT](#)” and a win for research [61,62]. However, others maintain that informed consent in the study was inadequate. In a [New York Times article](#), Dr. Jerry Menikoff, director of OHRP, is quoted as saying, “The consent form was inadequate at the time of the study, and the court ruling doesn’t change that.”

Ethical issues similar to those surrounding SUPPORT, including ones involving consent, also [arose in August of 2013](#) concerning another clinical trial conducting in premature infants—the [Transfusion of Prematures \(TOP\)](#) study.

Bibliography

1. Institute of Medicine. *Responsible Research: A Systems Approach to Protecting Research Participants*. Washington, DC: National Academies Press; 2002.
2. NBAC. *Ethical and Policy Issues in Research Involving Human Participants, Volume 1*. Rockville, MD: US Government Printing Office; 2001.
3. Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of informed consent in cancer clinical trials: a cross-sectional survey. *Lancet* 2001;358:1772-7. [PMID: 11734235](#). doi: 10.1016/S0140-6736(01)06805-2.
4. McCarty CA, Nair A, Austin DM, Giampietro PF. Informed consent and subject motivation to participate in a large, population-based genomics study: the Marshfield Clinic Personalized Medicine Research Project. *Community Genet* 2007;10:2-9. [PMID:17167244](#). doi: 10.1159/000096274.
5. Ormond KE, Cirino AL, Helenowski IB, Chisholm RL, Wolf WA. Assessing the understanding of biobank participants. *Am J Med Genet A* 2009;149A:188-98. [PMID: 19161150](#). doi: 10.1002/ajmg.a.32635.
6. Jefford M, Mileskin L, Matthews J, et al. Satisfaction with the decision to participate in cancer clinical trials is high, but understanding is a problem. *Support Care Cancer* 2011;19:371-9. [PMID: 20333413](#). doi: 10.1007/s00520-010-0829-6.
7. Bergenmar M, Molin C, Wilking N, Brandberg Y. Knowledge and understanding among cancer patients consenting to participate in clinical trials. *Eur J Cancer* 2008;44:2627-33. [PMID: 18818068](#). doi: 10.1016/j.ejca.2008.08.013.

8. Bergenmar M, Johansson H, Wilking N. Levels of knowledge and perceived understanding among participants in cancer clinical trials – factors related to the informed consent procedure. *Clin Trials* 2011;8:77-84. [PMID: 21109583](#). doi: 10.1177/1740774510384516.
9. Rahm AK, Wrenn M, Carroll NM, Feigelson HS. Biobanking for research: a survey of patient population attitudes and understanding. *J Community Genet* 2013. [PMID: 23605056](#). doi: 10.1007/s12687-013-0146-0.
10. Getz KA. Informed consent process: a survey of subjects assesses strengths and weaknesses. *Appl Clin Trials* 2002:30-6.
11. Mackintosh DR, Molloy VJ. Opportunities to improve informed consent. *Appl Clin Trials* 2003:42-8.
12. Albala I, Doyle M, Appelbaum PS. The evolution of consent forms for research: a quarter century of changes. *IRB* 2010;32:7-11. [PMID: 20590051](#).
13. Armstrong N, Dixon-Woods M, Thomas A, Rusk G, Tarrant C. Do informed consent documents for cancer trials do what they should? A study of manifest and latent functions. *Sociol Health Illn* 2012;34:1230-45. [PMID: 22443456](#). doi: 10.1111/j.1467-9566.2012.01469.x.
14. Beardsley E, Jefford M, Mileskin L. Longer consent forms for clinical trials compromise patient understanding: so why are they lengthening? *J Clin Oncol* 2007;25:e13-4. [PMID: 17369564](#). doi: 10.1200/JCO.2006.10.3341.
15. Breese P, Burman W, Rietmeijer C, Lezotte D. The Health Insurance Portability and Accountability Act and the informed consent process. *Ann Intern Med* 2004;141:897-8. [PMID: 15583246](#). doi:10.7326/0003-4819-141-11-200412070-00034.
16. Cheung WY, Pond GR, Heslegrave RJ, Enright K, Potanina L, Siu LL. The contents and readability of informed consent forms for oncology clinical trials. *Am J Clin Oncol* 2010;33:387-92. [PMID:19884804](#). doi: 10.1097/COC.0b013e3181b20641.
17. Cressey D. Informed consent on trial. *Nature* 2012;482:16. [PMID: 22297946](#). doi: 10.1038/482016a.
18. Grossman SA, Piantadosi S, Covahey C. Are informed consent forms that describe clinical oncology research protocols readable by most patients and their families? *J Clin Oncol* 1994;12:2211-5. [PMID: 7931491](#).
19. Kass NE, Chaisson L, Taylor HA, Lohse J. Length and complexity of US and international HIV consent forms from federal HIV network trials. *J Gen Intern Med* 2011;26:1324-8. [PMID: 21748435](#). doi: 10.1007/s11606-011-1778-6.

20. LoVerde ME, Prochazka AV, Byyny RL. Research consent forms: continued unreadability and increasing length. *J Gen Intern Med* 1989;4:410-2. [PMID: 2795264](#).
21. Paasche-Orlow MK, Taylor HA, Brancati FL. Readability standards for informed-consent forms as compared with actual readability. *N Engl J Med* 2003;348:721-6. [PMID: 12594317](#). doi: 10.1056/NEJMsa021212.
22. Paasche-Orlow MK, Brancati FL, Taylor HA, Jain S, Pandit A, Wolf MS. Readability of consent form templates: a second look. *IRB* 2013;35:12-9. [PMID: 23926857](#).
23. Sharp SM. Consent documents for oncology trials: does anybody read these things? *Am J Clin Oncol* 2004;27:570-5. [PMID: 15577434](#).
24. White LJ, Jones JS, Felton CW, Pool LC. Informed consent for medical research: common discrepancies and readability. *Acad Emerg Med* 1996;3:745-50. [PMID: 8853668](#). doi: 10.1111/j.1553-2712.1996.tb03509.x.
25. Mann H, Reyes M. Identifying the human research subject in cluster randomized controlled trials. *IRB* 2008;30:14-8. [PMID: 18953772](#).
26. McRae AD, Weijer C, Binik A, et al. When is informed consent required in cluster randomized trials in health research? *Trials* 2011;12:202. [PMID: 21906277](#). doi: 10.1186/1745-6215-12-202.
27. McRae AD, Weijer C, Binik A, et al. Who is the research subject in cluster randomized trials in health research? *Trials* 2011;12:183. [PMID: 21791064](#). doi: 10.1186/1745-6215-12-183.
28. Sim J, Dawson A. Informed consent and cluster-randomized trials. *Am J Public Health* 2012;102:480-5. [PMID: 22390511](#). doi: 10.2105/AJPH.2011.300389.
29. Edwards SJ, Braunholtz DA, Lilford RJ, Stevens AJ. Ethical issues in the design and conduct of cluster randomised controlled trials. *BMJ* 1999;318:1407-9. [PMID: 10334756](#). doi: <http://dx.doi.org/10.1136/bmj.318.7195.1407>.
30. Vaught J, Rogers J, Myers K, et al. An NCI perspective on creating sustainable biospecimen resources. *J Natl Cancer Inst Monogr* 2011;2011:1-7. [PMID: 21672889](#). doi: 10.1093/jncimonographs/lgr006.
31. Kaufman D, Murphy J, Scott J, Hudson K. Subjects matter: a survey of public opinions about a large genetic cohort study. *Genet Med* 2008;10:831-9. [PMID: 19011407](#). doi: 10.1097/GIM.0b013e31818bb3a.
32. Vermeulen E, Schmidt MK, Aaronson NK, et al. A trial of consent procedures for future research with clinically derived biological samples. *Br J Cancer* 2009;101:1505-12. [PMID: 19861997](#). doi: 10.1038/sj.bjc.6605339.

33. Kaufman D, Murphy J, Erby L, Hudson K, Scott J. Veterans' attitudes regarding a database for genomic research. *Genet Med* 2009;11:329-37. [PMID: 19346960](#). doi: 10.1097/GIM.0b013e31819994f8.
34. Beskow LM, Dean E. Informed consent for biorepositories: assessing prospective participants' understanding and opinions. *Cancer Epidemiol Biomarkers Prev* 2008;17:1440-51. [PMID: 18559560](#). doi: 10.1158/1055-9965.EPI-08-0086.
35. Bryant RJ, Harrison RF, Start RD, et al. Ownership and uses of human tissue: what are the opinions of surgical in-patients? *J Clin Pathol* 2008;61:322-6. [PMID: 18256118](#). doi: 10.1136/jcp.2007.053173.
36. Hamilton S, Hepper J, Hanby A, Hewison J. Consent gained from patients after breast surgery for the use of surplus tissue in research: an exploration. *J Med Ethics* 2007;33:229-33. [PMID: 17400623](#). doi:10.1136/jme.2006.016006.
37. Wendler D. One-time general consent for research on biological samples. *BMJ* 2006;332:544-7. [PMID: 16513715](#). doi: http://dx.doi.org/10.1136/bmj.332.7540.544.
38. Simon CM, L'Heureux J, Murray JC, et al. Active choice but not too active: public perspectives on biobank consent models. *Genet Med* 2011;13:821-31. [PMID: 21555942](#). doi: 10.1097/GIM.0b013e31821d2f88.
39. Murphy J, Scott J, Kaufman D, Geller G, LeRoy L, Hudson K. Public perspectives on informed consent for biobanking. *Am J Public Health* 2009;99:2128-34. [PMID: 19833988](#). doi: 10.2105/AJPH.2008.157099.
40. Vermeulen E, Schmidt MK, Aaronson NK, et al. Opt-out plus, the patients' choice: preferences of cancer patients concerning information and consent regimen for future research with biological samples archived in the context of treatment. *J Clin Pathol* 2009;62:275-8. [PMID: 19017681](#). doi: 10.1136/jcp.2008.061069.
41. Lipworth W, Morrell B, Irvine R, Kerridge I. An empirical reappraisal of public trust in biobanking research: rethinking restrictive consent requirements. *J Law Med* 2009;17:119-32. [PMID: 19771992](#).
42. Treweek S, Doney A, Leiman D. Public attitudes to the storage of blood left over from routine general practice tests and its use in research. *J Health Serv Res Policy* 2009;14:13-9. [PMID: 19103912](#). doi: 10.1258/jhsrp.2008.008016.
43. Kaphingst KA, Janoff JM, Harris LN, Emmons KM. Views of female breast cancer patients who donated biologic samples regarding storage and use of samples for genetic research. *Clin Genet* 2006;69:393-8. [PMID: 16650074](#). doi: 10.1111/j.1399-0004.2006.00614.x.

44. Mello MM, Wolf LE. The Havasupai Indian tribe case—lessons for research involving stored biologic samples. *N Engl J Med* 2010;363:204-7. [PMID: 20538622](#). doi: 10.1056/NEJMp1005203.
45. Beskow LM, Friedman JY, Hardy NC, Lin L, Weinfurt KP. Simplifying informed consent for biorepositories: stakeholder perspectives. *Genet Med* 2010;12:567-72. [PMID:20697289](#). doi: 10.1097/GIM.0b013e3181ead64d.
46. DuBois JM, Beskow L, Campbell J, et al. Restoring balance: a consensus statement on the protection of vulnerable research participants. *Am J Public Health* 2012;102:2220-5. [PMID: 23078487](#). doi: 10.2105/AJPH.2012.300757.
47. Lo B, Barnes M. Protecting research participants while reducing regulatory burdens. *JAMA* 2011;306:2260-1. [PMID: 22110108](#). doi: 10.1001/jama.2011.1727.
48. Allyse M, Karkazis K, Lee SS, et al. Informational risk, institutional review, and autonomy in the proposed changes to the common rule. *IRB* 2012;34:17-9. [PMID: 22830179](#).
49. Dresser R. Research ethics. Aligning regulations and ethics in human research. *Science* 2012;337:527-8. [PMID: 22859472](#). doi: 10.1126/science.1218323.
50. Federal Register. September 8, 2015. Federal Policy for the Protection of Human Subjects. Available at: <https://www.federalregister.gov/articles/2015/09/08/2015-21756/federal-policy-for-the-protection-of-human-subjects>. Accessed September 10, 2015.
51. Finer N, Leone T. Oxygen saturation monitoring for the preterm infant: the evidence basis for current practice. *Pediatr Res* 2009;65:375-80. [PMID: 19127213](#). doi: 10.1203/PDR.0b013e318199386a.
52. SUPPORT Study Group. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-69. [PMID: 20472937](#). doi: 10.1056/NEJMoa0911781.
53. Carlo WA, Bell EF, Walsh MC. Oxygen-saturation targets in extremely preterm infants. *N Engl J Med* 2013;368:1949-50. [PMID: 23593943](#). doi: 10.1056/NEJMc1304827.
54. Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT. *N Engl J Med* 2013;368:1929-31. [PMID: 23593944](#). doi: 10.1056/NEJMe1304996.
55. Magnus D, Caplan AL. Risk, consent, and SUPPORT. *N Engl J Med* 2013;368:1864-5. [PMID: 23597408](#). doi: 10.1056/NEJMp1305086.
56. Hudson KL, Guttmacher AE, Collins FS. In support of SUPPORT—a view from the NIH. *N Engl J Med* 2013;368:2349-51. [PMID:23738511](#). doi: 10.1056/NEJMp1306986.
57. Wilfond BS, Magnus D, Antommaria AH, et al. The OHRP and SUPPORT. *N Engl J Med* 2013;368:e36. [PMID: 23738513](#). doi: 10.1056/NEJMc1307008.

58. Macklin R, Shepherd L, Dreger A, et al. The OHRP and SUPPORT – Another View. N Engl J Med 2013 [ePub ahead of print]. [PMID: 23803135](#). doi: 10.1056/NEJMc1308015.

59. [No authors]. Subject to question. Nature 2013;500:377. [PMID: 23977685](#).

60. Looney v. Moore. Case No.: 2:13-cv-00733-KOB. United States District Court for Northern District of Alabama.

61. Lantos JD. Vindication for SUPPORT. N Engl J Med 2015; Epub ahead of print. [PMID: 26332442](#). doi: 10.1056/NEJMp1510876.

62. Drazen JM, Solomon CG, Morrissey S, Greene MF. Support for SUPPORT. N Engl J Med 2015; Epub ahead of print. [PMID: 26332278](#). doi: 10.1056/NEJMe1511158.

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